The cost-effectiveness of cervical screening in Australia: what is the impact of screening at different intervals or over a different age range?

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Abstract

Objective: To estimate the cost-effectiveness of altering the currently recommended interval and age range for cervical screening of Australian women.

Methods: The cost and effectiveness estimates of alternative screening strategies were generated using an established decision model. This model incorporated a Markov model (of the natural history of cervical cancer and pre-cancerous lesions) and decision trees which: 'mapped' the various pathways to cervical cancer screening; the follow-up of abnormal Pap test results; and the management of confirmed lesions. The model simulated a hypothetical large cohort of Australian women from age 15 to age 85 and calculated the accumulated costs and life-years under each screening strategy.

Results: Our model estimated that moving from the current two-yearly screening strategy to annual screening (over the same age range) would cost $379,300 per additional life-year saved. Moving from the current strategy to three-yearly screening would yield $117,100 of savings per life-year lost (costs and effects both discounted at 5% per year), with a relatively modest (<5%) reduction in the total number of life-years saved by the program.

Conclusions: Although moving to annual screening would save some additional lives, it is not a cost-effective strategy. Consideration should be given to increasing the recommended interval for cervical screening. However, the net value of any such shift to less effective (e.g. less frequent) and less costly screening strategies will require better evidence about the cost-effectiveness of strategies that encourage non-screeners or irregular screeners to have a Pap test more regularly.

Key words: Mass screening; cost-benefit analysis; program evaluation.

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The regular screening of women using cervical smears and Pap testing to detect pre-cancerous lesions has been one of the most widely adopted strategies for preventing deaths due to cancer. In Australia since the 1960s, there has been a continuous fall in mortality from cervical cancer,[1] and it is estimated that 70% of squamous carcinomas of the cervix are prevented by screening.[2] Australia's National Cervical Screening Program (including State-based Pap test registries) began in 1991 and has been an important factor in increasing the participation of women in regular screening, improved laboratory standards, and better follow-up of detected abnormalities. Prior to the program (from 1982-91), the age-standardised incidence of cervical cancer was declining at an average of 0.7% per year and mortality was declining at 2.7% per year. From 1991 to 2003 the average annual decline in cervical cancer incidence and mortality were 5.2% and 5% respectively.[3]

Although regular screening using Pap tests is of proven efficacy, there is still debate about the optimum frequency and age range for screening programs.[4,5] This is partly a reflection of continuing scientific uncertainty about the biology of cervical cancer and the accuracy of the screening tests, but also, in some countries, the attachment of professional groups to particular screening intervals. Screening policies in Western countries range from those recommending annual screening (some United States professional organisations) to those with three- or five-yearly recommended screening intervals (most European countries and some Canadian provinces).[5] Australia, with a two-yearly recommended screening interval (since 1990), is at the more frequent end of the spectrum of existing national programs.

Debate about the optimum screening strategy should involve consideration of cost-effectiveness (i.e. efficiency). National screening programs – together with all the ensuing diagnostic and treatment activities – are expensive: the annual cost to Australia's governments (Federal and State) of providing or following up cervical screening is estimated to be more than $A140 million (in

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2001).[9] Moreover, some of the resources allocated to screening for cervical cancer might save more lives or life-years if invested in other health programs.

There are also implicit trade-offs between costs and benefits/harms in the different types of cervical screening strategy that could be used. Because the incidence and prevalence of cervical pre-cancerous lesions are highly age dependent and their progression is relatively slow, both the costs and effectiveness of conventional screening by Pap test critically depend on the frequency and age range of regular screening. For example, instead of screening more frequently, could more cancers be prevented by stopping screening when women are older, and at what extra cost? Conversely, could substantial resources be saved by reducing the number of unnecessary early re-screens or lengthening the screening interval, and the additional resources used more effectively in targeting women who have never had a Pap test or who screen irregularly? This paper aims to quantitatively estimate some of these trade-offs to inform decisions about the optimum cervical screening strategy for Australia.

Cost-effectiveness findings are not easily transferred between countries or health systems.[6] Analyses need to be nationally specific in order to reflect the specific testing technologies in common use and the local costs and effectiveness of the prevailing patterns of clinical practice and provider payment. In order to integrate the various data and assumptions about the natural history of cervical cancer, the performance of the screening tests, and simulate the cost and effectiveness of diagnostic and therapeutic follow-up under alternative strategies, it is necessary to use a modelling approach.[7,8]

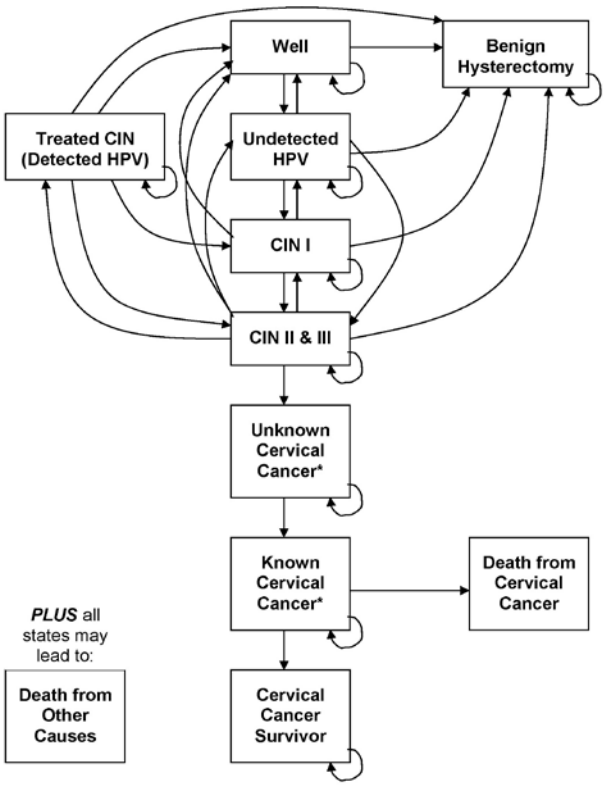
This paper presents the results of a modelling-based cost-effectiveness study of cervical screening in Australia. The study was commissioned by the National Advisory Committee (NAC) of the National Cervical Screening Program (NCSP). Specifically, the study aimed to compare the costs and effectiveness (life-years saved) of the present Australian screening policy – which recommends two-yearly screening between the ages of 20 and 69 – with screening women at alternative intervals (annually,

Table 1: Description of the model's 20 Markov or disease states.

State	Definition
Well	Never infected with HPV, no history of CIN
Benign hysterectomy	Hysterectomy for cause other than cervical cancer or CIN
Undetected HPV	Undiagnosed cervical HPV infection
Detected HPV	Diagnosed cervical HPV infection, OR post-treatment for CIN
CIN I	Cervical Intraepithelial Neoplasia grade I
CIN II & III	Cervical Intraepithelial Neoplasia grade II or III
Unknown Stage I	Undiagnosed Stage I cervical cancer
Detected Stage I	Stage I cervical cancer diagnosed by Pap or symptoms
Stage I survivor	Five years after initial diagnosis of Stage I cancer
Unknown Stage II	Undiagnosed Stage II cervical cancer
Detected Stage II	Stage II cervical cancer diagnosed by Pap or symptoms
Stage II survivor	Five years after initial diagnosis of Stage II cancer
Unknown Stage III	Undiagnosed Stage III cervical cancer
Detected Stage III	Stage III cervical cancer diagnosed by Pap or symptoms
Stage III survivor	Five years after initial diagnosis of Stage III cancer
Unknown Stage IV	Undiagnosed Stage IV cervical cancer
Detected Stage IV	Stage IV cervical cancer diagnosed by Pap or symptoms
Stage IV survivor	Five years after initial diagnosis of Stage IV cancer
Death from cervical cancer	Death from cervical cancer
Death from other cause	Death from cause other than cervical cancer

Notes:
The stage definitions of cervical cancer are:
I – Cancer confined to cervix.
II – Cancer involving upper two-thirds of vagina or parametrial tissues but not to pelvic sidewall.
III – Cancer involving lower one-third of vagina or parametrial tissues to pelvic sidewall.
IV – Cancer spread outside of the pelvis.

Figure 1: Markov model for the natural history of cervical carcinogenesis.



** Both Known Cervical Cancer and Unknown Cervical Cancer are divided into four Markov states: one for each stage of cancer diagnosis, I to IV. Abbreviations: HPV = Human Papillomavirus; CIN = Cervical Intra-epithelial Neoplasia.*

three-yearly or five-yearly) and/or screening over five different age ranges.

Methods

The model used to generate the cost-effectiveness estimates was first developed by researchers at Duke University (North Carolina) for evaluating cervical screening policies in the United States,[9,10] and has been adapted to the Australian policy and clinical context with their assistance. It is built in DATA™ 3.5 for Healthcare (TreeAge Software Inc., MA, USA) and allows simulation of a large, hypothetical cohort of women from a particular age and over their lifetime. Below we describe parameter values and changes made to the original model to reflect Australian epidemiological data or screening and clinical management practices. For a full description of the model, see Myers et al. 2000 or the 1999 AHCPR report.[9,10]

Model structure

The model is based on a 20-state 'Markov model' of the natural progression of cervical cancer and pre-cancerous lesions in a hypothetical cohort of unscreened women (see Table 1 and Figure 1). Markov models comprise a finite range of disease or health states and specify the probabilities for simulated individuals of moving between different states during each 'Markov cycle' (usually, each year of life). In combination with decision trees, they have proved the most adaptable way of simulating the long-term prognosis and care costs of patients under different assumptions, especially where the disease process is a gradual one.[11,12]

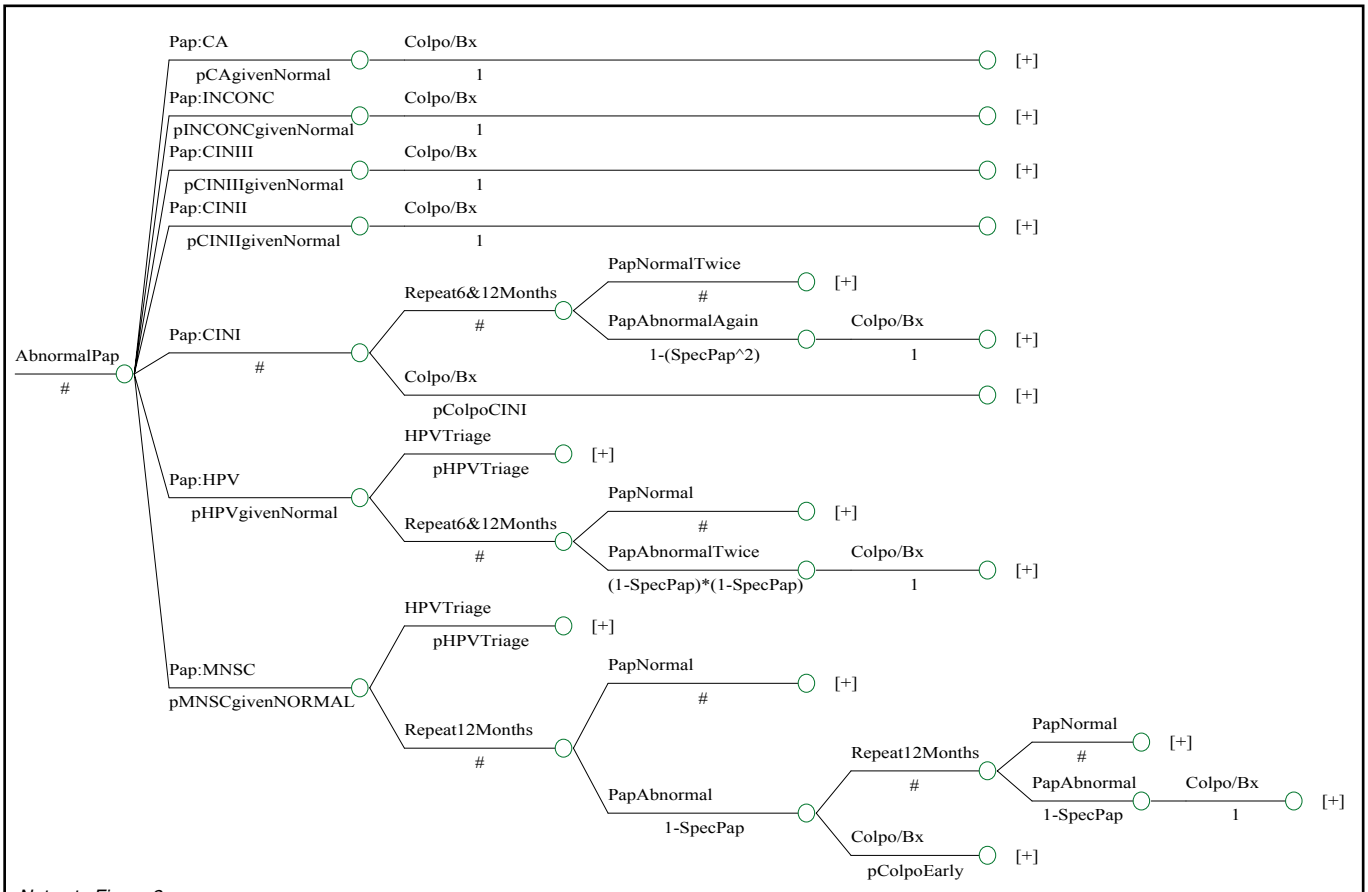
Within each Markov state in the model, decision trees reflect the possible clinical/screening pathways that women who are screened or not screened may experience, and if screened, the different results of Pap tests and how they are followed up. For example, there are some branches within the model which represent the treatment of different confirmed lesions following screening. It is after these treatment branches that the Markov transition probabilities differ from the 'natural history' model.

The main structural changes to the Australian-adapted model were (see Note 1 at end of paper):

- Modification of the possible types of Pap test results to reflect the classification system used in Australia – normal, plus seven types of abnormal result:

— MNSC (Minor Non-Specific cell Changes).
— HPV effect.
— CIN I (Cervical Intra-epithelial Neoplasia, grade I lesion).

Figure 2: Decision tree branches showing follow-up pathways for those with an abnormal Pap test result.



Notes to Figure 2:

Note that pHPVTriage=0 and therefore these branches of the tree are effectively 'switched off' (i.e. we did not evaluate HPV testing as a component of the follow-up of abnormal Pap test results).

Abbreviations and symbols: CIN = Cervical Intra-epithelial Neoplasia; HPV = Human Papillomavirus; MNSC = Minor Non-Specific cell Changes; Colpo/Bx = Colposcopy with Biopsy.

NB: In decision tree software the '#' symbol represents a probability of one minus the summed probability of all the other branches from the same node.

— CIN II.
— CIN III.
— Cancer.
— Inconclusive (usually, between CIN III and Cancer, or between CIN II and CIN III).

- Use of diagnostic follow-up and treatment protocols for each type of detected abnormality to reflect the Australian NHMRC guidelines.[13] For example, for detected CIN I lesions two branches reflected the two main management strategies, observational (i.e. repeat Pap tests) and active management (i.e. ablative or excisional therapy).

Since this analysis was conducted, both the classification system for abnormal cytological results and Australian guidelines for their follow-up and management have been updated, and the implications of this will be discussed. Figure 2 shows the basic structure of the tree for 'well' women after an abnormal Pap test result. (The full decision tree, with all Markov states and policy alternatives, contained more than 6,000 branches, so it is only possible to show selected parts of the structure.)

Data sources and probabilities

The biological processes underlying the natural history of cancer

Table 2: Probability estimates for the natural history Markov model.

Parameter	Base case
Prevalence of HPV infection at age 15	0.1
Prevalence of CIN I at age 15	0.01
Age-specific incidence of HPV infection	
15	0.1
16	0.1
17	0.12
18	0.15
19	0.17
20	0.15
21	0.12
22	0.10
23	0.10
24-29	0.05
30-49	0.01
50 +	0.005
Age-specific regression rate, HPV to Well age	
15-24	0.7/18 months
25-29	0.5/18 months
30 +	0.15/18 months
Progression rate, HPV to CIN I	0.2/3 years
Proportion of HPV infections progressing directly to CIN II/III	0.1
Probability of progression after treatment for CIN	0.05
Regression rate, CIN I to unknown HPV, age	
15-34	0.65/6 years
35+	0.4/6 years
Progression rate, CIN I to CIN II/III, age	
15-34	0.1/6 years
35+	0.35/6 years
Regression rate, CIN II/III to unknown HPV[a]	
15-39	0.4/6 years
40+	0.35/6 years
Progression rate, CIN II/III to Stage I cancer[a]	
15-34	0.25/12 years
35-44	0.3/12 years
45+	0.4/12 years
Progression rates between undetected cancer stages:	
from Stage I to II	0.9/4 years
from Stage II to III	0.9/3 years
from Stage III to IV	0.9/2 years
Annual probabilities of symptomatic detection of cancer:	
Stage I	0.15
Stage II	0.225
Stage III	0.6
Stage IV	0.9
Annual probability of survival by cancer stage, and by year post-diagnosis[b]	
Stage I: Year 1	0.9712
Year 2	0.9549
Year 3	0.9568
Year 4	0.9784
Year 5	0.9785
Stage II: Year 1	0.9075
Year 2	0.8769
Year 3	0.9234
Year 4	0.9341
Year 5	0.9614
Stage III: Year 1	0.7070
Year 2	0.7385
Year 3	0.8618
Year 4	0.9239
Year 5	0.9150
Stage IV: Year 1	0.3627
Year 2	0.4534
Year 3	0.6951
Year 4	0.7873
Year 5	0.7819

Notes:
Sources: All Markov transition probabilities are as per the model of the natural history of cervical cancer in US women (Myers et al. 2000),[11] except:
(a) These two transition rates were adjusted slightly from the original parameters in the US model in order to improve the fit between modelled and actual age-specific cervical cancer mortality.
(b) The annual survival rates by cancer stage are derived by adjusting the US year-specific survival probabilities so that they result in the estimated five-year survival rates (post-diagnosis) of: 85% for Stage I cervical cancer, 66% for Stage II, 38% for Stage III, and 7% for Stage IV cancer. These in turn are derived from NSW Cancer Council five-year survival data for the years 1980 to 1995 (84.9% for localised cancer [assumed equivalent to Stage I], 49.5% for regional cancers [assumed equivalent to Stages II & III], and 6.5% for distant cancers [assumed equivalent to Stage IV]). This data was the only Australian data we could find relating cancer survival to the spread or stage of disease.
Also, the following parameters (not shown in the above table) were derived directly from Australian sources:
Age-specific hysterectomy fractions, from: ABS (1995) cited in Table D2 in: Cervical Screening in Australia 1997-1998, Australian Institute of Health and Welfare (2000), Cancer Series No. 14. AIHW, Canberra.
Age-specific all-cause mortality, from Table 1.3 (Underlying cause, age-specific rates) in: Australian Bureau of Statistics (2000) 1999 Causes of Death (Cat. No. 3303.0).

were assumed to be similar to those of US women, so the basic Markov model structure and allowable transitions were the same in the Australian-adapted model. However, where Australian data were available, some transition probabilities were altered (e.g. age-specific hysterectomy fractions, age-specific all-cause mortality, and five-year cervical cancer survival; see Table 2). While many of the remaining transition probabilities were predominantly from populations of US women, with a different ethic mix to Australian women, no alternative data sources were available. In a calibration exercise,[14] this natural history model still over-estimated the cancer incidence rate among young Australian women, so we also (a) changed the rate of regression from CIN II/III (to 'detected HPV'), and (b) made the rate of progression and regression from CIN II/III age-dependent, until the model-generated age-specific incidence rates were close to Australian estimates. (NB. Similar adjustments were necessary in the MISCAN model in order to obtain an improved fit between modelled and actual data on age-specific cervical cancer mortality.[15]) Tree probabilities (i.e. not state transition probabilities) are shown in Table 3. The cost of different screening, diagnostic and therapeutic activities are shown in Table 4 (data sources are shown in the table footnotes).

Table 3: Probability estimates related to screening.

Parameter	Base case	Range
Pap test sensitivity[a]	0.8[a]	0.75-0.85[c]
Pap test specificity[a]	0.994[a]	0.991-0.997[c]
Probability of observational follow-up (instead of direct referral for colposcopy) following abnormal Pap test result of CIN I	0.5[d]	0.3-0.7[d]
Probability of having a colposcopy a year early when being followed up observationally (following abnormal Pap test result of Minor Non-Specific Changes)[b]	0.1[d]	0-0.5[d]
Probability of active treatment (rather than observational management by repeat smears) following colposcopic diagnosis of CIN I histology	0.3[d]	0.2-0.5[d]
Sensitivity of colposcopy for detecting true disease status: CIN I, CIN II & III, and cancer	0.9[d]	0.9-1[d]
Probability of CIN I treatment being effective if true histological disease status is CIN II or III	0.95[d]	0.9-0.97[d]

Notes:

(a) These sensitivity and specificity estimates are for conventional Pap tests, and are for cytology threshold MNSC or above at detecting histology of CIN I or higher grade lesions. Our parameter values reflect relatively positive assumptions about test accuracy, and are based on expert opinion with: Soost HJ et al. Acta Cytologica. 1991: 35(1):8-14, and van Oortmarssen G and Habbema J. British Journal of Cancer. 1991:64(3):559-65.

(b) Although NHMRC guidelines advise that following a Pap result of MNSC a colposcopy is not required until there have been two further abnormal annual smears, it is likely that a proportion of women receive colposcopies early (i.e. after one other abnormal smear).

(c) Pap test sensitivity and specificity were varied together in the sensitivity analysis, since they tend to be inversely correlated.

(d) Expert opinion of a highly experienced cervical cytologist/cancer epidemiologist, and a gynaecological surgeon.

Interventions/service models, study subject and setting

The choice and specification of alternative screening programs was determined by the commissioners of the research. The analysis

Table 4: Cost estimates in the model and ranges for sensitivity analysis.

Parameter	Base case	Range
Cost of a Pap test (including: weighted doctor visit fee, smear reading fee, and PEI fee)	$52[a]	+25% & -25%
Cost of a colposcopy (including: specialist consultation fee, procedure fee, and – for a proportion – biopsy and histopathology cost)	$136[a]	+25% & -25%
Cost of ablative therapy (including: specialist consultation fee, procedure fee, and average costs for hospitalisation, anaesthesia and histopathology [for some])	$229[a]	+25% & -25%
Cost of excisional therapy (including: specialist consultation fee, procedure fee, and average costs for hospitalisation, anaesthesia and histopathology [for some])	$596[a]	+25% & -25%
Cost of hysterectomy – not for cancer (including: specialist consultation fee, procedure fee, and average costs for hospitalisation, and anaesthesia)	$4,355[a]	+25% & -25%
Cost of simple hysterectomy for cancer (including costs as above, plus histopathology costs)	$7,050[a]	+25% & -25%
Cost of radical hysterectomy for cancer (including costs as above, plus histopathology costs)	$7,558[a]	+25% & -25%
Cancer work-up and treatment costs by stage (weighted average of various diagnostic procedures and therapies – see table footnote b):		
Stage I work-up	$477	+25% & -25%
Stage I treatment	$10,161	
Stage II work-up	$708	+25% & -25%
Stage II treatment	$11,958	
Stage III work-up	$767	+25% & -25%
Stage III treatment	$10,469	
Stage IV work-up	$767	+25% & -25%
Stage IV treatment	$8,378	
Cost of terminal care (assumed for all cancer deaths, in last year of life only)	$15,000[c]	$10,000 to $25,000[c]

Key to data sources:

(a) 85% of the relevant MBS schedule fee (or a weighted average of a range of the relevant MBS item fees), as well as relevant AN-DRG (v4.1) standard in-patient care costs for a proportion of some procedures requiring hospitalisation (e.g. 25% of women having surgical excision of lesions; all having hysterectomies). Details available from the authors.

(b) Work-up costs were estimated by applying MBS schedule item fees to the type and number of diagnostic tests provided in the US treatment model. Treatment costs included the relevant AN-DRG standard costs for chemotherapy, radiotherapy and/or surgery, adjusted for the probable length of stay for treating cervical cancers, and also adjusted for the proportion who received combinations of these therapies or none of them.

(c) In the absence of other reliable Australian data sources, the cost of terminal care was crudely extrapolated from a 1991 study of the cost of terminal care for breast cancer patients and another of people with hepatitis C (Salkeld G and Gerard K, Australian Journal of Public Health, 1994:18(4):388-93; Shiell A et al. Medical Journal of Australia, 1999:171(4):189-93.

was designed to compare the recommended screening strategy (two-yearly screening from age 20 to 69) with: three alternative screening frequencies (annual, three-yearly, and five-yearly); one alternative starting age (25, instead of 20); and two alternative stopping ages (64 or 74, instead of 69), thus defining a matrix of 23 [= (4 × 2 × 3) – 1] possible alternatives to the current screening strategy.

Total accumulated costs and life-years were estimated by simulating a hypothetical cohort of 15-year-old women and following them through the model for 70 cycles (years) – that is, until they reached 85 years old, or died. Since the screening policies being compared ended – at the latest – at age 74, it was assumed that the effects of screening would not be very different beyond age 85.

The main basis for determining which diagnostic and management procedures women experience was the 1994 NHMRC Treatment Guidelines for the Management of Women with screen-detected abnormalities.[13] This information was supplemented by additional information from the published literature, input from clinicians, and data from Health Insurance Commission (see notes to Table 3).

Measuring effectiveness

The critical parameters that determine the effectiveness of screening include: the sensitivity and specificity of the primary test (conventional Pap test and cytological reading); the sensitivity and specificity of any further diagnostic tests (e.g. cell sample histology and direct colposcopy of cervix); and the assumed effectiveness of treatments. These estimates are shown in Table 3 together with their sources.

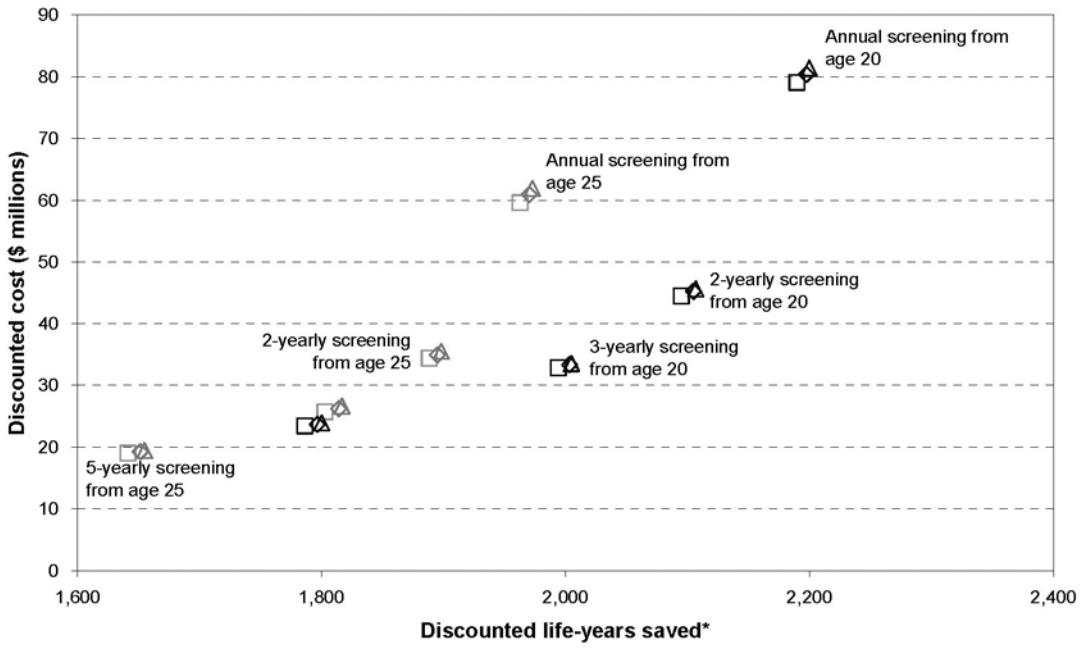
Measuring and valuing resource use

The model includes the variable costs of screen-taking, reading and the various follow-up, diagnostic and treatment procedures that may follow abnormal test results or symptomatic diagnosis. Table 4 shows the cost (Australian $, 1998) of the various screening, diagnosis and treatment activities that are included in the model. The cost data sources are indicated in the table footnotes. Future costs and life-years were both discounted to their present value in the main ('base case') analysis at a rate of 5% per year.

Data analysis and sensitivity analysis

Unfortunately, this model did not easily allow the simulation of distinct cohorts of women with different screening behaviours (such as high or low compliance with recommended screening intervals). For simplicity, we therefore simulated cohorts of women who all totally complied with each policy's specified age range and frequency of screening. Also, without individual-specific data on screening-related costs and effectiveness (e.g. as typically comes from clinical trials), this is a 'deterministic' rather than a 'stochastic' cost-effectiveness analysis; it used the best available point estimates of the cost, effectiveness and probability parameters.[16] We therefore produce base case estimates of cost-effectiveness ratios and explore how simple changes in the base case parameters alter these estimates (i.e. one-way and two-way sensitivity analysis).

Figure 3: Cost and life-years saved[a] under each screening strategy (both discounted at 5% per year).



Notes:
(a) For a hypothetical cohort of 100,000 women from age 15 till age 85 or death.

Key to symbols: shape of symbol denotes age at which screening finishes (Square=64, Diamond=69; Triangle=74). Lighter coloured symbols denote screening strategies starting at age 25.

The parameter ranges for performing sensitivity analyses were sometimes based upon published literature. For some parameters these were adjusted in line with expert opinion (e.g. Pap test sensitivity and specificity). Otherwise, fairly arbitrary ranges were used (e.g. in the absence of sample distributions for most cost estimates, these parameters were simply varied between -25% and +25%; the cost of terminal cancer care in the final year of life (base case $15,000) was varied between $10,000 and $25,000 to reflect the very broad range of estimates in the literature).

Results

The results presented below relate only to the incremental effectiveness, and cost-effectiveness in terms of the cost per life-year saved, of moving to alternative screening strategies from the recommended strategy of two-yearly screening between age 20 and 69. Cost-effectiveness results in terms of the cost per cancer case detected or cost per cancer death avoided are available from the authors.

Effectiveness and costs of the current strategy

The model estimates that in a cohort of 100,000 women from age 15 to 85 years the present screening strategy prevents 451 cancer cases, 144 cancer deaths and saves 2,100 life-years, relative to no cervical screening. (If these outcomes are *not* discounted at 5% per year, the effectiveness estimates are 2,587, 912, and 21,400 respectively.) Over the 70 years of these women's modelled lives the present strategy costs an estimated $45 million ($131 million without discounting) in both screening and cervical pre-cancer/cancer treatment costs.

Incremental cost-effectiveness analysis

The incremental effectiveness and cost-effectiveness of moving to either *more* effective or *less* effective screening strategies are shown in Table 5 and Table 6 respectively, and in Figure 3. The results for six 'dominated' strategies are not shown; these would not be recommended because they are both less effective and more costly than one of the other strategies evaluated. Moving from the present strategy to more effective and more costly screening strategies saves more life-years, but at considerable cost for each additional life-year saved. Each additional life-year saved by moving to annual screening would cost between $380,000 and $400,000. Also, by extending the age range of two-yearly screening to 74, the few extra life-years gained (only two) cost $197,500 each (see Table 5).

Moving from the present screening strategy to less effective and less costly strategies yields savings, but at the same time increases the number of cancer cases and cancer deaths and reduces the number of life-years saved due to screening (i.e. 'life-years lost'). For example, moving from the present screening strategy to three-yearly screening (but over the same age range) yields $117,100 of savings for each of the 102 life-years lost (a total saving, discounted over 70 years, of $12 million) (see Table 6). This total saving is achieved with a small (<5%) reduction in the number of discounted life-years saved in the modelled cohort.

Sensitivity analysis

The cost-effectiveness estimates presented in the tables are most sensitive to changes in the assumed performance of the Pap test (i.e. specificity and sensitivity), the rate used to discount costs and life-years, and the cost of Pap tests. For example, more conservative estimates of Pap test sensitivity (0.75) and specificity (0.997) result in a substantially lower incremental cost-effectiveness ratio for changing to three-yearly screening ($100,700). Alternatively, with a higher discount rate of 10% the same policy change would yield $267,900 of savings for each life-year lost. If the cost of Pap tests was $100 (rather than the $52 assumed in the base case analysis) then the same incremental

Table 5: Incremental cancers prevented, deaths avoided, life-years saved and cost per life-year saved with shifts from current to more effective strategies.

Screening interval and age range		Incremental effectiveness[a] and cost-effectiveness[a] (relative to the current strategy in a birth cohort of 100,000 women from age 15 to 85)				
Screening starts	**Screening ends**	**Cancers prevented**	**Deaths avoided**	**Life-years saved (LYS)**	**Cost per LYS**	**Total additional cost per annum**
Annual screening						
from age 20	to age 64	28	4.1	85	$397,900	$33.8m
	to age 69	34	5.7	93	$379,300	$35.3m
	to age 74	38	6.5	95	$380,200	$36.1m
from age 25	to age 64, 69, 74	= Dominated strategies				
Two-yearly screening						
from age 20	to age 74	3	0.7	2	$197,500	$395,000
from age 25	to age 64, 69, 74	= Dominated strategies				

Notes:
(a) Incremental = relative to the current strategy of two-yearly screening from age 20 to age 69; effectiveness and cost-effectiveness are for a simulated cohort of 100,000 women from age 15 to age 85, with future costs and effects both discounted at 5% per year.
'Dominated strategies' are those which are both more costly and less effective than any one (or more) of the other strategies. Dominated strategies would therefore never be chosen on cost-effectiveness grounds.
Roundings: All cost-effectiveness estimates have been rounded to the nearest $100.

cost-effectiveness ratio for moving to three-yearly screening would be $223,213. However, other factors had a surprisingly small impact on the cost-effectiveness ratios, including: the incidence of cervical cancer (both by varying the progression rate from CIN II/III to Stage I cancer, and by doubling the initial prevalence of HPV infection); the proportion of women with confirmed CIN I who received active management (as opposed to repeat Pap tests); and the cost of ablative or excisional therapy. The full results of the sensitivity analyses are available from the authors.

Discussion

This modelling exercise has made explicit the key trade-offs implied in moving away from the present cervical screening strategy in Australia to screening at different intervals and over a different age range. The incremental cost-effectiveness of moving from two-yearly to annual screening creates modest gains in life-years at substantial cost: almost $400,000 per additional life-year saved. This is over three times the cost of life-years gained by moving from three-yearly to two-yearly screening ($117,000) (or, conversely, over three times the savings yielded per life-year lost by moving from two-yearly to three-yearly screening).

Of the 23 alternative policies evaluated, we have identified six policy shifts – all those to screening annually from age 25, or two-yearly from age 25 – that would not be chosen because they are both less effective and more costly than other strategies. Of the remaining 17 alternative screening policies, our analyses have shown that moving to annual from two-yearly screening provides limited extra life-years at substantial additional cost. It is very difficult to say whether the estimated cost of saving particular life-years is good value for money in a particular population and health system. However, if the precedent of decisions made by the Pharmaceutical Benefits Advisory Committee is taken as an indication of the Australian Government's willingness to pay for additional life-years, then moving to annual screening is clearly unaffordable (between 1991 and 1996 new drugs that achieved incremental cost-effectiveness ratios of more than $80,000 per life-year gained were very likely to be rejected for listing[28]). Moreover, by the same logic, over-screening (i.e. screening more frequently than two-yearly when not at higher risk) should be actively discouraged as a highly inefficient use of government resources.[29] At present, almost 30% of Australian women with a negative Pap test re-screen earlier than recommended (i.e. have another test within the following 21 months), but it is not known what proportion of these were justified on clinical grounds.[3]

The implication, then, is that Australia could consider increasing the recommended interval for cervical screening. However, since this would involve sacrificing life-years in order to yield savings – estimated to be more than $110,000 per life-year lost by moving to three-yearly screening over the same age-range – to be efficient, such a policy decision should also involve (a) cost-effectiveness information showing that the alternative strategies that the savings could be re-invested in would produce additional life-years (or quality-adjusted life-years) more cheaply, and (b) appraisal of whether the savings would be actually realised and useable in ways that will generate more health gains (either within the National

Table 6: Incremental cancers, deaths, life-years lost and cost per life-year lost by shifts from current to less effective strategies.

Screening interval and age range		Incremental effectiveness[a] and cost-effectiveness[a] (in a birth cohort of 100,000 women from age 15 to 85)				
Screening starts	**Screening ends**	**Cancers**	**Deaths**	**Life-years lost (LYL)**	**Incremental savings per LYL**	**Total savings per annum**
Two-yearly screening:						
from age 20	to age 64	7	2	10	$79,200	$792,000
Three-yearly screening:						
from age 20	to age 64	39	8.2	111	$111,800	$12.4m
	to age 69	33	6.3	102	$117,100	$11.9m
	to age 74	31	5.8	100	$116,900	$11.7m
from age 25	to age 64	85	19.1	302	$64,600	$19.5m
	to age 69	78	17.0	291	$65,300	$19.0m
	to age 74	75	16.1	288	$64,600	$18.6m
Five-yearly screening:						
from age 20	to age 64	97	21.8	318	$68,500	$21.8m
	to age 69	92	20.0	308	$69,900	$21.5m
	to age 74	88	19.0	305	$70,000	$21.4m
from age 25	to age 64	130	29.9	463	$56,600	$26.2m
	to age 69	124	28.1	453	$57,300	$25.9m
	to age 74	121	27.1	450	$57,300	$25.8m

Notes:
(a) Incremental = relative to the current strategy of two-yearly screening from age 20 to age 69; effectiveness and cost-effectiveness are for a simulated cohort of 100,000 women from age 15 to age 85, with future costs and effects both discounted at 5% per year.
Roundings: All cost-effectiveness estimates have been rounded to the nearest $100.

Cervical Screening Program or in other disease or service areas). This implication also assumes that a society's willingness to pay for new health gains from new investment (e.g. as reflected in previous Pharmaceutical Benefits Advisory Committee decisions) is the same as a society's willingness to accept financial compensation for forgoing health benefits that are already being received. Some analysts have shown that this may not be the case, and therefore that for disinvestment decisions, a higher willingness-to-pay threshold should be employed.

Unlike our modelled, policy-complying hypothetical cohorts, in reality there are still considerable numbers of Australian women who have never had a Pap test (11% of the target age group), who screen irregularly (e.g. one-quarter of eligible women in New South Wales, 1998 data), or who re-screen earlier than necessary.[17,18] In another paper, we have used the results presented here to model this variation in actual screening behaviour and to assess its impact on cost-effectiveness.[19] However, there is a related need to evaluate the effectiveness and cost-effectiveness of strategies that encourage such women to have a Pap test or, if they have already had a test, to become regular screeners.

There are a number of other limitations to this modelling exercise. Any modelling exercise requires certain simplifying assumptions about disease processes and health care activities. For example, we have assumed that the spectrum of cancerous and pre-cancerous cervical cancer can be divided into the four distinct cancer stages, three CIN categories, and HPV infection. The model has also used the same cervical cancer survival rates for all ages, which is known not to be the case in reality. Although the natural history model was based on Australian data sources wherever possible and was adjusted to predict Australian outcome estimates (cancer incidence at different ages), many of the remaining input parameters to do with the progression and regression of disease are from US data sources. Given the different ethnic mix of Australian women, this may add to the uncertainty in our results.

Our analysis has also assumed that cytological abnormalities would be followed up exactly in accordance with 1994 NHMRC guidelines. Since this analysis was conducted the NCSP, through the NHMRC, has issued new guidelines that include a different classification system for cervical cytological abnormalities and different (although largely similar) recommendations concerning the follow-up of different types of abnormality. Interestingly, the revised classification system was introduced in part to reflect increased understanding of the natural history of cervical cancer, with the early stages being characterised as a primarily infective rather than neoplastic process. Our model could be seen as already reflecting this since it involved significant regression as well as progression between the main pre-cancerous states. Although it is difficult to judge whether the use of the new cytology classification system and management guidance would greatly alter our cost-effectiveness results, there are two reasons to suspect they might not. First, most of the cost differences arise from the cost of the initial screening tests, rather than follow-up tests and treatment. Second, our sensitivity analysis varied the proportion of women found with CIN I who had active management (mostly ablative therapy) versus observational management (two repeat smears at six-monthly intervals) from 20% to 80%; this had a very small effect on the incremental cost-effectiveness ratios. As most changes in management have been recommended at the less severe end of the disease spectrum, we conclude that the impact on incremental costs and life-years would not be great.

Another limitation of the model is that the results are based on a hypothetical single birth cohort of 15-year-old women who follow the alternative screening strategies until age 85, or death, whichever comes first. Although single birth cohort simulations are conventional for evaluating cervical screening,[20-24] in reality, any change in screening policy would affect not just those *about to enter* the screening age range but all women of screening age. This issue has been highlighted by van Oortmarsen et al.,[7] and recent empirical analysis by one of the present authors suggests that modelling more realistic, multi-age cohorts can have a significant impact on the incremental cost-effectiveness estimates of alternative strategies.[25]

The model includes the variable costs of Pap test taking, reading and various follow-up, diagnostic and treatment procedures that may follow abnormal test results or symptomatic diagnosis. We have therefore assumed that the costs of running the screening program(s) at the national and State level are fixed, whatever the strategy chosen. This may be true for the monitoring and screening promotion activities of the NCSP, but the State/Territory Pap test registries would possibly incur lower costs if a policy of recommending less frequent screening intervals was adopted (e.g. fewer reminder letters needed, less data entry, etc.).

We have assumed that the cost of performing the Pap test, and the sensitivity and specificity of the test results, are those of a conventional Pap test. This means that the sample cells are taken from the cervix using a standard spatula and/or an endocervical brush; the cells are then transferred to a slide, and sprayed with (or immersed in) a preserving solution; the cells are then stained (using the Papanicolaou method) and examined visually, under magnification, by a cytologist. The process therefore does not include new technologies that may improve slide preparation or automate slide analysis, but will also be more costly. The uptake in Australia of the new technologies to improve Pap test screening has been rapid and is likely to continue.[26] At present the additional cost of using these technologies is borne by the patient and is not reimbursable under the MBS schedule. If they could be demonstrated to increase the sensitivity or specificity of the Pap test, particularly in under-screened groups, then the cost-effectiveness results would be different.

Conclusion

Cost-effectiveness analyses are fundamentally a decision-informing, rather than decision-making, analytical tool; they aim to make explicit the trade-offs between the resources committed (costs) and outcomes achieved (effectiveness) for any given policy or practice choice.[27] Unambiguous policy implications from cost-effectiveness studies are therefore rare.

Despite this caveat, we are able to conclude that moving to a policy of annual from two-yearly screening would provide limited extra life-years at substantial additional cost. For the same reason, screening more frequently than two-yearly when not at higher risk ('over-screening') is highly inefficient. Australia could, conversely, consider increasing the recommended interval for cervical screening. Such a policy shift should, however, also be based on adequate empirical evidence of the cost-effectiveness of strategies for encouraging never-screeners to have a Pap test, or for encouraging irregular screeners to screen more regularly. Only then will it be possible to clearly judge whether the estimated savings from lengthening the recommended screening interval could, if reinvested in such strategies, result in an overall net reduction of cancer deaths and net gain in life-years.

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Note 1: The classifications used here are based on the 1994 NHMRC guidelines. These have since been rescinded and replaced with *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities* (NHMRC 2005).