



Projected impact of HPV vaccination and primary HPV screening on cervical adenocarcinoma: Example from Australia



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ABSTRACT

Cytology-based cervical screening appears to have had a limited effect on the incidence of adenocarcinoma, however HPV vaccination and HPV-based screening will likely play a role in reducing future burden. Using Australia as an example, we estimated the future burden (2015–2040) of adenocarcinoma in the absence of other interventions; and the impact of HPV vaccination (introduced 2007) and HPV-based screening (commencing 2017).

Future burden was estimated considering underlying trends in adenocarcinoma, using national data (1982–2010). The relative reduction in adenocarcinoma due to HPV vaccination and HPV-based screening was derived from observed clinical data.

Adenocarcinoma incidence rates have been increasing since the early-mid 2000s (average annual increases from 3.0%(25–49 years) –8.1%(20–24 years)). If these trends continue, rates would increase from 1.4 to 2.4/100,000 in < 50 years and from 2.2 to 4.4/100,000 in 50+ years by 2040. Taking into account coverage, HPV vaccination will reduce 2040 incidence by 36–39%, mainly in women < 50 years (61% reduction). Taking into account uncertainties in trends and screening effectiveness, HPV-based screening will reduce incidence by an additional 19–43%, mainly in women 50+ years (additional 30–68% reduction). Together, these interventions will reduce incidence by 55–81%.

1. Introduction

Cervical cancer screening programs have been established in many developed countries for a number of decades and this has been followed by a fall in cervical cancer incidence and mortality [1,2]. However, these reductions have primarily occurred in squamous cell cancers (SCC), with limited reductions in adenocarcinomas, which arise in glandular cells [2–5]. Potential explanations offered for this differential impact include that glandular cells are harder to sample, and that cytological interpretation of glandular abnormalities is more difficult [6].

Two interventions have the potential to reduce adenocarcinoma in the future: prophylactic HPV vaccination and HPV-based screening. Current generation HPV vaccines protect against HPV 16 and 18, the types associated with over 80% of HPV-positive adenocarcinomas [7–11]. In addition to efficacy data from trials, there are also now data from many settings where HPV immunisation programs have been implemented, showing impact on infections with vaccine-included HPV types and other endpoints [12–14], but no documented impact

of vaccination on cervical cancer has yet been reported. Screening using a molecular assay for HPV has been shown to improve detection of precancerous lesions. A pooled analysis of data from four European randomised controlled trials of HPV-based versus cytology-based screening which combined recruited women over the period 1997–2004 and followed them up for a median period of 6.5 years found substantially lower rates of invasive adenocarcinoma in the HPV-based screening arm compared to the cytology-based screening arm (pooled rate ratio: 0.31; 95% CI: 0.14–0.69) [15].

Australia will be the first country in the world where both of these interventions are implemented in overlapping age cohorts. A National HPV Vaccination Program (NHVP) was implemented in Australia in 2007, using the quadrivalent vaccine (HPV4). It initially targeted females aged 12–13 years but included an extensive catch-up program in females aged up to 26 years from 2007 to 2009. Since 2013, boys have also been included in the routine program. Three-dose uptake in the target age group has been approximately 71–79% in girls and 71–72% in boys [16].

The organised National Cervical Screening Program (NCSP) has

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been in place in Australia since 1991 (preceded by opportunistic screening), and since that time cervical cancer incidence has approximately halved, but this has predominantly occurred in SCC [6,17]. Adenocarcinomas do not appear to have reduced to the same extent as SCC; consequently, adenocarcinomas have increased from 11.4% of all cervical cancer in Australia in 1982 to 22.0% in 2010 [6]. Major changes are scheduled to occur in the NCSP from 2017, based on the recommendations of a major review of cervical screening [18]. These include a switch from two-yearly cytology-based screening in women 18–69 years to five-yearly HPV-based screening in women aged 25–74 years, with partial genotyping for HPV 16/18 and referral of women positive for these types to colposcopy. Direct colposcopy referral for women testing positive for HPV 16/18 may make the Australian program even more effective in reducing adenocarcinoma than predicted by the European trials, given the strong association between adenocarcinoma and these types.

Therefore, the aim of this study was to estimate the impact of HPV vaccination and HPV-based cervical screening on the future burden of adenocarcinoma, using Australia as an example. In order to do this we first aimed to characterise trends in the incidence of adenocarcinoma in Australia since the introduction of the screening program, and use these findings to estimate the potential future burden of adenocarcinoma in the absence of change.

2. Material and methods

2.1. Trends in adenocarcinoma since the introduction of the current screening program

National incidence data for cervical adenocarcinoma were obtained from the Australian Institute of Health and Welfare (AIHW), for the period 1982–2010 (the most recent year for which data were available). Reporting of all cancers (other than basal and squamous cell carcinomas of the skin) is mandated by legislation in Australia. Three-year average age-specific rates were calculated using population estimates from the Australian Bureau of Statistics [19]. Broad age groups were examined (20–24; 25–49; 50–69; 70+) to allow for the possibility that the impact of screening varied by age, as suggested by previous international and local studies [17,20].

2.1.1. Statistical analysis

Joinpoint regression was used to examine whether trends had been consistent over time and estimate the annual percentage change (APC) in adenocarcinoma incidence. Joinpoint analysis fits the simplest trend model (fewest changes in trends) consistent with the observed data. To avoid overfitting, we restricted analyses to a maximum of 3 joinpoints (4 trends) over the period, based on a visual inspection of the data. Age-standardised rates and standard errors were calculated using established methods and the Australia 2001 Standard Population (which is still used and recommended for routine program reporting) [21,22]. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC) and Joinpoint 4.2.0.2 (Surveillance Research, National Cancer Institute, Bethesda, MD).

2.2. Potential future burden and impact of HPV vaccination and of the new screening program

The potential future burden of adenocarcinoma (in the absence of any intervention change) was estimated from 2015 to 2040 under two assumptions: i) that rates remained steady at their most recently observed level (the three-year average over the period 2008–2010; “stable underlying rates”); or ii) that any significant trends in rates which were observed in the most recent time period continued (“current trends continue”). Standard methods were used in the latter case [23]. Briefly, Joinpoint was used to identify the time period of the most recent trend period using the observed data from the period

1982–2010; linear models were fitted to age-specific rates over the identified time period to ascertain whether trends were significant. Where significant trends were identified, projections assumed a linearly increasing trend, while a log-linear model was used to project significant decreasing trends. Where the trends were not significant, the mean incidence rate over the most recent trend period was used. Case numbers were then estimated by applying future population estimates [24].

The potential impact of HPV vaccination and HPV-based screening used an incidence-based approach – that is, relative reductions were applied to the underlying age-specific incidence rates of adenocarcinoma, using observed clinical data to estimate the relative reductions.

To estimate the potential impact of HPV4 vaccination, we assumed that 76.6% of adenocarcinomas were attributable to vaccine-included HPV types, based on the proportion of adenocarcinoma which were positive for HPV16/18 in the Australian Cervical Cancer Typing Study (ACCTS) [25]. In addition to detection using polymerase chain reaction (PCR), ACCTS used laser capture microdissection to resolve tumours where multiple types were detected. We assumed that the remaining fraction of adenocarcinomas (23.4%; comprising those positive only for non-vaccine HPV types and those where HPV was not detected) were not vaccine-preventable and so their underlying incidence rates for would be unaffected by HPV4 vaccination. For the vaccine-preventable fraction, we estimated the reduction in adenocarcinoma incidence based on observed reductions in vaccine-included type infections in a repeat cross-sectional prevalence survey of young women who in the second period had previously been offered vaccination [13]. Prevalence ratios (adjusted for age and hormonal contraceptive use) were reported for women who were fully (three doses), partially (one or two doses), or not vaccinated [13]. These prevalence ratios were combined with the estimated proportions of women in birth cohorts offered vaccination at school who are fully, partially or not vaccinated of 72%, 8% and 20% respectively, based on published vaccine register data [26]. The resulting estimated reduction was applied to all age-specific incidence rates of vaccine-preventable adenocarcinoma in those cohorts (up to 2040). We conservatively only applied these reductions to cohorts of females who were offered vaccination at school (born 1990 or later), because prior exposure is more likely to have occurred in those vaccinated at an older age during the catch-up phase of the program. In a supplementary analysis, we estimated the impact of a next-generation nonavalent HPV vaccine (HPV9) that protects against an additional five oncogenic types (31/33/45/52/58), as HPV9 has been registered for use in Australia, and may in future be used in the national vaccination program. For this supplementary analysis, we assumed that 84.8% of adenocarcinomas were attributable to vaccine-included types, based on the proportion of adenocarcinoma in ACCTS positive for any of the nine types targeted by HPV9 [25] and that the incidence of the remaining 15.2% (those positive for other types or with no HPV detected) would be unaffected by HPV9 vaccination. For both the HPV4 and supplementary HPV9 analysis, we also conservatively assumed no vaccine cross-protection against non-vaccine-included HPV types.

The potential impact of HPV-based screening was estimated using the point estimate for the relative reduction in a pooled analysis of four European trials [15], applied to women aged 25 and older (since from 2017 cervical screening will no longer be recommended for women aged less than 25). A lower impact estimate was also calculated using the upper end of the 95% confidence interval for the rate ratio. In both cases, however, we conservatively assumed no reduction would be observed over the first round (five years) of HPV-based screening in Australia, as cumulative detection of invasive cervical carcinoma was similar in both the cytology-based and the HPV-based arms in the European trials for approximately the first two years from enrolment.

Details of how these reductions were applied in different birth cohorts, depending on their eligibility for HPV vaccination and screening, are provided in [Supplementary Table 2](#).

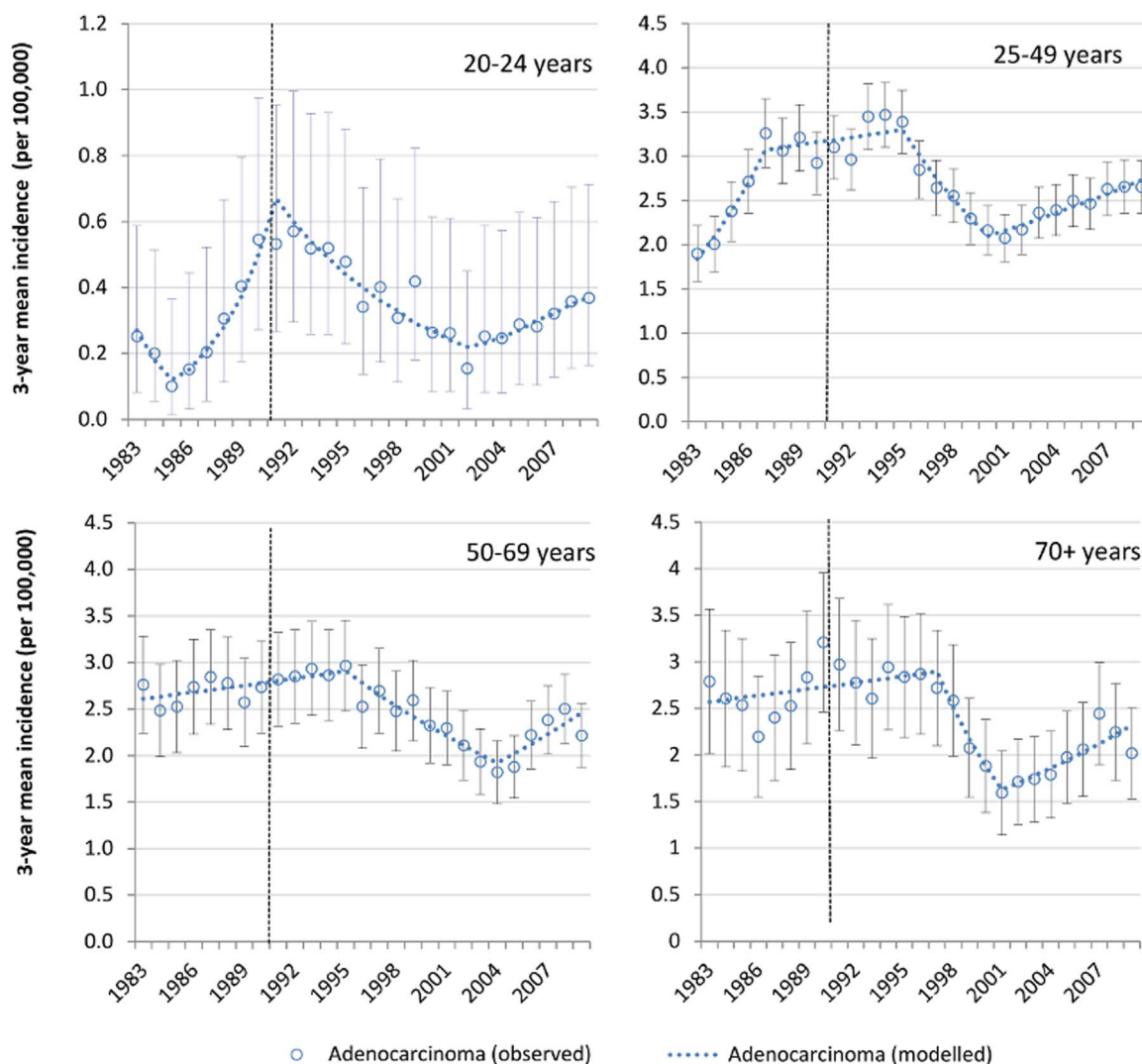


Fig. 1. Three-year mean incidence of cervical adenocarcinoma in Australia (per 100,000 women), by age group. Dotted line indicates approximate start of NCSP in Australia (1991). Incidence is three-year mean incidence centred around the plotted year. Rates for women aged 25–49, 50–69 and 70+ are standardised using the Australia 2001 Standard Population. Total cases in period 1982–2010: 20–24 years =66 cases; 25–49 years =2539 cases; 50–69 years =1253 cases; 70+ years =593 cases.

3. Results

3.1. Trends in adenocarcinoma since the introduction of the current screening program

Between 1982 and 2010, there were 4460 cases of adenocarcinoma in Australia. Broadly similar patterns in adenocarcinoma trends were observed in all four age groups examined (Fig. 1). Data was suggestive of an increase during the 1980s (although this was only significant in women aged 20–24 and 25–49 years)(Table 1). In all four age groups, there was evidence of a fall starting from around the mid-late 1990s, with average annual declines varying from 3.0% (25–49 years) to 13.4% (70+ years); and then an increase in incidence starting from around the early to mid-2000s, with average annual increases from 3.0% (25–49 years) to 8.1% (20–24 years).

3.2. Potential future burden and impact of HPV vaccination and HPV-based screening

In the absence of HPV vaccination and any change to cervical screening, an expected 6436 adenocarcinomas would be diagnosed in Australia over the period 2015–2040, if underlying incidence rates remained stable at 2008–2010 levels (54% of these cases in women <

Table 1

Estimated annual percentage change (APC) in three-year average incidence of cervical adenocarcinoma by age.

Age group	Period	APC	(95% confidence interval)	P
20–24	1983–1985	–34.46	(–51.5, –11.4)	< 0.01
	1986–1991	33.90	(25.2, 43.2)	< 0.001
	1992–2002	–9.67	(–11.8, –7.5)	< 0.001
	2003–2009	8.11	(3.8, 12.6)	< 0.001
25–49	1983–1987	13.69	(8.3, 19.4)	< 0.001
	1988–1995	0.88	(–0.7, 2.5)	0.25
	1996–2000	–8.65	(–12.2, –5.0)	< 0.001
	2001–2009	2.97	(1.8, 4.2)	< 0.001
50–69	1983–1995	0.90	(–0.2, 2.0)	0.09
	1996–2004	–4.49	(–6.3, –2.7)	< 0.001
	2005–2009	5.06	(1.3, 9.0)	0.01
70+	1983–1997	0.86	(–0.3, 2.1)	0.15
	1998–2001	–13.41	(–23.5, –2.0)	0.03
	2002–2009	4.51	(1.7, 7.4)	< 0.01

50 years). If the recently observed trends for increasing incidence rates continued, up to 9887 cases would be expected (50% in women < 50 years).

Table 2
Estimated rates and cases of cervical adenocarcinoma diagnosed in Australia, 2015–2040, and predicted impact of HPV vaccination and screening, by age.

	< 50				50+				All ages			
	Rates steady		Observed trends continue		Rates steady		Observed trends continue		Rates steady		Observed trends continue	
	N	% reduction	N	(% reduction)	N	(% reduction)	N	(% reduction)	N	(% reduction)	N	(% reduction)
No change												
Rate (2040)	1.42		2.40		2.15		4.36		1.63		2.97	
Cases (Total 2015–2040)	3499		4989		2937		4898		6436		9887	
Vaccination only												
Rate (2040)	0.55	61.3%	0.93	61.3%	2.10	2.6%	4.30	1.3%	0.99	39.0%	1.90	36.0%
Cases (Total 2015–2040)	2315	33.8%	3042	39.0%	2935	0.1%	4895	0.1%	5250	18.4%	7937	19.7%
cases averted	1183		1947		3		3		1186		1950	
Screening program change (lower impact)												
Rate (2040)	0.99	30.1%	1.70	29.5%	1.49	31.0%	3.01	31.0%	1.13	30.5%	2.07	30.1%
Cases (Total 2015–2040)	2697	22.9%	3814	23.6%	2230	24.1%	3654	25.4%	4927	23.4%	7469	24.5%
cases averted	801		1175		707		1244		1509		2419	
Screening program change (higher impact)												
Rate (2040)	0.47	67.1%	0.83	65.6%	0.67	69.0%	1.35	69.0%	0.52	67.8%	0.98	67.0%
Cases (Total 2015–2040)	1715	51.0%	2374	52.4%	1363	53.6%	2130	56.5%	3078	52.2%	4504	54.4%
cases averted	1783		2615		1575		2768		3358		5383	
Vaccination + screening program change (lower impact)												
Rate (2040)	0.38	73.0%	0.64	72.7%	1.45	32.8%	2.97	31.9%	0.69	57.7%	1.32	55.5%
Cases (Total 2015–2040)	1845	47.3%	2411	51.7%	2228	24.1%	3653	25.4%	4073	36.7%	6063	38.7%
cases averted	1653		2578		709		1245		2362		3824	
Vaccination + screening program change (higher impact)												
Rate (2040)	0.18	87.5%	0.29	86.7%	0.65	69.8%	1.33	69.4%	0.32	80.6%	0.61	79.4%
Cases (Total 2015–2040)	1269	63.7%	1637	67.2%	1362	53.6%	2129	56.5%	2631	59.1%	3766	61.9%
cases averted	2229		3352		1575		2769		3805		6121	

“Higher impact” estimates use the point estimate for the relative reduction in adenocarcinoma incidence in a pooled analysis of four European randomised trials of HPV-based screening [15]; “Lower impact” estimates use a lower end estimate for the relative reduction in adenocarcinoma incidence, based on the upper end of the 95% confidence interval for the rate ratio from the European trials

HPV vaccination (in the absence of screening change) is estimated to reduce rates of adenocarcinoma in 2040 by 39.0% compared to 2008–2010 levels, corresponding to 1186 cases averted over the period 2015–2040 assuming stable underlying rates; or alternatively to reduce rates by 36.0% (1950 cases averted) if recent increasing trends were assumed to continue (Table 2). Virtually all of this impact would occur in women aged less than 50 years, in whom the rate is predicted to be 61.3% lower than 2008–2010 levels (and cases 33.8–39.0% lower than would otherwise be expected over the period 2015–2040) (Fig. 2). As a consequence, the majority of adenocarcinoma cases in this period would be expected to shift to occur in women aged 50+ in the absence of screening changes (56% of cases, compared to 46% in the absence of HPV vaccination, assuming stable underlying rates; or alternatively 62% of cases, compared to 50% in the absence of HPV vaccination, if current trends continue).

In the context of a switch to HPV-based screening, however, it is predicted that adenocarcinoma rates in 2040 would be an additional 18.7–41.6% lower than in 2008–2010 assuming stable underlying rates, or an estimated 19.5–43.4% lower than they would be if current trends in incidence were to continue. Compared to the effect of vaccination alone, an additional 1177–4171 cases could be averted, taking into account uncertainties in both the underlying incidence rates

(stable or increasing) and the effectiveness of screening in preventing adenocarcinoma. This reduction would affect both women aged < 50 and also those aged 50+, in whom rates are respectively predicted to be a further 11.8–26.2% and 30.2–68.1% lower in 2040 than in 2008–2010, taking into account uncertainties in both the underlying incidence rates and the effectiveness of screening in preventing adenocarcinoma (Fig. 3). The combination of HPV vaccination and the new screening program has the potential to reduce overall rates of adenocarcinoma in 2040 by 55.5–80.6%, and to reduce cases over the period between 2015 and 2040 by 36.7–61.9% (2362–6121 cases) (Table 2).

Over the period 2015–2040, the effect of the new screening program in women aged 50 or older (an estimated 30.2–68.1% reduction in rates; 24.1–56.5% reduction in cases; and absolute reduction of 707–2766 cases) is predicted to be broadly comparable to the impact of HPV vaccination in women aged less than 50 (an estimated 61.3% reduction in rates; 33.8–39.0% reduction in cases; and absolute reduction of 1183–1947 cases).

The absolute number of cases averted was sensitive to the assumptions about whether underlying adenocarcinoma rates would remain stable or whether current increasing trends would continue, but the relative reductions in incidence rates and cases were relatively insensi-

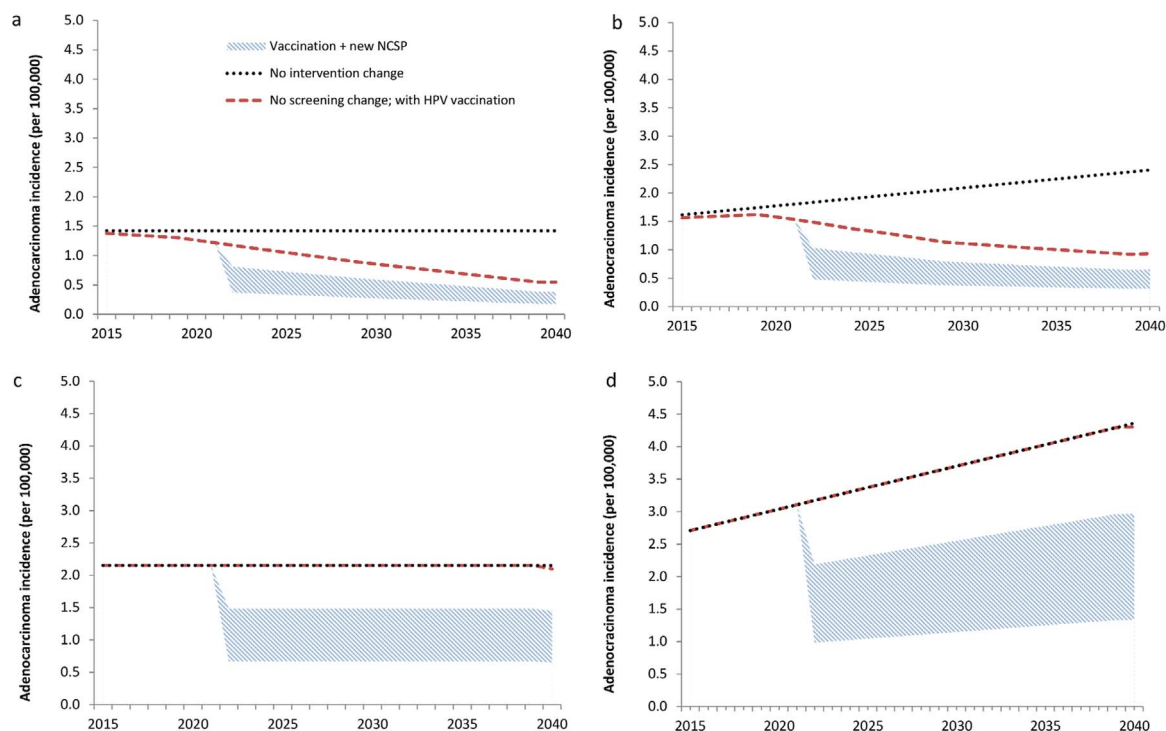


Fig. 2. Estimated incidence of cervical adenocarcinoma in Australia (per 100,000 women), 2015–2040, a) Women aged less than 50 years, assuming stable underlying rates, b) Women aged less than 50 years, assuming current trends continue, c) Women aged 50 years or older, assuming stable underlying rates, d) Women aged 50 years or older, assuming current trends continue. Rates are age-standardised using the Australia 2001 Standard Population. Shaded area represents the range of predictions, taking into account uncertainties in the effectiveness of HPV-based screening in preventing adenocarcinoma [15].

tive to these assumptions; the relative reductions were more sensitive to the assumed impact of the screening program in preventing adenocarcinoma (Table 2, Supplementary Fig. 1).

In a supplementary analysis where we considered the potential impact of HPV9, the effect of vaccination alone increased from a 36.0–39.0% reduction in incidence to 2040 compared to 2008–2010 from HPV4 to a 39.8–43.2% reduction from HPV9, driven by a greater reduction in women aged less than 50 of 67.8% (compared to 61.3% for HPV4) (Supplementary Table 1). However, the combined impact of HPV vaccination and HPV screening on 2040 incidence rates and cases over the period 2015–2040 was only slightly higher than was predicted for HPV4 (a 58.2–82.0% reduction in incidence rates compared to 2008–2010; versus 55.5–80.6% for HPV4, and a 38.1–62.7% reduction in cases over the entire period 2015–2040; versus 36.7–61.9% for HPV4) (Supplementary Table 1, Supplementary Fig. 2). This is largely because, although the additional relative reduction due to screening is the same in the context of either HPV4 or HPV9, the absolute incremental reduction due to screening is smaller when HPV9 is used, as there is less remaining disease.

4. Discussion

We found that an initial decrease in adenocarcinoma incidence after the commencement of organised screening in Australia in the 1990s was followed by significantly increasing rates since the early-mid 2000s in women in all age groups, with recent average annual increases from 3.0% (25–49 years) to 8.1% (20–24 years). If these trends continue, rates would increase from 1.4 to 2.4/100,000 in women < 50 years and from 2.2 to 4.4/100,000 in women 50+ years by 2040. However, HPV vaccination will reduce 2040 incidence by 36–39%, mainly in women aged <50 years (61% reduction). HPV-based screening will reduce incidence by a further 19–43%, mainly in women aged 50+ years (30–68% reduction). The combination of these two interventions will reduce incidence by 55–81%. The combined impact of vaccination and HPV-based screening was predicted to be slightly

greater in the context of HPV9 (58–82% reduction in incidence rates) compared to the current generation vaccines. The relatively small incremental increase in the combined impact is because vaccination and screening work together; as more disease is prevented by vaccination, there is less left to be prevented by screening, and the absolute impact of screening is smaller even if the relative reduction due to screening is the same.

The strengths of this study include the use of national routinely-collected data to estimate future trends in adenocarcinoma, and the direct incorporation of observed clinical data to estimate impact of HPV vaccination and HPV-based screening [13,15]. The observed data on vaccine impact incorporated both the direct and indirect effects of HPV vaccination [13]. We took into account a range of possible trends in adenocarcinoma incidence, grounded in an analysis of past trends over a 20 year period since the introduction of the organised cytological screening program.

One limitation of this study is that the impact of vaccination may have been underestimated. Coverage improved in females aged 12–13 years in 2013 and 2014 (the most recent years for which data are available), however we took a conservative approach as it was unclear whether or not this higher coverage would be sustained. We also assumed no direct impact of vaccination in women who were vaccinated when aged 18–26 years. This is also likely to be conservative as substantial reductions in genital warts have been reported in women aged 21–30 in 2011 (17–26 in 2007) [27], although herd effects are likely stronger for HPV types related to genital warts (HPV 6/11) compared to HPV 16 [28]. Additionally, the observed reductions in HPV16/18 used to estimate the impact of HPV vaccination [13] were measured in 2010–2012, relatively soon after the period of the catch-up program (2007–2009) and before boys were included. It is possible the relative reductions in these cohorts could increase over time, as suggested by other studies [12,29,30], as some of the infections detected in vaccinated women may have been present prior to them being vaccinated, and protection in unvaccinated females is also likely to increase in future as more of the community is vaccinated. Finally,

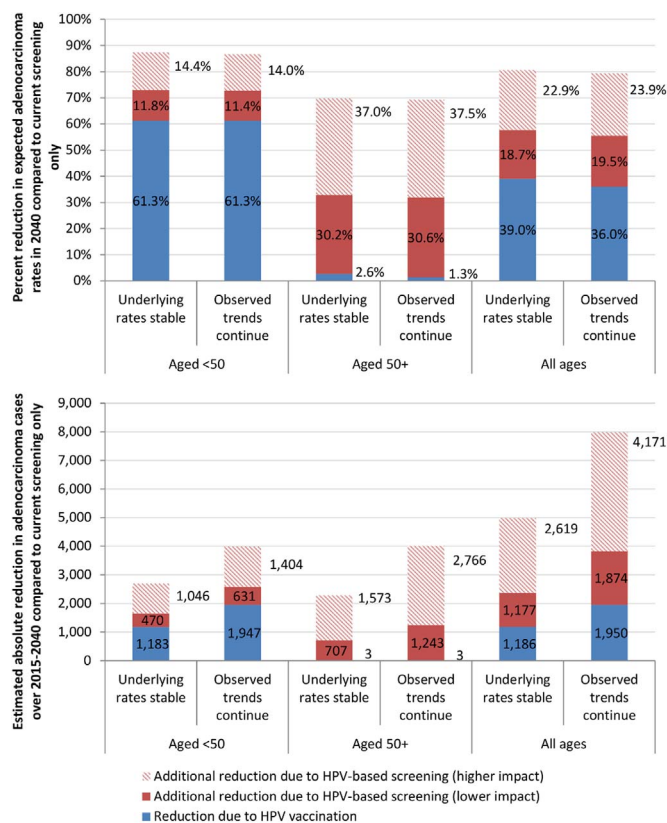


Fig. 3. Estimated reduction in adenocarcinoma due to HPV4 vaccination and HPV-based screening, compared to current screening only, by age. Upper panel shows percentage reduction in age-standardised rates in 2040; lower panel shows absolute reduction in adenocarcinoma cases over the period 2015–2040. HPV4= quadrivalent HPV vaccine. “Higher impact” estimates use the point estimate for the relative reduction in adenocarcinoma incidence in a pooled analysis of four European randomised trials of HPV-based screening [15]; “Lower impact” estimates use a lower end estimate for the relative reduction in adenocarcinoma incidence, based on the upper end of the 95% confidence interval for the rate ratio from the European trials.

we conservatively used the proportion of adenocarcinomas which were positive for HPV16/18 across all ages in the Australian typing study, ACCTS; however the proportion was higher than 76.6% in younger women, who were the main group affected by vaccination in the timeframe we considered [25].

Although the majority of our assumptions around vaccination were thus conservative, in one aspect, the impact of HPV vaccination is uncertain. In all cohorts offered vaccination, the age-specific incidence of adenocarcinoma was assumed to be reduced up until 2040. Depending on the timing of when the vaccine was given, this could mean a period of up to 33 years between vaccination delivery and diagnosis of adenocarcinoma. Given that there is a lag between acquisition of infection and development and diagnosis of adenocarcinoma, it is likely that in many cases infections which would (in the absence of vaccination) cause adenocarcinoma in 2040 would have been acquired much earlier than 2040, and thus much closer to the time of vaccination than 33 years. Trial data have demonstrated protection for HPV4 out to eight years [31]; stable antibody titers [31,32]; and robust anamnestic responses to booster doses given five years after the original vaccine course, indicating the existence of vaccine-induced immune memory [33]. These data suggest that HPV vaccines are likely to provide long-term protection [34,35]; however if protection wanes within around 20–25 years (assuming time between infection acquisition and diagnosis of adenocarcinoma is around a decade), then the impact of HPV vaccination in women vaccinated in the first decade of the vaccination program would be overestimated for the later years of our analysis.

A recent study found 15.6% of adenocarcinoma were HPV negative, even when highly sensitive tests were used, and samples with poor quality DNA or relating to extracervical tumours were excluded; however it was not able to determine whether the tumours truly arose in the absence of HPV, or whether they may have initially been HPV positive (i.e. with precursor lesions that may have been preventable by HPV vaccination or detectable by HPV screening, even if HPV is not later detectable in the cancer itself) [36]. This is broadly consistent with the proportion of adenocarcinoma which were HPV negative based on the Australian data which is incorporated into our assumptions (13.1%) [25], and also an earlier Australian meta-analysis (16.9%; but based on fewer samples than ACCTS). A larger international study reported a higher proportion of HPV-negative adenocarcinoma (37.2%), although the authors identified some reasons for their lower HPV detection rate – such as the inclusion of older tissue samples (cases were diagnosed from 1940 to 2009), regional differences in tissue-fixing protocols, and the use of formalin-fixed tissue rather than fresh-frozen biopsies – and also noted the inherent greater technical difficulties in detecting HPV in adenocarcinoma, compared to SCC [11]. Whether or not HPV negative adenocarcinomas affect our estimated impact of screening is uncertain, and would depend to what extent data from the pooled European analysis reflects adenocarcinoma that were HPV negative at the time of cancer diagnosis. However, this effect is likely to have been accounted for in the overall trial-based estimates of the effectiveness of HPV-based screening relative to cytology-based screening. When we re-estimated impact using international estimates for the proportion of adenocarcinomas which could be prevented by HPV vaccination (51.8%) [11], the impact of vaccination was predicted to be smaller, but the combined impact of vaccination and HPV-based screening was broadly similar, especially for a higher impact screening program (incidence reduced by 47–77%, compared to 55–81%).

Our assumed impact of screening may be somewhat overestimated because women included in the four European trials were screened at least once and screening coverage is not directly taken into account in this analysis. However, we performed our analysis in the context of a highly organised screening program that will implement invitation-based call-and-recall HPV screening, and explored a wide range of assumptions for overall screening program effectiveness against adenocarcinoma; this is conservative since we included only the lower end of the 95% confidence interval of trial-based effectiveness, rather than both the upper and lower ends. It should be borne in mind that it is possible that the Australian HPV screening program might also prove to be more effective in reducing adenocarcinoma than the European trials, because women testing positive for HPV 16/18 will be referred directly for colposcopy.

In common with other studies to date which have estimated the impact of HPV vaccination and/ or HPV-based screening, this analysis does not explicitly model the natural history of adenocarcinoma and its precursor lesions. The natural history of adenocarcinoma is less well documented and understood than that of squamous cell carcinoma, making adenocarcinoma more challenging to model. It is likely for this reason that, to our knowledge, this is the first study which has attempted to estimate the impact of either HPV vaccination or HPV-based screening on adenocarcinoma specifically. This impact is likely to be important and the relative impact on adenocarcinoma could be greater than the impact on cervical cancer overall (as was suggested for HPV-based screening by the European trials [15]). Use of an incidence-based approach, rather than directly modelling natural history, may have some effect on our estimates; for example if the proportion of adenocarcinoma which is vaccine-preventable varies by age, this might affect the timing of observed changes. Given that we assumed vaccination would only prevent adenocarcinoma in women born in 1990 or later, and in the timeframe of the current analysis those women are aged 50 or less, the adenocarcinomas affected by vaccination in this analysis are in relatively young women, among whom the vaccine-

preventable fraction is - if anything - likely to be higher than we assumed [25]. This would imply that the impact of vaccination may be greater in the next few decades than we have estimated. Our approach also assumes that the effectiveness of HPV-based screening in preventing adenocarcinoma does not vary by age. Pooled data from the European screening trials were suggestive of a larger relative reduction in cervical cancer overall due to HPV-based screening among women aged 30–34 than older women, however this was not significant, and not broken down by histological type [15].

The findings relating to the relative reduction in incidence of adenocarcinoma are likely to be broadly applicable to other settings with similar vaccine coverage in females (these findings do not include the additional indirect effect of vaccinating boys in Australia, as the vaccine impact used was measured prior to males being included the program). This includes settings with a less extensive age range of catch-up vaccination of females than Australia (where it included women aged up to 26), because we conservatively did not include the direct effects of vaccinating women aged 18–26. They may also apply to settings with moderate uptake in both females and males, as a recent modelling meta-analysis found that in the long term, the impact of vaccinating 60% of girls and boys was similar to the impact of vaccinating 80% of girls only [28].

We have previously reported that rates of squamous cell carcinoma and cervical cancer overall have declined dramatically in women aged 25 years or older since the inception of the NCSP in Australia [17], but trends in the incidence of adenocarcinoma in the same time period have been less clear. This is consistent with findings from other settings of a limited impact of organised cytology-based cervical screening on rates of adenocarcinoma [3,4]. One recent case-control study concluded that, while cytology-based screening was inefficient at preventing adenocarcinomas, it did appear to be effective in detecting them earlier, leading to downstaging and therefore likely reduced mortality [37]. We did not aim to directly examine the impact of cytology-based screening on adenocarcinoma, but rather to estimate the future burden in the absence of change, and also the potential impact of HPV vaccination and screening on cervical cancer incidence. It is possible that adenocarcinoma incidence (and mortality) is lower in Australia than would have occurred in the absence of cytology-based screening, however incidence nonetheless appears to be increasing in absolute terms. Nevertheless, our predictions encompass a range of assumptions around future underlying incidence rates - from no increase, to a continuation of observed increasing trends.

As the impact of cytology-based screening on adenocarcinoma has been limited, the potential future impact of HPV vaccination and changes to cervical screening on adenocarcinoma will be important. We found that over the next 25 years, HPV vaccination is predicted to substantially reduce rates and cases of adenocarcinoma, but in this time period virtually all of the reduction is likely to occur in women aged less than 50. However, if HPV-based screening is as effective at reducing adenocarcinoma as was observed in the four European randomised controlled trials [15], it will play an important role in bringing forward the reduction in adenocarcinoma, and in reducing adenocarcinoma in women aged 50 or older. In terms of reducing adenocarcinoma over the next 25 years, the changes to the NCSP may be as important in older women as HPV vaccination will be in younger women. These findings demonstrate the continuing importance of cervical screening in the coming decades, especially for older women who are likely to receive very limited benefit from HPV vaccination programs in this timeframe. Even in the context of a relatively extensive catch-up vaccination program in Australia, women aged 50 and older will be comprised of cohorts who were outside the age range offered HPV vaccination for some time.

In addition to highlighting the ongoing importance of screening in the next 25 years, especially for older women, these findings also suggest it will be important to monitor adenocarcinoma specifically (as well as cervical cancer overall, or by HPV type) in the coming decades.

This monitoring would provide a mechanism to verify the effectiveness of both HPV vaccination and HPV-based screening against adenocarcinoma in particular, to confirm that expectations based on trials are being met in the context of real-world programs and participation. Surveillance of women at elevated risk for adenocarcinoma is likely to be an important part of achieving the full benefit of HPV-based screening suggested by the European trials and the current study. The implementation of HPV-based screening will alter the population of women who are seen at colposcopy [38], especially in settings where women who are positive for HPV 16/18 are referred for colposcopy regardless of cytological findings (such as Australia). An important research question raised by HPV-based screening is the optimal management of women who test positive for HPV where no lesion is identified colposcopically. Surveillance is likely to be important for this group of women in order to for the full benefit of HPV-based screening to be realised, especially against adenocarcinoma, since glandular lesions may be missed by cytology and colposcopy. With this in mind, clinical management guidelines for the new HPV-based screening program in Australia recommend careful surveillance of women who are HPV positive, even where cytology and colposcopy are negative, particularly those who are positive for HPV 16/18; however there was little direct clinical evidence on the optimal approach [39]. Studies which provide insight into this, or which identify useful markers which could identify women harbouring glandular lesions, are needed.

5. Conclusions

Both HPV vaccination and HPV-based screening are anticipated to have a substantial effect on adenocarcinoma in the coming decades. HPV-based screening will play a particularly important role in reducing adenocarcinoma in women aged 50 or older, who are likely to experience limited benefits from HPV vaccination in the next 25 years.

Competing interest statement

Competing interests: no specific support from any organisation for the submitted work, however KC receives salary support from the National Health and Medical Research Council Australia (CDFs APP1007994 and APP1082989); KC is co-principal investigator of an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass') (NCT02328872), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc. USA. KC is also a PI on Compass in New Zealand, ('Compass NZ') (ACTRN12614000714684) which is conducted and funded by Diagnostic Medlab, now Auckland District Health Board. DML received an equipment and a funding contribution for the Compass NZ trial from Roche Molecular Systems. However, neither KC nor her institution on her behalf (Cancer Council NSW) receive direct funding from industry for this trial or any other project.

Author contribution statement

Study conception: KC, MAS. Study design: MAS, KC. Data analysis: MAS. Interpretation of data: All authors. Drafted the manuscript: MAS. Critically reviewed all drafts of the manuscript: KC. Approved the final version: all authors. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. MAS is guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

Ethical approval statement

As this study used only aggregated non-identifiable data, ethics approval was not required.

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Data sharing

Aggregate data are available from the Australian Institute of Health and Welfare <http://www.aihw.gov.au/cancer-data-requests/>.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.pvr.2017.04.003](https://doi.org/10.1016/j.pvr.2017.04.003).

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