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Title:
Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination?

Date:
2019-06-15

Citation:
Sultana, F., Winch, K., Saville, M. & Brotherton, J. M. L. (2019). Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination?. International Journal of Cancer, 144 (12), pp.2964-2971. https://doi.org/10.1002/ijc.32050.

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**+Title:** Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination?

**Short title:** PPV of high-grade cytology

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**Key words:** Positive predictive value, Cytology, High-grade squamous intra-epithelial lesion, Adenocarcinoma-in-situ, HPV vaccination

**Abbreviations**
HGD: high grade cervical disease
CIN NOS: cervical intra-epithelial neoplasia not otherwise specified
CIN II: cervical intra-epithelial neoplasia grade II
CIN III: cervical intra-epithelial neoplasia grade III
PPV: positive predictive value
VCSR: Victorian Cervical Screening Registry
LSIL: Low-grade squamous intra-epithelial lesion
HSIL: High-grade squamous intra-epithelial lesion
ASCUS: Atypical squamous cells of undetermined significance
AIS: Adenocarcinoma in situ

**Appropriate article category:** Cancer Epidemiology

**Novelty and Impact (75 words):** A decline in the positive predictive value (PPV) of cervical cytology following population level decreases in cervical lesion prevalence was predicted following HPV vaccination. Using routinely collected registry data, we demonstrated a decline in the PPV of cytology in cohorts where vaccine impact has been documented. The findings have implications for the effectiveness of continued screening using cytology in populations with high vaccine uptake and support explicit reconsideration of cervical screening strategies as vaccine coverage rises.

**Introduction:** The National Cervical Screening Program in Australia, based on conventional cervical cytology (Pap) testing every 2 years, has been successful in reducing cervical cancer incidence and mortality since its inception in 1991.[1] However, developments in our understanding of the cause of cervical cancer, which is due to persistent infection with oncogenic types of human papillomavirus (HPV), have resulted in recent advances in the field of cervical cancer prevention. These are 1) development and introduction of HPV vaccines and 2) development and implementation of HPV based cervical screening programs.[2]

Australia started a government-funded, school-based HPV vaccination program, with extensive initial catch-up vaccination in April 2007.[3] The program initially provided quadrivalent HPV vaccine for all females aged 12-26 years until end December 2009. From 2009 the Program offered HPV vaccination routinely to females in the first year of high school (usually at 12-13 years). From 2013, males were also offered HPV vaccination routinely in the first year of high school (age 12-13 years), with a catch-up program available for males aged 14-15 years in 2013 and 2014.[3-5] Since the commencement of the program in Australia, HPV related infection and HPV related cervical disease have started to decline in cohorts offered vaccination.[6-11] Prior to the program it was noted that HPV vaccination could potentially decrease the performance of cytology based cervical screening programs.[12] This is because it will cause a decreased prevalence of HPV infection and subsequently of HPV related high-grade lesions in the screening population. Decreasing the prevalence of underlying disease, whilst maintaining the sensitivity and specificity of the test, results in a fall in the positive predictive value (PPV) of the test i.e. a larger proportion of the women who test positive do not have the disease (false-positive) and have to undergo unnecessary clinical interventions, incurring both health care costs and psychosocial impacts. Other potential concerns post-vaccination include the possibility of a reduction in sensitivity if screeners become less familiar with recognising high-grade cervical lesions and a possible loss of specificity if lesions are relatively overcalled in a low prevalence environment, potentially resulting in a further decline in the PPV of cytology.[13] Simulation studies have shown that when sensitivity and specificity are maintained, the PPV of an abnormal smear to predict disease decreases from current estimates of 50-70% to 10-20% in settings where most women being screened have received the vaccination. The declines in PPV would be far more pronounced with concomitant decreases in sensitivity and specificity in low prevalence settings.[14, 15] However, empirical evidence for the above prediction is lacking.

To date, no assessment has been made in Australia of the PPV of cytology over time since the vaccination program commenced in 2007. This is despite such concerns being one of the reasons supporting a change to primary HPV testing in the renewed cervical screening program. In this study, we assess whether there is any evidence of a decline in the PPV of high-grade cytology in predicting high-grade cervical disease, since the introduction of the HPV vaccination program in Australia.

**Materials and Methods:**

*Study design:* An ecological study was conducted in Victoria, Australia.

*Study population:* De-identified cervical cytology and histology episodes occurring between January 1, 2000 and December 31, 2016 were extracted from the Victorian Cervical Screening Registry (VCSR) (formally known as the Victorian Cervical Cytology Registry) on May 12th, 2017.[16] VCSR is one of Australia's eight Pap test registers, which supported the cytology based cervical screening program until the program switched to HPV based screening, partial genotyping and reflex cytology

in December 2017. It recorded almost all cytology and histology tests performed in Victoria, unless a woman opted off the Register (VCSR has <1% opt-off rate).[17] Cytology tests with a high-grade intraepithelial abnormality and subsequent histology taken within six months of this cytology were included in the analyses. In Australia, neither a single ASCUS nor LSIL cytology result were a routine indication for colposcopy referral, which was only recommended for previously under-screened women aged over 30 or with repeated low grade results. We therefore could not estimate in this study the PPV of low grade cytology or ASCUS for the presence of high grade cervical disease. Where more than one histology report fell within the six-month period of the high-grade cytology, the histology report with the highest grade of abnormality was considered. HPV testing, liquid-based cytology triage tests, and high-grade cytology where only a colposcopy report was available without a histological diagnosis were excluded.

*Australian National Cervical Screening Program (pre-renewal):* The National Cervical Screening Program in Australia recommended a cervical cytology test every 2 years, beginning at age 18 years (or 2 years after the onset of sexual activity, whichever is later) until the age of 69 years. However, this policy changed to 5 yearly HPV testing starting December 1, 2017.[1, 18] Under the previous policy, follow-up and management of abnormal smears was as per the 2005 national guidelines for the management of asymptomatic women with screen-detected abnormalities;[19] now replaced by new guidelines where follow-up and management is dependent on the HPV testing results.[20] According to the 2005 guidelines, women with incident squamous low-grade abnormalities were followed up with another cytology test after 12 months to determine if the abnormality had resolved or whether a colposcopy was required, whereas women with possible or definite high-grade squamous intra-epithelial lesions were directly referred for colposcopy.[19] Colposcopy assessment, however, was always recommended if the cervical cytology suggested a glandular lesion.[19]

The National Cervical Screening Program uses the 2004 Australian Modified Bethesda System for reporting cytology, which is equivalent to the 2001 Bethesda System (TBS).[19] Histology results are received from reporting laboratories and coded according to an in-house coding schedule with coding checked by a second staff member at VCSR for quality assurance. Based on this coding, histology results are classified as either negative, atypia, low-grade, high-grade, micro-invasion or invasion. For the purpose of this study, we classified high-grade cervical disease (HGD) as any high-grade, squamous high-grade or glandular high-grade. Squamous high-grade disease includes high-grade cervical intra-epithelial neoplasia (CIN) not otherwise specified (high-grade CIN NOS), CIN grade II (CIN II), CIN III, micro-invasive and invasive squamous cell carcinoma; glandular high-grade disease includes high-grade endocervical abnormality, AIS, mixed adenosquamous carcinoma in situ, micro-invasive and invasive endocervical adenocarcinoma, adenosquamous carcinoma and carcinoma of the cervix – others and any high-grade disease includes any high-grade squamous or glandular disease (including micro-invasive and invasive cancers) as specified above.[17] All cytology and histology reporting is consistent with the Australian Institute of Health and Welfare (AIHW) national reporting indicators for the National Cervical Screening Program.[1]

*Primary outcome:* For the primary analysis, we calculated the PPV of definite high-grade intraepithelial abnormality in cytology (which includes high-grade squamous intraepithelial lesion (HSIL) and/or adenocarcinoma-in-situ (AIS)) in predicting any HGD for each calendar year from 2000 to 2016, age standardised to the Australian population at 30 June 2001. We also estimated the PPV within each calendar year by different age groups. PPV standards are as per the performance measures for Australian laboratories reporting cervical cytology, the National Pathology Accreditation Advisory Council (NPAAC) performance indicator (3a), according to which at least 65% of cytology

specimens reported as definite high-grade intra-epithelial abnormality (i.e. HSIL/AIS) must be confirmed as having a high-grade intraepithelial abnormality or malignancy (i.e. any HGD) in the histology performed within 6 months.[21] Of note, this indicator is intended for routine screening samples in the target age group 20-69 years. For the purpose of this analysis only, we have applied the standard across women of all ages.

*Secondary outcome:* In secondary analyses, we estimated separately the PPV of HSIL cytology alone in predicting any HGD and squamous HGD and the PPV of AIS cytology alone in predicting any HGD and glandular HGD. The latter are consistent with annual routine VCSR statistical reporting but not requirements of the national standard.[17]

Furthermore, we also estimated the PPV of a possible high-grade intra-epithelial abnormality predicted by cytology (which includes possible HSIL equivalent to atypical squamous cells, possible high-grade lesion (ASC-H) in TBS and/or possible high-grade glandular cytology equivalent to atypical endocervical cells, possibly neoplastic in TBS) in predicting any HGD. According to the NPAAC performance indicator 3b, the PPV for a cytology result classified as 'possible' should not exceed 65% or fall below 40%.[21]

**Statistical analysis:** PPV was calculated for each age group (<20, 20-24, 25-29, 30-34, 35-39, 40-49, 50-59, 60-69, 70+ years) and calendar year, where paired cytology and histology results were available, using the formula below and expressed as a percentage.

= (Number of histologically confirmed high-grade disease/Number of high-grade cytology)*100

Results were graphed to indicate changes in PPV per age group over time (i.e. calendar year). The time period was further divided into pre-vaccination (2000-2006) and post-vaccination period (2007-2016). The $x^2$ (chi-square) test for trend was estimated to assess if there was a decreasing (or increasing) trend in the PPV overtime for the different age groups in the pre-vaccination and the post-vaccination periods. For age groups <20 and 20-24 years we anticipated a decrease in PPV in the post-vaccination period (on the basis of the observed decrease in HGD prevalence in these age groups in Victoria of almost 75% in women <20 between 2007 and 2015 and a 43% decrease in 20-24 year olds over the same period).[10, 17] All analyses were conducted using STATA version 12 and a p-value$\leq$0.05 was regarded as significant.

The Victorian Department of Health and Human Services approved the study as the data custodian. As a legislated public health register, no ethics approval was required to analyse the de-identified data.

**Funding source:** There was no funding source for this study. FS, KW and JB had full access to the data. JB conceived the study, KW extracted the data and FS conducted the analyses. FS wrote the manuscript with contribution from JB, MS and KW. The corresponding author (FS) had the final responsibility for the decision to submit for publication.

**Results:** A total of 9,707,921 cytology episodes performed between calendar years 2000 and 2016 were extracted from the VCSR. A total of 9,564,836 episodes were excluded: 6,439 were reflex LBC tests, 215,968 were unsatisfactory or had an error reported, 497,714 were low grade, 4,298 were other abnormalities including micro-invasive and invasive cancers and 8,840,417 were negative smears. Of the included 143,085 high-grade cytology, 76,968 (54%) were definite HSIL/AIS. Of the 76,968

definite HSIL/AIS cytology, 65,791 (85%) had a histology performed within 6 months of the cytology. Similarly of the 66,117 possible HSIL/glandular high-grade cytology, 42,889 (65%) had a histology done within 6 months of the cytology (**Figure 1**). The proportion of definite high-grade cytology with histology reporting within 6 months ranged between 81% and 90% and has been consistently above 85% for the last 12 years**..**

**PPV of HSIL/AIS cytology: Table 1** shows the PPV of high-grade cytology in predicting HGD in the different categories. The overall PPV of a HSIL/AIS cytology in predicting any HGD was 75%, which is well above the NPAAC performance measure of 65%. The age-standardized PPV of HSIL/AIS cytology in predicting any HGD was consistently above the NPAAC requirement across the calendar years except calendar years 2014 and 2015 (**Figure 2**). When stratified by age, there was a decreasing trend in the PPV of HSIL/AIS cytology in predicting any HGD in women aged <20 years ($p_{trend}$=0.0006) in the post-vaccination period (2007-2016). The PPV, for women aged <20 years, was consistently below the NPAAC requirements after 2008. A similar decreasing trend in PPV of HSIL/AIS cytology in predicting any HGD was observed in the post-vaccination period ($p_{trend}$=0.0004) in women aged 20-24 years, although, for this age group, the PPV was maintained at least for the period of observation. No such decreasing trend in PPV of HSIL/AIS cytology in predicting any HGD was observed in the pre-vaccination period (2000-2006) in women aged <20 years ($p_{trend}$=0.82) and 20-24 years ($p_{trend}$=0.73) or in either the pre-vaccination or the post-vaccination periods in women aged 25-29 years, 30-34 years, 35-39 years, 40-49 years and 50-59 years. An increasing trend in PPV of HSIL/AIS cytology in predicting any HGD was observed in women aged 35-39 years in the post-vaccination period ($p_{trend}$=0.01). We also observed a decreasing trend in the PPV of HSIL/AIS cytology in predicting any HGD in women aged 60-69 years ($p_{trend=}$0.02) in the post-vaccination period. In women aged 70+ years, there was a decreasing trend in the PPV in the pre-vaccination period (**Figure 3**). The overall PPV of AIS cytology alone in predicting any HGD and glandular HGD was also high at 85% and 75% respectively (**Table 1**)**.**

**PPV of possible HSIL/possible high-grade glandular:** The overall PPV of possible HSIL or possible high-grade glandular cytology in predicting any HGD was 47%, within the NPAAC requirement of 40-65% (**Table 1**).

**Discussion:**

We found a decreasing trend in PPV of HSIL/AIS cytology in predicting HGD in both the <20 and 20-24 years age groups following the implementation of the HPV vaccination program in 2007. For the <20 years age group, the PPV was consistently below the national standard starting 2008. No such decreasing trend in PPV of HSIL/AIS cytology was observed in the pre-vaccination period in women aged <20 and 20-24 years or in the pre- and post-vaccination periods in the other age groups with the exception of the very oldest women. We observed a generally lower PPV with increasing age of women screening but the small number of women in the 70+ age group, an age by which most women had routinely exited the program under the cytology based program, limits our ability to interpret the unstable trends in this age group.

Our study confirms the findings of previous modelling studies that predicted a decline in PPV of cervical cytology following a decline in cervical lesion prevalence consequent to HPV vaccination.[14] The coverage with HPV vaccination, as recorded on the National HPV Vaccination Program Register, rose dramatically during the initial catch up period from 2007-2009 with 1st/2nd/3rd dose coverage in women aged 15-19 in 2007 of 75/67/56%. For women aged 20-24 years the coverage of $1^{st}/2^{nd}/3^{rd}$

dose in 2007 was 58/47/33% respectively. By 2016, women in these age groups had mostly been offered vaccine in the higher uptake school programs and coverage had risen to 81/78/72% in 15-19 year olds and 71/68/62% in 20- 24 year olds.[5] Substantial declines in histologically confirmed HGD in women <20 years (from 11 per 1000 women screened in 2008 to 3 per 1000 in 2015) and 20-24 years (from 21.1 per 1000 women screened in 2008 to 9.2 per 1000 in 2015) have been documented whereas for the 25-29 years age group, these rates have only started to decline recently (i.e. in 2014).[6, 10, 17] It is possible therefore that the fall in PPV observed in these age groups is due to falling prevalence of high grade lesions in young women due to vaccination.

In our study, the decrease in PPV of HSIL/AIS cytology in women aged under 20 was pronounced, progressive, and consistently below the national performance measures post-vaccination. The decline in HSIL was observed within 3 years of the start of the vaccination program in this age group.[6] Many of these women were vaccinated at school and likely prior to sexual debut, meaning that they were more likely than older women to benefit fully from vaccine derived protection against HPV infection and disease. The greater fall in PPV in women under 20, compared to the 20-24 year old age group in whom declines in PPV appear to be smaller and more recent, corresponds with the earlier and much greater impacts on lesion prevalence observed in the younger women. HSIL detection rates amongst women 20-24 years actually increased during the HPV vaccination catch up program, during which time a high level of concurrent screening and vaccination was observed,[22] and it is only since 2011 that rates have declined below pre-vaccination levels.[17] A separate and specific analytical study across several rounds of screening in the post vaccination period, amongst women with complete follow up, would be required to determine whether there was any loss in the sensitivity and specificity of cytology in the cytology screening program in the post vaccination environment.

Marked declines in the prevalence of targeted HPV types at the cervix have been documented in young women in Australia, with a recent study finding a decline of 92% in types 16, 18, 6 and 11 since the pre-vaccine period amongst women aged 18-24 years attending for routine cervical screening.[11] A possible consequence of remaining HGD being predominantly caused by the less aggressive oncogenic HPV types (i.e. not types 16 and 18) could be more difficult in identifying dysplastic cells in cytology specimens if underlying lesions are smaller and progress less rapidly.[23, 24] Australia's switch to HPV based cervical screening, with cytology reserved as a reflex test in HPV positive women, will also have consequences for the performance of cytology, given that the selection of cytology samples being screened will now have a much higher rate of underlying disease. This knowledge could result in changes in scientist's thresholds for cytological predictions. It will not be possible to use routine screening data in Australia to monitor the PPV of cytology in any way that is comparable to its performance previously.

Our results are consistent with a study in Scotland, which utilises liquid based cytology with image assistance in contrast to the conventional cytology used in Australia. HPV vaccination and cervical screening outcome data, including colposcopy reports, in Scottish registries were linked for individual women aged 20 years.[25] Women in the study had been offered the bivalent HPV vaccine in a national catch up vaccination program. The authors found a significant decrease in the PPV of HSIL cytology in detecting CIN2+ in fully immunised women compared to non-immunised women (65.69% versus 76.55%; p=0.002) and that 35% more immunised women than non-immunised women had to be referred following abnormal cytology (this includes borderline and persistent low-grade in addition to high-grade) to detect one case of CIN2+.[25]

The decrease in HPV infection and lesion prevalence could also reduce the PPV of HPV testing as suggested by a Scottish analysis, which noted the change in the ratio of HPV16/18 to other oncogenic HPV types in vaccinated women, which will reduce the overall underlying risk of current/future HSIL for HPV positive women. [26]. In Australia, the HPV based screening program routinely uses partial genotyping to differentiate those with 16/18 from other oncogenic HPV types, with more intensive pathways for those who are 16/18 positive than others.[20] This approach may be more likely to preserve the distinction in risk between women with the most oncogenic HPV 16/18 infections and those with less oncogenic HPV types and therefore the predictive value of HPV testing amongst vaccinated women.. Given that most studies of primary HPV testing have been performed in unvaccinated women, and include prevalent round screening which is relatively enriched for persistent HPV and related lesions, future studies should monitor the performance of HPV testing across multiple screening rounds and as vaccinated cohorts undergo screening. This will be especially critical once cohorts vaccinated with the nonavalent HPV vaccine, which protects against a further 5 oncogenic HPV types compared to the quadrivalent HPV vaccine, enter screening. The Compass trial, which is specifically assessing HPV based screening compared to cytology based screening among vaccinated cohorts in Australia, will provide sentinel information about the performance of both cytology and HPV screening amongst vaccinated cohorts.[27]

Although ecological in design, as appropriate for measuring population level PPV for the program, the study has several strengths. The long study duration (2000-2016) allowed us to analyse PPV trends over time and explain these changes in relation to HPV vaccination implementation in Australia. The study included the use of routinely collected, high quality and almost complete population-based data about cervical screening related outcomes from a well- established state-wide registry (VCSR). The analyses were restricted to those with histology reporting completed within 6 months, permitting valid and unbiased estimates of PPV. The same women who were eligible for population based HPV vaccination were also eligible for population based cervical screening.

In summary, our findings of a decreasing trend in PPV of HSIL/AIS cytology after 2007 in the younger age cohorts, in whom a significant decrease in HGD prevalence has been documented, is likely to be an effect of HPV vaccination and supports Australia's decision to switch to primary HPV testing starting at age 25. Other countries considering transition to primary HPV testing for cervical screening, given its superior impact in preventing cervical cancer,[28] will need to consider the characteristics of their HPV vaccination program and current starting age for screening to inform whether a declining PPV is likely to become problematic for existing cytology based screening in the near term. Australia achieved a high and rapid HPV vaccine coverage and experienced immediate overlap with screening cohorts. Herd impacts were substantial in Australia, due to the extensive catch up program,[29] but notable herd protection is seen even with low HPV vaccine coverage.[30] Countries who utilise bivalent HPV vaccine may observe even larger impacts on cervical lesion prevalence in young women, due to the marked cross-protection against types 31/33/45 provided by the vaccine.[31] Similarly cohorts vaccinated with nonavalent HPV vaccine will have greater declines in lesion prevalence than with quadrivalent vaccine. A further consideration is the suggestion that even one dose of HPV vaccine may be effective, which could accelerate reductions in cervical disease beyond current predictions.[32, 33]

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**Acknowledgments and COI**

JMLB and MS are chief investigators of the NHMRC Centre for Research Excellence in Cervical Cancer Control (APP1135172) from which FS receives salary support. JB and MS are investigators of a trial of primary HPV screening in Australia (Compass) that has received a part funding contribution from Roche Molecular Systems, Ventana Inc. USA. VCSR acknowledges the support of the Victorian Government.

**Figures and Tables**

Table 1: Overall Positive Predictive Value (PPV) of high-grade intra-epithelial abnormality cytology in predicting high-grade disease (HGD), Victoria, Australia, 2000-2016

Figure 1: Flow chart of the cytology and histology episodes included in the study

Figure 2: Positive Predictive Value (PPV) of HSIL/AIS cytology in predicting high-grade disease, Victoria, Australia (2000-2016)

[Insert Figure 2]

Legend: PPV HSIL/AIS-Any HGD: PPV of HSIL/AIS cytology in predicting any high-grade disease
NPAAC ref: National Pathology Accreditation Advisory Council require at least 65% of HSIL/AIS cytology to be confirmed with cervical histopathology performed within 6 months, as having high-grade disease
PPV is age-standardised to the Australian Population at 30 June 2001

Figure 3: Positive Predictive Value (PPV) of HSIL/AIS cytology in predicting any HGD¥ in Victoria, Australia (2000-2016)

[Insert Figure 3]

Legend: Red bold line: NPAAC reference for performance; blue dotted line separates the pre- and the post-vaccination periods.
¥Any high-grade disease (HGD) includes high-grade CIN NOS, CIN II, CIN III, micro-invasive and invasive squamous cell carcinoma, high-grade endocervical abnormality, AIS, mixed adenosquamous carcinoma in situ, micro-invasive and invasive endocervical adenocarcinoma, adenosquamous carcinoma and carcinoma of the cervix – others