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ORIGINAL ARTICLE

The impact of primary HPV screening on the incidence of cervical cancer in New Zealand

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Sensitivity

Introduction Our objective was to evaluate the impact on the incidence of cervical cancer in New Zealand of 5-yearly human papillomavirus (HPV) primary screening compared with 3-yearly cytology.

Materials and methods Unbiased estimates of the screening test sensitivity of HPV and cytology screening, and screening coverage, were used to calculate the reduction in cervical cancer incidence obtained by current cytology screening and the new HPV screening policy.

Results HPV screening in New Zealand is predicted to increase the incidence of cervical cancer in women being screened by 81.7% (95% CI: 38.9%-124.7%). The overall increase in the population incidence of cervical cancer in New Zealand was estimated to be 46.7% (95% CI 42.6%-50.8%), leading to about 57 more women developing cervical cancer each year.

Conclusions The results indicate that lengthening the screening interval concurrently with changing to HPV testing may reduce the protection from invasive cervical cancer for women. Women in New Zealand should continue to be screened by cytology every 3 years. Changes to screening policy should be carefully designed so that changes in screening effectiveness can be accurately measured.

Introduction

The New Zealand Ministry of Health intends to replace 3-yearly cytology with 5-yearly human papillomavirus (HPV) screening in 2021.[1] The main evidence used to justify this

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change is an Australian simulation model of cervical screening suggesting a 12% to 16% reduction in the incidence of cervical cancer from 5-yearly HPV screening.[2] Unfortunately, the calculations of the model used the detection sensitivity of the screening tests, an inappropriate measure of screening performance, for the assessment of the public health impact of screening.[3-6]

The primary aims of screening are to reduce the mortality and incidence of invasive cervical cancer, so it is the effect of screening on cervical cancer that is the primary measure of effectiveness.[7-9] However, the effect of screening on the surrogate measure of high-grade abnormalities is often used to try to predict the effectiveness of screening on invasive cancer.[10] Cytology detected CIN3 and its precursors, some of which may not have been detected by HPV screening, have already been largely removed from currently screened populations.

The disease that is sought at the time of screening is a lesion that will progress into an invasive cancer[11] and not, as proposed by the Australian modellers,[12] all high-grade abnormalities. We have indicated that the change to 5-yearly HPV screening in Australia may reduce protection from cervical cancer[13] and a more cautious introduction of HPV screening has been recommended.[6,13] Our assessment of the 5-yearly HPV screening policy in Australia[13] has been identified as contributing to successful advocacy for changes to the draft cervical screening policy of the US Preventive Services Task Force.[14]

There are several common, but very different, measures of cervical screening performance that use the word sensitivity.[3-5] First, the *detection sensitivity*, sometimes called prevalence sensitivity in public health, is the probability of detection of prevalent preinvasive disease. The detection sensitivity is a fundamental measure of sampling and laboratory performance to identify preinvasive disease that may progress to invasive cancer, may regress, or may persist unchanged, but does not distinguish between these clinical outcomes. Detecting disease that will regress, or does not progress to invasive cancer may be considered a failure of screening.[3,4] The probability that the test detects that subset of disease that will progress to life-threatening invasive cancer is the screening test sensitivity. In the presence of overdiagnosis or regression of disease, detection sensitivity is higher than screening test sensitivity and its use considerably overestimates the benefit of the screening test.

The published randomized controlled trials of HPV and cytology screening[6,15-24] have, mostly, reported the detection rates of preinvasive disease (CIN2+ or CIN3+) or have insufficient follow-up for the assessment of interval cancers.[20-24]

Several trials reported the occurrence of the combination of interval and screen-detected cancers but this mixes the assessment of the ability of the test to detect cancer with its ability to prevent cancer.[5] A meta-analysis of 4 of these trials found, overall, the number of cancers identified to be lower with HPV screening compared with cytology screening ≥2.5 years from enrollment.[25] Two[6,15] of the 5 randomized trials[6,25] found the incidence of cervical cancer to be higher in women after being screened with HPV tests than with cytology. However, only 1 randomized trial measured the screening test sensitivity of HPV and conventional cytology screening without overdiagnosis bias.[6] The screening test sensitivity was estimated to be 87% (95% CI: 74%-95%) and 93% (95% CI: 82%-98%) for HPV screening and cytology screening, respectively. As similar screening test sensitivity for both HPV and cytology screening was found, we estimated the potential change in the incidence of invasive cervical cancer of changing from 3-yearly cytology to 5-yearly HPV screening in New Zealand.

Materials and methods

This proportional incidence ratio is the incidence of cervical cancer for women screened divided by the incidence of cervical cancer in a comparable unscreened population. This was calculated from the relative protection (RP) from screening for time since last negative smear[26,27] for women aged 35 to 64 years of age, shown in Table 1. Women with 120 or more months since their last negative smear or whom had never been screened are herein referred to as "unprotected" women for convenience and their RP assumed to be 1.

Table 1 Geometric mean relative protection against cervical cancer for women 35 to 64 years of age participating in 10 organized screening programs.[26,27]

Months since last negative smear	Relative protection[a]	95% confidence interval
0-11	15.3	10.0-22.6
12-23	11.9	7.5-18.3
24-35	8.0	5.2-11.8
36-47	5.3	3.6-7.6
48-59	2.8	1.9-4.0
60-71	3.6	2.1-5.9
72-119	1.6	0.6-3.5
120+	0.8	0.3-1.6
Never screened	1.0	

[a]The incidence rate in women never screened relative to the incidence rate in women since last negative smear.

The proportional incidence ratio for the 3 years after a negative smear is the average of the inverse of the RPs from less than 12 months, 12 to 23 months, and 24 to 35 months since the last negative screening episode from Table 1. It is

$$(1/15.3 + 1/11.9 + 1/8)/3 = 0.092$$

Therefore, women 35 to 64 years of age screened every 3 years have only 9.2% of the incidence of unscreened women and a reduction in incidence of 90.8%.[27]

The RPs shown in Table 1 were applied to women aged 30 to 69 years of age. The proportional incidence ratios were then used to estimate the potential impact of the new HPV screening policy on the incidence of cervical cancer.[13] The age-specific 3-yearly and 5-yearly cervical screening coverage of women without hysterectomy in the New Zealand National Cervical Screening Programme[28] was used to estimate the proportion of eligible women with different screening frequencies. To use the RPs listed in Table 1, we estimated the coverage of frequent screening (smears taken within 24 months), an interval of 60 to 119 months, and among unprotected women. About 13% of eligible women were not screened within the previous 5 years or were never screened. For women with 60 or more months since their last screen or who had never been screened, we assumed that, of these, 10% had 60 to 119 months since their last negative smear and the other 90% were unprotected women. This assumption was tested by sensitivity analysis assuming that a much larger percentage, 80%, of these women had 60 to 119 months since their last negative smear and only 20% were unprotected.

A further cytology test <30 months since last cervical smear occurred for about 16% of women[28]; many of these tests were not screening tests as they were likely to be part of the investigation of symptoms or follow-up of previous abnormalities. Of eligible women whose last negative smear was <36 months (screened within the 3-year screening interval), we assumed that 5% had been screened at less than 24-month intervals. Sensitivity analysis with an increased percentage of 15% for this group was also undertaken. The age-specific 3-yearly coverage of current cytology screening was assumed to be the same as the 5-yearly coverage for the new HPV screening policy. These proportions were used to estimate the proportion of women by time since last negative screening episode for both screening policies.

As reported previously,[13] the change in incidence of cervical cancer when moving from policy 1 to policy 2 was calculated as

$$\Delta I = (PF_1 - PF_2)/(1 - PF_1)$$

where PF_1 is the prevented fraction of screening policy 1 and PF_2 the prevented fraction of screening policy 2.

The effect of screening policy on cervical cancer incidence in women 30 to 69 years of age is presented, assuming unprotected women had the same or 2-fold greater

Table 2 Estimated proportional screening frequency of current cervical screening policy and the 5-yearly HPV policy.

Screening frequency					
Age group (y)	<24 mo	24-35 mo	36-59 mo	60-119 mo	120+ mo or never
Relative protection from screening, current coverage	0.075	0.091	0.164	0.360	1.00
20-24	2.7%	51.1%	4.0%	4.2%	38.0%
25-29	3.3%	63.4%	15.8%	1.7%	15.7%
30-34	3.6%	68.6%	15.8%	1.2%	10.8%
35-39	3.8%	72.8%	15.3%	0.8%	7.2%
40-44	4.0%	75.2%	14.5%	0.6%	5.7%
45-49	4.0%	76.7%	14.4%	0.5%	4.4%
50-54	4.0%	76.9%	13.8%	0.5%	4.7%
55-59	4.0%	76.0%	12.6%	0.7%	6.6%
60-64	3.9%	74.6%	11.7%	1.0%	8.8%
65-69	3.7%	70.3%	11.9%	1.4%	12.6%
Total	3.7%	70.1%	13.0%	1.3%	11.9%
5-yearly HPV policy					
25-29	4.4%	0.7%	63.4%	15.8%	15.7%
30-34	4.1%	0.7%	68.6%	15.8%	10.8%
35-39	3.9%	0.7%	72.8%	15.3%	7.2%
40-44	3.9%	0.7%	75.2%	14.5%	5.7%
45-49	3.8%	0.7%	76.7%	14.4%	4.4%
50-54	4.0%	0.6%	76.9%	13.8%	4.7%
55-59	4.2%	0.5%	76.0%	12.6%	6.6%
60-64	4.5%	0.4%	74.6%	11.7%	8.8%
65-69	4.8%	0.3%	70.3%	11.9%	12.6%
Total	3.6%	0.5%	64.0%	12.5%	19.3%

Coverage derived from a report of the 1.08 million individual screening records of the National Cervical Screening Register.[28]

inherent risk of cervical cancer compared with screened women. The reductions in the incidence of cervical cancer for different periods of time since the last negative screen in each 5-year age group were calculated.

The average annual number of women developing cervical cancer for the 2008 to 2012 time period was calculated,[29] and the expected annual age-specific incidence rates of current screening, 5-yearly HPV screening, and the effect of a 15% relative increase in coverage for both policies estimated.

The precision of the prevented fraction (PF), and therefore the percentage change in protection when changing policy, is determined by the variance of the independent RPs of the groups of women with different screening histories. The PF is a simple weighted sum of RPs with lognormal distributions and, because the central limit theorem thus indicates rapid iterative convergence for estimates of the average value and standard deviation, the mean and standard deviations of the PF were obtained from 30 Monte Carlo simulations. The logarithms of the estimates of RP and their confidence intervals were used to estimate the 95% confidence interval for the relative change in the incidence of cervical cancer from changing screening policies.

Results

Not all women strictly adhere to screening policy and a range of screening frequencies occurs in practice. The estimated screening coverage of screen-negative women without hysterectomy under current screening policy and the proposed HPV screening policy, and RPs from cytology screening are shown in Table 2.

A last screening episode 36 months or more previously, but less than 120 months previously, was more common for women less than 35 years of age and women 65 or more years of age than for women 35 to 64 years of age. The estimated reduction in the incidence of cervical cancer in the New Zealand population achieved by the screening policies and the increase in incidence when changing from current screening to 5-yearly HPV screening are shown in Table 3.

Cytology screening in New Zealand was estimated to reduce the overall incidence of cervical cancer by 83% and the HPV 5-yearly primary screening policy by 75%. The overall population increase in cervical cancer for eligible women 30 to 69 years of age, screened and unscreened combined, was 46.7% (95% CI: 23.8%-69.7%) with the HPV screening policy. Increasing the proportion screened within 24 months to 15% from 5% resulted in an estimated 48.5% increase in cervical cancer incidence, and decreasing the proportion of unprotected women from 90% to 20% —an estimated 47.3% increase in cervical cancer incidence, for a change from 3-yearly cytology to 5-yearly HPV screening. When confined to screened women with less than 10 years since their last negative screen, the increased risk of cervical cancer was 81.7% (95% CI: 42.1%-121.4%).

When the inherent risk of cervical cancer in "unscreened" women compared to screened women was assumed to be the same and there was a 15% relative increase in participation, the reduction in cervical cancer achieved by screening women 30 to 69 years of age fell from 84.1% (95% CI: 81.7%-86.5%) for current screening to 78.1% (95% CI: 72.8%-83.3%) for 5-yearly HPV screening. If "unprotected" women had a 2-fold greater inherent risk of cervical cancer, then changing to the 5-yearly HPV policy increased overall cervical cancer incidence in the population by 59.5% (95% CI: 50.7%-68.2%). Even if the 5-yearly HPV policy achieved a 15% relative increase in coverage, the incidence of cervical cancer was still estimated to increase by 29.7% (95% CI: 24.0%-35.5%), whereas a 15% relative increase in current cytology screening coverage in New Zealand produced a decrease in cervical cancer incidence of 6.0% (95% CI: 2.6%-9.3%).

Fig. 1 shows the expected average annual age-specific incidence rates of cervical cancer under current and the proposed 5-yearly HPV screening policy, as well as the expected rates from a 15% increase in coverage for both policies in New Zealand. Little change in incidence for

Table 3 Reduction in incidence from screening and relative increase in incidence of cervical cancer for women 30-69 years of age compared with current screening with different inherent risk in "unprotected" women.

Inherent risk in "unprotected" women relative to screened women				
Screening	The same risk		2-fold greater risk	
	Reduced incidence (%)	Relative increase in incidence (%)	Reduced incidence (%)	Relative increase in incidence (%)
Current 3-yearly cytology screening in coverage	83.1 (81.7 to 84.5)	reference	73.5 (70.6 to 76.3)	reference
3-yearly cytology with 15% increase	84.1 (81.7 to 86.5)	−6.0 (−9.3 to −2.6)	74.1 (69.3 to 78.8)	−2.3 (−9.0 to 4.4)
HPV primary screening 5-yearly	75.2 (71.9 to 79.5)	46.7 (24.0 to 69.5)	57.7 (51.1 to 64.2)	59.5 (50.7 to 68.2)
HPV policy with 15% increase in coverage	78.1 (72.8 to 83.3)	29.7 (24.0 to 35.5)	60.8 (50.3 to 71.2)	47.8 (36.3 to 59.3)

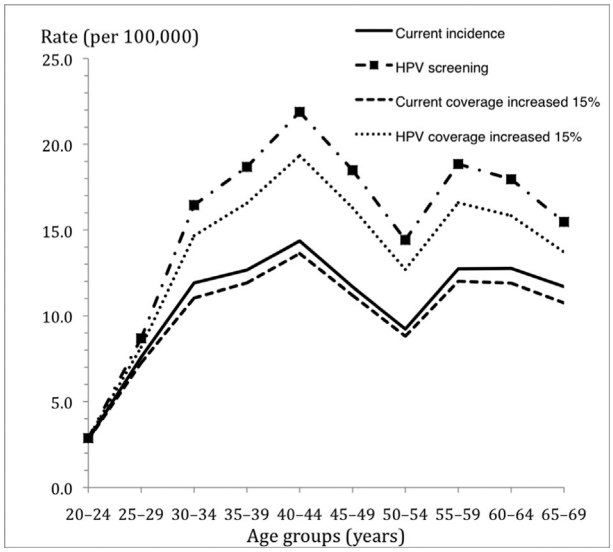

Figure 1 Current age-specific cervical cancer incidence rates, effect of 5-yearly HPV and 3-yearly cytology screening policies, and a 15% increase in coverage.

women less than 30 years of age was predicted from the proposed change in policy due to the lower effectiveness of screening in that age group. The larger increases in incidence from the 5-yearly HPV policy occurred for women 35 to 44 and 55 to 64 years of age. These same age groups had the greatest reduction in incidence from a 15% increase in coverage by cytology screening.

Discussion

If the screening test sensitivity of HPV and cytology screening is similar, there are considerable risks in lengthening the cervical screening interval. The incidence of cervical cancer has been found to be higher after HPV screening than cytology screening in 2 of 5 randomized trials that have reported the incidence of cancer.[6,15] The 2[15,17] of the 3 European trials[15-17] that used population-based cancer registries during follow-up did not find lower incidence rates of invasive cervical cancer more than 2.5 years after baseline with HPV, compared with cytology, screening.[25] These were also the 2 trials that did not exclude women with CIN previously detected by cytology,[15] thus reducing bias from a reduction in the pool of cytology-detectable lesions before randomization.

We estimated that the proposed 5-yearly HPV screening policy may increase the overall incidence of cervical cancer by 47% in the population 30 to 69 years of age and without hysterectomy. This is equivalent to 57 more women developing cervical cancer each year compared with the current annual average of 123 women in this age group.

Between 2008 and 2016, HPV immunization was free for girls and women less than 20 years of age, including non-residents under the age of 16 years and living in New Zealand for 8 months or more. From the beginning of 2017, HPV immunization became free for everyone, male and female, aged 9 to 26 years, including non-residents under the age of 18 years. Vaccination coverage for women is currently 65%. The assessment was restricted to women 30 to 69 years of age because the effect in younger women is lower and more inconsistent than for older women[30] and women currently 30 to 69 years of age have not been offered HPV vaccination. HPV vaccination is not expected to begin to affect cervical cancer incidence for women 30 or more years of age until at least 2020 and its effects will depend on whether women were born since about 1990 and, therefore, likely to have been offered HPV vaccination before exposure to HPV.

There are no recent estimates of the percentage of eligible women who have not been screened. However, the sensitivity analysis indicated that the estimated increase in incidence of the HPV screening policy was not appreciably altered when either the proportion of women unprotected was reduced or the proportion screened within 24 months increased.

The molecular basis of the HPV test is considerably different from the cellular assessment provided by cytology, raising concern that it cannot be assumed that it will detect more of the subgroup of CIN3 that progresses to invasive cancer than cytology. If the mean lead time from the detection of preinvasive disease that would progress to symptomatic invasive cancer without intervention is greater for HPV than cytology screening, then the increase in cervical cancer incidence from moving to a 5-yearly HPV policy would be lower than we have predicted. However, the increase in lead time over cytology screening would need to be about 2 years (the difference in the screening intervals) before the 5-yearly HPV screening policy with similar screening test sensitivity reached equipoise with the impact on cervical cancer incidence from cytology screening. In the presence of the greater overdiagnosis in HPV testing, it is difficult to assess differences in mean lead time between the two screening tests unless an analysis of incident cancers is used.[31]

Our predicted increase in cervical cancer incidence differs from the results of the simulation model used to underpin the proposed change in New Zealand policy.[2] We used estimates of the observed direct effects of screening on the incidence of cervical cancer and did not require assumptions or modelling of the sexual behavior of the population, the prevalence of HPV infection, the immunological response to HPV infection, HPV type replacement, or the natural history of cervical neoplasia. The assessment of the quality of simulation models involves review of the research that validates each of the assumptions used. The inclusion of assumptions that can not be validated, or the use of imputation, weakens the value of the results compared to direct observations from trials of health service practice.

A large series of US patients who had a cervical biopsy within a year of a screening utilizing liquid-based cytology

and from-the-vial HPV cotesting found that 18.6% of 526 women with cervical cancer had a negative HPV test compared with only 12.2% who had negative cytology.[32] In China, 7.5% to 15.5% of patients with invasive cervical cancer had previous negative HPV tests,[33] and in the meta-analysis of the 4 European studies 8 of 19 (42%) women who developed cancer with HPV screening ≥2.5 years after enrollment appear to have been HPV-negative at baseline.[25] Two other large US studies of women developing cervical cancer after cytology and HPV cotesting have reported HPV-negative screening test results in women tested more than twelve months before the diagnosis of cervical cancer.[34,35] In addition, negative preceding HPV tests have been reported in 8.3% of women with high-grade dysplasia detected at biopsy.[36] It has also been shown that high-risk HPV negative cervical cancer has a significantly poorer prognosis than high-risk HPV positive cancer,[37] suggesting that 5-yearly HPV screening may have a lower effect on cervical cancer mortality than 3-yearly cytology screening.

The Australian simulation model of the New Zealand cervical screening policy used a detection sensitivity of 96.4%,[2] not screening test sensitivity.[8] The use of detection sensitivity results in overestimation of the comparative benefit of HPV screening because of greater overdiagnosis in HPV compared with cytology screening[5,6] and is the most likely reason the simulation model results differ from ours. The greater overdiagnosis associated with HPV screening also contributes to the increased initial detection of CIN3 with HPV screening but, the same cumulative detection of CIN3 as cytology screening after 6 years of follow-up.[16,17]

All cervical screening in New Zealand uses liquid-based cytology and only 1 randomized controlled trial compared HPV screening with liquid-based cytology.[15] Conventional cytology was the predominant comparator of the other trials. The estimates of RP from cytology screening we used were published over 30 years ago but recent estimates of RP from squamous cell carcinoma of the cervix by cytology screening interval are similar.[38,39]

The 5-yearly HPV screening policy of the New Zealand National Screening Unit was reviewed by the National Cervical Screening Advisory Group and the National Screening Advisory Committee. The National Cervical Screening Advisory Group is largely composed of representatives of relevant professional medical colleges. The results of a simulation model, however, with all the assumptions contained therein, should not be valued more highly than the results of randomized trials comparing HPV and cytology screening in public health practice. This would be a major departure from the standard practice of considering the results of randomized controlled trials to be the strongest evidence for medical practice. In addition, as in other fields of medicine, the principle of "first, do no harm" should apply in public health medicine. Our assessment suggests that lengthening of the screening interval at the same time as changing the screening test may increase the incidence of cervical cancer in New Zealand. New policies can be introduced in a controlled randomized manner so that their effectiveness on disease can be accurately assessed[40] and this should be, whenever possible, a fundamental component of the ongoing management of cancer screening programs.

The change to HPV screening in New Zealand represents a major shift in government funding from the cytology workforce to the manufacturers and suppliers of HPV tests. Several of the randomized trials comparing HPV and cytology screening[15,20] and their effects on colposcopy services[22] have received funds from the diagnostics industry. The research and assessment that contributes to decisions about whether HPV screening is introduced and which HPV tests are approved for a government funded HPV screening program need to be independent of the manufacturers and suppliers of HPV tests.

There appears sufficient evidence that an increased incidence of cervical cancer may eventuate from the proposed 5-yearly HPV screening policy. Australia is introducing 5-yearly HPV screening and, because more women develop cervical cancer in Australia than New Zealand, any increased incidence of cervical cancer resulting from the change in policy would be evident sooner in Australia. It would be prudent to heed the advice of the world experts who have suggested that "implementation of HPV testing needs to be reconsidered especially in countries with well organized programmes",[6] maintain the current cytology screening policy, assess progress in Australia and elsewhere, and re-evaluate the value of HPV screening in 5 to 10 years.

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Conflict of interest disclosures

None.

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