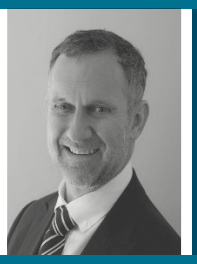
CERVICAL CANCER

THE AUSTRALIAN PROGRAM

Dr **JOHN CUMMINS** Medical Director



SCOR
The Art & Science of Risk

Introduction

Cancer of the cervix is the third most common cancer diagnosed and the fourth most common cause of cancer death globally. Approximately half of sexually active people will get cervical cancer resulting in many individual cases of pain and suffering. The disease is a global burden on health care systems and a significant contributor to claims experience in the life insurance industry.

Various strains of human papillomavirus (HPV), a sexually transmitted infection, plays a role in causing most cervical cancer. Australia has developed an improved screening program and nine valent vaccine that has been 100% effective at curing cervical cancer in women. Combining these remedies with the current cervical cancer immunisation program can lead to the eventual elimination of the disease.

In Australia, by 2020, cancer of the cervix is set to become rare and will likely be eliminated by 2028 – a world first. This article outlines why and how this can be achieved and what this means for cancer of the cervix globally.

Background

Each year, somewhere between 250,000-310,000 women are estimated to die from cancer of the cervix.[1] Carcinomas of the cervix are most often of squamous cell origin (squamous cell carcinomas i.e. SCC) whereas adenocarcinomas, while less frequent, have been increasing in prevalence globally and now cause more than 25% of all cervical cancers.[2] Adenocarcinomas have been historically more difficult to detect by routine Pap screening as squamous lesions are more likely to be visually apparent than adenocarcinomas and adenocarcinomas tend to occur higher in the cervix or be unevenly distributed ('skip lesions').[3]

Virtually all (99.7%) cases of cervical cancer carcinoma are caused by (sexually transmitted) chronic human papillomavirus (HPV) infection. While most often HPV infection is benign and has no potential for carcinogenesis, some HPV variants are more likely to become chronic and cause cancer than others. For example, HPV types 16 and 18 are responsible for approximately 70% of all cervical cancer,[4] with type 16 found in approximately 50% of patients. Other factors frequently associated with an increased risk of cervical cancer include: stress, immunosuppression, chronic exposure to tobacco, and oral contraceptive therapy, the latter for both SCC and adenocarcinoma of the cervix.

Timeline of Carcinoma of the cervix screening and prevention in Australia

There are three historic components to the screening/prevention program in Australia.

❶ PAP SMEAR TESTING

Australia introduced a national cervical screening program in 1991, which involved a Papanicolaou (Pap) smear test every two years examining cervical cells microscopically (i.e. cytology) for precancerous/cancerous changes. Abnormalities would lead to further investigation by a Specialist and generally locally ablative therapy of any offending lesion discovered.

❷ MASS HPV VACCINATION OF TEENAGERS

The first HPV vaccine was created by Researchers Ian Frazer and Jian Zhou at the University of Queensland and approved by the US Federal Drug Administration in 2006.This was a quadrivalent vaccine protecting against four four strains of oncogenic HPV virus.

The free national HPV vaccination program was first offered to Australian schoolgirls aged 12 to 13 in 2007, with a catch-up program for women aged up to 26. Between 2007 and 2009, 72% of girls aged 14–15 had received three doses of the quadrivalent vaccine over six months.[5] In 2013, the program was extended to cover both boys and girls aged 12–13. (Figure 1).

In 2018 Australia commenced using the new nonavalent HPV vaccine, Gardasil 9, replacing the quadrivalent vaccine, thereby protecting against an additional five strains of HPV (types 6, 11, 16, 18, 31, 33, 45, 52 and 58). The program began in line with the school year and reduces the number of doses from three to two (spaced 6–12 months apart).

A recent study suggested that up to 93% of cervical cancers in Australia are associated with the HPV types covered by the new vaccine.[6] In addition, by moving to the nonavalent vaccine and decreasing the number of recommended doses, the rate of compliance with the vaccination schedule is expected to increase.[7]

FIGURE 1: NATIONAL HPV VACCINATION COVERAGE FOR FEMALE ADOLESCENTS TURNING 15 YEARS OF AGE

Year	Coverage Dose 1	Coverage Dose 2	Coverage Dose 3
2012	82.7	79.2	71.5
2013	82.1	78.4	71.7
2014	83.7	80.3	74.1
2015	86.4	83.7	78.0
2016	86.5	83.8	78.6

Notes

1. Coverage is calculated as doses administered and reported to the HPV Register/ Estimated Resident Population expressed as a percentage.
2. Year is the year in which females turn 15 years of age; 15 years of age is used as the age for routine review of vaccination coverage that provides the best comparison to allow for these varying ages in administration, as per World Health Organization (WHO) recommendations.

Source: National HPV Vaccination Register 2017; Victorian Cytology Service 2017.

❸ HPV TESTING

In late 2017 Australia moved from a biannual Pap smear program to a five yearly HPV testing program. International randomised trials comparing HPV DNA testing with cytology for primary screening have shown HPV testing for those strains known to be more likely to lead to high grade lesions to be superior.[8] For HPV-positive women, liquid-based cytology testing will be reflexively performed on the sample.

The advantages of HPV screening over the traditional Pap tests include:

- A significant false-negative rate for Pap versus HPV tests (30% vs 2-3%) required more frequent Pap screening to minimise failure to detect disease
- Women who test HPV negative are at very low risk for cervical cancer for at least the following five years. Compared with cytology, HPV testing provides 60–70% greater protection against invasive cervical cancers[8] and significantly reduces the incidence of adenocarcinoma
- Opportunity for self-collection (for women who for a variety of reasons decline to be examined by a practitioner) in under-screened populations

Hence the participation rate is expected to increase in concordance with a higher diagnostic rate.

In addition, the increasing percentage of women being vaccinated with an anticipated much lower prevalence of HPV transmission was another reason for updating the national cervical cancer screening program.

RESULTS

As a result of the initial cervical screening program with Pap smears, the incidence of cervical cancer in Australia halved from approximately 13 cases per 100,000 women in 1991 to seven cases per 100,000 women in 2002. The death rate has dropped to two per 100,000.[9]

Due to the latency period of 10 to 15 years between HPV exposure and cervical cancer development, it was not thought to be likely that there would be significant decreases in cervical dysplasia or cancer for many years after the implementation of vaccination programs. Surprisingly however, reporting around the world has shown:

- A reduction of 90% for HPV types 6, 11, 16 and 18
- A decrease by 85% for high-grade cervical abnormalities
- And a lowering of 45% for low-grade abnormalities[10]

In countries such as Australia that have achieved vaccination rates greater than 70%, there has already been a 47% reduction in high-grade cervical neoplasia.[11] Early data from the Victorian Cervical Cytology Registry (Australia) showed a decrease in high-grade cervical abnormalities in girls younger than 18 years within 30 months of the introduction of the vaccine.[12]

A recent study published in the *Journal of Infectious Diseases*[13] showed that among women aged 18 to 24 the rate of HPV infection dropped from 22.7% to just 1.5% by 2015. Recent research has also shown a decline in HPV among males.

"We are forecasting that over the next 30 to 40 years, rates of cervical cancer will drop from around the current 930 cases a year in Australia to just a few", says the author of the study Professor Garland.

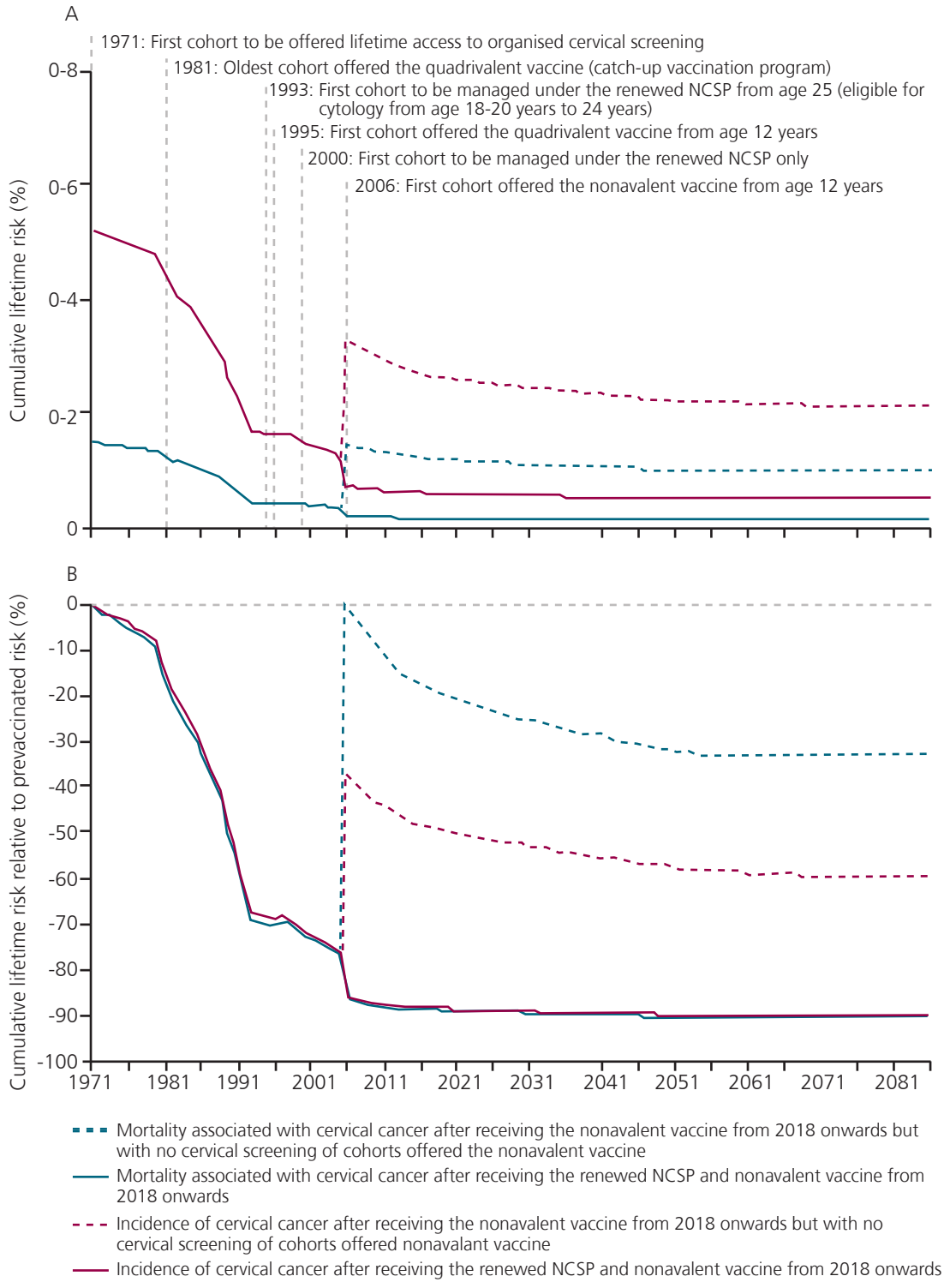
The screening program has been shown to be 100% effective at preventing cervical cancer for women who take full part in the program. So there is a real possibility that by combining the cervical cancer immunisation program now with the new nine valent vaccine and the improved screening program, the 200 cases of cervical cancer that occur in Australia each year will drop over the next few years to negligible numbers.

Despite the success of the previous program based on two-yearly Pap smears, there had been no change in the incidence and mortality associated with adenocarcinoma of the cervix. It's important to note that the prevalence rate of any HPV infection is 72% in adenocarcinoma.[14] The renewed program, based on five-yearly HPV testing is predicted to deliver an additional decline of 24–36% in the incidence and mortality from cervical cancer by enhancing the rate of detection of HPV precursors of both adenocarcinoma and squamous cell cervical cancers. In Australia in 2008, 65.1% of cervical cancers were squamous cell carcinoma and 25.7% were adenocarcinoma, with adenosquamous (3.3%) and other cervical cancers (5.9%) making up the remainder.[15]

If current practices continue, the disease will be eliminated as a public health problem in Australia by 2028 and all but eradicated by 2066 globally with about one case per 100,000. By 2100 there would be just three deaths per million women (compared to 21 deaths per million, or about 260 deaths each year today).[16]

As Figure 2, in addition to demonstrating the time course of the prevention program, it remains critically important for a woman to still have HPV screening despite completing the vaccination program[16] as there will be some oncogenic viruses not covered by the Gardasil 9. Nonetheless, if one had the full vaccine regimen and one was not screened thereafter, the odds of developing cancer of the cervix is still as low as a woman born after 1971 participating in the older Pap smear program prior to vaccinations and HPV testing.

FIGURE 2: CUMULATIVE LIFETIME RISK OF INCIDENCE OF INVASIVE CERVICAL CANCER AND ASSOCIATED MORTALITY IN AUSTRALIAN WOMEN BY BIRTH YEAR



Data are (A) cumulative lifetime risk, and (B) cumulative lifetime risk, relative to the prevaccinated risk. The prevaccinated risk refers to cumulative lifetime risk calculated for the 1971 birth cohort (i.e. the first Australian cohort who received organised cervical screening and were not offered human papillomavirus vaccination). NCSP=National Cervical Screening Program.

Going Global

As of May 2017, more than 270 million doses of HPV vaccines have been administered worldwide. More than 10 million doses of Gardasil 9 have been given in the US in the past year. Nearly 50% of girls and boys in the US are now receiving the cervical cancer vaccines, and universal immunisation programs are in place in many European countries and Canada.

While dozens of countries around the world now vaccinate their teenagers from HPV, many are still missing out as the vaccine remains relatively expensive even when offered at a lower price in some countries.

Gardasil inventor Ian Frazer and the University of Queensland have waived millions of dollars in royalties on sales of the cervical cancer vaccine in 72 western countries. Professor Frazer said the decision, along with initiatives by the charitable Frazer Family Foundation (run by Professor Frazer and his wife Caroline), the Bill and Melinda Gates Foundation and the World Health Organisation, would help ensure the vaccine was available in the developing world at the heavily subsidised cost.[17]

Professor Frazer notes that education programs are important before introducing the vaccine, and the logistics for delivering Gardasil in some countries needed to be worked out carefully before it could be introduced.

Other Cancers

It is also crucial to note that HPV is the reputed agent in a number of other cancers and conditions. Oncogenic HPVs cause almost 100% of cervical cancers, 90% of anal, 70% of vaginal, 40% of vulvar, 50% of penile and 13% to 72% of oropharyngeal cancers, and HPV16 predominates in all of these non-cervical HPV-related cancers. HPV6 and HPV11, which are classified as low-risk genotypes, cause 90% of genital warts as well as the rare but debilitating recurrent respiratory papillomatosis.[18]

It is anticipated that the cancers and diseases noted above will also fall in incidence at a rate similar to the causative contribution of HPV.

CONCLUSION

By combining the cervical cancer immunization program with the new nine valent vaccine and the improved screening program, there is a potential for this virus induced cancer to be eradicated from Australia and quite likely globally within the next few decades.

Understanding disease causation and prevention so that public health initiatives can be utilized to their maximum extent will improve claims experience for cancer of the cervix. A determination to apply the information gathered may also lead to a decrease in other cancers caused by the same oncogenic virus.

The consequences of increased exposure to health care systems will enhance primary prevention using diligent interventions such as basic health checks and vaccinations.

Modern medicine is transforming the prevalence and outcomes of cancer medicine which will have significant impacts on future claims as well as underwriting experience.

References

1 Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and Trends. Cancer Epidemiol Biomarkers Prev. 2017; 26(4); 444–57.

2 Tornesello ML, Losito S, Benincasa G, et al. Human papillomavirus (HPV) genotypes and HPV16 variants and risk of adenocarcinoma and squamous cell carcinoma of the cervix. Gynecol Oncol. 2011;121(1):32-42.

3 del Carmen M, Schorge JO. Cervical adenocarcinoma in situ. Goff B, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/cervical-adenocarcinoma-in-situ. (Accessed on December 18, 2018 .)

4 Muñoz N, Bosch FX, de Sanjosé S, Herrero R, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518–27.

5 Brotherton, JML; Winch, KL; Bicknell, et al HPV vaccine coverage is increasing in Australia The Medical Journal of Australia Volume 206 issue 6 2017

6 Brotherton JML, Tabrizi SN, Phillips S, et al. Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination. Int J Cancer 2017;141(8):1576–84.

7 Australian Institute of Health and Welfare 2018. Cervical screening in Australia 2018. Cat. no. CAN 111. Canberra: AIHW.

8 Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014; 383 (9916):524-532.

9 Australian Institute of Health and Welfare 2014. Cervical screening in Australia 2011–2012. Cancer series no.82. Cat. no. CAN 79. Canberra: AIHW.

10 Garland SM, Kjaer SK, Muñoz N, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clin Infect Dis. 2016;63(4):519-27.

11 Lee LY, Garland SM. Human papillomavirus vaccination: the population impact. F1000Res. 2017;6:866. 2017 Jun 12.

12 National Cervical cancer screening program renewal : Evidence review November 2013 Medical Services Advisory Committee Application no 1276 . Assessment report

13 Machalek DA, Garland SM, Brotherton JML, et al. Very Low Prevalence of Vaccine Human Papillomavirus Types Among 18- to 35-Year Old Australian Women 9 Years Following Implementation of Vaccination, The Journal of Infectious Diseases, 2018; 217,(10)1590–1600.

14 Tornesello ML, Losito S, Benincasa G, et al. Human papillomavirus (HPV) genotypes and HPV16 variants and risk of adenocarcinoma and squamous cell carcinoma of the cervix. Gynecol Oncol. 2011;121(1):32-42.

15 Australian Institute of Health and Welfare 2012. Cervical screening in Australia 2009–2010. Cancer series 67. Cat. no. CAN 63. Canberra: AIHW.

16 Hall M, Math M, Simmons K, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study Lancet Public Health 2018 Open Access https://doi.org/10.1016/S2468-2667(18)30183-X

17 https://www.couriermail.com.au/news/queensland/gardasil-inventor-ian-frazer-and-the-university-of-queensland-waive-millions-of-dollars-in-royalties/news-story/5e6bda679d490d0a081300827839dea9

18 Lee LY, Garland SM. Human papillomavirus vaccination: the population impact. F1000Res. 2017;6:866. Published 2017 Jun 12. doi:10.12688/f1000research.10691.1

Editor
Paolo De Martin

life@scor.com

SCOR
The Art & Science of Risk

SCOR
5, avenue Kléber - 75795 Paris Cedex 16
France

www.scor.com