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# Hormonal contraceptive use and smoking as risk factors for high-grade cervical intraepithelial neoplasia in unvaccinated women aged 30–44 years: A case-control study in New South Wales, Australia

Huilan Xu[a,1], Sam Egger[b,1], Louiza S Velentzis[b,c,1], Dianne L O'Connell[a,b,d], Emily Banks[e,f], Jessica Darlington-Brown[b], Karen Canfell[a,b,g,*], Freddy Sitas[a,h]

[a] Sydney School of Public Health, University of Sydney, Camperdown, NSW, Australia
[b] Cancer Research Division, Cancer Council NSW, Woolloomooloo, Sydney, NSW, Australia
[c] Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics, University of Melbourne, Melbourne, Victoria, Australia
[d] School of Medicine and Public Health, University of Newcastle, Australia
[e] National Centre for Epidemiology and Population Health, Australian National University, Canberra, ACT, Australia
[f] The Sax Institute, Sydney, Australia
[g] Prince of Wales Clinical School, Faculty of Medicine, University of New South Wales, NSW, Australia
[h] School of Public Health and Community Medicine, University of New South Wales Australia, Kensington, Australia

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ABSTRACT

*Background:* Human papillomavirus (HPV) vaccines protect against HPV types 16/18, but do not eliminate the need to detect pre-cancerous lesions. Australian women vaccinated as teenage girls are now entering their mid-thirties. Since other oncogenic HPV types have been shown to be more prevalent in women ≥30 years old, understanding high grade cervical lesions in older women is still important. Hormonal contraceptives (HC) and smoking are recognised cofactors for the development of pre-malignant lesions.

*Methods:* 886 cases with cervical intraepithelial neoplasia (CIN) 2/3 and 3636 controls with normal cytology were recruited from the Pap Test Register of NSW, Australia. All women were aged 30–44 years. Conditional logistic regression was used to quantify the relationship of HC and smoking to CIN 2/3 adjusted for various factors.

*Results:* Current-users of HC were at higher risk for CIN 2/3 than never-users [odds ratio (OR) = 1.50, 95%CI = 1.03–2.17] and risk increased with increasing duration of use [ORs:1.13 (0.73–1.75), 1.51 (1.00–2.72), 1.82 (1.22–2.72) for < 10, 10–14, ≥15 years of use; p-trend = 0.04]. Ex-users had risks similar to never-users (OR 1.08, 95%CI = 0.75–1.57) regardless of duration of use. Current smoking was significantly associated with CIN 2/3 (OR = 1.43, 95%CI = 1.14–1.80) and risk increased with increasing number of cigarettes/day (p-trend = 0.02). Among ex-smokers, the risk of CIN 2/3 decreased with increasing time since quitting (p-trend = 0.04).

*Conclusions:* In this benchmark study, current, long term users of HC and current smokers of ≥5 cigarettes/day were each at increased risk of developing CIN 2/3. Findings support smoking cessation in relation to decreasing the risk of pre-cancerous lesions and reinforce the continuing need for cervical screening for cancer prevention in vaccinated and unvaccinated populations.

## 1. Introduction

Australia was one of the first countries to implement a publicly funded National HPV Vaccination Programme. The programme commenced in 2007 and involved administering 3 doses of the quadrivalent vaccine (Gardasil™, Merck) to 12–13 year old schoolgirls and until 2009 included a catch-up phase, where women aged up to 26 years were also offered vaccination. In 2013 the vaccination programme was extended to include boys aged 12–13 years and a 2-year catch-up phase for males aged 14–15 years. More than a decade since the implementation of the

*Abbreviations:* CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; IUD, intra-uterine device; LSIL, low grade squamous intraepithelial lesion; NSW, New South Wales; PTR, Pap Test Register

* Corresponding author at: Cancer Research Division, Cancer Council NSW, 153 Dowling Street, Woolloomooloo, NSW, 2011, Australia.
*E-mail address:* karen.canfell@nswcc.org.au (K. Canfell).

[1] Joint first authors.

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vaccination programme in Australia, reductions of 65%, 40% and 13% have been observed in histologically confirmed high grade cervical abnormalities in women aged < 20 years, 20–24 years and 25–29 years [1], respectively. A 78% fall in population prevalence of vaccine-included HPV types in women 18–24 years [2] and a 73–90% decline in the incidence of anogenital warts in females 12–26 years [3] have also been reported. However, HPV vaccination will not eliminate the need to detect and treat pre-cancerous cervical lesions. In the catch-up phase, adult females were not tested for HPV16/18 infections prior to vaccination and administration of the vaccine after exposure has been found not to impact clearance of existing infections [4]. Also, in its current form, the HPV vaccine does not protect against oncogenic HPV types other than HPV 16 and 18. Although cervical HPV16/18 DNA is more prevalent in women under 30 years of age, studies have shown that other high risk HPV types become prevalent in women above 30 years [5–7]. Furthermore, taking into consideration that the majority of women worldwide have not been vaccinated against HPV, it is still important to understand the occurrence and determinants of high grade cervical lesions in women aged over 30 years.

Infection with oncogenic HPV types is required for the development of high grade cervical intraepithelial neoplasia (CIN) and cervical cancer, however, not all infected women develop pre-cancerous lesions. The International Agency for Research on Cancer (IARC) has classified smoking and combined oral contraceptives as carcinogenic to humans and its evaluation of the evidence has shown a causal association between these agents and cervical cancer [8–10]. Two collaborative analyses of data from international epidemiological studies on the relationship between the pattern of use of these agents and cervical cancer reported elevated risks of cervical cancer and CIN3 associated with smoking and the use of combined oral contraceptives [11,12]. However, no Australian data were included in the collaboration on smoking and less than 100 cases from Australia were included in the collaboration on oral contraceptives. With temporal changes in the formulation of oral contraceptives in terms of oestrogen dose and progestagen type, investigating the association between pre-cancer and oral contraceptive use in a more recent cohort is warranted. Based on survey data from Australian General Practices, among women aged 35–44 years, 64 out of 1000 consultations were for contraceptive management and over half of these (58%) concerned the use of oral contraceptives [13]. Furthermore, about 14% of women aged 25–44 years reported being current smokers, with higher prevalence found among women living in areas of most disadvantage [14].

The aim of the current study was to measure the effects of hormonal contraceptive use and smoking history on the risk of developing high-grade cervical lesions for Australian women above 30 years of age.

## 2. Methods

### 2.1. Setting and subjects

Data for this analysis were obtained from the Cervical Health Study, described previously [15]. Briefly, women were recruited from the NSW Pap Test Register (PTR) [16]. The PTR was established in 1996 and is a centralised database of NSW cytology results. It contains information on name, address, date of birth and cervical screening history of women who have had a Pap test, and each of their cytology and histology results except those for < 1% of women who opt-out. Study recruitment was conducted between December 2006 and July 2011 and women were eligible if they were aged 20–64 years when they entered the study. Preliminary cases were defined as women with high-grade squamous intraepithelial lesions (HSIL), including a cytological prediction of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) during the study period. The date of the first abnormality was regarded as the date of entry into the study and this test was referred to as the index test. The preliminary cases were frequency-matched by 5-year age band and date of index test to three preliminary controls (women with a normal Pap test result). Preliminary controls were selected at random from the women meeting these criteria. For preliminary controls, the date of the test which was used to match them to the corresponding preliminary case was referred to as the index test date.

### 2.2. Definition of cases and controls

Cases and controls were then selected from their corresponding preliminary lists. Women with hysterectomy were excluded since the cervix is generally removed and so the risk of CIN 2/3 is negligible. Incident cases of CIN 2/3 were women with a CIN 2/3 smear cytology index test (i.e. the preliminary cases) that was also confirmed by a histology test within 3 months after the index test. Cases with CIN 2/3 cytology or positive histology within 5 years prior to the index test were excluded since they were considered to be prevalent cases. Controls were women with a normal index smear cytology test and no CIN 2/3 cytology or histology test within 5 years prior to the index test.

For this analysis, cases and controls aged 30–44 years were selected. The age limit of 44 was used as women aged 44 or older are less likely to be using oral contraceptives for prevention of pregnancy. Controls and cases were matched by 5-year age band (30–34, 35–39, 40–44) and date of index test (2-month periods).

### 2.3. Data collection and measurements

Questionnaires and consent forms were mailed to women who were registered with the NSW PTR and were eligible for the study. A help line was established to respond to participants' queries about the study, consent or assistance with questionnaire completion. Non-respondents were followed up after two weeks with a repeat mailing.

A self-administered questionnaire sought information on demographic and relevant medical details, hormonal contraceptive use, history of smoking, alcohol consumption, reproductive and sexual history, use of menopausal hormone therapy and cervical screening history. In addition, data from the NSW PTR were used to ascertain previous frequencies of Pap smears and the corresponding test results. Hormonal contraceptives included the combined pill, progestagen-only pill, injections, IUDs with hormones, implants and vaginal rings. Current hormonal contraceptive users and/or smokers were defined as those who were using/smoking at the time of having the index Pap smear test or who had stopped less than a year before the date of the index test. Most of the questions used in the questionnaire have been used previously and validated in the UK Million Women Study [17]. Similar questions regarding use of injectable/implanted contraceptives were also included.

Increased attendance for cervical screening has been found to be associated with having children, having ever-used oral contraceptives and not currently smoking [18]. Therefore it is important to adjust for the number of Pap smear tests when assessing the potential risk factors for cervical disease. In Australia, it is recommended that cervical screening is carried out every second year; women with a smear result suggesting a low grade cervical lesion or a possible low grade squamous intraepithelial lesion (LSIL) are recommended to have a repeat cytology test at 12 months after the index smear; those aged over 30 years without a history of negative cytology in the preceding two to three years and with a low grade cervical lesion or a possible LSIL smear result are recommended to have a repeat cytology test within 6 months [19]. Hence, women with prior equivocal smears may have more subsequent smear tests over a relatively short period of time and an increased number of smear tests overall. To account for this, tests conducted up to 1.5 years prior to the index test in this study were not included in the number of prior Pap tests. That is, the number of Pap smear tests was counted for the period 1.5–5 years prior to the index text.