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Condom and oral contraceptive use and risk of cervical intraepithelial neoplasia in Australian women

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Objective: To assess the association between condom use and oral contraceptive consumption and the risk of cervical intraepithelial neoplasia (CIN).
Methods: A cross-sectional study was conducted in Perth clinics. A total of 348 women responded to the structured questionnaire. Information sought included demographic and lifestyle characteristics such as the use of condom for contraception, consumption of oral contraceptive, and duration of oral contraceptive usage. Crude and adjusted odds ratio (OR) and associated 95% confidence interval (CI) were calculated using unconditional logistic regression models and reported as estimates of the relative risk.
Results: The prevalence of CIN was found to be 15.8%. The duration of oral contraceptive consumption among women with abnormal Papanicolaou (Pap) smear result indicating CIN was significantly shorter than those without abnormal Pap smear result (mean±SD, 5.6±5.2 years vs. 8.2±7.6 years; p=0.002). Comparing to ≤3 years usage, prolonged consumption of oral contraceptive for ≥10 years reduced the risk of CIN (p=0.012). However, use of condom for contraception might not be associated with a reduced risk of CIN after accounting for the effects of confounding factors (adjusted OR, 0.52; 95% CI, 0.05 to 5.11; p=0.577).
Conclusion: Use of oral contraceptives, but not condoms, for contraception appeared to be inversely associated with CIN. Prolonged use of oral contraceptive demonstrated its benefits of reducing the risk of CIN.

Keywords: Australia, Cervical intraepithelial neoplasia, Comparative study, Condom, Oral contraceptive

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is initiated by human papillomavirus (HPV) infection [1]. Sexual and reproductive behaviours, as well as hormone levels and hormone receptors, are known to affect the development of CIN [1]. Besides vaccination, use of condoms is an effective barrier against HPV infection [2], and may reduce the risk of CIN among women highly susceptible to HPV infection [3]. Its protective effect needs to be ascertained on other women.

The transforming zone of the cervix, where HPV initiates CIN, is sex-hormone dependent [1]. Steroid hormones including progesterone, influence HPV actions and indirectly contribute to HPV-related CIN [1]. Despite the widespread use of oral contraceptives and its protective effect against cancers affecting female, such as endometrial cancer [4,5], there is no consensus on the use of oral contraceptives and the health of the cervix [6-8]. While a joint report by the World Cancer Research Fund and the American Institute for Cancer Research suggested a possible increased risk of cervical cancer [9], the World Health Organization did not recommend discontinuing the use of oral contraceptives as its use outweighed its risk [10]. Indeed, evidence is lacking on the relationship between oral

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contraceptive consumption and the risk of CIN [11,12]. Therefore, the present study aims to investigate whether the use of non-clinical contraception, particularly condoms and oral contraceptives, is associated with any risk of CIN in Australian women.

MATERIALS AND METHODS

Community-dwelling adult women within metropolitan Perth, Western Australia who had a Papanicolaou (Pap) smear test at five medical centres and clinics (Parkwood Medical Centre; Murdoch Health and Counselling Service; Fremantle Women's Health; Women's Health Services, Northbridge; Women's Health Service Incorporation, Gosnells) were approached by their general practitioners. Temporary residents, women below 18 years of age, women who had a history of breast, ovarian or endometrial cancer, and those with a chronic debilitating disease, were excluded from this study. Following consecutive referrals from the general practitioners, and further screening and subsequent withdrawals, a total of 348 women were eventually recruited and signed the informed consent form. An appointment for interview was made with each participant by the third author. These face-to-face interviews were held at either the clinic of recruitment or the participants' residences. All participants were assured of confidentiality but blinded to the research hypothesis. The study protocol was approved by the Human Research Ethics Committee at Curtin University (approval number HR 118/2006).

A structured questionnaire was used to collect information on demographic and lifestyle characteristics. In relation to contraception, information sought included the use of condom for contraception (no, yes), consumption of oral contraceptive (never, ever), and duration of oral contraceptive usage (years). Specifically, the participants were asked "What form of contraception, if any, do you use?" The choices were: "I use condoms (categorized as 'yes')," "I use another method of contraception (categorized as 'no')," and "None, I don't use contraception (categorized as 'no')." For the 'consumption of oral contraceptive,' the participants were asked "Are you currently using, or have used, the oral contraceptive pill?" In the context of 'duration of oral contraceptive usage,' the participants were asked "How many years in total have you ever taken the oral contraceptive pill?" Information about other sexual history was not asked as it did not contribute directly to CIN [13-15] and may cause embarrassment and burden to the participants. The Pap smear test outcome was classified as "normal" or "CIN" based on the result reported by the accredited St John of God Pathology, Murdoch, Western Australia, Australia. The Pap smear status was defined according to the Australian Modified Bethesda System 2004 [16].

Descriptive statistics were first used to summarize the characteristics of the participants. Chi-square and independent samples t-tests were then applied to compare the variables between women with normal Pap smear status and with abnormal Pap smear result indicating CIN. To assess the effects of condom and oral contraceptive use on CIN risk, including duration of oral contraceptive consumption, the Pap smear test outcome was analysed by three separate unconditional logistic regression models. Duration of cumulative oral contraceptive consumption was categorized based on the distribution of women with normal Pap smear status into three increasing levels of exposure (≤3 years, 3.1 to 9.9 years, and ≥10 years). Each fitted multivariable model included terms for age (years), age of first pregnancy (years), smoking duration (years), annual family income (<AUD $15,000, AUD $15,000 to 60,000, >AUD $60,000), hormone replacement therapy (never use, ever use), and number of pregnancies. These confounding variables were plausible risk factors identified from the literature or from our univariate analyses. Crude and adjusted odds ratio (OR) and associated 95% confidence interval (CI) were reported as estimates of the relative risk. All statistical analyses were performed using the IBM SPSS ver. 20 (IBM Co., Armonk, NY, USA).

RESULTS

Table 1 presents characteristics of the 348 participants by CIN status. The prevalence of CIN was found to be 15.8% (55/348) in the present study. Most of the participants were married (99%) and never smoked (62%). Women with CIN (n=55) tended to be younger (p<0.001) and earned less (p=0.019) than those without CIN (n=293). Body mass index, lifestyle and reproductive characteristics were similar between the two groups (p>0.05).

The duration of cumulative oral contraceptive consumption among women without CIN was significantly longer than those with CIN (mean±SD, 8.2±7.6 years vs. 5.6±5.2 years; p=0.002). Logistic regression results in **Table 2** further showed that long term consumption of oral contraceptive for at least 10 years was associated with a reduced risk; the adjusted OR was 0.17 (95% CI, 0.04 to 0.69) when compared to 3 years or less usage. However, use of condom for contraception might not be associated with a reduced risk of CIN after accounting for the effects of confounding factors (adjusted OR, 0.52; 95% CI, 0.05 to 5.11).

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Table 1. Characteristics of participants by CIN status

Variable	Without CIN (n=293)	With CIN (n=55)	p-value*
Age (yr)	46.8±13.7	38.8±15.2	<0.001
Age of first menarche (yr)	13.0±1.5	13.2±1.6	0.300
Age of first pregnancy (yr)	25.2±5.3	24.5±5.5	0.435
No. of pregnancies	2.1±1.6	1.9±1.9	0.361
Body mass index (kg/m^2)†	26.1±5.42	25.1±5.0	0.223
Smoking duration (yr)†	8.5±10.05	10.7±6.6	0.111
Smoking status			0.143
Never smoked	187 (63.8)	29 (52.7)	
Current smoker	29 (9.9)	10 (18.2)	
Ex-smoker	77 (26.3)	16 (29.1)	
Marital status			0.119
Never married/*de facto*	2 (0.7)	2 (3.6)	
Married	291 (99.3)	53 (96.4)	
Nationality			0.149
Australia/New Zealand	189 (64.5)	41 (74.5)	
Others	104 (35.5)	14 (25.5)	
Annual family income (AUD $)†			0.019
<15,000	14 (4.8)	7 (12.7)	
15,000–60,000	135 (46.6)	30 (54.5)	
>60,000	141 (48.6)	18 (32.7)	
Hormone replacement therapy†			0.290
Never use	213 (73.2)	44 (80.0)	
Ever use	78 (26.8)	11 (20.0)	

Values are presented as mean±SD or number (%).
AUD, Australian dollar; CIN, cervical intraepithelial neoplasia.
*Chi-square or t-test for difference between two groups. †Missing data present.

Table 2. Association between contraception use and risk of CIN in Australian women

Variable	Without CIN (n=293)	With CIN (n=55)	Crude OR (95% CI)	Adjusted* OR (95% CI)	p-value
Duration of cumulative oral contraceptive consumption (yr)					0.012
≤3	99 (33.8)	25 (45.5)	1.00	1.00	
>3 and <10	83 (28.3)	18 (32.7)	0.859 (0.438–1.682)	0.339 (0.093–1.235)	
≥10	111 (37.9)	12 (21.8)	0.428 (0.204–0.897)	0.169 (0.042–0.689)	
Consumption of oral contraceptive					0.221
Never use	243 (82.9)	43 (78.2)	1.00	1.00	
Ever use	50 (17.1)	12 (21.8)	1.356 (0.668–2.755)	0.256 (0.029–2.267)	
Use of condom for contraception					0.577
No	261 (89.1)	50 (90.9)	1.00	1.00	
Yes	32 (10.9)	5 (9.1)	0.816 (0.303–2.195)	0.523 (0.054–5.108)	

Values are presented as number (%).
AUD, Australian dollar; CI, confidence interval; CIN, cervical intraepithelial neoplasia; OR, odds ratio.
*Adjusted for age (yr), age of first pregnancy (yr), smoking duration (yr), annual family income (<AUD $15,000, AUD $15,000–60,000, >AUD $60,000), hormone replacement therapy (never use, ever use), and number of pregnancies.

DISCUSSION

In this study, cumulative use of oral contraceptive was longer amongst women with CIN. After controlling for plausible confounding factors, prolonged oral contraceptive consumption was found to be inversely associated with the risk of CIN in Australian women, consistent with a previous report of a decreased risk of CIN with use over 5 years [17]. The potentially protective mechanism may be attributable to the hormonal effect of oral contraceptive on HPV DNA expression and the viscosity of the cervical mucus [18,19]. Estrogen can protect the mucosal immune system against early HPV infection [17], while the viscosity of the mucus affects the penetration of foreign bodies including HPV [19]. The inverse association of the risk of CIN with long term oral contraceptive consumption could also be due to the relatively stable sexual relationships among middle-aged women, who tended to prefer oral contraception to the use of condoms [20]. Previous studies have found the use of oral contraceptive to be not associated with the risk of CIN [21-26], while some studies reported that an increased risk was plausible for high grade CIN [27,28].

The association between use of condom for contraception and risk of CIN was not significant. Nevertheless, the potential beneficial effect of condom use against CIN has been demonstrated in other studies [19,29]. Evidence showed that barrier methods of contraception such as condom could increase the clearance of HPV infection [30,31], thereby reducing the risk of CIN [3]. The relatively small sample size of this study might explain the apparent lack of association observed.

The strength of this study includes using standardized questionnaire, classification of the Australian Modified Bethesda System and the accredited pathology. The face-to-face interviews by a single investigator (third author) also eliminated inter-interviewer bias. A major limitation is the small sample cross-sectional retrospective design so that cause-effect relationship cannot be established. Another limitation is the one-off assessment of Pap smear status as HPV infection can be transient and CIN may regress [32]. In addition, the types of oral contraceptive used by the participants were not recorded. Interaction between the estrogen and progesterone receptors and the oral contraceptive can affect the physiology of the cervical epithelium [33]. Similarly, ethnicity may play a role in the disease etiology. Large-scale multiethnic longitudinal age-matched studies including detailed information on sexual history and behavior, together with periodical assessments of Pap smear status, are recommended to confirm the association of risk of CIN with various use of contraception for women from various backgrounds. Both developed and developing countries should be targeted for consideration. Despite these limitations, the present study found that prolonged oral contraceptive use was associated with a decreased risk of CIN. As the protective benefits of oral contraceptives, and possibly that of condom, outweighed the adverse effect, their use should not be discontinued without consultation with general practitioners.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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