

Review

Estro-progestin Contraceptives and Risk of Cervical Cancer: A Debated Issue

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Abstract. *Steroid contraceptive hormones may promote human papilloma virus (HPV) - DNA integration into the host genome, may bind to specific HPV-DNA sequences within transcriptional regulatory regions, and may modulate cell apoptosis. Most epidemiological studies, reported in this narrative review, have shown that oral contraception is associated with a 1.5-3.3-fold higher relative risk of cervical cancer, but only in users for >5 years and especially in HPV-positive women. The relative risk declines with increasing time since last use and is not different from that of never users after >10 years. Ten-year oral contraceptive use from the age of 20 years is associated with an increase in the cumulative incidence of invasive cervical cancer at the age of 50 years of approximately 1 case per 1,000. Oral contraception has a very small negative impact on the absolute risk of cancer of the uterine cervix.*

Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries have detected 569,847 new cases of cervical cancer and 311,365 deaths due to this tumor in 2018 (1). It is caused by persistence of high-risk human papillomavirus (HPV) infection (2). HPV-16 is the most common type, responsible for about 55% of all tumors, HPV 18 accounts for another 15%, and HPV types 31, 33, 35, 45, 52, and 58 are responsible for an additional 18% of cases (3). Most cervical cancers arise in the transformation zone (4). Low-grade cervical lesions, generally harboring episomal HPV, have a low risk of progression, whereas a minority of persistent infections after integration of HPV-DNA into the

host genome may cause a high-grade cervical lesion and then, an invasive cervical cancer (5). The genome of HPV includes early genes (E1, E2, E4, E5, E6, E7) involved in the regulation of the vegetative and productive phases of the virus life cycle, late genes encoding the capsid proteins, and a non-coding regulatory region involved in transcription regulation and viral replication (6). The HPV E2 protein regulates the transcription of the E6 and E7 genes, whereas the malignant transformation triggered by HPV-DNA integration into the host genome is accompanied by disruption of the E2 gene and deregulated expression of E6 and E7 (7). High-risk HPV E6 protein degrades the p53 protein and high-risk HPV E7 protein induces phosphorylation and degradation of the retinoblastoma protein pRB, thus leading to the release of E2F family of transcription factors and subsequent activation of genes promoting cell proliferation (8).

Mechanisms used by HPV to escape immune surveillance include the non-lytic replication that limits innate immune responses that would occur in response to cell death, the lack of a viremic phase, the low expression of viral proteins until later stages of epithelial differentiation, and the down-regulation of important receptors on cells of the innate immune system (9). Furthermore, HPV inhibits the expression of proinflammatory proteins that are critical for activating cytotoxic T cells.

Smoking, infection with other sexually transmitted agents such as *Chlamydia trachomatis* and human herpes simplex virus, multiparity and hormonal contraception have been investigated as cofactors for the development of high-grade cervical lesions and invasive cervical cancer, whereas there is a controversial evidence for a role of intrauterine device (IUD) in HPV-related carcinogenesis (10-22). A recent US retrospective cohort analysis of 10,674 women who received IUDs reported that copper IUD users had a lower risk of cervical neoplasms compared with levorgestrel-releasing IUD users [relative risk (RR)= 0.38, 95% confidence interval (CI)=0.16-0.78] (20).

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In vivo studies have shown that estrogen may enhance the onset and progression of cervical cancer in human HPV transgenic mouse models (23). The combination of low-dose 17 β -estradiol and low-level HPV gene expression biases transformation zone reserve cells toward squamous cell rather than glandular cell differentiation (24). Transitional zone is five-fold more sensitive to the induction of squamous cell carcinogenesis by estrogen compared to other genital tract sites. Immunohistochemical studies on hysterectomy specimens from young women undergoing surgery for non-cervical benign uterine disease, have revealed that the expression of estrogen receptors and progesterone receptors is significantly higher in the transformation zone compared with the ectocervix (25).

Steroid contraceptive hormones may also promote HPV-DNA integration into the host genome, and may bind to specific HPV-DNA sequences within transcriptional regulatory regions, thus increasing or suppressing the transcription of different genes and possibly modulating cell apoptosis (10-12, 14, 26, 27). Estrogen and progesterone increase the levels of apoptosis induced by HPV16 E2 and E7 proteins and therefore these hormones might protect cells from malignant transformation (26).

Conversely, in the absence of HPV-16 E2 protein following HPV-DNA integration into the host genome, steroid hormones could enhance carcinogenesis.

Estrogens may be genotoxic agents that are hydroxylated by a specific cytochrome P450 (28, 29). 4-hydroxyestrone and 16 α -hydroxyestradiol are considered to be carcinogenic (30). Cervical cells, especially those of the transformation zone, are able to 16 α -hydroxylate estradiol, and both cervical and foreskin cells immortalized with HPV-16 are greatly enhanced in the 16 α -hydroxylation of estradiol compared with normal cells (31). Moreover, *in vitro* studies have shown that 17 β -estradiol may enhance Bcl-2 expression and prevent oxidative stress-induced apoptosis in keratinocytes (32).

Experimental investigations in animal models of human multiple sclerosis have shown that 17 β -estradiol decreases tumor necrosis factor- α , interferon- γ and interleukin -12 production in mature dendritic cells (33) and that 17 β -estradiol-exposed dendritic cells inhibit the expansion of CD4⁺ T cells and increase the number of regulatory T cells and CD4⁺CD28⁻ suppressor T cells (34). The altered dendritic cell function may contribute to the persistence of HPV by preventing infected cells from being eliminated by cytotoxic T cells.

The International Agency for Research on Cancer (IARC) has classified oral contraceptives as carcinogenic for the uterine cervix (35). Oral contraceptive users are more likely to be exposed to HPV than women using barrier methods (36). In a prospective population-based cohort study including 170 patients aged 25-40 years with histologically proven cervical intraepithelial neoplasia (CIN) 2-3, a regression to \leq CIN1 in cone specimen was detected in 22%

of the women who underwent conization after a minimum of 12 weeks (37). On multivariate analysis, condom use was found to be an independent predictor of CIN regression.

Oral contraceptives used in 1960s and 1970s contained higher doses of ethinylestradiol and different types and doses of progestins than the currently used formulations, and long-term users would have probably started with higher dose oral contraceptives with a progressive switch to lower dose oral contraceptives pills (36). In this review, we critically analyzed the available literature data about oral contraception use and risk of carcinoma of the uterine cervix.

Oral Contraception and HPV Infection

Conflicting data are available in the literature regarding the risk of HPV infection in oral contraceptive users (Table I). In a population-based study including 15,145 women aged >15 years from 14 areas worldwide, Vaccarella *et al.* (38) detected no significant differences in HPV positivity between ever [odds ratio (OR)=1.08; 95%CI=0.94-1.25] and never users after adjustment for age, lifetime number of sexual partners, and study area.

Syrianen *et al.* (39), who assessed a cohort of 3,187 women enrolled in a Soviet Union screening trial, reported that no contraceptive users, non-oral contraceptive users, and oral contraceptive users had identical prevalence of high-risk HPV.

Maucourt-Boulch *et al.* (40) found that oral contraceptive use was not associated with HPV persistence in 2,408 women with equivocal or mildly abnormal cytology followed for 24 months. A cohort study on more than 12,000 Brazilian and Argentinian women showed that the length of oral contraceptive use was not an independent predictor for high-risk HPV infections (41). A pooled analysis of 16,573 women with cervical cancer and 35,509 controls from 24 studies worldwide confirmed that neither ever pill use nor use for >5 years correlated significantly with high-risk HPV infection (RR for HPV positive *versus* HPV negative=1.19, 95%CI=0.92-1.52, and 1.21, 95%CI=0.89-1.63, respectively) (42).

A Swedish study on 972 women found no association between low-dose oral contraceptive use and HPV infections, whereas high-dose oral contraceptives were an independent risk factor for these infections after adjustment for age, number of lifetime sexual partners, number of sexual partners during the last 6 months and age at sexual debut (OR=2.8) (43).

A prospective study on the natural history of HPV assessed 1,070 HIV-negative Thai women aged 20-37 years who at enrollment had a prevalence of 19.8% and 11.5% of any HPV and high-risk HPV infections, respectively (14). After adjustment for age, sexual behaviors, sexual transmitted infections and cytology, pill use for >6 years was associated with a significantly increased RR of infection with any HPV

Table I. Oral contraceptive use and risk of HPV infection.

Unchanged risk	Increased risk
Vaccarella (38)	Sikstrom (high-dose oral contraceptives) (43)
Marks (14)	Cotton (44)
Syrianen (39)	Rudolph (45)
Maucort-Boulch (40)	Catarino (46)
Longatto-Filho (41)	
Appleby (42)	
Sikstrom (low-dose oral contraceptives) (43)	

Table II. Oral contraceptive use and risk of cervical intraepithelial neoplasia (CIN).

Unchanged risk	Increased risk
Syrianen (39) CIN2-3	Roura (15) CIN 3
Longatto-Filho (41) CIN1-3	Xu (18) CIN 2-3
Adhikari (49) CIN 1 (reduced risk)	Loopik (21) CIN 3
Volpato (51) CIN 2-3	Volpato (51) CIN 1

(1.88, 95%CI=1.21-2.90) and any high risk-HPV (2.68, 95%CI=1.47-4.88) compared to never users. The overall age-standardised prevalence of high-risk HPV was 34.2% among 5,038 UK women aged 20-59 years with a low-grade smear included in the Trial Of Management of Borderline and Other Low-grade Abnormal smears [TOMBOLA] and the risk of this infection was significantly related to current pill use on multivariate analysis (OR=1.54, 95%CI=1.30-1.84) (44). Similarly, in a Mexican population-based study including 30,829 women aged 30-64 years, high-risk HPV positivity was 11% and hormonal contraception was an independent risk factor for this infection (OR=1.10; 95%CI=1.01-1.20) (45). Hormonal contraception significantly correlated with HPV infection on multivariate analysis (OR=1.97, 95%CI=1.21-3.17) in two sequential Cameroonian studies including 838 women aged 25-65 years with an overall HPV prevalence of 39% (46).

In conclusion, there is no clear relationship between HPV positivity and oral contraception. The limited data available, the great heterogeneity among studies, the presence of confounding factors (*i.e.* sexual activity and smoking habit), and the use of different hormone contraceptive formulations do not allow firm conclusions to be drawn (47).

Oral Contraception and Cervical Cancer

The PAPilloma TRIal against Cancer In young Adults (PATRICIA) is a double-blind, randomised study that has demonstrated the efficacy of HPV-16/18 AS04-adjuvanted vaccine against high-risk HPV infections and precancerous lesions of the uterine cervix (48). Adhikari *et al.* (49)

assessed the relationship between oral contraceptive use and cervical atypias in a cohort of 999 originally non-HPV vaccinated 16-17-year-old women participating in PATRICIA for 4 years. After adjusting for smoking and age at sexual debut, the RR of CIN 1 in women who had started pill use for more than 1 year was 0.2 (95%CI=0.1-0.7) (Table II). Syrianen *et al.* (39) reported that no contraceptive users, non-oral contraceptive users and oral contraceptive users had the same incidence of cervical smear abnormalities and CIN histology. Oral contraception was a predictor of HSIL or CIN2-3 in neither HPV-positive nor HPV-negative women. According to Longatto-Filho *et al.* (41), the duration of oral contraceptive use was associated neither with low-grade SIL (LSIL), atypical squamous cell of unknown significance (ASCUS) and high-grade SIL (HSIL) on cervical smear nor with high-grade CIN on histologic samples. Oral contraception has not been found to increase the relapse rate of CIN after conization (50).

A case-control study, including 101 women with HPV-related cervical lesions and 101 controls, found that users of oral contraceptives containing ethinyl-estradiol doses >0.03mg had a 2.1-fold higher risk of LSIL ($p=0.036$), but no increased risk of HSIL and invasive cancer compared with never users (51).

The European Prospective Investigation into Cancer and Nutrition (EPIC) showed that, in a cohort of 308,036 women, current oral contraceptive use was associated with a 1.8-fold higher RR (95%CI=1.4-2.4) of CIN 3 compared to never users (15).

An Australian case-control study, including 886 women with CIN 2-3 and 3,636 controls aged 30-44 years, revealed

Table III. Oral contraceptive use and risk of invasive cervical cancer.

Unchanged risk	Increased risk
Lasey ¹ (57)	Roura ² (15)
Moreno ³ (56)	Loopik ⁴ (21)
	Appleby ² (42)
	Vessey ⁵ (58)
	Smith ⁶ (59)
	Hannafor ⁷ (61)
	Asthana ⁸ (62)

1Associations between oral contraceptive use and invasive adenocarcinomas and squamous cell carcinomas disappeared after accounting for HPV infection, sexual history, and cytological screening; ²use >5 years; ³use >5 years in HPV- positive women; ⁴use for at least 5 uninterrupted years; ⁵use >4 years; ⁶any duration of use for all women and use>5 years in HPV- positive women; ⁷use >97 months; ⁸use >2 years.

that current hormonal-contraceptive users had a higher risk for CIN 2-3 than never users (OR=1.50, 95%CI=1.03-2.17) and that the risk increased with increasing duration of use (18). In fact, the OR for CIN 2-3 was 1.13 (95%CI=0.73-1.75), 1.51 (95%CI=1.00-2.72) and 1.82 (95%CI=1.22-2.72) for <10 years, 10-14 years and ≥15 years of use (p <0.001). However, past users had the same risk as never users (OR=1.08, 95%CI=0.75-1.57), regardless of the time since last use and the length of use.

A Surveillance, Epidemiology, and End Results (SEER) population-based case-control study, including 150 women with cervical adenocarcinoma *in situ* (ACIS) and 651 controls, revealed an increased incidence of ACIS in ever oral contraceptive users (OR=2.7; 95%CI=1.2-5.8) (52). The risk increased linearly with the length of use (p <0.001 for trend), reaching an OR of 5.5 (95%CI=2.1-14.6) for a use of >12 years. Long-term oral contraceptive use may contribute to the pathogenesis of cervical adenocarcinoma. However, we must take into consideration that this malignancy has a wide histopathological spectrum and can be classified into 7 subtypes (53, 54). No meaningful clinical data are currently available as for the hormonosensitivity of each subtype.

According to a meta-analysis of 16 case-control studies, oral contraception was not a risk factor for cervical cancer (OR=1.12; 95%CI=0.90-1.38), except for Asian women (OR=1.43; 95%CI=1.14-1.79) (55).

Most papers have reported that a long-term use of oral contraception is associated with a higher risk of invasive cervical cancer (15, 21, 42, 56-62) (Table III).

A Dutch retrospective population-based cohort study, which analyzed 702,037 women aged 29-44 years attending a screening program, detected 6,705 cases of CIN 3 and 559 cases of cervical cancer after a median follow-up of 9.7 years (21). Oral contraceptive use correlated significantly with an increased risk of CIN 3 (RR=2.77, 95%CI=2.65-3.00) and cervical cancer (RR=2.06, 95%CI=1.52-2.79). Unfortunately, the RR was not adjusted by sexual behaviour,

HPV status and smoking habit, because of the retrospective design of the study.

An IARC multicentric case-control study assessed 1,853 patients with cervical squamous cell cancer and 1,916 controls, of whom 1,676 and 255, respectively, were HPV-positive (56). Women who had taken oral contraceptives for <5 years, 5-9 years or >10 years had an OR of 0.73 (95%CI=0.52-1.03), 2.82 (95%CI=1.46-5.42) and 4.03 (95%CI=2.09-8.02) of developing cervical cancer compared with never users. The age at which women started to use oral contraceptives was not significantly associated with cervical cancer after adjustment for length of use. In women who had taken oral contraceptives for >5 years, an increased risk persisted for 5-14 years after stopping use. Therefore, long-term oral contraception could increase cervical carcinoma risk in HPV-positive women.

In a multicenter case-control study including 124 patients with cervical adenocarcinoma, 139 with cervical squamous cell carcinoma and 307 controls, oral contraceptive use was significantly associated with adenocarcinoma and weakly associated with squamous cell carcinoma (57). Adjustment for HPV status, sexual history and screening, eliminated the positive correlation between oral contraceptives and invasive adenocarcinoma, squamous cell carcinoma *in situ* and invasive squamous cell carcinoma and confirmed a positive association only between current oral contraceptives and ACIS.

The Oxford Family Planning Association contraceptive study, including 17,032 women aged 25-39 years, found that the RR of cervical cancer was 4.2 (95%CI=1.8-12.0) for ever oral contraceptive users *versus* non users, ranging from 2.9 (95%CI=0.9-9.9), to 3.3 (95%CI=1.2-10.4) and to 6.1 (95%CI=2.5-17.9), for an oral contraceptive use up to 48 months, 49-96 months, and >97 months, respectively (58).

The assessment of 12,531 women with cervical carcinoma enrolled in 28 studies showed that oral contraceptive use for <5 years, 5-9 years, and >10 years was associated with a RR of this tumor of 1.1 (95%CI=1.1-1.2), 1.6 (95%CI=1.4-1.7) and 2.2 (95%CI=1.9-2.4) in all women,

and, of 0.9 (95%CI=0.7-1.2), 1.3 (95%CI=1.0-1.9) and 2.5 (95%CI=1.6-3.9) in HPV-positive women, respectively (59). The results were similar for invasive and *in situ* cancers, as well as for squamous cell carcinoma and adenocarcinoma.

A reanalysis of individual data on 8,097 women with invasive squamous cell carcinoma, 1,374 women with invasive adenocarcinoma and 26,445 controls from 12 epidemiological studies, showed that in current oral contraceptive users, there was an increased RR per each year of use of 1.08 (95%CI=1.06-1.09) for squamous cell carcinoma and 1.07 (95%CI=1.04-1.11) for adenocarcinoma (60). A subsequent pooled analysis of 24 studies detected that among current users, the RR of invasive cervical cancer was 1.90 (95%CI= 1.69-2.13) for >5 year use *versus* never use (42). The RR declined with increasing time since last use and was not different from that of never users after >10 years. Each year of use in current users was associated with a change in RR by a factor of 1.07 (95%CI=1.05-1.08).

The Royal College of General Practitioner's oral contraception study, based on approximately 339,000 woman years of observation for never users and 744,000 woman years for ever users, showed that oral contraception was associated with a non- statistically significant increase in RR of cervical cancer (1.33, 95%CI=0.92-1.94) (61). The RR was 1.10 (95%CI=0.64-1.90), 1.45 (95%CI=0.84-2.49) and 2.73 (95%CI=1.61-4.61), for pill use <48 months, 46-96 months and >97 months, respectively. The RR progressively decreased after discontinuation, ranging from 1.99 (95%CI=1.26-3.15) to 1.25 (95%CI=0.65-2.39) to 0.65 (95%CI=0.23-1.83) for current or recent (<60 months) users, past users (61-120 months) and long-term past users (>181 months), respectively.

The EPIC study detected that oral contraceptive use had a RR of cervical cancer of 2.0 (95%CI=1.3-3.0), 1.6 (95%CI=1.0-2.6) and 1.8 (95%CI=1.1-2.9), after a length of use of 5-9 years, 10-14 years and >15 years, respectively (15).

A recent review of 14 case-control and 5 cohort studies reported that oral contraception was associated with a 1.51-fold higher risk of cervical cancer (95%CI=1.35-1.68) (62). According to the length of use, there was a non-significantly increased incidence if the use was <2 years (OR=1.27; 95%CI=0.98-1.65). Conversely, a statistically significant increased risk was detected for an oral contraceptive use of 2-5 years (OR=1.34, 95%CI=1.20-1.50), 5-10 years (OR=1.93, 95%CI=1.56-2.36) and >10 years (OR=2.24, 95%CI=1.45-3.48), respectively (62). According to the histological type, the risk was greater for adenocarcinoma (OR=1.77; 95%CI=1.4-2.24) than for squamous cell carcinoma (OR=1.29, 95%CI=1.18-1.42).

Conclusion

Most epidemiological studies have shown that oral contraception may enhance cervical carcinogenesis, but only

in users for >5 years, and especially in HPV-positive women who should be encouraged to attend cervical screening programmes accurately (15, 18, 21, 42, 56-63).

The Royal College of General Practitioner's oral contraception study found that oral contraception to be associated with a 12% reduction in the RR (0.88, 95%CI=0.83-0.94) of any cancer (61). This study reported a significant reduction in the RR of endometrial cancer (0.58, 95%CI=0.42-0.79), ovarian cancer (0.54, 95%CI=0.40-0.71) and large bowel cancer (0.72, 95%CI=0.58-0.90) and an unchanged RR of gallbladder or liver cancer, lung cancer, melanoma, and breast cancer. Conversely, a non-statistically significant increase was detected in the RR of cancers of the central nervous system (1.34, 95%CI=0.73-2.47) and uterine cervix (1.33, 95%CI=0.92-1.94). Cervical cancer risk increased significantly only after 97 months.

It has been calculated that 10 yearf of oral contraceptive use from the age of 20 years is associated with an increase in the cumulative incidence of invasive cervical cancer at the age of 50 years from 7.3 to 8.3 per 1,000 in less developed countries and from 3.8 to 4.5 per 1,000 in more developed countries (42). Therefore, the potential increase in terms of absolute risk is very limited. Taking into consideration both the overall harms and benefits, the World Health Organization does not recommend any change in oral contraceptive practice as far as cervical carcinogenesis risk is concerned (63). We must take into consideration that two very effective prevention strategies are available for cervical cancer, *i.e.* primary prevention with HPV vaccination and secondary prevention with HPV screening followed by treatment of precancerous lesions (64, 65). Widespread coverage of both HPV vaccination and at least two cervical screenings in the lifetime from 2020 onwards, has the potential to avoid up to 12.5-13.4 million cases by 2069 and could obtain an average cervical cancer incidence of <4 per 100,000.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Writing – original draft: AG; Data curation, Formal analysis, Methodology, Writing-review & editing: AG, SC, FF.

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