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Correlation of cervical cancers with long-term use of hormonal oral contraceptive pills - A retrospective observational multicentric study in suburban-based medical colleges in West Bengal

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ABSTRACT

Background: Hormonal oral contraceptive pills (OCP) may increase the risk of carcinoma cervix by changing the susceptibility of cervical cells to persistent infection with high-risk human papilloma virus. There is a causal and promoting association with long-term use of these pills for more than 5 years of use, and the association is diminished 10 years after last use. **Aims and Objectives:** In this study, retrospective data were collected to analyze the risk of association of carcinoma cervix with hormonal contraceptive pill use. **Materials and Methods:** Interview-based retrospective observational study to enquire about the history of hormonal OCP use and duration of intake in all diagnosed cases of cervical carcinoma attending gynecology and oncology outpatient departments over the period of 2 years in two medical colleges in suburban West Bengal. **Results:** Of the total 401 subjects, 119 have a history of intake of hormonal OCPs, and 198 have a history of other methods of contraception. Among the subjects, 67.58% had squamous cell carcinoma (SCC), 31.67% had adenocarcinoma of the cervix, and 0.75% had other varieties. There is no correlation between the duration of hormonal OCP use and SCC cervix (P = 0.269), whereas there is a significant correlation between adenocarcinoma of the cervix and duration of intake of hormonal OCP (P = 0.002). **Conclusion:** Studies have shown that women who have used OCPs for 5 or more years have a higher risk of cervical cancer than women who have never used oral contraceptives. This study reported a statistically significant increase in the relative risk of adenoca of the cervix but not of the SCC of the cervix, even after long-term use of hormonal OCPs.

Key words: Hormonal oral contraceptive pills; Carcinoma cervix; Adeno carcinoma

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INTRODUCTION

Cervical cancer is a malignant tumor of the lower-most part of the uterus, the cervix. It usually presents as menstrual irregularities, inter-menstrual bleeding, post-coital bleeding, foul-smelling white discharge, low back or lower abdominal pain, and in some cases, there may be no symptoms. Almost 99% of all cervical cancers are linked to infection with the high-risk human papillomavirus (HPV), transmitted through sexual contact, although other causal relationships exist, like immune system deficiency, age from mid-thirties onwards, lower socioeconomic status, multiple sexual partners, and exposure to diethylstilbestrol. Research continues to look into what factors cause cervical cancer,

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including ways to prevent it and what people can do to lower their personal risk.

It was estimated that in 2020, the total number of cancer cases around the world would be about 18 million, with 9.5 million in men and 8.5 million in women. Cervical cancer was the fourth most common cancer in women, contributing 6.9% of the total number of new cases; the most common was breast cancer, which contributed to 25.8% of the total number of new cases diagnosed in 2020. The projected incidence of patients with cancer in India among males was 679,421 (94.1/100,000) and among females 712,758 (103.6/100,000) for the year 2020. The projected 5 most common cancers in 2020 for males (lung, mouth, prostate, tongue, and stomach) constitute 36% of all cancers, and for females (breast, cervix uteri, ovary, corpus uteri, and lung), they constitute 53% of all cancers.[1] Data from West Bengal revealed that breast cancer (18.84%) and cervix cancer (17.27%) were the most common and threatening in different types of female carcinoma in the population. Both of them proportionally increased in successive years from 2003 to 2010.[2]

Oral contraceptive pills (OCPs) are classified by the International Agency for Research on Cancer (IARC/World Health Organization [WHO]) as a cause of cervical cancer (CaCx). OCP may increase the risk of Ca Cx by changing the susceptibility of cervical cells to persistent infection with high-risk HPV types.[3] OCPs promote HPV-DNA integration into the host genome and bind to specific HPV-DNA sequences within transcriptional regulatory regions, thereby modulating cell apoptosis. Benefits and risks of OCP use on cancer were reviewed in 1998 by working groups of the IARC/WHO, which concluded that hormonal OCPS are carcinogenic. Early and recent studies demonstrated a causal and promoting association with long-term use of hormonal OCPs for more than 5 years of use. The association has diminished 10 years after its last use.[4] Most epidemiological studies had shown that OCP was associated with a 1.5–3.3-fold higher relative risk of Ca Cx for OCP users for more than 5 years, especially in HPV-positive women.

The present study was conducted to determine the relation of hormonal OCP with the incidence of cervical cancer and to estimate whether both squamous cell carcinoma (SCC) and adenocarcinoma of the cervix separately have an association with the intake of hormonal contraceptive pills.

Aims and objectives

To statistically analyse data collected retrospectively from diagnosed cervical cancer patients of different histological variety and to find positive and negative risk of association with long term as well as short term use of oral hormonal contraceptives.

MATERIALS AND METHODS

The research question is to find any causal relation between incidences of cervical carcinoma (Ca Cx) of different histological varieties in long-, mid-, or short-term hormonal OCP users.

Research hypothesis type of study: Interview-based retrospective observational study to enquire about the history of hormonal OCP use in diagnosed cases of cervical carcinoma as per the histology for any statistically significant association.

The study period was from January 01, 2017 to December 31, 2019.

Study population

The subjects registered in present study were selected from patients attending Gynecology and Obstetrics OPD and Oncology OPD of Burdwan Medical College and Diamond Harbour Government Medical College respectively with histopathological evidence of cancer cervix. The number of patients attending the study was 401, maintaining inclusion and exclusion criteria and after both verbal and written consent. A pre-determined structured interview was conducted, and data were encoded. All diagnosed patients attending the OPD were initially included, and the study was done with patient data that satisfied both the inclusion and exclusion criteria.

Inclusion criteria

Female patients who were known CaCx either after cervical biopsy or after hysterectomy, either institutionally or from outside, were willing to participate in the study.

Exclusion criteria

The exclusion criteria were: advanced carcinoma requiring intensive supportive lifesaving management. Patients with post-operative complications after type 2 hysterectomy in CaCx and those patients who refused to be interviewed or gave voluntary consent for the study.

RESULTS

The sociodemographic variables distribution study among the total study subjects of 401 reveals 249, i.e., most of the patients are in the age group of 35–60 years (62.09%). Most of them are housewives with primary level education (41.90%) in the background of middle-class socioeconomic status (58.10%) from mostly rural areas (52.62%). Multiple

pregnancies were 84.7% in 340 of our cancer patients, and tobacco addiction in the form of zarda, gutkha, and nashi was found in 71.8% of cases, as many as 288 patients among 401.

As we analyzed the distribution of marital status and sexual practices according to study subjects, 202 of our subjects had their marriage and first pregnancy below 19 years (52.60%); contrary to common belief, only 17 patients, i.e., 4.23%, had a history of sexual promiscuity. 261 patients gave a clinical history of chronic white discharge vaginally along with chronic pelvic pain, and 78 patients presented with symptoms of acute pelvic inflammatory disease among our study subjects. 7 patients were found to have a direct link with sexually transmitted diseases (STDs), mainly Herpes simplex, and 22 patients had HPV. We found immunodeficiency in 20 patients with CaCx; 2 were HIV positive, 17 were getting steroid therapy, and one patient was under chemotherapy for breast carcinoma.

Most of our patients suffered from abnormal menstrual bleeding patterns (267 out of 401) and contact bleeding (126 out of 401). Presenting clinical features were irregular menses and vaginal bleeding after intercourse, between periods or after menopause in maximum (228 out of 401), watery, bloody vaginal discharge with or without foul smell (176 out of 401), and pelvic pain and pain during intercourse (119 out of 401). We found cervical growth extended beyond the cervix in 206 patients, visible or palpable cervical growth limited to the cervix (<4 cm) in 102 patients, and no visible or palpable cervical growth in 93 patients.

Among 383 symptomatic patients, 271 had SCC and 127 had adenocarcinoma (Adeno Ca) of the cervix (67.58 and 38.67%, respectively). According to the latest FIGO clinical staging, 311 out of 401 or 77.56%, were stage II or more. In maximum numbers, i.e., 270, no histological grade was written in the available biopsy report.

Sixty-nine and 19 patients had histories of taking high-dose and low-dose COC pills, respectively, while 31 used either oral non-hormonal pills or injectable hormonal contraceptives (Table 1). We found 62 patients used hormonal contraceptive pills for <5 years, 41 for 5–15 years, and 16 for more than 15 years. In Table 2, we surveyed the interrelationship between oral contraceptive use and the incidence of cervical carcinoma according to study subjects (n=401) and found that 119 patients had a history of OCP use of variable duration, while 282 subjects never used OCP. Among users, 60 patients developed SCC and 59 Adeno Ca, the maximum numbers. SCC developed after a shorter duration of pill use, i.e., 5 years, and maximum numbers of Adeno Ca developed after a longer duration of pill use, i.e., 5–15 years (Figure 1). Among 282 non-users, most suffered from SCC. Statistical analysis of the association between OCP use and the incidence of CaCx (n=401) deduced Chi-square value, df is 2.149, 2 and P=0.001, which is statistically significant association, there exists a significant difference between the incidence of types of cervical carcinoma (i.e., SCC and Adenoca) in terms of duration of OCP use (Table 3). A statistical analysis of the correlation between study variables according to study subject (n=401) was calculated in Tables 4 and 5. According to the correlation coefficient calculated in Table 4, a highly positive

Table 1: Practice of oral hormonal contraceptives (n=119)

Type of pill used	High dose hormonal OCP	Low dose hormonal OCP	Oral non hormonal pills, injectable hormonal contraceptives etc.
	69	19	31
Duration of pill used	<5 years 62	5–15 years 41	>15 years 16

OCP: Oral contraceptive pills

Table 2: Relation of oral contraceptive use and incidence of cervical carcinoma according to study subjects (n=401)

Biopsy proved cervical cancer study population									
OCP (both high and low dose) user						No history of any type of OCP used			
119						282			
<5 years		5–15 years		>15 years		Any contraceptive other than OC pill		No history of any kind of contraceptive	
SCC	Adeno ca	SCC	Adeno ca	SCC	Adeno ca	SCC	Adeno ca	SCC	Adeno ca
43	19	12	29	05	11	72	31	126	53

Types of cervical carcinoma	<5 years	5–15 years	>15 years
SCC	43	12	05
Adeno ca	19	29	11

SCC: Squamous cell carcinoma, OCP: Oral contraceptive pills

Table 3: Association of oral contraceptive use and incidence of cervical carcinoma (n=401)

Types of cervical carcinoma	<5 years	5–15 years	>15 years	Chi-square value, df	P-value
SCC	43	12	05	2.149, 2	**0.001***
Adeno ca	19	29	11		

SCC: Squamous cell carcinoma.
There exists a statistically significant difference between the incidence of types of cervical carcinoma (i.e., SCC and Adeno ca) in terms of duration of oral contraceptive pills use

Table 4: Correlation between duration of OCP and Adeno ca study variables according to study subject (n=401)

Variables	Correlation (r value)	P value	Remarks
Duration of OCP and Adeno ca	+0.739	**0.002***	Highly positive correlation

OCP: Oral contraceptive pills.
This test were consider at 95% confidence interval, Consider P<0.05 as a level of significant. According to above correlation coefficient table, it indicates that duration of OCP and Adeno carcinoma there exist a highly positive correlation with (r=0.793) also noted that *P*<0.05, as a level of significance

Table 5: Correlation between duration of OCP and SCC study variables according to study subject (n=401)

Variables	Correlation (r value)	P value	Remarks
Duration of OCP and SCC	0.104	0.269	No correlation

OCP: Oral contraceptive pills, SCC: Squamous cell carcinoma.
This test was considered at a 95% confidence Interval, Consider P<0.05 as a level of significant. According to the above correlation coefficient table, it indicates that Duration of OCP and SCC there does not exist any correlation between them (r=0.104)

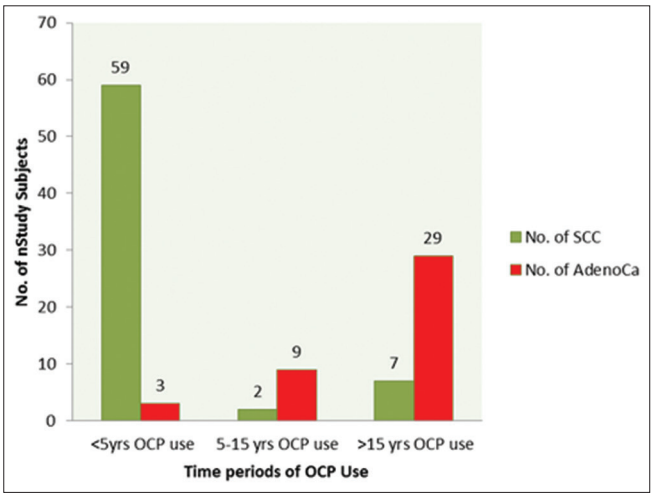

Figure 1: Association of oral contraceptive use and incidence of cervical carcinoma (n=119)

correlation exists between the duration of OCP use and the incidence of Adeno Ca (r=0.793), and there is not exist any correlation between the duration of OCP use and the incidence of SCC (r=0.104), as shown in Table 5.

DISCUSSION

In 2020, the WHO set a goal to eliminate cervical cancer as a public health problem globally by 2120. To reach this goal, WHO's Member States should strive to meet the following interim scale-up targets by 2030: ("90,70,90" strategy), i.e., 90% of girls are to be fully vaccinated with the HPV vaccine by 15 years of age; 70% of women are screened using a high-performance test by 35 years of age and again by 45 years of age; 90% of women with pre-cancer are treated; and 90% of women with invasive cancer are managed.

HPV, smoking, STDs, i.e., C. trachomatis and HSV, multiparity, and most recently, hormonal contraception, especially OCPs, have emerged as cofactors for the development of high-grade cervical lesions and invasive cervical cancer. *In vivo* studies have shown that estrogen may enhance the onset and progression of cervical cancer in human HPV transgenic mouse models.[5] as low-dose 17β-estradiol in the background of HPV gene expression may replace transformation zone (TZ) reserve cells toward squamous cells rather than glandular cells.[6] TZ is five fold more sensitive to 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 diseases have revealed that the expression of estrogen and progesterone receptors is significantly higher in the TZ than the ectocervix.[7] Steroid contraceptive hormones, those that contain estrogen, may promote both HPV-DNA-induced and HPV-DNA-independent carcinogenesis, as estrogens may be converted into 4-hydroxyestrone and 16α-hydroxyestradiol by cytochrome P450,[8] which are considered to be carcinogenic.[9]

In a review article by Smith et al., Lancet, 2003, 28 eligible studies were identified, including 12531 women with cervical

cancer. The relative risks of cervical cancer increased with the increasing duration of use of OCPs compared with non-users of oral contraceptives. Women who have used OCPs for 5 or more years have a higher risk of cervical cancer than women who have never used oral contraceptives. The longer a woman uses OCPs, the greater the increase in her risk of cervical cancer. In a study of long-term use of oral contraceptives and risk of invasive cervical cancer published in the International Journal of Cancer in 1986, Brinton et al., found a 10% increased risk for <5 years of use, a 60% increased risk with 5–9 years of use, and a doubling of the risk with 10 or more years of use. However, the risk of cervical cancer has been found to decline over time after women stop using oral contraceptives.[10]

In a case-control study of colored and black women in the western Cape Province, South Africa, 524 incident cases of clinically evident invasive cervical cancer (Stages 1b–1V) were compared with 1541 controls. It was found that neither injectable progestogen-only nor combined estrogen/progestogen oral contraceptives increase the risk of clinically evident invasive cancer of the cervix.[11]

In a review article by an international collaboration of epidemiological studies of cervical cancer et al., Lancet, 2007, individual data for 16,573 women with cervical cancer and 35,509 without cervical cancer were reanalyzed centrally, and it was found that among current users of oral contraceptives, the risk of invasive cervical cancer increased with increasing duration of use (relative risk for 5 or more years' use versus never use). The risk declined after use ceased, and by 10 or more years, it had returned to that of non-users. A similar pattern of risk was seen both for invasive and *in-situ* cancer and in women who tested positive for high-risk human papillomavirus. The relative risk of cervical cancer is increased in current users of oral contraceptives and declines after use ceases. 10 years' use of oral contraceptives from around age 20–30 years is estimated to increase the cumulative incidence of invasive cervical cancer by age 50 from 7.3 to 8.3/1000 in less developed countries and from 3.8 to 4.5/1000 in more developed countries.[12]

In a multicentre study by Moreno et al., Lancet, 2002, Pooled data from eight case-control studies of patients with invasive CaCx and from two studies with carcinoma *in situ* (CIS) and compared with the data about the use of OCPs obtained from personal interviews. OC users <5 years did not have an increased risk of CaCx, but use for 10 years or more could be a cofactor that increases the risk of CaCx by up to fourfold in women who are HPV DNA positive. They concluded that extra effort should be made to include long-term users of oral contraceptives in cervical screening programs.[13]

In a systematic review of prospective studies on OCP use as a risk factor for cervical dysplasia with HPV infection documented before outcome assessment, including PubMed and EMBASE records between January 2000 and February 2020, it was found that there was no consistent evidence of OC use associated with increased risk for cervical dysplasia or cancer after controlling for HPV infection.[14] There were too few studies of progestin-only injectables, implants, or Hormone releasing intra uterine devices to assess their effect on cervical dysplasia and cancer risk. In their meta-analysis to evaluate the risk of cervical cancer in OC users and non-users through a comprehensive systematic review from January 1990 until August 2019, Asthana et al., included 19 studies. The overall risk of invasive cancer from OC use was found to be significant with the unknown status of HPV. Adenocarcinoma, SCC, and CIS had significant associations. They concluded that OC pill use had a definite associated risk of developing cervical cancer, especially adenocarcinoma, and a longer duration of OC pill use.[15]

In a population-based study including 15,145 women aged >15 years from 14 areas worldwide, Vaccarella et al., detected no significant differences in HPV positivity or CaCx between users and non-users of OCPs after adjustment for age, lifetime number of sexual partners, and study area.[16] Similarly, Syrianen et al., who assessed a cohort of 3,187 women enrolled in a Soviet Union screening trial, reported that no contraceptive users, non-oral contraceptive users, or oral contraceptive users had identical prevalences of high-risk HPV, but they concluded that oral contraception was a predictor of high-grade squamous intraepithelial lesion (HSIL) or CIN2-3 in neither HPV-positive nor HPV-negative women.[17] Maucort-Boulch et al., followed a cohort of 2,408 OC users for 24 months and found that OC use was not associated with HPV persistence with equivocal or mildly abnormal cytology.[18] A cohort study on more than 12,000 Brazilian and Argentinian women showed that the length of oral contraceptive use does not predict high-risk HPV infection or high-risk CaCx. The duration of oral contraceptive use was associated neither with a low-grade squamous intra epithelial lesion, an atypical squamous cell of unknown significance, or HSIL on a cervical smear nor with a high-grade CIN on histologic samples.[19] A pooled analysis of 16,573 women with cervical cancer and 35,509 controls from 24 studies worldwide confirmed that neither pill use nor use for more than 5 years correlated significantly with high-risk HPV infection.[12] 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.[20]

A reanalysis of individual data on 8,097 women with invasive SCC, 1,374 women with invasive adenocarcinoma, and 26,445 controls from 12 epidemiological studies showed that OCP users have an increased RR of 1.08 for SCC and 1.07 for Adeno Ca each year.[21] A subsequent pooled analysis of 24 studies detected that among current users, the relative risk of invasive cervical cancer was 1.90 for more than 5-year use versus never-use. The relative risk declined with increasing time since last use and was not different from that of never users after 10 years of use.[19]

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 the relative risk of cervical cancer.[22]

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. According to the length of use, there was a non-significantly increased incidence if the use was <10 years. According to the histological type, the risk was greater for adenocarcinoma than for SCC.[23]

Limitations of the study

Because of the limited period of this study, we were unable to observe whether the association remains long after the use of hormonal contraceptives has ceased, neither it was properly reflected in any of the related published data. As we have observed the effect of using hormonal contraceptives and not distinct pills by their hormonal constituents, our observations could not reflect the understanding of whether some compositions of OCPs have an increased risk or some have a bit less risk for cervical cancer. Methodologically rigorous studies with different contraceptive pills, differentiated by their compositions, are needed to improve our understanding of the etiology of cervical cancer in terms of OCP use.

CONCLUSION

Most epidemiological studies have shown that oral contraception may enhance cervical carcinogenesis, but only in users for >5 years, especially in HPV-positive women who should be encouraged to attend cervical screening programs. This study reported a statistically significant increase in the relative risk of adenocarcinoma of the cervix but not of SCC of the cervix, even after long-term use of OCPs.

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PSM- Literature survey, Prepared first draft of manuscript, implementation of study protocol, data analysis and preparation of figures; **MB-** Data collection, clinical protocol and manuscript preparation; **PG-** Design of study and statistical Analysis; **JS-** Concept, data collection, clinical protocol, manuscript revision, editing, and submission; **DS-** Coordination and Manuscript review.

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