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Risk Factors for Cervical Cancer in a Sample Comprising Three Generations of Brazilian Women

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Abstract

Background: Cervical cancer is the main cause of cancer deaths in some developing countries. Age-related cervical cancer incidence has been fundamental for understanding the different stages of carcinogenesis concepts. No Brazilian study explored the environmental risk factors involved on cervical cancer, according to age groups taking 70's sexual revolution in Brazil as reference. **Aim:** To determine the prevalence of epidemiological and clinical aspects related to cervical cancer development in a sample of three age groups of Brazilian women based on 70's sexual revolution. **Methods:** A cross-section study was proceeded in a hospital-based cohort of women with altered Pap-test refereed to the National Cancer Institute for Colposcopy and treatment from October 2004 to May 2006. Two register nurses interviewed all patients ascertaining risk factors and clinical characteristics. Biopsy, partial ablation were used for CIN-1, and conization was the treatment for CIN-2/3. **Results**: From 318 women included in the study, 42.8% were 18 - 30 years old (born after 1975), 43.4% were 31 - 49 years old (born 1955-1975), and 13.8% were 50 - 68 years old (born 1936-1954). Pregnancies (OR = 1.16; CI95%: 1.01 - 1.34) and menarche under 12 years old (OR = 1.95; CI95%: 1.17 - 3.25) were independently associated to CIN2-3/cancer in 18 - 30 age group; menopause age (OR = 1.21; CI95%: 1.04 - 1.41) and current smoking habit (OR = 1.37; CI95%: 1.10 - 1.70) were associated to CIN2-3/cancer in 31 - 49 age group; no statistical significance was observed for 50 - 68 age group. **Conclusion:** Brazilian women present distinct risk for cervical cancer according to the generation they belong, when taking the Brazilian sexual revolution on 70's as a reference.

Keywords

Cervical Cancer, Cross-Section Study, Epidemiology, Sexual Revolution, Brazil

1. Introduction

Cervical cancer is the second major cause of cancer deaths among women worldwide, and is still the main cause of cancer deaths in some developing countries [1] [2]. Studies of historical trends show that cervical cancer incidence in Brazil has changed since 1980, but still is a public health problem in this country [3] [4]. Known risk factors for cervical cancer include HPV infection, age, early sexual exposure, multiple sexual partners, and sexual contact with high-risk males [5]. Besides sexual behavior, cigarette smoking has also been reported as an environmental risk factor for cervical cancer, which interacts with HPV as a carcinogenic co-factor [6] [7].

Age-related incidence has been fundamental for understanding the different stages of carcinogenesis concepts [8]. European and North American trend studies demonstrated an increased incidence rate of cervical adenocarcinoma among women who were born between 1953 and 1957, and therefore were 30 - 34 years old at the end of 70s and early 80s, compared to those who were born between 1937 and 1941. Furthermore, age cohort effect was also found in this population, revealing an increased adenocarcinoma incidence rates among young women [9] [10] [11].

However, the reason for this exponential increase in the cervical cancer rates among young women in 70s and 80s is still unknown. Although there is evidence of a change in the screened population over time from younger to older women, it provides a partial explanation for these age-specific trends in cervical cancer mortality [12]. Therefore, this increasing incidence may also be related to changes in sexual behavior including early age at onset of sexual intercourse, multiple sexual partner and changes in sexual habits, and increasing transmission of HPV among younger women [13] [14]. A well-documented report on premarital sexual activity among teenage women in the United States concluded that young teenagers continued to engage in intercourse at earlier ages and in increasing partner number since the sexual revolution of the late 1960s [15].

In Brazil, it has been reported a high prevalence of high-risk HPV—16 (49.2%), 58 (13.4%), 31 (11.2%)—among all levels of lesions, and an increasing tobacco smoking prevalence among women under 18 years old [16] [17]. However, there are few Brazilian studies exploring the environmental risk factors involved on cervical cancer, according to age groups taking the 70 decade as a reference, when sexual revolution occurred in Brazil.

Thus, the purpose of this study was to determine the prevalence of epidemiological and clinical aspects related to cervical cancer development in a sample of three age groups of Brazilian women based on 70's sexual revolution, seeking possible specific co-factors associated with this neoplasia. As a whole, this study aimed to explore the sexual pattern modifications observed among women in Brazil, trying to elucidate their possible role in cervical cancer pathogenesis experienced in such population.

2. Material & Methods

2.1. Study Population

All cervical cytological and histological diagnosis and cervical cancer treatment are carried out at Hospital of Cancer II of Brazilian National Cancer Institute, wherein this investigation was performed using available recorded data. These data enabled the es-

tablishment of three different age groups of women as follow: women had born between the years 1976-88; women born between the years 1956-75; and those born between 1937-55. Therefore, considering 1970 as the year of the significant turning point of sexual behavior in Brazil, the studied population was comprised of women who were 18 - 30 years old, 31 - 49 years old, and 50 - 70 years old at the time of the interview from October 2004 to May 2006.

Patients were eligible if they were older than 18 years old, had not undergone any cervical treatment in the past 6 months, were free of any psychiatric disease, were either literate or brought a literate relative to witness the informed consent explanation. Women who refused to sign the informed consent or were left untreated because they had no lesion at the time of the colposcopy test were excluded from this study.

All enrolled patients signed the informed consent before being interviewed to ascertain exposures to risk factors and clinical characteristics, following the colposcopy test. Biopsy, partial ablation with diathermy and electrocauterization were used for CIN-1, and conization was the treatment of choice for CIN-2/3. Present study was approved by the Ethical Committee of both, National Cancer Institute in Brazil and the National School of Public Health, Oswaldo Cruz Foundation.

2.2. Sampling

Considering the cervical lesions prevalence in the State of Rio de Janeiro in 2002 (56.5% of CIN I, 21.4% of CIN II, 15.12% of CIN III, 2.8% of squamous cancer, 0.33% of adenocarcinoma *in situ,* and 0.82% of invasive adenocarcinoma) and a difference of 5% - 15% of each lesion degree prevalence as the worse expected value, a survey including samples of 42 women with CIN-1, 61 women with CIN-2, 49 with CIN-3, and 113 with cervical cancer were required to obtain statistically significant estimates (*error I* = 0.05; power = 80%) in the studied population.

2.3. Clinical Tests

After signing an informed consent and answering the questionnaire, patients underwent washing of the cervix and lower genital tract with 4% - 6% acetic acid solution, and visual inspection under colposcopy. Colposcopy impressions, lesion size and suspected grade were reported. Biopsies were made of suspicious lesions; and a Pap smear test was carried out if the colposcopy evaluation was unsatisfactory. When the result of the Pap exam at the time of colposcopy was altered, endocervical curettage (ECC) was performed.

Histological diagnosis was made through slides stained with hematoxylin and eosin(HE) for grading of the cervical lesion according to the Bethesda System [18] in condylomata, ASCUS/AGUS and cervical intraepithelial neoplasia grade I (CIN-1); in CIN-2 and CIN-3/*in situ* carcinoma(SCC). Histological normal tissues presenting only reactive/reparative changes were classified as negative (disease-free). Biopsy specimens were colposcopically directed, obtained with a punch biopsy device, placed in 10% formalin, and embedded and stained in a routine manner.

Two oncology gynecology surgeons performed the colposcopic exams and Pap smear tests. Histological and cytological specimens were evaluated at the Department of Pa-

thology, Brazilian National Cancer Institute.

2.4. Data Collection Protocols

Age, self reported skin color, education level, age at menarche, age at first sexual intercourse, parity, number of abortions, menopausal status, number of sexual partners, Marital status (if live in the same house with a sexual partner or not), history of sexually transmitted diseases (STD), contraceptive method use, co-morbidity diseases history (diabetes mellitus, hypertension), HIV *status* (yes/no), HBS-Ag (yes/no), HCV (yes/no), smoking status (current, former, and never smoking) and previous Pap smear tests were obtained from an interview-administered questionnaire. Region of birth was also collected, since this variable may reflect cultural differences in sexual behavior related to different regions of Brazil (e.g. women born in Northeast region at 1937-55, could be more conservative than those who had born in Southeast in the same years). All patients were interviewed by two trained nurses applying standardized procedures.

Tobacco consumption was classified as never smoked, no passive smoking; former smoker, and current smoker. Smoking habit variables were defined as the cumulative exposure of daily cigarette packs smoked, expressed as pack-year. For this analysis, we considered 1 g of tobacco for 1 cigarette, 4 cigarettes for each cigar, and 3 cigarettes for each pipe [18]. Smoking *status* was only assigned for those women who had smoked 100 cigarettes or more during their whole life, and former smokers were classified only as those who quit smoking at least 6 months before the interview date [19].

2.5. Statistical Analysis

Comparisons between frequencies among age groups were performed using *Chi-Square* test, and variables expressed as means were evaluated using independent Student's t-test. Mantel-Haentszel procedures were performed for trend analysis between the age groups. Significant level considered in each analysis was 5%.

Association between CIN 2-3/cancer and selected risk factors at the diagnosis was first ascertained using a cross-sectional approach. Odds ratios (OR) and their 95% confidence intervals were obtained to evaluate the magnitude of association between CIN 2-3/cancer development and risk factors, using a bivariate analysis. Multivariate analysis was accomplished to obtain adjusted OR using logistic regression analysis (CI: 95%). Associations between each variable and disease susceptibility (negative/CIN-1 vs. CIN 2-3/Cancer) were adjusted by age at first sexual intercourse, pack-year smoked (when indicated), number of sexual partners and contraceptive use. Age at menopause, number of pregnancy and pack-year smoked were evaluated as continuous variables.

All analyses were proceeded using STATA program (5.0 version, Stata Press, College Station, TX).

3. Results

From October 2004 to May 2006, 463 women met the inclusion criteria and 18 patients (3.9%) refused to participate. From 445 patients who agreed to sign the informed consent, 318 patients (71.5%) were submitted to the lesion excision or biopsy (**Table 1**),

Table 1. Characteristics of women included in the study, Rio de Janeiro, Brazil.

Variables	N*	%	IC (95%)
Total	**318**	**100.00**	
Age (Years)			
18 - 30	136	42.8	(37.3 - 48.2)
31 - 49	138	43.4	(37.9 - 48.8)
50 - 68	44	13.8	(10.0 - 17.6)
Birth Region			
State of Rio de Janeiro	207	65.1	(59.9 - 70.3)
Other southeast/South states	36	11.3	(7.8 - 14.8)
North/Northeast side	75	23.6	(18.9 - 28.3)
Occupation			
House wife	98	30.9	(25.7 - 35.9)
House keeper	71	22.4	(17.7 - 26.9)
Unskilled worker	15	4.8	(2.4 - 7.0)
Student	15	4.8	(2.4 - 7.0)
Others	119	37.5	(32.1 - 42.7)
Ethnicity			
White	95	29.9	(24.8 - 34.9)
Black	64	20.1	(15.7 - 24.5)
Multiethnic	159	50.0	(44.5 - 55.5)
Education Level			
Incomplete Elementary school	167	52.6	(47.0 - 58.0)
Complete Elementary/Middle school	85	26.8	(21.9 - 31.6)
Complete High School	53	16.7	(12.6 - 20.8)
Complete/incomplete College Degree	13	4.1	(1.9 - 6.3)
Marital Status			
with no partner	104	32.7	(27.5 - 37.9)
with a partner	214	67.3	(62.1 - 72.5)
Reference Cytology			
CIN 1	16	5.1	(2.6 - 7.4)
CIN 2	132	41.5	(36.1 - 46.9)
CIN 3	112	35.3	(30.0 - 40.5)
ASCUS/AGUS	50	15.8	(11.7 - 19.7)
Invasive cancer/Adenocarcinoma	8	2.6	(0.8 - 4.2)
HIV			
Yes	6	1.9	(0.4 - 3.4)
No	312	98.1	(96.6 - 99.6)
HCV			
Yes	10	3.2	(1.2 - 5.1)
No	304	96.9	(93.3 - 97.9)
HBS-Ag			
Yes	23	7.3	(4.4 - 10.1)
No	291	92.7	(88.4 - 94.6)
Diabetes Mellitus			
Yes	12	3.8	(1.7 - 5.9)
No	306	96.2	(91.4 - 98.3)
Hypertension			
Yes	47	14.8	(10.9 - 18.7)
No	271	85.2	(81.3 - 89.1)

*Totals may change according to missing values.

and 127 (28.5%) were left untreated because they had no visible lesion at the colposcopy test and presented no changes at the Pap smear test taken at the time of colposcopy exam.

Demographic and clinical characteristics of enrolled women are presented at Table 2. According to this table, comparing the younger women (18 - 30 years old at enrollment) to the intermediate age group (31 - 49 years old,), histological results of cervical cancer and negative results were more frequent among women 31 - 49 years old ($p \leq 0.05$). On the other hand, the histological result of NIC-1 is significantly more frequent among younger women. ASCUS/AGUS and cancer cytological results were statistically significantly more frequent among the oldest group (50 - 68 years old).

Table 3 presents the distribution of epidemiological and clinical characteristics according to the lesion grade and age group. Among older women, mean age at menopause was statistically higher among women with CIN 2-3/Cancer than those with normal/CIN-1 results (50 ± 2.8 $_{vs}$ 46.5 ± 7.5, $p \leq 0.05$). Mean of pack-year smoked differences between Normal/CIN-1 (12 ± 10.6) and CIN 2-3/Cancer (19.2 ± 15.9) groups were only observed in the group of women aged 31 - 49 years ($p \leq 0.05$). Mean number of pregnancies was statistically higher in CIN 2-3/Cancer (2.3 ± 1.5) as compared to the Normal/ CIN-1 (1.6 ± 1.5) only in the youngest group of women (18 - 30 years old), who also presented statistically significant differences in the frequencies of parity > 1 (CIN 2-3/Cancer = 51.9% $_{vs}$ Normal/CIN-1 = 29.1, $p \leq 0.05$), and oral contraceptive use for over 60 months (CIN 2-3/Cancer = 44.4% $_{vs}$ Normal/LSIL = 30.9, $p \leq 0.05$). Frequencies of early age of sexual onset (≤16 years old), high number of sexual partners (>2 partners), and current tobacco smoking was statistically higher in the CIN 2-3/Cancer than the Normal/CIN-1 among women of 31 - 49 years old. Besides menopause age, only current contraceptive use frequencies was statistically different between CIN 2-3/Cancer (54.2%) and Normal/CIN-1 (30%) in the oldest group of 50 - 68 years old ($p \leq 0.05$).

Crude and adjusted odds ratio (OR) for CIN 2-3/cancer development, according to age group, are presented in Table 4. Among women 18-30 years old, number of pregnancy (OR = 1.16; CI95%: 1.01 - 1.34) and menarche under 12 years old (OR = 1.95; CI95%: 1.17 - 3.25) were independently associated to CIN 2-3/cancer. Among intermediate age group (31-49 years old), menopause age (OR = 1.21; CI95%: 1.04 - 1.41) and current smoking habit (OR = 1.37; CI95%: 1.10 - 1.70) were independently associated to CIN 2-3/cancer. However, among the oldest group, although menopause age, number of children (>1), number of abortion (>1), and number of sexual partners (3-4) were positively associated to CIN 2-3/cancer, no statistical significance was observed.

4. Discussion

Observed increase in the incidence of adenocarcinoma and adenosquamous carcinoma since the early 1970s has been attributed to the sexual revolution in the late 1960s [4] [7] [12] [13]. However, in Brazil sexual revolution occurred on early 70's, instead of 60's, and mostly in the main capitals of the country (specially, Rio de Janeiro and São Paulo). Therefore, different patterns of risk factors distribution among age groups would be expected since sexual revolution could differently affect the sexual values, be-

Table 2. Demographic and clinical characteristics of enrolled women, according to age group, Rio de Janeiro, Brazil.

Variables	18 - 30 years old N = 136		31 - 49 years old N = 138		50 - 68 years old N = 44		
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	*p-trend*
Birth region							
State of Rio de Janeiro	104 (76.5)*φ	(69.3 - 83.6)	87 (63.0)*π	(55.0 - 71.1)	16(36.4)φπ	(2.21 - 50.6)	**P = 0.0000**
Southeast/South states	12 (8.8)φ	(4.1 - 13.6)	13 (9.4)	(5.1 - 15.2)	10 (22.7)φ	(10.3 - 35.1)	**P = 0.0360**
North/Northeast side	20 (14.7)*φ	(8.8 - 20.7)	37 (26.8)π	(19.4 - 34.2)	18 (40.9)φ	(26.4 - 55.4)	**P = 0.0002**
Occupation							
House wife	48 (35.3)	(27.3 - 43.3)	38 (27.5)	(20.1 - 35.0)	12 (27.3)	(14.1 - 40.4)	*P* = 0.2062
House keeper	19 (14.0)*φ	(8.1 - 19.8)	39 (28.3)*	(20.7 - 35.8)	13 (29.5)φ	(16.1 - 43.0)	**P = 0.0048**
Unskilled worker	06 (4.4)	(1.0 - 7.9)	08 (5.8)	(1.9 - 9.7)	01 (2.3)	-	*P* = 0.8014
Student	14 (10.3)	(5.2 - 15.4)	0 (0.0)	-	01 (2.3)	-	*P* = 0.0010
Others	49 (36.0)	(28.0 - 44.1)	53 (38.4)	(30.3 - 46.5)	17 (38.6)	(24.2 - 53.0)	*P* = 0.6854
Ethnicity							
White	46 (33.8)	(28.0 - 44.1)	33 (23.91)	(16.8 - 31.0)	16 (36.4)	(22.1 - 50.6)	*P*= 0.6572
Black	30 (22.1)	(15.1 - 29.0)	26 (18.84)	(12.3 - 25.4)	08 (18.2)	(6.8 - 29.6)	*P* = 0.4829
Multiethnic	60 (44.1)φ	(35.8 - 52.5)	79 (57.25)*	(49.0 - 65.5)	20 (45.4)	(30.7 - 60.2)	*P* = 0.3329
Education Level							
Incomplete Elementary school	53 (39.0)*φ	(30.8 - 47.2)	79 (57.1)*π	(49.0 - 65.5)	35(79.5)φπ	(67.6 - 91.5)	**P = 0.0000**
Complete Elementary/Middle school	50 (36.8)φ	(28.7 - 44.9)	31 (22.4)*	(15.5 - 29.4)	04 (9.1)	-	**P = 0.0001**
Complete High School	27 (19.8)	(13.1 - 26.6)	22 (15.9)	(9.8 - 22.0)	04 (9.1)	-	*P* = 0.0967
Complete/incomplete College Degree	06 (4.4)	(1.0 - 7.9)	06 (4.3)	(0.9 - 7.8)	01 (2.3)	-	*P* = 0.6134
Marital Status							
with no partner	48 (35.3)	(27.3 - 43.3)	44 (31.9)	(24.1 - 39.7)	12 (27.3)	(14.1 - 40.4)	
with a partner	88 (64.7)	(56.7 - 72.7)	94 (68.1)	(60.3 - 75.9)	32 (72.7)	(62.2 - 87.8)	*P* = 0.3089
Reference Cytology							
CIN-1	12 (8.8)	(4.1 - 13.6)	4 (2.9)	-	0 (0.0)	-	*P* = 0.0065
CIN-2/3	107 (78.7)φ	(71.8 - 85.6)	106 (76.8)π	(69.8 - 83.9)	08(18.2)φπ	(6.8 - 29.6)	**P = 0.0000**
Ascus/Agus	17 (12.5)φ	(6.9 - 18.1)	23 (16.7)π	(10.4 - 22.9)	33(75.0)φπ	(62.2 - 87.8)	**P = 0.0000**
Câncer	0 (0.0)	-	03 (2.2)	-	03 (6.8)	-	*P* = 0.0120
Histological results							
Negative	20 (14.7)*φ	(8.8 - 20.7)	37 (26.8)*	(19.4 - 34.2)	17(38.6)φ	(24.2 - 53.0)	**P = 0.0004**
CIN-1	35 (25.7)*	(18.4 - 33.1)	19 (13.8)*	(8.0 - 19.5)	03 (6.8)	-	*P* = 0.0011
CIN-2/3	76 (55.9)	(46.8 - 63.5)	67 (48.5)	(40.2 - 56.9)	18 (40.9)	(26.4 - 55.4)	**P = 0.0024**
Cancer	05 (03.7) *	(1.0 - 7.9)	15 (10.9)*	(5.7 - 16.1)	06 (13.6)	(3.5 - 23.8)	**P = 0.0120**
Diabetes Mellitus							
Yes	0 (0.0)	-	05 (3.6)	-	07 (15.9)	(5.1 - 26.7)	*P* = 0.0000
No	136 (100)		133 (96.4)	-	37 (84.1)	(73.3 - 94.9)	
Hypertension							
Yes	3 (2.2)	-	23 (16.7)π	(10.4 - 22.9)	21 (47.7)π	(33.0 - 62.5)	*P* = 0.0000
No	133 (97.8)		115 (83.3)π	(77.1 - 89.6)	23 (52.3)π	(37.5 - 67.0)	

*$p \leq 0.05$ (Between 18 - 30 years vs 31 - 49 years old);φ $p \leq 0.05$ (Between 18 - 30 years vs. 50 - 68 years old); π $p \leq 0.05$ (Between 31 - 49 years old vs. 50 - 68 years old).

Table 3. Distribution of epidemiological and clinical characteristics according to the lesion grade and age group, Rio de Janeiro.

Variables	18 - 30 years old N = 136		31 - 49 years old N = 138		50 - 68 years old N = 44	
	Normal/CIN-1 (n = 55)	CIN 2-3/Cancer (n = 81)	Normal/CIN-1 (n = 56)	CIN 2-3/Cancer (n = 82)	Normal/CIN-1 (n = 20)	CIN 2-3/Cancer (n = 24)
Menopause (Mean ± SD)	-	-	**46.7 (0.6)***	**42.5 (0.7)***	**46.5 (7.5)***	**50.0 (2.8)***
Number Pregnancies (Mean ± SD)	**1.6 (1.5)***	**2.3 (1.5)***	3.2 (2.0)	3.7 (2.2)	4.1 (2.1)	4.2 (3.1)
Pack-year smoked (Mean ± SD)	3.4 (4.5)	5.9 (6.7)	**12.0 (10.6)***	**19.2 (15.9)***	33.0 (41.5)	22.0 (26.0)
Menarche						
≤12 years	28 (50.9)	50 (61.7)	39 (69.6)	52 (63.4)	12 (60.0)	14 (58.3)
>12 years	27 (49.1)	31 (38.3)	17 (30.4)	30 (36.6)	08 (40.0)	10 (41.7)
Age at sexual onset						
≤16 years	35 (63.6)	61 (75.3)	**15 (26.8)***	**39 (47.6)***	05 (25.0)	07 (29.2)
>16 years	20 (36.4)	20 (24.7)	41 (73.2)	43 (52.4)	15 (75.0)	17 (70.8)
Parity						
0 - 1	39 (70.9)	39 (48.1)	16 (28.6)	16 (19.5)	02 (10.0)	06 (25.0)
>1	**16 (29.1)***	**42 (51.9)***	40 (71.4)	66 (80.5)	18 (90.0)	18 (75.0)
Number of Abortions						
0 - 1	49 (89.1)	72 (88.9)	47 (83.9)	64 (78.0)	14 (70.0)	14 (58.3)
>1	06 (10.9)	09 (11.1)	9 (16.1)	18 (22.0)	06 (30.0)	10 (41.7)
Number of Sexual Partners						
1 - 2	21 (38.2)	25 (30.9)	21 (37.5)	15 (18.3)	11 (55.0)	09 (37.5)
3 - 4	16 (29.1)	29 (35.8)	**13 (23.2)***	**33 (40.2)***	03 (15.0)	10 (41.7)
≥5	18 (32.7)	27 (33.3)	**22 (39.3)***	**34 (60.7)***	06 (30.0)	05 (20.8)
Oral Contraceptive						
Current use	38 (69.1)	57 (70.4)	29 (51.8)	42 (51.2)	**6 (30.0)***	**13 (54.2)***
Former use	07 (12.7)	17 (21.0)	17 (30.3)	27 (32.9)	9 (45.0)	4 (16.7)
Never use	10 (18.2)	07 (8.6)	10 (17.9)	13 (15.9)	5 (25.0)	7 (29.2)
Duration of contraceptive use						
0	10 (18.2)	07 (8.6)	11 (19.6)	14 (17.1)	05 (25.0)	07 (29.2)
1 - 60	28 (50.9)	38 (47.0)	16 (28.6)	31 (37.8)	06 (30.0)	08 (33.3)
≥60	**17 (30.9)***	**36 (44.4)***	29 (51.8)	37 (45.1)	09 (45.0)	09 (37.5)
Tobacco Smoking						
Current smoker	10 (18.2)	20 (24.7)	**14 (25.0)***	**39 (47.6)***	4 (20.0)	8 (34.8)
Former smoker	04 (7.3)	14 (17.3)	13 (31.2)	18 (22.0)	9 (45.0)	8 (34.8)
Never smoke	41 (74.5)	47 (58.0)	29 (51.8)	25 (30.5)	7 (35.0)	7 (30.4)
Duration of tobacco smoking						
≤15	14 (100)	30 (88.2)	10 (37.0)	11 (19.3)	04 (30.8)	06 (37.5)
>15	0 (0.0)	04 (11.8)	17 (63.0)	46 (80.7)	09 (69.2)	10 (62.5)

*$p \leq 0.05$ (between groups: Negative/LSIL vs. HSIL/Cancer.

Table 4. Crude and adjusted odds ratios for CIN 2-3 and cancer development, according to age group, among Brazilian Women.

Variables	18 - 30 years old		31 - 49 years old		50 - 68 years old	
	crudeOR (CI:95%)	*adj. OR (CI:95%)	crude OR (CI:95%)	*adj. OR (CI:95%)	crude OR (CI:95%)	*adj. OR (CI:95%)
Menopause age	-	-	0.44 (0.25 - 0.76)	**1.21 (1.04 - 1.41)**	1.08 (0.99 - 1.18)	1.13 (0.98 - 1.32)
Number Pregnancy	**1.10 (1.02 - 1.20)**	**1.16 (1.01 - 1.34)**	1.04 (0.98 - 1.11)	1.03 (0.98 - 1.09)	1.01 (0.91 - 1.11)	1.03 (0.89 - 1.20)
Pack-year smoked	1.02 (0.99 - 1.04)	1.02 (0.99 - 1.05)	1.01 (1.00 - 1.019)	1.00 (0.99 - 1.01)	0.99 (1.00 - 1.01)	0.99 (0.98 - 1.01)
Menarche						
>12 years	1.00	1.00	1.00	1.00	1.00	1.00
≤12 years	1.03 (0.85 - 1.25)	**1.95 (1.17 - 3.25)**	1.12 (0.84 - 1.49)	1.22 (0.94 - 1.57)	1.03 (0.59 - 1.81)	0.89 (0.38 - 2.09)
Age at sexual onset						
>16 years	1.00	1	1	1	1	1
≤16 years	1.27 (0.92 - 1.76)	1.06 (0.65 - 1.73)	**1.41 (1.07 - 1.86)**	1.20 (0.95 - 1.51)	1.10 (0.60 - 2.01)	0.81 (0.35 - 1.87)
Parity						
0 - 1	1	1	1	1	1	1
>1	1.45 (1.09 - 1.91)	1.26 (0.82 - 1.91)	1.24 (0.88 - 1.77)	1.02 (0.78 - 1.32)	0.67 (0.35 - 1.26)	0.65 (0.23 - 1.80)
Number of Abortions						
0 - 1	1	1	1	1	1	1
>1	1.01 (0.65 - 1.57)	1.43 (0.80 - 2.59)	1.16 (0.83 - 1.62)	1.26 (0.97 - 1.65)	1.25 (0.71 - 2.19)	1.44 (0.58 - 3.59)
Number of Sexual Partners						
1 - 2	1	1	1	1	1	1
3 - 4	1.18 (0.84 - 1.67)	0.67 (0.39 - 1.17)	**1.72 (1.16 - 2.55)**	1.09 (0.81 - 1.48)	1.71 (0.91 - 3.21)	1.41 (0.57 - 3.49)
≥5	1.10 (0.78 - 1.57)	0.91 (0.57 - 1.44)	1.46 (0.98 - 2.15)	1.05 (0.79 - 1.41)	1.01 (0.47 - 2.17)	0.89 (0.31 - 2.49)
Oral Contraceptive						
Never use	1	1	1	1	1	1
Former use	1.72 (0.98 - 3.03)	1.11 (0.64 - 1.83)	1.08 (0.71 - 1.66)	0.89 (0.64 - 1.24)	0.53 (0.22 - 1.24)	0.42 (0.13 - 1.36)
Current use	1.46 (0.88 - 2.41)	1.08 (0.57 - 0.44)	1.05 (0.70 - 1.56)	0.93 (0.70 - 1.24)	1.17 (0.62 - 2.23)	1.15 (0.44 - 2.99)
Duration of contraceptive use						
0	1	1	1	1	1	1
1 - 60 months	1.40 (0.83 - 2.35)	0.99 (0.57 - 1.73)	1.18 (0.78 - 1.77)	0.90 (0.67 - 1.22)	0.98 (0.48 - 1.99)	0.77 (0.27 - 2.21)
≥60 months	1.65 (0.98 - 2.78)	1.22 (0.69 - 2.18)	1.00 (0.67 - 1.49)	0.93 (0.69 - 1.27)	0.86 (0.43 - 1.71)	0.82 (0.29 - 2.32)
Tobacco Smoking						
Never smoke	1	1	1	1	1	1
Former smoker	1.46 (0.99 - 2.14)	1.44 (0.97 - 2.13)	1.25 (0.85 - 1.85)	1.20 (0.94 - 1.54)	0.94 (0.46 - 1.93)	1.20 (0.54 - 2.65)
Current smoker	1.25 (0.89 - 1.75)	1.31 (0.93 - 1.87)	**1.59 (1.15 - 2.20)**	**1.37 (1.10 - 1.70)**	1.33 (0.65 - 2.73)	1.19 (0.55 - 2.60)
Duration of tobacco smoking						
≤15 years	1	1	1	1	1	1
>15 years	1.47 (0.82 - 2.61)	1.43 (0.76 - 2.72)	1.39 (0.96 - 2.03)	1.13 (0.90 - 1.43)	0.88 (0.43 - 1.77)	0.74 (0.35 - 1.60)

*Odds Ratio adjusted by Number of Sexual Partners, Contraceptive use, Age at sexual onset and Pack-year smoked.

havior, and habits of women who were at age of 15 - 30, under 15, and those who were born on an already changed society. Such sexual changing could modulate the risk of acquitting HPV infection between age groups, leading to a different pattern of co-factors distribution and different risk of CIN 2-3/cancer according to age groups [16] [20] [21].

In the present study, we observed a smaller contribution of affected women born on 1937-1955 years (13.8%) as compared to those born on 1956-75 and 1976-88, respectively, 43.4% and 42.8%. Until 1998 cervical cancer screening in Brazil was opportunistic, and only after 1998 screening for cervical cancer has been mainly strengthened as a systematical program. So, our results could be explained by the low Pap test coverage of the 50 - 70 years old group. Also, it could result from different reasons, such as behavioral differences among generations to undergo the Pap exam, as a consequence of their poorer survival after diagnosis by the screened women, or lower incidence of precursor lesion among the oldest women [22].

The varying development of cervical cancer according to age groups because of behavioral, cultural, social and educational differences is highlighted by the observation that 40.9% of women from the oldest group, compared to 14.7% among the youngest, were migrants and showed lower education.

As expected, CIN-1 was statistically more frequent (25.7%) and cancer was statistically less frequent (03.7%), among the youngest women, as compared to the oldest women (6.8% and 13.3%, respectively). Nevertheless, considering the latency needed to develop CIN 2-3, a higher frequency of these lesions would be expected among older women. Thus, unexpectedly, a higher frequency of CIN 2-3 (55.9%) was only seen in the youngest women as compared to the older women (CIN 2-3 1956-75: 48.6%; CIN 2-3 1937-55: 40.9%), with a significant linear trend between them ($p\text{-}trend = 0.0024$).

Epidemiological and clinical characteristics distributions were statistically different among the studied age groups. Known risk factors such as number of pregnancy and early age at menarche were statistically associated to CIN 2-3/cancer in the youngest group. In Brazil, 20.8% of pregnancies in 1994 occurred in adolescents, reaching 26% in 2000 [23]; and it has been observed that sexual initiation generally occurs before the end of adolescence between 15 and 19 years old, and right after menarche [24] [25]. In this sense, it has been reported that early sexual onset is associated with drug use, more sexual partners, and less selectiveness towards partners [15] [26]. However, other behavioral risks factors such as age at sexual onset, smoking, oral contraceptive use and number of sexual partners showed no statistical significance in such group of women, despite of the association observed. Effects of such factors will probably be further depicted when this cohort reaches the next decades as they will probably have a higher number of lifelong sexual partners than currently seen among older women. Our results corroborate the findings of Hofferth *et al.* [13], who reported an increasing number of sexual partners and an earlier age at sexual onset among teenager women in US. If the above female sexual behavior scenario had also occurred in Brazil, younger birth cohorts would be likely to continue to be at higher risk for developing cervical cancer.

On the other hand, finding age at menopause and current smoking habit independently associated to CIN 2-3/cancer in the group from 31 to 49 years old, could suggest

that older women who are sexually active might be at higher risk of cancer development. Cruikshank *et al.* [19] developed a case-control study in the United Kingdom, seeking to identify those risk factors associated with the development of an abnormal Pap smear over the age of 50. Authors found that HPV positivity was significantly associated with the change of sexual partner after age 40, which probably results from new infection, but could be a surrogate marker for previous sexual behavior. In parallel of sexual revolution, smoking habit was a symbol of independence among women. Thus, women who were under 15 years old on 70's would probably have grown up considering smoking habit as a reference of independence and success.

Surprisingly, none of the sexual behavior and environmental habits (smoking and oral contraceptive use) evaluated were significantly associated to CIN2-3/cancer among the oldest women group (50 - 68 years old). Since those women were aged 15 to 30 years old on 70's sexual revolution, such findings could be probably due to both, either small number of older women in the sample study or a more conservative sexual behavior, such as late sexual onset, smaller number of sexual partner, stable marital status, late use of oral contraceptive and smoking habits. Since 1982, Murphy *et al* (1993) [27] observed in Scotland that incidence and mortality due to invasive cervical cancer amongst single women, with a dramatic increase in carcinoma *in situ*, exceeded of the married, widowed and divorced women. Authors found that such increase must partially reflect changes in screening and diagnostic classification, but also consistent with the later occurrence of the sexual revolution in Scotland. Another important finding was that in overall Britain, data on patterns of smoking and oral contraceptive use are broadly consistent with a role for them in determining the current disease pattern associated with marital status but their possible involvement cannot be disentangled from the more likely effect of changing levels of sexual activity increasing the risk of sexual transmitted disease. However, as marital status becomes a less important social indicator of sexual behavior, it has also become a much less reliable marker of cervical cancer risk.

Besides diffusion of health promotion, including health education related to safe sexual behavior, smoking habits should also be considered in such programs. Current smoking habits were independently associated to the risk of developing CIN-2/3 and cancer among women from 31 to 49 years old, showing that special care must be taken about this issue. Because the health effects of smoking only become fully evident many years after the widespread uptake of smoking, the full global impact of smoking on women health will not be fully pictured for some decades. Many women, even in developed countries, are unaware of the extension of the risk of cervical cancer. In this sense, our study can provide evidence to support tobacco control programs focused on Brazilian women who are at higher risk of developing cervical cancer all over the country.

Present study limitations that must be addressed includes those inherent to cross-sectional studies, where exposures and outcomes are evaluated in a point of time. Thus, it is not possible to stablish causal association between exposures and outcome. Nevertheless, because of the latency period for cervical cancer development, the prevalence of known co-factors that may cumulatively affect the risk of this neoplasia (e.g. tobacco

smoking, oral contraceptive use); and of those behavioral characteristics that may be a proxy of HPV infection opportunity in a lifetime (e.g. number of sexual partners, early menarche, late menopause, parity), may enable us to hypothesize about the changings occurred in the society concerning to risk of cervical cancer. Moreover, when such prevalence differ according to the generation based on a well described behavioral-impacting sociological event, such as the Sexual Revolution, such hypothesis become stronger. However, in order to test such hypothesis, analytical studies with greater sample size are required.

5. Conclusion

Present study suggests that risk factors for CIN-2/3/cervical cancer may have played different roles among generations of Brazilian women in Rio de Janeiro. In this sense, our data suggest that Brazilian women present distinct risk for cervical cancer according to the age group they belong, when taking the Brazilian sexual revolution on 70's as a reference. Thus, among women from 18 to 30 years old, number of pregnancies and early age at menarche would be independently associated with CIN 2-3/cancer. However, among women from 31 to 49 years old, the independent risk factors for CIN 2-3/cancer would be age at menopause and smoking habits; while known behavioral risk factors would have smaller effect among women from 50 to 68 years old. Such findings suggest that cervical cancer control programs in Brazil should include smoking prevention among young women and smoking cessation among the oldest women. Pap smear exam adherence should be accomplished among all women sexually active, regardless their age, and public health advertisement must reach each age group of women, considering their cultural and generational differences.

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