

## Risk Factors of Cervical Cancer in Two Reference Hospitals of Douala: A Case-Control Study

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Received: 23 May 2020; Accepted: 28 June 2020

**Citation:** Engbang Ndamba Jean Paul, Essome Henri, Mve Koh Valère, et al. Risk Factors of Cervical Cancer in Two Reference Hospitals of Douala: A Case-Control Study. *Cancer Sci Res.* 2020; 3(2): 1-6.

### ABSTRACT

**Background:** Cervical cancer is the second most common cancer in women. Few data are available in the city of Douala. Our objective is to determine risk factors for cervical cancer at Laquintinie Hospital and Douala General Hospital.

**Patients and Methods:** This was a case-control study of patients seen from 02/02/2016 to 31/05/2018 in both sites of the study. The cases were women with histological evidence of cervical cancer, those with no cervical cancer at visual inspection with acetic acid and lugol (IVA-IVL). The odds ratio with 95% confidence interval were used to measure the association between cervical cancer and the variables of interest.

**Results:** We included 250 cases of cervical cancer and 1000 controls. In cases, 82.8% had metrorrhagia. The most recovered FIGO stages were stages IIIb and Iva with 22.8% and 18.4% respectively. Squamous cell carcinoma accounted for 91.2% of the histological types and 64.0% received concomitant neoadjuvant chemotherapy. The risk factors found were tobacco (OR = 25,  $P < 0.0001$ ), STIs (OR = 13.7,  $P < 0.0001$ ), number of sexual partners  $\geq 2$  (OR = 4.4), HIV seropositivity (OR = 8.6,  $P = 0.0001$ ), age  $\geq 50$  years (3.6), low socio-economic status (OR = 3), sexual intercourse before the age of 18 (OR = 2.8), delivery before age 20 (OR = 2.56), oral contraceptive use over 5 years or more (OR = 2.3).

**Conclusion:** The study carried out within the framework of our thesis, despite its limitations, constitutes a source of information for scientific research on cervical cancer. It contributes to the improvement of cervical cancer knowledge, allows us to define at-risk populations, and subsequently allows us to set up an early diagnosis algorithm.

### Keywords

Cervical cancer, Risk factors, Sexually transmitted infection.

### Introduction

Cervical cancer is considered as a non communicable disease with an estimated global prevalence of 2.3 million women [1]; With an incidence of 528,000 new cases it represents the 4th most common malignant tumor in women worldwide after breast, colorectal and lung cancers [2]. It is also the 4th leading cause of cancer deaths with 266,000 deaths in 2012 [2,3].

However, there is significant inequality in the distribution of incidence across countries. In fact, about 85% of cervical cancers are registered in developing countries, where access to testing and care is totally different from that of developed countries [2,4]. In Europe, this pathology occupies the 9th rank of female cancers in terms of incidence and the 12th rank in terms of mortality. With approximately 3,000 new cases and 1,100 deaths per year, cervical cancer represents the 12th leading cause of cancer and the 10th leading cause of cancer death among women in France [5]. In America, Canada has diagnosed 1,550 new cases in 2017 and in

the United States in the African-American population there are 6 new cases per 100,000 population [5,6]. In Africa and mainly in sub-Saharan Africa, cervical cancer has become more and more common in the last two decades with more than 75,000 cases diagnosed in 2013 and nearly 50,000 deaths related to it during the same year [7].

Cervical cancer is a multifactorial disease, the most important of which is Human Papillomavirus (HPV) infection; it is the necessary etiopathogenic factor and more than 90% detected in the diagnosis of this malignant tumor [10,11]. However other cofactors have been found including the precocity of first intercourse, the multiplicity of sexual partners, smoking and alcohol, hormonal contraception and immunosuppression potentiating the oncogene character of Human Papillomavirus [8-11,13-15]. In Cameroon, cervical cancer is the leading women genital cancer, 40.18% of cervical cancers are diagnosed in urban areas [16,17]. Engbang et al. reported from 2005 to 2014, 2559 cases of genital cancer in women with 2078 cases of cervical cancer, giving 82.26% in Cameroon [18]. Given these works in the literature, it seemed important for us to study the risk factors for cervical cancer at Laquintinie Hospital in Douala and Douala General Hospital. In fact, very little data is available on the risk factors for cervical cancer, while knowledge of these will help to improve prevention.

### Patients and Methods

This is a descriptive cross-sectional and analytical study. Data collection was done from subjects at the time of cancer screening through the use of a standardized questionnaire. The study population consisted of women aged from 18 years old who were screened for cervical cancer in two references centers, Douala Laquintinie Hospital and Douala General Hospital from March 2010 to May 2013.

The included cervical cancer cases were patients from the selected recruitment centers in our study. Witnesses were also recruited from the centers selected in our study. For each case of cervical cancer, four controls were matched by age (<50 years and ≥50 years) and residence. We defined as controls, women at least 18 years old, sexually active, consenting, consultants in recruitment centers, with IVA (visual inspection after application of acetic acid) and IVL (visual inspection after application of lugol). The recruitment of controls was done on the basis of age-matched (± 5 years) cases. Concerning controls, a sensitization of the women through the messages and communicators sent in different communities (Churches, meetings) of the city of Douala was carried out. Participants were enumerated and recorded daily for mass screening.

After validation of the informed consent, a chart abstraction instrument was elaborated for collecting data from participant files. Information in files was collected by trained providers during systematic screening, and data were extracted retrospectively from those files stored in the two sites by providers from the respective sites. The collection of the data of the various participants followed by the IVA and IVL screening test was done individually in a

soundproof room.

One dependent variable of interest was chosen, cervical cancer was defined as a binary variable. Independent variables included: Sociodemographic variables (age, region, social level, level of education, marital status), Clinical variables (hypertension, diabetes, serological status, blood type, STI, family history of cervical cancer, tobacco), Variables in reproductive life (age of first coitus, number of pregnancies, number of deliveries, number of abortions, number of partners, contraception), Family history (history of cervical cancer in the family, history of other cancers in the family).

For 1:4 allocation ratios the required number of controls were 250, hence 1000 individuals were included in the study. Data analysis was done using statistical package for social sciences software. Data is summarized in form of tables. Univariate logistic regression analysis was used to evaluate the factors significantly associated with cervical cancer. Multiple Logistic Regression was used to calculate the adjusted Odds ratio with 95% CI.

## Results

### Distribution by age

In case group, the age of cases ranged from 25–82 year with mean age of cases is  $53.29 \pm 12.71$  years. In control group the mean age of the participants was  $40.38 \pm 12.20$  years from 17 to 77 years.

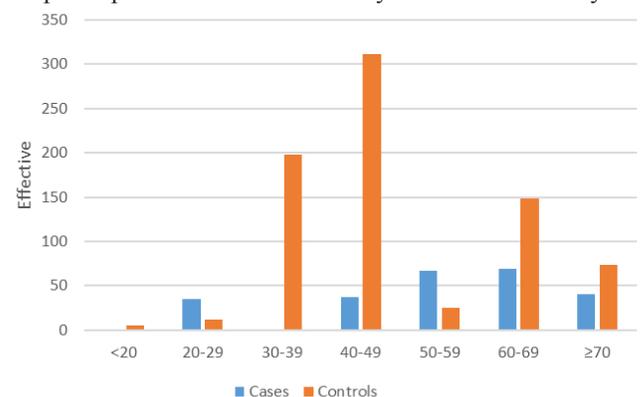


Figure 1: Age distribution of cases and controls.

### Univariate Logistic regression analysis

#### Socio-demographic characteristics of women screened for cervical cancer

As shown in table I, the distribution by age, low socio-economic level and level of education was significant ( $P < 10^{-3}$ ,  $P = 0.002$  and  $P < 0.0001$ ).

Variables		Cases		Controls		P	RC (IC 95%)
		N	%	n	%		
Age	< 50 years	105	42	764	76,4	0	0,22 [0,16-0,29]
	≥ 50 years	145	58	235	23,5		4,49 [3,36-6]
Socio-économic status	Low level	161	69,6	437	49,3	0,002	2,05 [1,78-3,32]
	Middle level	68	29,4	449	50,6		0,4 [0,3-0,5]
	High level	2	0,8	22	4,7		0,24 [0,05-1,11]

Education	Primary	79	33,8	227	22,9	0,03	1,42 [1,02-1,98]
	Secondary	105	44,9	429	43,2		0,7 [0,5-1]
	University	50	21,4	337	33,9		0,42 [0,28-0,62]

**Table 1:** Univariate Logistic regression analysis for socio-demographic variables.

**Medical and toxicological history in relation to cervical cancer** HIV seropositivity, STIs, high blood pressure, smoking, family history of cancer was all significant.

Variables		Cases		Controls		P	*RC (IC 95%)
		n	%	n	%		
HIV Status	Négative	172	71,9	854	94,1	<0,001	0,16 [0,11-0,24]
	Positive	67	28,1	54	5,9		6,16 [4,15-9,14]
Diabète	No	233	98,7	938	97,2	0,189	2,22 [0,8-7,14]
	Yes	3	1,3	27	2,8		0,45 [0,14-1,5]
**STI	Yes	41	17,4	672	67,2	<0,001	0,10 [0,07-0,14]
	No	195	82,6	328	32,8		9,7 [6,78-13,98]
Arterial hypertension	Yes	175	73,8	836	85,1	<0,001	0,21 [0,1-0,3]
	No	62	26,2	146	14,9		4,73 [3,24-6,91]
Tabacco	Yes	186	78,2	989	99,2	0	0,02 [0,01-0,06]
	No	52	21,8	8	0,8		34 [16,04-73,44]

**Table 2:** Variables of medical and toxicological antecedents in relation with cervical cancer.

### Reproductive and sexual factors

Age at first sexual intercourse was significant (P = 0.02), hormonal contraception was significant (P = 0.03), multi sexual partnership was significant (P = 0.03).

Variables		Cases		Controls		P	RC (IC 95%)
		N	%	N	%		
Age of first intercourse	< 18 years	152	67,9	420	46,3	0	2,36 [1,76-3,16]
	≥ 18 years	86	38,4	560	61,7		0,42 [0,31-0,56]
Gravidity	≤ 3	51	20,4	504	50,4	0	0,25 [0,18-0,355]
	> 3	199	79,6	496	49,6		3,96 [2,84-5,52]
Parity	≤ 3	74	29,6	643	64,3	0	0,23 [0,17-0,3117]
	> 3	176	70,4	357	35,7		4,28 [3,17-5,78]
Age of the first pregnancy	< 20 years	129	56,6	258	31,7	0,001	2,81 [2,08-3,8]
	≥ 20 years	99	43,4	556	68,3		0,36 [0,27-0,49]
Number of sexual partners	< 2	25	10,33	537	35,7	0,001	0,2 [0,13-0,31]
	≥ 2	217	90,77	642	64,28		4,8 [3,13-7,45]
Abortion	None	123	52,1	480	48,1	0,27	1,17 [0,88-1,56]
	At least one	113	47,9	517	51,9		0,85 [0,64-1,13]
Oral contraceptive pills	Yes	184	73,6	830	83	0,001	0,57 [0,74-0,74]
	No	66	26,4	170	17		1,75 [1,35-2,42]

**Table 3:** Univariate Logistic regression analysis for reproductive and

sexual factors.

### Multivariate regression

Age at first coitus of <18 years showed high significance (p = < 0.001) with cervical cancer with OR of 5.44 (2.73–10.86). Low economic status was significantly associated with risk of cervical cancer. Age at first pregnancy, consumption of tobacco and other factors also had significant association with risk of cervical cancer (Table 4).

Variables	P value ajusté	Odds Ratio
Age ≥ 50 ans	<0,0001	3,6
Low economic status	0,002	3
HIV status	0,0001	8,2
Tobacco	0,0001	25
STI	<0,0001	13,5
Age at first intercourse < 18ans	0,02	2,8
Age of the first pregnancy < 20ans	0,01	2,56
Number of sexual partners ≥ 2	0,03	4,4
Oral contraceptive pills	0,03	2,3

**Table 4:** Risk factors of cervical cancer.

### Discussion

In the study, in case group, the age of cases ranged from 25–82 year with a mean age cases of 53.29 ± 12.71 years. In control group the mean age of the participants was 40.38 ± 12.20 years from 17 to 77 years. These results are similar to those found by Biswas et al. (participants from the age range of 25–70 year), Pragati Sharma et al., whose participants ages range from 35 to 78 years [19,20]. Shields et al. included women from 20 to 74 years [21].

In our study the flagship sign was metrorrhagia with a frequency of 82.8% seconded by pelvic pain with a frequency of 46.4%. These data of metrorrhagia corroborate with 94,2 %, 92,2 % and 88, 7% found by Diaki, Sahraoui and Nguyen [22-24] respectively. Dem reported only 19.50% cases with pelvic pains [25]

Regarding the FIGO classification, 22.8% of women were in stage IIIB followed by 18.4% in stage IVA at the time of diagnosis. Results lower than 65,9% at stage IIIB followed by 8,8 % at stage IV found by Diakite in Mali and 65% for stages III and IV found by Tonato Bagnan et al. in 2013 in Benin [22,26]. This result can be explained by the fact that patients at risk do not consult frequently and are therefore screened late.

As for the histological type, squamous cell carcinoma was the most represented with 91.2% and adenocarcinoma with 8.8% which corroborates with 94.2 % and 5.1% respectively found by Ell Diakite in 2019 in Mali, with 81.18% and 12.95% found by Engbang et al. in 2016, in Cameroon and differs from 62% of squamous cell carcinoma found by Tonato Bagnan et al. in 2013 in Benin [18,22,26].

In our study, the average age was 53 ± 12 years. Women over the

age of 50 were 3 times more likely to develop cervical cancer (OR = 3.6; 95% CI = [3.34-7.3]) result that agrees with the literature stipulating of this affection being that of elderly women [27]. The disease caused by HPV infection is very slow (around 15 years). Over time, this development can be potentiated by the presence of multiple cofactors. In addition, it can in some cases be slowed down or eradicated by immunity, but reinfections associated with other factors will cause the cycle to resume with late onset of the disease [28].

Regarding socioeconomic level, 64.4% of cases had a low socioeconomic level. In our study, the low socioeconomic level increased the risk of cervical cancer 3 times (OR = 3; 95% CI = [1.51-6.21]). As with many other infectious diseases, poverty is the strongest determinant of the incidence of and mortality from cervical cancer around the world [29]. The human development index and poverty rates have shown a clear association (inverse and direct, respectively) with incidence and mortality, thus explaining about 52% of variability in cervical cancer globally [30,31]. In our context, the low socioeconomic level exposes women to promiscuity, precociousness of sexual intercourse, and sometimes sexual vagrancy which all together potentiates the occurrence of infection. In addition, women of this same level are for the most part not in a position to ensure medical follow-up.

Regarding HIV infection, 28% of the cases were infected. In our study, immunosuppression to HIV increased the risk of cervical cancer by 8 times (OR = 8.6; 95% CI = [3.84-20]). Women immunocompromised with HIV see their immunity weaken over time. As a result, they will be more vulnerable to infections than the general population and not at the same time to eradicate HPV for those who come into contact [29]. Abraham et al. in 2013 in a study done in North America found that women infected with HIV with reference CD4 + T lymphocytes  $\geq 350$ , 200-349 and  $<200$  cells /  $\mu\text{L}$  had an increase in incidence of cervical cancer 2.3 times, 3.0 times and 7.7 times respectively compared to women not infected with HIV (P = 0.001) [32].

For STIs, 82.6% of the cases had a history of STIs. In our study, STIs increased the risk of cervical cancer by 13 times (OR = 13.5; 95% CI = [6.62-33.33]). According to the literature, STIs (chlamydia and herpes simplex2) constitute a risk factor because they potentiate HPV infection which over time leads to changes in the mucosa and the occurrence of cancer [33].

Regarding tobacco, 21.8% of cases were smoking. In our study, tobacco increased the risk of developing cervical cancer by 25 times (OR = 25; 95% CI = [7.24-83.33]). According to various studies have shown that smoking is one of the most important risk factors for CIN 3 and invasive cervical cancer [34,35]. Smoking can increase the risk of cervical neoplasia through several mechanisms. One of the mechanisms is the local induction of immune suppression by tobacco metabolites. In addition, chemicals in cigarettes, such as nicotine and its metabolites, can cause DNA damage in squamous cells [36]. Smoking can cause epigenetic changes in the epithelium of the cervix and contribute

to the pathogenesis of neoplasia in the cervix and in many other parts of the body [37].

In terms of sexual behavior, at the age of first sexual intercourse, 67.9% of cases had their first sexual intercourse before the age of 18 years and 56.6% of the cases had given birth before the age of 20 years. In our study, the first report before 18 years as well as the first delivery before the age of 20 were risk factors (OR = 2.8; 95% CI = [1.52-5.36]). Sharma et al. Age at first coitus of  $<18$  years showed high significance (p =  $< 0.001$ ) with cervical cancer with OR of 5.44 (2.73–10.86) [20]. Similar findings were observed in a study by Biswas N et al. which showed OR of 2.7 (0.8–8.9) with p = 0.005 for age at 1st coitus of  $<18$  years [19]. Cervical cancer is extremely rare in women younger than the age of 20. However, many young women become infected with multiple types of human papilloma virus, which then can increase their risk of getting cervical cancer in future. Early age at first intercourse is consistently found to be a risk factor in most of the early epidemiological studies of cervical cancer [19,38]. Cervical cancer risk is double in women who first had sexual intercourse at the age of 14 or less, compared to those who did at 25 or more [38]. This could be explained by the immaturity of the cervix (transition zone) in adolescence and therefore a sensitivity to aggression. Furthermore, the first coitus before 18 years of age will lead to a long sexual life, consequently an increased risk for STIs and a long time of exposure to the carcinogen (HPV) [26].

With regard to hormonal contraception, 26.4% of the cases had used hormonal contraception. In our study, hormonal contraception increased 2 times the risk of occurrence of cervical cancer (OR = 2.3; 95% CI = [1,11-5]). It has been reported by some authors that the use of oral contraceptive method for 5 years or more can double the risk of cancer. However, there is a slight increase in the incidence of invasive cervical cancer in those who used only injectable progesterone for 5 years or more [39]. Moreno et al. affirmed that among women who tested positive for HPV DNA, the risk of cervical cancer increased by 3 times if they have used oral contraceptive pills for 5 years or more. The results of this study showed that the risk of cancer does not depend on the first time use of OC pills [40].

## Conclusion

Cervical cancer is a pathology with an infectious basis that affects older women much more and whose diagnosis in our context is made much later. Several factors increasing the occurrence of cervical cancer have been determined, namely age  $\geq 50$  years, low socioeconomic level, tobacco, HIV immunosuppression, STIs, multi sexual partnership, age  $<18$  years at first sexual intercourse, oral contraceptive. These factors will then allow us to set up an algorithm allowing us to define the patients at high, medium and low risk. This will allow us to improve the policy of early detection which will guarantee the fall in the incidence of cervical cancer in our country.

## Author's Contributions

Author ENJP designed the study, wrote the protocol and wrote the

first draft of the manuscript. Authors EH and NNJP participated in data collection supervision and analysis. Author MKV contributed in literature search. Author FP reviewed the final manuscript. All authors read and approved the final.

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