HEALTH SCIENCES AND DISEASES
The Journal of Medicine and Health Sciences

Original Article

Oncogenic Human Papillomavirus Genotypes 16 and 18 Prevalence Among Women with Normal Cervical Cytology and Neoplasia in Cameroon: A Systematic Review

Prévalence des génotypes oncogènes de papillomavirus humain 16 et 18 chez les femmes ayant une cytologie cervicale normale et une néoplasie cervicale au Cameroun: une revue systématique

Gilbert Doh[1*], George Mondinde Ikomey[1], Duncan Njenda[2], Josiah Gichana[2], Mary Grace Katusiime[2], Valantine Ngum Ndze[3], Michelle Zeier[4], Martha Mesembe[1], Charles Fokunang[5], Marie Claire Okomo Assoumou[5], Pierre-Marie Tebeu[5], Paul Adrien Atangana, Graeme Brendon Jacobs[2]

[1]Center for the Study and Control of Communicable Diseases (CSCCD), Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon
[2]Division of Medical Virology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa
[3]Centre for Evidence-Based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa.
[4]Department of Internal Medicine and Cardiology Academic Teaching Hospital Feldkirch, Austria
[5]Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon
[6]Centre Pasteur du Cameroun (CPC), Yaoundé
***Correspondence to:** Gilbert Doh, Center for the Study and Control of Communicable Diseases (CSCCD), Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon, P.O.Box 8445 Yaoundé, Cameroon
Telephone: +273 676 168 011/ 698 677 381; Fax: +273 32312733
E-mail: doh_gilbert@yahoo.fr

Key words: HPV, Genotypes, Cameroon
Mots clés: VPH, Génotypes, Cameroun

ABSTRACT

Introduction – Aim. Cervical cancer, although largely preventable, remains the most common cause of cancer mortality amongst women in low-resource countries. Epidemiological and clinical studies have clearly established human papillomavirus (HPV) types 16 and 18 as the main cause of invasive cervical cancer (ICC). Despite the high burden of HPV (39.0%), high mortality due to cervical cancer in Cameroon, and availability of vaccines, quality reviews on HPV to inform effective public health control strategies are lacking. **Methods**. We carried out systematically search of 12 major electronic databases for published articles and grey literature up to May 2016 as per PRISMA guidelines. We included studies without language restriction that reported the prevalence of HPV genotypes 16 and 18 among Cameroonian women. Data was extracted and study quality appraised from 5 articles. **Results**. Our search strategy resulted in five eligible articles, including a total of 1856 women, age ≥18 years tested for HPV. The overall HPV prevalence in Cameroon observed in our systematic review was 36.3% (673/1856). The prevalence of HPV 16 and 18 were 13.0% and 6.5% in women with normal cytology, 18.2% and 4.6% in ASCUS, 29.7% and 27.0% in HSIL, 22.2% and 5.3% in women with ICC respectively. **Conclusion**. Our study shows that HPV16 and 18 account for 27.5% of ICC cases among Cameroonian women with a high HPV prevalence in women > 25 years of age. These findings greatly support increased efforts in screening for high risk HPV genotypes and the introduction and roll out of HPV prophylactic vaccines in Cameroon.

RÉSUMÉ

Objectifs. Malgré le fardeau élevé du virus du papillomavirus humain (VPH) (39,0%), la mortalité élevée due au cancer du col de l'utérus au Cameroun et la disponibilité des vaccins, les revues de qualité sur le VPH pour renforcer l'efficacité des stratégies de contrôle en santé publique font défaut. **Méthodes**. Nous avons fait une revue systématique à la recherche de 12 bases de données électroniques majeures pour les articles publiés et la littérature grise jusqu'en mai 2016, conformément aux lignes directrices de PRISMA. Notre critère d'inclusion était les études sans restriction de langue qui ont signalé la prévalence des génotypes du VPH 16 et 18 parmi les femmes camerounaises. **Résultats**. Notre stratégie de recherche a abouti à cinq articles éligibles, donnant 1856 femmes, âgées de 18 ans testées pour le VPH. La prévalence globale du VPH au Cameroun observée dans notre étude était de 36,3% (673/1856). VPH 16 et 18 représentaient 6,25% et 3,28% respectivement. La prévalence du VPH 16 et 18 était de 13,0% et 6,5% chez les femmes ayant une cytologie normale et 5,3% chez les femmes avec cancer invasif du col (CIC). **Conclusion**. Notre étude montre que HPV 16 et 18 représentent 27,5% des cas de CIC chez les femmes camerounaises avec une forte prévalence du VPH chez les femmes > 25 ans. Ces résultats appuient grandement les efforts accrus dans le dépistage des génotypes de HPV à haut risque et l'introduction et le déploiement des vaccins prophylactiques contre le VPH au Cameroun.

INTRODUCTION

Cervical cancer remains a leading cause of morbidity and mortality in women worldwide [1,2] and it is the leading cause of cancer mortality in Africa [3,4]. It predominantly affects women between the ages 15 and 44 years old [5]. Twelve highly carcinogenic human papillomavirus (HPV) genotypes have been recognized as the causative agent of cervical cancer [6,7]. In Cameroon, over 1474 women are diagnosed with cervical cancer each year and approximately 995 women die from the disease annually [8]. Despite this, comprehensive data on HPV genotype prevalence and distribution in Cameroon are lacking [9]. The use of Papanicolaou (Pap) smear screening and HPV prophylactic vaccines are effective in preventing cervical cancer by allowing high risk women to seek treatment when needed [10,11,12]. However, their use in Cameroon remains very limited due to a variety of socio-economic and logistical barriers, such as the readiness of vaccine distribution clinics, available infrastructure, cost involved for successful dispensation [13,14–16]. Several global meta-analyses studies have found that HPV16, 18, 31, 52 and 58 are the most prevalent genotypes in women with normal cytology [16,4] and they are the most prevalent genotypes in women with cervical neoplastic diseases [17–25]. HPV16 and 18 were identified as the predominant oncogenic genotypes, causing approximately 70% of global cervical cancer cases. In women co-infected with HIV, HPV16 is the most dominant strain, followed by HPV58 [4,19,24,26].

The vast majority of HPV data come from studies done on infected women from Europe, North America [19–22,24–26], Asia [17] and more recently Latin America and the Caribbean [18]. Data for studies on Cameroonian women are highly variable and incomplete. Most studies are geared towards sensitization, creating awareness, evaluating education efforts, the epidemiology of cervical cancer and HIV and assessing the effectiveness of sensitization [27–33]. Therefore a critical assessment on the prevalence and distribution of HPV genotypes in Cameroon among women with normal cervical cytology, neoplastic lesions and invasive cervical cancer (ICC) is required.

In May 2013, the Global Alliance for Vaccine and Immunization (GAVI) announced the availability of HPV vaccines (Gardasil and Cervarix) for a reduced price of $4.50 per dose to low-income countries that meet the eligibility criteria [16,28]. With clear indications that the GAVI Alliance is committed to subsidizing HPV vaccines for low-income countries [16,27–29], many African nations, including Cameroon are beginning to design effective strategies that address the potential challenges of vaccine delivery and screening for HPV and cervical cancer [16,31,32].

Epidemiological information on the prevalence and distribution of genital HPV infection in Cameroon is critical for planning for vaccine implementation, evaluating the possible impact of existing prophylactic HPV vaccines and determining the relevant tools for HPV screening to prevent cervical cancer. The goal of this review is to establish the overall prevalence and HPV genotypes among women with normal cervical cytology, neoplastic cervical lesions and cancer, by systematically reviewing eligible articles, to inform cancer prevention and control policies in Cameroon.

METHODS

Search strategy

We used a comprehensive literature search strategy to identify studies on HPV among women in Cameroon that met the following criteria: (a) the article and relevant data were accessible, (b) cervical cytology / histology was confirmed by exfoliated cervical cells or fixed / fresh biopsy, (c) HPV genotype-specific prevalence of at least two HPV genotypes were calculated and (d) HPV genotype prevalence was calculated separately for each cervical lesion according to the 2001 Bethesda classification method [40,41]. Studies not meeting these criteria were excluded in this review.

Two authors (D.G. and D.N.) independently screened the search output for inclusion, using a pre-defined relevance criteria form [35,4], obtained the full-text of potentially relevant articles and screened their eligibility. Discrepancies were resolved by discussion and with the involvement of a third author when there was need. There were no restrictions on the type of HPV assay method used. HPV genotypes were determined by molecular methods; PCR based reverse-line strip test for HPV, qualitative polymerase chain reaction (PCR) using the Cobas R4800 system and reverse-blot hybridization [39,42–45]. The methodological quality assessment of observational studies was assessed by a checklist of essential items as outlined in [47, 48]. The quality assessment tool consisted of the sampling strategy, sensitivity of sampling, timing of sampling, non-response bias, outcome reporting bias and conflict of interest. A summary list of the five included studies quality assessment is provided in **S2**; Quality assessment tool for included studies.

Data extraction

Two authors (D.G. and D.N.) independently extracted data using a pre-tested data extraction form and discrepancies were resolved by discussion, see **S3;** Data extraction form. Data extracted for analysis included: study characteristics (method of study, period of data collection, sample size), participant characteristics (population, mean or age range,

standard deviation of age), place where the samples were analyzed and genotyped, region, HPV detection and genotyping method, number of HPV positive women and overall HPV prevalence. We focused on both high risk (HR) HPV and low risk (LR) and intermediate types commonly recognized to be associated with cervical cancer. These included the following HR types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82; intermediate types including HPV 26, 53, 66 and LR types including HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108. We equally included studies with multiple infections with any HPV genotype with exception being those with specimens negative for beta globin. The data is summarized in study characteristics **Table 1.**

Characteristics of included studies.

We used the Bethesda classification system and classified cases using the five grades of cervical diagnosis by cytology and / or histology as outlined. This included women with: (1) normal cervical cytology; (2) atypical squamous cells of undetermined significance (ASCUS); (3) low-grade intraepithelial lesion (LSIL), including cervical intra-epithelial neoplasia grade 1 (CIN1); (4) high-grade squamous intraepithelial lesion (HSIL), including CIN2-3, and (5) invasive cervical cancer (ICC), including squamous cell carcinoma (SCC) and adeno/adenosquamous carcinoma [33,39]**,** see **S4**; Bethesda classification system.

Statistical analysis

Studies in which age was not reported were recorded and analyzed as missing age. Studies reporting the age-specific prevalence of HR HPV infection were analyzed and variation due to time of data collection, HPV detection methods and study location was noted. In order to ensure consistency across studies, only studies that collected samples in routine screening, such as routine Papanicolau test were included in the analysis. These results were described narratively to view the wide heterogeneity observed across studies.

HPV prevalence among routine screening populations were defined as the proportion of individuals who were positive for HPV infection divided by the total population tested for HPV infection (the number of HPV positive women / the total number tested)*100. HPV type-specific prevalence among routine screening populations was defined as the proportion of females testing positive for the specific HPV type among all of those testing for HPV infection. These analyses only included studies of females engaged in routine screening. HR HPV prevalence and HR HPV type-specific prevalence was also calculated from those who tested positive for HPV infection [25,45]. Similarly, HPV type-specific prevalence by cytology or histology was also calculated for those testing positive for the specific HPV type by cytological category according to the 2001 Bethesda System [41]. Studies using routine screening, those returning after a previous abnormal cytological test, as well as those receiving a biopsy were included in this analysis. Individuals diagnosed with squamous cell carcinoma of the cervix and /or adenosquamous carcinoma of the cervix were included in the confirmed cancer category.

Estimates of type-specific prevalence of HR HPV infection were derived using a random-effects model [46,25]. The 95% CIs were derived based on a normal distribution. In order to produce conservative prevalence estimates and corresponding 95% CIs, studies reporting zero for the number of positives were imputed as being 0.5 [23]. Each HR HPV type was considered individually; hence prevalence estimates might include concomitant infection with other HPV types. All analyses were conducted using the Cochrane Collaboration Review Manager statistical software (http://ims.cochrane.org/RevMan).

Ethical statement

No ethical clearance approval was required for this study.

RESULTS

Studies considered in the review

Our search strategy resulted in 31 potentially eligible studies and 5 eligible studies were reviewed. Data was extracted from the 5 included epidemiological studies, with individual-level data that met the inclusion criteria. The study flow chart is shown in **Figure 1.**

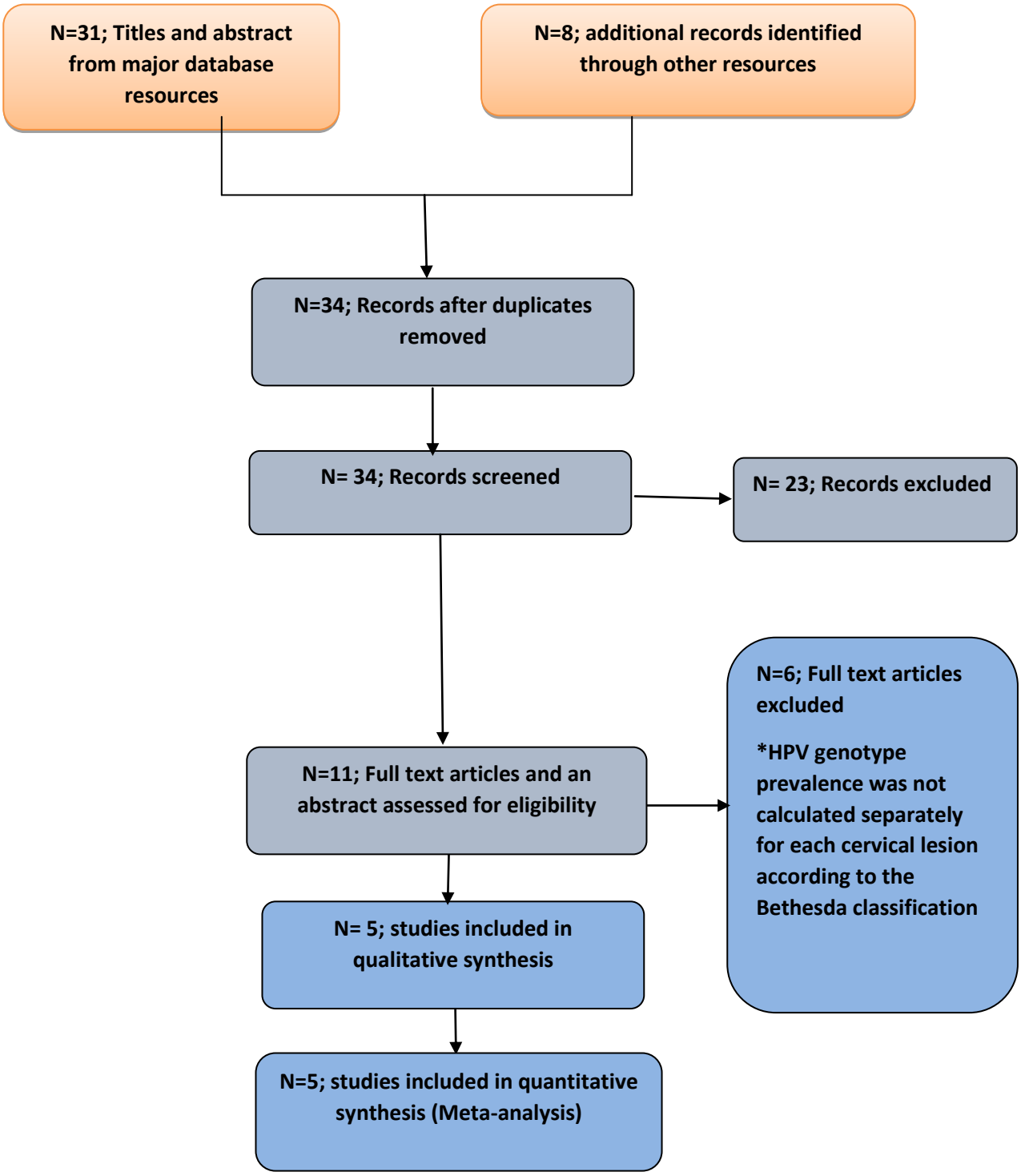

Figure 1: The study flow chart

Study characteristics

Data were collected from studies between 2009 [41] and 2015 [45]. With the exception of one study, where the place for participant HPV genotyping was not indicated [45]. Most of the studies laboratory analysis were performed in laboratories in Europe, (Lausanne and Geneva, Switzerland) [42–44] and one in South Dakota, USA [41]. Three studies reported infection with multiple HPV types [41,43,45] and two studies reported information on HPV16 and 18 only [42,44]. A total of 1856 Cameroonian women from three regions (Centre, South West and Littoral) were tested for HPV in the 5 studies and 809 samples were tested for β globin, of which 351 were positive.

With the exception of one study that was not relevant to the non-response bias [44], three studies (60%) did address non-response bias [41,43,45]. We found one study that did not use a representative sampling strategy [42]. This study included individuals with various risk factors for HPV and their results cannot be generalized to the normal population. The quality assessment for each individual methodological quality components for each study are reported in **S2;** Methodological quality of the included studies.

Of the 1856 women, 348 had normal cytology; 97 were classified as ASCUS; 10 were diagnosed with LSIL; 37 were HSIL-positive and 181 had ICC, as shown in **Table 2.** The overall HPV prevalence observed in our systematic review was 36.3% (673/1856) among the general population. HPV prevalence according to each of the individual studies varied from 30.6% [43] to 83.78% [42]. Two studies calculated the prevalence of six different types of HPV [41,42], while two others only characterized HPV16 and 18 [43,45] and the other HPV types as other HR HPV (31.64%). One of the studies reported the percentage prevalence of HPV16 (88%), HPV45 (32%) and HPV18 (14.2%) without reporting the actual number of cases [44]. The prevalence of HPV16 and 18 from four studies was 6.25% and 3.28 respectively [41-43,45]. The prevalence of other HR HPV, HPV33 and HPV35 was 2.94% and 8.82% respectively, as reported by two studies [41,42]. In one of the studies HPV45 was reported to have a high prevalence (32.0%) after HPV16 and before HPV18 [44]. All the five studies were carried out in the Centre, Littoral and South West region of Cameroon.

Results analysis according to Bethesda Classification

The analysis of HPV type-specific prevalence by lesion types according to the Bethesda classification of women with normal cervical cytology and other cervical lesions (ASCUS, LSIL, HSIL and ICC) are presented in **Table 3.** The most prevalent HPV type among those classified as negative for intraepithelial lesion or normal cytology was HPV16 (13.0%) after other HR HPV (72.0%). Among those classified with ASCUS, the three most prevalent types were other HR HPV (90.3%), HPV16 (18.2%) and HPV18 (4.2%). For LSIL, only other HR HPV was reported with a prevalence of 80.0%. Among those classified with HSIL, the prevalent HR HPV types were HPV16 (29.7%), HPV18 (27.0%), HPV45 (16.2%), HPV33 (8.1%), HPV 35 (5.4%) and LR HPV types, HPV68 (2.7%), HPV 11(5.41%), HPV53 (2.7) and HPV74 (2.7%). Among those with confirmed cervical cancer, the highest prevalence was observed for other HR HPV (35.7%), followed by HPV 16 (22.2%) and HPV 18 (5.3%). Among other HR HPV as defined by authors, the prevalence generally increased as the type of cervical lesion approached cervical cancer. The observed prevalence of combined HR HPV types for those with negative cytology was 53.2%, 34.0% for ASCUS, 80.0% for LSIL, 83.3% for HSIL and 93.8% for ICC.

Table 3: Prevalence of HPV by Bethesda classification system

HPV Type	Bethesda classification	# Studies	# Cases	Sample Size	Prevalence (%) at 95% CI
Other HR HPV	Normal Cytology	1	85	118	72.03
	ASCUS	1	28	31	90.32
	LSIL	1	8	10	80.00
	HSIL	0	0	0	00
	ICC	0	0	0	00
HPV 16	Normal Cytology	1	10	77	12.99
	ASCUS	1	4	22	18.18
	LSIL	0	0	0	00
	HSIL	1	9	37	29.0
	ICC	1	79	285	27.72
HPV 18	Normal Cytology	1	5	77	6.49
	ASCUS	1	1	22	4.55
	LSIL	0	0	0	00
	HSIL	1	8	37	25.8
	ICC	1	36	285	12.63

Age-specific HPV prevalence

Two studies [43,45] reported age-specific prevalence of HPV. The HPV prevalence was highest in the age group 25 – 34 years, ranging from 43.6% to 43.8%. The prevalence is lower in the age group 35 - 44 years (41.0%), in the 45 – 54 years age group (31.8%) [45] and in the >54 years age group in one study (9.3%) [45], but was higher among the >54 years age group in one study (43.8%) [43]. Two studies reported HPV16 with highest prevalence among all the age groups [43,45]. HPV16, along with HPV18, was equally reported to be the most predominant genotypes in two studies [39,42]. The prevalence of HPV16 for the age group 25 - 34 was 7.0% for one of the studies [43] and 9.6% and 9.3% for the age group >54 years in two studies

[43,45] respectively. The prevalence of HPV18 was 3.7% for the age group 25 – 34 years, 4.1% for the age group <35 years and 2.7% for the age group >54 years in two studies [43, 45]. We found that multiple infections occurred in all five studies [41–45].

DISCUSSION

Comprehensive data on the distribution and prevalence of specific HPV genotypes in women with all grades of cervical cancer diagnosis are required to provide information on the baseline burden of disease, the future impact of HPV vaccines on cervical cancer prevention and the identification of optimal HPV screening tools. The data is also useful for health economic evaluations and epidemiological modeling research. Baseline prevalence data could only be obtained by synthesizing highly heterogeneous individual studies. In this review we report on the first analysis of HPV genotype distribution and prevalence in Cameroonian women. Five studies were included for the systematic review which fairly matched the inclusion criteria. The ten regions in Cameroon were not fairly represented, all the studies were performed in only three regions (Centre, South West and Littoral), with the Centre region having the highest percentage.

The overall HPV prevalence observed in our systematic review was 36.3% among the general population. This varies between HIV infected and non-HIV infected women, age range 18 years and above. HPV prevalence was high in younger women (≤ 25 years of age), decreased with age and peaked again in women aged ≥54 years. This is inconsistent with other reviews in other African countries [19,23]. Compared to different regions throughout the world, HPV prevalence in Cameroon is high. One review found that the highest prevalence of HPV among middle-aged women (35-50 years) was observed for Africa, Central and South America, and the United States (approximately 20%), while a lower prevalence was observed in Asia, Australia, Europe, Middle East, and Canada (approximately 15%) [59]. Furthermore, the proportion of cancer cases associated with HPV16 and 18 was found to be highest in Africa (94.2%), moderate in North America (89.2%), and the lowest in Asia (68.0%) [21].

The observed HPV prevalence from our analysis in women with normal cytology was 53.2%, ASCUS (34%), LSIL (80%), HSIL (83.8%) and ICC (55.5%). The HPV prevalence among women with ICC is quite higher than what was observed in other reviews [4, 26] Contrary to other reviews carried out in other African countries and in Europe, the prevalence of ICC is lower in Cameroon [4,26]. This could be attributed to the very few number of studies and the fact that some of the studies included ICC amongst the HSIL grade [42]. The prevalence of any HPV infection among women by cervical disease grade could not be efficiently determined as most of the studies did not actually report the HPV type specific prevalence with cervical grade lesions. However, it increases among women with normal cytology to ICC, although the accuracy might be influenced by the variation in the sensitivity of the techniques used.

The five most common genotypes identified in our study were HPV16 (6.3%), HPV18 (3.3%), HPV33 (2.9%), HPV35 (8.8%) and HPV45 (20.6%). The prevalence rates were not identical from normal cytology through HSIL and ICC. This might be due to the fact that most of the studies were focused on a particular cervical grade, while others only reported on HPV16 and 18 and the rest as other HR HPV. Not all the studies actually reported the HPV type specific prevalence with cervical grade lesion. All this makes interpretation difficult.

There was an inconsistent relationship between HPV prevalence in HSIL and ICC cases across different HPV types. For example, we found a higher HPV prevalence in HSIL versus ICC (including squamous cell carcinoma of the cervix and/or adeno/adenosquamous carcinoma of the cervix) for HPV16 (29.7% for HSIL versus 22.2% for ICC) and HPV18 (27.0% for HSIL versus 5.3% for ICC). The relationship between HSIL and ICC could not be explored for the other HPV types due to insufficient data. Furthermore, many of the cervical cancer estimates were based on a small number of studies, making these results difficult to interpret. Multiple infections occurred in all the five studies. Factors that can explain the difference in multiple infections across reviews include different duration of specific types of infection (natural clearance of one or several types, but persistence of the main one); and/or potentially different number of new sexual partners during the last months in females with LSIL, HSIL and those with cervical cancer or HIV.

The HPV vaccines protect against oncogenic strains HPV16 and 18. They contributed a combined prevalence of 4.4% for HR HPV infection and 13.8% for cervical cancer, which can potentially be prevented by the vaccines, assuming 100% efficacy and long-lasting immunity. These estimates are lower than previous reviews that reported this estimate as being approximately 70.0% [4,21,23,25,53,54]. Emerging data showing cross-protection against several non-vaccine HR HPV types is encouraging. In recent years, there has been substantial mobilization toward mass vaccination against HPV, with either Gardasil or Cervarix [55]. Until now there was insufficient data to demonstrate the high prevalence of HPV16/18 in cases of ICC in Cameroon. Data from this present study suggest that vaccines currently available could prevent less than70.0% of cervical cancer cases in the country. This is similar to a previous review on HPV in Africa where the same observation was made [4].

According to recent studies a polyvalent vaccine in Phase III clinical trials, known to protect against HPV16, 18, 31, 33, 35, 45, 51, 52 and 58, could prevent nearly all cases of cervical cancer in African women. Unfortunately, because

most African countries, including Cameroon, are currently unprepared to implement HPV vaccination, even the availability of this polyvalent vaccine would leave an entire generation unprotected in Africa [4,56].

The implementation of one lifetime screening test at the age of 35, with either visual inspection with acetic acid or HPV DNA testing, would reduce the risk of developing cervical cancer by 25.0%. This would cost less than $500 per person per year of life saved [4,14]. However, the lack of laboratory infrastructure for HPV genotyping in nearly the entire country, as shown in our study, should be a major concern for the prevention and control of cervical cancer in Cameroon and across the globe. In our systematic review all the HPV DNA genotyping was performed out of Cameroon. HPV DNA testing is currently the most sensitive and reproducible cervical screening test [4,60]. Therefore, there is an urgent need to build the infrastructure in Cameroon, and in Africa as a whole, to facilitate efficient cervical screening.

The major contribution of our study to the current body of literature is the assessment of 1856 women from three regions of whom 673 (36.3 %) were HPV infected. A further stratification of specific HPV genotype prevalence by disease severity will help identify appropriate tools for HPV genotyping and assess the future impact of HPV vaccines. However, the applicability of this data throughout the country is limited, since all the studies were obtained only from three regions, partially attributable to the lack of well-designed studies in the other part of the country.

Limitations of this systematic review include: (1) the analyses were based on each HPV type individually, so may include concomitant infection. (2) Inclusion of studies that used HIV-seropositive patients in the analysis; (3) Data were collected across studies using different tests to measure the presence of HPV (PCR based reverse-line strip test, reverse-blot hybridization and Real-time PCR). These tests vary in their sensitivity and specificity. (4) The methodological quality of the included studies was variable; less than half used a representative sampling strategy and many had small sample sizes. High-quality, population-based HPV prevalence studies are primordial. These studies should report age-specific prevalence, overlap between single and multiple infection and HPV type-specific infection.

Conclusion

We found high HPV prevalence in women > 25 years of age and this increases up to the age of 30 years. Data from this review are useful for future impact of HPV vaccines on cervical cancer prevention and the identification of optimal HPV screening tools.There is an urgent need to build infrastructure in Cameroon to facilitate efficient cervical screening.

Conflict of interest

None

Funding

This review was not funded.

Electronic supplementary material

S1: The search strategy for PubMed used in the systematic review.
S2: Methodological quality of the included studies.
S3: Data extraction form.
S3: Bethesda classification system.
S5: Methodological quality and risk of bias tool.

Authors' contributions

G.B.J. and G.D. conceived the review. G.D., G.B.J., M.G.K., and V.N.N. contributed in study design, study selection and screening. G.D., D.N., V.N.N., J.G., M.M., C.F., M.Z., O.A. P.M.T., A.P.A., and G.M.I. contributed in data extraction, data analysis, drafted the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. SP Cerón, Shelley L Deeks, LG Dilsa, Domínguez. MC EFD. Prevention. Progress toward implementation of human papillomavirus vaccination—the Americas 2006-2010.2011;60(40) 1382–1384. ISSN: 1545-861X.
2. Ferlay, J.; Shin, HR.; Bray, F.; Forman, D.; Mathers, C.; Parkin, DM. GLOBOCAN 2008, v12.Lyon FIA for R on C 2010. Cancer Incidence and Mortality Worldwide. Int J Cancer. 2010;127(11):2893–917. http://globocan.iarc.fr (accessed 14.04.2016).
3. Eduard R. Bos, Dean T. Jamison, Florence Bainga, Richard G. A. Feacham, Malegapuru Makgoba KJH and hama OR. Diseases and mortality in Sub-Saharan Africa. 2006. 1-410. http://dx.doi: 10.1596/978-0-8213-6397-3
4. Ogembo RK, Gona PN, Seymour AJ, Park HS-M, Bain PA, Maranda L, et al. Prevalence of human papillomavirus genotypes among African women with normal cervical cytology and neoplasia: a systematic review and meta-analysis. PLoS One. 2015;10(4):e0122488. http://dx.doi:10.1371/journal. pone.0122488
5. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J cancer. 2006;118(12):3030–44. http://dx.doi 10.1002/Ijc.21731
6. Emma J. Crosbie, Mark H. Einstein, Silvia Franceschi HCK. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;382(9895):889–99. http://dx.doi.org/10.1016/S0140-6736(13)60022-7
7. N Munoz, F X Bosch, S de Sanjose, R Herrero, X Castellsague, K V Shah, P J F Snijders, Cjlm Meijer CIARCM. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348:518–27. http://dx.doi:10.1056/NEJMoa021641
8. International Agency for Research on Cancer I. Handbooks on Cancer Prevention, Cervix Cancer Screening. 2005. 201-212. ISBN 92 832 3010 2
9. Jemal A, Bray F, Center MM, Ferlay J, Ward E FD. Global cancer statistics. CA: a cancer J Clin. 2011;61(2):69–90. http://dx.doi:10.3322/caac.20107
10. Gakidou E, Nordhagen S OZ. Coverage of cervical cancer screening in 57 countries: low average levels and large

inequalities. PLoS Med. 2008;5(6):863–8. http://dx.doi: org/10.1371/journal.pmed.0050132
11. Baldur-Felskov B, Dehlendorff C, Munk C KS. Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia—Nationwide Follow-up of Young Danish Women. J Natl Cancer Inst. 2014;106(3):1. http://dx.doi: 10.1093/jnci/djt460
12. Sepehr N. Tabrizi, Julia M L Brotherton, John M. Kaldor, S. Rachel Skinner, Eleanor Cummins, Bette Liu, Deborah Bateson, Kathleen McNamee, Maria Garefalakis SMG. Fall in human papillomavirus prevalence following a national vaccination program. J Infect Dis. 2012;206(11):1645–51. http://dx.doi: 10.1093/infdis/jis590
13. Agosti JM GS. Introducing HPV vaccine in developing countries, Äîkey challenges and issues. N Engl J Med. 2007;356(19):1908–10. http://dx.doi: 10.1056/NEJMp078053
14. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahé C, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med. 2005;353(20):2158–68. http://dx.doi: 10.1056/NEJMsa044278
15. Perlman S WROJMSNKFL. Achieving High Uptake of Human Papillomavirus Vaccine in Cameroon: Lessons learned in overcoming challenges. J Vaccine. 2014;32(35):4399–403. http://dx.doi: 10.1016/j.vaccine.2014.06.064.
16. Perlman S, R G Wamai, P A Bain, T Welty, E Welty, J G Ogembo. Knowledge and Awareness of HPV Vaccine and Acceptability to Vaccinate in Sub-Saharan Africa. PLoS One. 2014;9(3):e90912. http://dx.doi: 10.1371/journal.pone.0090912
17. Bhatla N, Lal N, Bao YP, Ng T QY. A meta-analysis of human papillomavirus type distribution in women from South Asia: Implications for vaccination. J Vaccine. 2008;26(23):2811–7. http://dx.doi: 10.1016/j.vaccine.2008.03.047
18. Ciapponi A, Bardach A, Glujovsky D, Gibbons L PM. Type-specific HPV prevalence in cervical cancer and high-grade lesions in Latin America and the Caribbean: Systematic Review and Meta-analysis. PLoS One. 2011;10(6):e0025493. http://dx.doi: 10.1371/journal.pone.0025493
19. Clifford GM, Gonp ßalves MAG FS. Human papillomavirus types among women infected with HIV: a meta-analysis. AIDS. 2006;20(18):2337–44. http://dx.doi: 10.1097/01.aids.0000253361.63578.14
20. de Sanjose S FSGPH-JRLNBL. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349–59. http://dx.doi: 10.1002/ijc.27485
21. Li N, Franceschi S, Howell-Jones R, Snijders PJ CG. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. Int J Cancer. 2011;128(4):927–35. http://dx.doi: 10.1002/ijc.25396
22. Jennifer S Smith, Lisa Lindsay, Brooke Hoots, Jessica Keys, Silvia Franceschi, Rachel Winer GMC. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. Int J cancer. 2007;121(3):621–32. http://dx.doi: 10.1002/ijc.22527
23. Tricco A.C., Ng C.H., Gilca V., Anonychuk A., Pham B. BS. Canadian oncogenic human papillomavirus cervical infection prevalence: Systematic review and meta-analysis. BMC Infect Dis. 2011;11(1):235. http://dx.doi: 10.1186/1471-2334-11-235
24. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer [Internet]. 2003;88(1):63–73. http://dx.doi: 10.1038/sj.bjc.6600688
25. Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer [Internet]. 2003;89(1):101–5. http://dx.doi.org/10.1038/sj.bjc.6601024
26. Tricco AC, Ng CH, Gilca V, Anonychuk A, Pham B, Berliner S. Canadian oncogenic human papillomavirus cervical infection prevalence: Systematic review and meta-analysis. BMC Infect Dis [Internet]. 2011;11(1):1–15. http://dx.doi.org/10.1186/1471-2334-11-235
27. Ayissi CA, Wamai RG, Oduwo GO, Perlman S, Welty E, Welty T, et al. Awareness, acceptability and uptake of human papilloma virus vaccine among Cameroonian School-attending female adolescents. J Community Health. 2012;37(6):1127–35. http://dx.doi: 10.1007/s10900-012-9554-z
28. Crofts V, Flahault E, Tebeu PM, Untiet S, Fosso GK, Boulvain M, et al. Education efforts may contribute to wider acceptance of human papillomavirus self-sampling. Int J Womens Health. 2015;7:149–54. http://dx.doi: 10.2147/IJWH.S56307
29. Wamai RG, Ayissi CA, Oduwo GO, Perlman S, Welty E, Manga S, et al. Assessing the effectiveness of a community-based sensitization strategy in creating awareness about HPV, cervical cancer and HPV vaccine among parents in North West Cameroon. J Community Health. 2012;37(5):917–26. http://dx.doi: 10.1007/s10900-012-9540-5
30. Domgue JBF, Tebeu PM, Vassilakos P, Petignat P. Effectiveness of a two-stage strategy with HPV testing followed by visual inspection with acetic acid (VIA) for cervical cancer screening in a low income setting. Asia Pac J Clin Oncol [Internet]. 2014;10:2–3. http://dx.doi: 10.1002/ijc.29250
31. Atashili J, Miller WC, Smith JS, Ndumbe PM, Ikomey GM, Eron J, et al. Age trends in the prevalence of cervical squamous intraepithelial lesions among HIV-positive women in Cameroon: a cross-sectional study. Biomedcentral Res Notes [Internet]. BMC Research Notes; 2012;5(1):590. http://dx.doi: 10.1186/1756-0500-5-590
32. Atashili J. Cervical precancerous lesions in hiv-positive women in cameroon: prevalence, predictors and potential impact of screening. 2009. UMI Number: 3352931
33. Nkegoum B, Belley Priso E, Mbakop a, Gwent Bell E. Precancerous lesions of the uterine cervix in cameroonian women. Cytological and epidemiological aspects of 946 cases. Gynecol Obstet Fertil. 2001;29(1):15–20. PubMed:11217188. ISSN: 1297-9589
34. Lancet T. GAVI injects new life into HPV vaccine rollout. Lancet. 2013;381(9879):1688. http://dx.doi: 10.1016/S0140-6736(13)61058-2
35. de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L MN. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007;7(7):453–9. http://dx.doi: 10.1016/S1473-3099(07)70158-5
36. Nicole G. Campos, Jane J. Kim, Philip E. Castle, Jesse D. Ortendahl, Meredith O'Shea, Mireia Diaz SJG. Health

and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa. Int J Cancer. 2012;130(11):2672–84. http://dx.doi: 10.1038/sj.bjc.6604462
37. GAVI Alliance. GAVI welcomes lower prices for life-saving vaccines. GAVI. 2011; http://www.gavi.org/library/news/press-releases/2011 (acessed 14.04.2016)
38. Kelly R (GAVI). 206,000 more girls to benefit from HPV vaccine with GAVI Alliance support. GAVI. 2015; http://www.gavi.org/library/news/press-releases/2014.(acessed 14.04.2016)
39. Schiffman M, Solomon D. Cervical-Cancer Screening with Human Papillomavirus and Cytologie Cotesting. N Engl J Med [Internet]. 2013;369(24):2324–31. http://dx.doi: 10.1056/NEJMcp1210379
40. Solomon N NR. The Bethesda System for reporting cervical cytology: definitions, criteria, and explanatory notes: Springe. Springer International Publishing,. 2015. 1-321 p. ISBN-13: 978-0387403588
41. Desruisseau AJ, Schmidt-Grimminger D, Welty E. Epidemiology of HPV in HIV-positive and HIV-negative fertile women in cameroon, West Africa. Infect Dis Obstet Gynecol. 2009;10:6. http://dx.doi:10.1155/2009/810596
42. Sando Z, McKee T, Claude Pache J, Kemajou H, Folem O, Rubbia – Brandt L, et al. Human Papillomavirus Genotypes in the High Grade Preinvasive Cervical Lesions in Yaounde (Cameroon). Am J Cancer Prev [Internet]. 2013;1(3):20–3. http://dx.doi:10.12691/ajcp-1-3-1
43. Jerome Bigoni, Melissa Gundar, Pierre-Marie Tebeu, Adamo Bongoe, Sonja Schafer, Joel Fokom-Domgue, Rosa Catarino, Evelyne Foguem Tincho, Stephanie Bougel PV and PP. Cervical cancer screening in sub-Saharan Africa: A randomized trial of VIA versus cytology for triage of HPV-positive women. Int J Cancer. 2015;137(1):127–34.http://dx.doi: 10.1002/ijc.29353
44. Pirek D, Petignat P, Vassilakos P, Gourmaud J, Pache J-C, Rubbia-Brandt L, et al. Human papillomavirus genotype distribution among Cameroonian women with invasive cervical cancer: a retrospective study. Sexually transmitted infections. 2015. p. 440–4. http://dx.doi: 10.1136/sextrans-2014-051642
45. Catarino R, Vassilakos P, Tebeu P-M, Schäfer S, Bongoe A, Petignat P. Risk factors associated with human papillomavirus prevalence and cervical neoplasia among Cameroonian women. Cancer Epidemiol [Internet]. Elsevier Ltd; 2015;40:60–6. http://dx.doi.org/10.1016/j.canep.2015.
46. Luff RD. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: Report of the 1991 Bethesda Workshop. Am J Clin Pathol. 1992;98(2):152–154. Doi: http://dx.doi.org/10.1093/ajcp/98.2.152 152-154
47. Sellors JW, Lorincz AT, Mahony JB, Mielzynska I, Lytwyn A, Roth P, et al. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. Cmaj. 2000;163(5):513–8. PMID:11006761
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88. http://dx.doi: 10.1016/0197-2456(86)90046-2
49. Smith JS, Melendy A, Rana RK, Pimenta JM. Age-Specific Prevalence of Infection with Human Papillomavirus in Females: A Global Review. J Adolesc Heal. 2008;43(4 SUPPL.):S5–25. http://dx.doi: 10.1016/j.jadohealth.2008.07.009
50. Guan P, Howell-Jones R, Li N, Bruni L, De Sanjosé S, Franceschi S, et al. Human papillomavirus types in 115,789 HPV-positive women: A meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349–59. http://dx.doi: 10.1002/ijc.27485
51. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer [Internet]. 2007;121(3):621–32. http://dx.doi.org/10.1002/ijc.22527
52. World Health Organization. WHO | Preparing for the introduction of HPV vaccines [Internet]. World Health Press. 2006. http://www.who.int/reproductivehealth/publications/cancers/RHR_06.11/en/ (accessed 10.05.2016)
53. Peres J. For cancers caused by HPV, two vaccines were just the beginning. J Natl Cancer Inst. 2011;103(5):360–2. http://dx.doi: 10.1093/jnci/djr053
54. Denny L, Kuhn L, Hu C-C, Tsai W-Y, Wright TC. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. J Natl Cancer Inst [Internet]. 2010;102(20):1557–67. http://dx.doi: 10.1093/jnci/djq342

Table 1: Characteristics of studies reviewed

	Reference	Study population	Year, data collection	Region	Sample size	Age	Nb of cases	Method of detection	HPV types	HPV prevalence	Methodological quality components
1	Desruisseau *et al*, 2009	HIV positive and negative women	2005 - 2006	Central and South West	61	27 - 29	41	PCR based reverse-line strip test South Dekota	**HR:** 16, 18, 31, 35, 39, 45, 51, 52, 53, 56, 58, 59, 68,73,84, 108 **LR:** 6, 11, 40, 42, 54, 55, 61, 62, 67, 70, 81, 82, 83	67.2% - 85.4%	**1: Y 2: Y 3: Y 4: U 5: Y 6: Y 7: Y**
2	Sando *et al*, 2013	Women with high-grade squamous preinvasive lesions of the uterine cervix	2009	Central	37	25	31	PCR based reverse-line strip test Geneva	**HR:** 16, 18, 45, 33, 35, 68 **LR:** 11, 53,74	83.8% - 83.8%	**1: N/A 2: Y 3: Y 4: U 5: Y 6: Y 7: U**
3	Bigoni *et al*, 2014	HPV positive women	2014	Central and Littoral	846	25 - 65	259	Qualittative PCR Cobas R4800 system Lausanne	**HR:** 16,18, others	38.5%	**1: Y 2: Y 3: Y 4: Y 5: Y 6: Y 7: U**
4	Pirek *et al*, 2015	Women with invasive cervical cancer	2014	Central	181	Not known	181	Reverse blot hybridization	Unknown	Unknown	**1: N/A 2: U 3: N/A 4: U 5: N 6: Y 7: U**
5	Catarino et al, 2015	Women with cervical neoplasia	2015	Central and Littoral	731	34 - 48	285	Real-time PCR Geneva	HR: 16,18, others	44.9%	**1: Y 2: Y 3: Y 4: Y 5: Y 6: Y 7: U**

Abbreviations

Y = Yes, **U** = Unclear**, N/A** = Not Applied. **HR** = High Risk, **LR** = Low Risk

Methodological quality components: A methodological quality and risk of bias tool, use to evaluate risk of bias in systematic review. It's establish consistency and avoid discrepancies in assessing the methodological quality of included studies in systematic reviews.

1. Describe efforts to address non-response bias
2. Study is free from outcome reporting bias
3. Response rate reported
4. Representative sampling strategy
5. Adequate timing of sampling
6. Use of a sensitive sample
7. Study is free from conflict(s) of interest

Table 2: Specific Distribution of Studies, Study Size and Prevalence of HPV DNA by Cervical Disease Grade

Studies (Reference)/Region	Total (studies=05)		Normal Cytology (studies=02)		ASCUS (studies=02)		LSIL (studies=01)		HSIL (studies=02)		ICC (studies=02)	
	Tested N	HPV(+) n	Tested N	HPV(+) n (%)	Tested N	HPV(+) n (%)	Tested N	HPV(+) n (%)	Tested N	HPV(+) n (%)	Tested N	HPV(+) n (%)
Andrew J. D. et al_2009 Centre and South West	61	41	41	15 (36.6%)	9	8 (88.9%)	10	8 (80%)	00	00 (00%)	00	00 (00%)
Zacharie Sando et al 2013 Centre Region	37	31	-	-	-	-	-	-	37	31 (83.8%)	-	-
Jérôme Bigoni et al 2014 Centre and littoral	846	259	307	170 (55.4%)	88	25 (28.4%)	-	-	-	-	-	-
David Pirek et al 2014 Centre Region	181	-	-	-	-	-	-	-	-	-	181	178
Rosa Catarino et al 2015 Centre and littoral	731	285	-	-	-	-	-	-	-	-	-	-
Total	**1856**	**616**	**348**	**185 (53.2%)**	**97**	**33 (34%)**	**10**	**8 (80%)**	**37**	**31 (83.8%)**	**181**	**178 (98.3%)**

Abbreviations:
ASCUS: Atypical squamous cells of undetermined significance;
LSIL: Low-grade squamous intraepithelial lesions;
HSIL: High-grade squamous intraepithelial lesions;
ICC: Invasive cervical cancer included both squamous cell carcinoma of the cervix and/or adenosquamous carcinoma of the cervix.