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The burden of HPV associated cancers in two regions in Nigeria 2012–2014

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Abstract

Introduction—HPV attributable cancers are the second most common infection-related cancers worldwide, with much higher burden in less developed regions. There are currently no country-specific estimates of the burden of these cancers in Nigeria just like many other low and middle income countries.

Methods—In this study, we quantified the proportion of the cancer burden in Nigeria that is attributable to HPV infection from 2012 to 2014 using HPV prevalence estimated from previous

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Author contributions

EJA, EOD, SNA, MO and EAO all contributed equally to this manuscript; by contributing to the concept and design, data acquisition, analysis and interpretation, drafting and revising the manuscript and approving the final version for submission. FI, TO, EE, RA contributed to the acquisition and analysis of data, providing revisions to the manuscript and approving the final version of the manuscript. FB took part in the analysis and interpretation of data, revising the manuscript critically for intellectual content and approving the final version to be submitted. CAA obtained funding, conceived the study and study design, provided critical revisions for intellectual content and guided all aspects of the paper. All authors read and approved the final manuscript.

studies and data from two population based cancer registries (PBCR) in Nigeria. We considered cancer sites for which there is strong evidence of an association with HPV infection based on the International Agency for Research on Cancer (IARC) classification. We obtained age and sex-specific estimates of incident cancers and using the World Standard Population, we derived age standardized incidence (ASR) rates for each cancer type by categories of sex, and estimated the population attributable fractions (PAF).

Results—The two PBCR reported 4336 new cancer cases from 2012 to 2014. Of these, 1627 (37.5%) were in males and 2709 (62.5%) in females. Some 11% (488/4336) of these cancers were HPV associated; 2% (38/1627) in men and 17% (450/2709) in women. Of the HPV associated cancers, 7.8% occurred in men and 92.2% in women. The ASRs for HPV associated cancers was 33.5 per 100,000; 2.3 and 31.2 per 100,000 in men and women respectively. The proportion of all cancers attributable to HPV infection ranged from 10.2 to 10.4% (442–453 of 4336) while the proportion of HPV associated cancers attributable to HPV infection ranged from 90.6% to 92.8% (442–453 of the 488 cases). In men, 55.3% to 68.4% of HPV associated cancers were attributable to HPV infection compared to 93.6% to 94.8% in women. The combined ASR for HPV attributable cancers ranged from 31.0 to 31.7 per 100,000. This was 1.4 to 1.7 per 100,000 in men and 29.6 to 30.0 per 100,000 in women. In women, cervical cancer (n = 392, ASR 28.3 per 100,000) was the commonest HPV attributable cancer, while anal cancer (n = 21, ASR 1.2 per 100,000) was the commonest in men.

Conclusions—HPV attributable cancers constitute a substantial cancer burden in Nigerian women, much less so in men. A significant proportion of cancers in Nigerian women would be prevented if strategies such as HPV DNA based screening and HPV vaccination are implemented.

Keywords

HPV; HPV associated cancers; Cancer registries; Cancer incidence; Nigeria

1. Introduction

Approximately 2 million (16%) of all new cancer cases that develop globally every year are attributable to infections but the proportion differs significantly between developed and developing countries. In developed countries, infections-attributable cancers account for 3.3% while they account for 32.7% of annual incident cancer cases in developing countries [1]. Close to 5% of global incident cancers are attributable to Human Papillomavirus (HPV) infections and the proportions differ comparing developed (2.1%) to developing countries (14.2%) [2,3]. The human papilloma virus is the second largest contributor to infections associated cancers worldwide after *Helicobacter Pylori*, with a much higher burden in less developed regions [2]. The International Agency for Research on Cancer [4] (IARC) and a wide range of other public health organizations [5–7] consider that there is strong evidence for a causal relationship between HPV infection and cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsils [8].

The population attributable fraction (PAF) which is the proportional reduction in disease incidence and mortality that would occur in a specific population if exposure to a risk factor is prevented, for HPV and cancer varies widely [9,2]. In 2008, the highest PAFs for HPV

infection and cancer were for India (15.5%) and Sub-Saharan Africa (14.2%) while the lowest PAFs were for North America (1.6%) and Australia/New Zealand (1.2%) [2]. In the reference paper on global estimates of cancer disease burden, the PAF for Sub-Saharan Africa was computed using global HPV prevalence estimates and cancer registry data from GLOBOCAN 2012 to which only one population-based cancer registry (PBCR) in Nigeria contributed [10]. Currently, there are no country-specific estimates for the burden of HPV associated cancers in Nigeria.

In this study we quantify the proportion of the cancer burden in Nigeria that is attributable to HPV infection for the period 2012 to 2014 using HPV prevalence estimates derived from meta-analyses [11–15] and data from Nigerian PBCR. Knowledge of the proportion of the cancers that can be prevented by reducing the prevalence of HPV infections provides a critical baseline for evaluating the effectiveness of interventions and contribute to analyses of the added value of such interventions [16]. HPV vaccinations, for example, will substantially reduce the burden of HPV associated diseases [17]. However many low and middle income countries, including Nigeria, are yet to implement HPV vaccination and HPV DNA test based screening programs [18].

2. Methods

2.1. Data sources

We retrieved data on cancer incidence from two out of six PBCR in Nigeria, the Abuja and Enugu cancer registries for the period 2012 to 2014 because only these 2 registries submitted data to the Nigerian National System of Cancer Registries (NSCR) during the period under consideration [19]. We obtained age and sex-specific estimates of new cancer cases reported for the time period under review.

The Abuja Cancer Registry (ABCR) at the National Hospital Abuja started as a hospital-based cancer registry (HBCR) in 2005 but with support from NSCR became a PBCR in 2009. The registry covers a defined population of 1,406,239 people. The method of case ascertainment in the Abuja cancer registry has been described elsewhere [20]. The Enugu Cancer Registry (ECR) in the Oncology Department of the University of Nigeria Teaching Hospital Ituku Ozalla, Enugu, Nigeria began in 1988 as a HBCR but was developed into a PBCR by the NSCR in 2012. The registry covers a population of 1,103,153. These 2 registries cover a combined population of 2,509,392. Both registries use ICD-O-3 for coding and classification of cancers. While the ECR uses CanReg5 software for data entry, processing and storage, ABCR uses CanReg4.

The data were checked and cleaned prior to analysis by two of the authors (EJA and MO). Quality control checks were performed using IARC's CanReg5 software to ensure uniformity, correctness of coding and completeness of information, including removal of duplicates. Information on cancer sites for which there is strong evidence of an association with HPV infection was based on the IARC Monograph 100b [8], a comprehensive review of published information on infectious agents that may be carcinogenic to humans [3]. The cancer sites (ICD-O code) considered in this study were; Cervix (C.53), Vulva (C.51), Vagina (C.52), Anus (C. 21), Penis (C.60) and Oropharynx (C.01, C.09, C10). Incidence

cases by year, sex and 5-year age group for the above cancers, were extracted from the cleaned cancer registries' databases.

2.2. Statistical analyses

We calculated age standardized incidence rates by cancer type and sex using the direct method based on the WHO World Standard Population. We obtained PAF estimates from previous studies published in the literature (Table 1). We did not use methods that require population prevalence estimates of HPV and relative risks given the absence of large population based surveys of cancer-specific HPV infection sites in Nigeria and few epidemiologic studies with relative risk estimates for the different cancers. Instead, we searched PubMed and found 34 studies of HPV prevalence from Africa with sample sizes greater than 50. Our search strategy included the following terms: Human papilloma-virus OR HPV and cancer* OR tumour* OR tumor* OR malignan* OR neoplas* OR carcinoma* OR adenocarcinoma* OR precancer* OR pre-cancer* OR dysplas* and (genital infection) OR cervix OR vagina OR vulva OR anus OR oropharynx OR penis and SSA OR SubSaharan Africa OR Sub Saharan Africa OR West Africa OR East Africa OR North Africa OR Central Africa OR South Africa and prevalence.

We used a PAF of 100% for cervical cancer, given that it is almost universally accepted that HPV is necessary for the development of the disease and that all cervical cancer cases can be attributed to HPV infection [11]. For vulvar cancer, we identified only one study in Africa; a study from Botswana which suggested an HPV prevalence of 100% among 35 cases of vulvar cancer. As a result of the small sample size and in the absence of other studies from Sub-Saharan Africa, we used a PAF of 40% for vulvar cancer based on meta-analyses [12]. We did not find any individual studies of HPV prevalence in anal cancer in Africa so we used a PAF range of 88% to 90% for anal cancer from two studies; a large intercontinental study than included cases from West Africa and a global study by Parkin et al. [13,21] We identified two studies from Uganda and Kenya that evaluated prevalence of HPV in penile cancer however, we used a PAF range of 40 to 48% from a meta-analysis, because of the limited sample sizes of 17 and 22 in the African studies [22,23,14]. We used a PAF range of 12 to 46% for oropharyngeal cancers [15,24]. The PAF estimates and their sources are provided in Table 1.

2.3. Sensitivity analyses

We obtained incidence estimates for cervical cancer from GLOBOCAN 2012 and used these to conduct sensitivity analyses in our study by comparing the ASR of HPV associated cervical cancer reported in GLOBOCAN 2012 with the findings from our analyses.

3. Results

3.1. Overview

A total of 4336 cases of cancer were reported by the ABCR and ECR registries from 2012 to 2014 (Table 2). Among these, 1627 (37.5%) were in males and 2709 (62.5%) in females. Of the total cancers in both sexes, 488 (11%) were HPV associated and most of these occurred in women (92.2%, 450/488) compared to men (7.8%, 38/488). (Table 2) HPV associated

cancers constituted 2% (38/1627) of all cancers in men and 17% (450/2709) of all cancers in women. (Fig. 1) The combined ASR for HPV associated cancers was 33.5 per 100,000 and it was 2.3 and 31.2 per 100,000 in men and women respectively. The proportion of the total cancers attributable to HPV infection ranged from 10.2 to 10.4% (442 to 453 of 4336) while the HPV associated cancers that were attributable to HPV infection ranged from 90.6 to 92.8% (442 to 453 of 488). In men, 55.3 to 68.4% (21 to 26 of 38) HPV associated cancers were attributable to HPV infection while in women 93.6% to 94.9% (421 to 427 of 450) HPV associated cancers were attributable to HPV infection (Table 3). The ASR for HPV attributable infections ranged from 31.0 to 31.7 per 100,000 and this was 1.4 to 1.7 per 100,000 in men and 29.6 to 30.0 per 100,000 in women (Table 3).

3.2. Cervical cancer

Some 392 cases of cervical cancer were reported by the two PBCR during this period. Cervical cancer was the most common HPV associated cancer overall and in women in this population (Fig. 1), with ASR of 28.3 per 100,000. Given a PAF of 100% for cervical cancer, all 392 cases reported by the registries are attributable to HPV infection (Table 3) so the ASR for HPV attributable cervical cancer in this population is 28.3 per 100,000

3.3. Oropharyngeal cancers

There were 23 cases of oropharyngeal cancer reported in both sexes by the registries. Of these, 15 (65.2%) occurred in men and 8 (34.7%) in women. The ASR for HPV associated oropharyngeal cancer was 0.8 per 100,000 in men and 0.5 per 100,000 in women. We used a PAF range of 12% to 46% [21,15] and estimated that 3 to 11 of the 23 cases of oropharyngeal cancer were attributable to HPV infection (Table 3). The ASR for HPV attributable oropharyngeal cancers ranged from 0.1 to 0.4 per 100,000 in men and 0 to 0.3 per 100,000 in women (Table 3).

3.4. Anal cancer

Some 38 cases of anal cancer were reported with 21 (55.3%) cases in men and 17 (44.7%) cases in females. The ASR for HPV associated anal cancer was 2.1 per 100,000. Using a PAF of 88% to 90% for anal cancer, we estimated that 33 of the 38 cases of anal cancer in both sexes were attributable to HPV infection (Table 3). The ASR for HPV attributable anal cancer in this population was 1.8 per 100,000. In men, anal cancer was the most common HPV attributable cancer with ASR of 1.2 per 100,000. In women, anal cancer was the third most common HPV attributable cancer after cervical and vulval cancers with an ASR of 0.6 per 100,000.

3.5. Vulvo-vaginal cancers

The registries reported 33 cases of vulvo-vaginal cancer from 2012 to 2014. Of these, 25 were vulva cancers and the ASR for HPV associated vulval cancer in this population was 1.3 per 100,000. We used a PAF of 40% from meta-analysis studies to compute attributable risk [12]. Therefore 10 of the 25 cases of vulva cancer were attributable to HPV infection. The ASR for HPV attributable vulval cancers was 0.5 per 100,000.

Only 8 cases of vaginal cancer were reported during the time period under review and of these, 6 cases were attributable to HPV infection based on PAF estimates of 70% from a meta-analysis by De Vuyst et al. [12]. The ASR for HPV associated vaginal cancers was 0.4 per 100,000 and the ASR for HPV attributable vaginal cancers ranged from 0.2 to 0.3 per 100,000.

3.6. Penile cancers

There were only two cases of penile cancer reported by the cancer registries giving an ASR for HPV associated penile cancer of 0.1 per 100,000 and HPV attributable penile cancer of 0.05 per 100,000.

3.7. Sensitivity analyses

We compared our findings to the GLOBOCAN 2012 database of IARC. The ASR for HPV associated and HPV attributable cervical cancer reported in GLOBOCAN was 29 per 100,000. This result is similar to our findings of 28.3 per 100,000 for the ASR for HPV associated and HPV attributable cervical cancer in Nigeria.

4. Discussion

Our study showed that Nigerian women had a higher burden of HPV attributable cancers compared to men, due to high incidence of cervical cancer. We found that 10.2 to 10.4% of all cancers and 90.6 to 92.8% of HPV associated cancers were attributable to HPV infection. The proportion of HPV attributable cancers in Nigeria is similar to findings from other developing countries [25] but much higher than in developed countries [26] mainly due to the higher burden of cervical cancer in Nigeria.

Cervical cancer was the most common HPV attributable cancer in our study. Similar incidence rates to our findings have been reported in West-Africa (29.3 per 100,000) and Central Africa (28 per 100,000) but the incidence rates in South Africa (38.2 per 100,000) and Eastern Africa (42.7 per 100,000) were much higher [27]. This is in contrast with developed regions such as Europe where much lower incidence rates (11.9 per 100,000) have been reported [27]. This difference with the developed world may be as a result of differences in the prevalence of risk factors for cervical cancer such as early age at first intercourse [28], total number of lifetime sexual partners, sexual practices [29], and early age at first pregnancy [28]. The widespread availability of population based screening programs for cervical cancer in developed countries has also contributed to reduced incidence while HIV infection in Africa is contributing to increased incidence [30,31].

Analysis of worldwide trends showed that the incidence of oropharyngeal cancers significantly increased between 1983 and 2002 in several countries around the world [32]. Given that countries with reduced or stable incidence of lung cancer had increased incidence of oropharyngeal cancer, Chaturvedi et al. [32] surmised that the increase in oropharyngeal cancer incidence in developed countries was due to factors other than smoking, notably HPV infection. HPV16 was shown to account for the vast majority (~95%) of HPV-positive oropharyngeal squamous cell carcinomas [33].

Our results showed that the incidence of HPV attributable oropharyngeal cancers is low in Nigerian men and women at this time. There is no data on time trends of oropharyngeal cancers, for most developing countries. A recent study of head and neck cancers from Nigeria analyzed blocks from 123 patients and did not find any to be positive for HPVHPV associated [34]. Oropharyngeal cancers were the second most common HPV attributable cancers in men after anal cancers, but were the least common HPV attributable cancers in women. The low prevalence of HPV attributable oropharyngeal cancers in Nigerian adults may be related to low prevalence of sexual behaviors that may be contributing to rising incidence of oropharyngeal cancer in other populations [35,36]. The gender difference that we observed in incident oropharyngeal cancers in our study may be due to lower prevalence of use of tobacco products and alcohol among women compared to men in the Nigeria. Other risk factors for oropharyngeal cancer are HIV infection [37], poor oral hygiene [38], diet [39,40] and occupational [41] exposures.

For the past three decades, the global incidence of anal cancer has been rising by about 2% per year among both men and women [42]. The increasing incidence of anal cancer may reflect changes in sexual behavior in the second half of the twentieth century that increases the risk of exposure to HPV in the anal canal [43]. In contrast to reports from other parts of the world where the incidence of anal cancers is higher in women, we found almost similar incidence in both sexes [44–47]. The ASR of anal cancer in our study was 1.4 and 0.7 per 100,000 in men and women respectively. Similarly low incidence rates have been reported in Uganda 0.2 per 100,000 in men and women and <0.1 per 100,000 in men and women in Zimbabwe [25]. Risk factors for anal cancers include chronic irritation in the form of fissures or fistulas, smoking and immunosuppression [43].

Vulvar and vaginal cancers are rare malignancies of the female genital tract. Worldwide, about 2% and 1.5% of the cancers attributable to HPV in 2008 were cancers of the vulva and vagina, respectively [12]. Although there are no previous studies in Nigeria reporting the incidence of vulva cancer, the incidence of vulva cancer in our study was similar to the results from previous studies conducted in Uganda and Zimbabwe [25]. The incidence of vaginal cancer was also very similar to findings from other African countries of 0.4 and 0.7 per 100,000 in Uganda and Zimbabwe respectively [25]. The risk factors for vulvo-vaginal cancers are multiple lifetime sexual partners, age at first intercourse, immunosuppression, cigarette smoking, chronic pessary use, surgical menopause, or prior hysterectomy [48,49]; however these factors have not been examined in relation to vulvo-vaginal cancers among Nigerian women, to the best of our knowledge. A study conducted in Nigeria about 25 years ago showed that vulvar carcinoma was more common among women of low socio-economic status [50].

A review of 31 studies on HPV and penile cancer revealed that about 50% of the cancers were associated with HPV 16 and 18 [51]. Although penile HPV prevalence is high, persistence is less likely [52], thus HPV is not a necessary cause of penile cancer. Penile cancer virtually occurs in only uncircumcised men. In Israel, where most males are circumcised during the neonatal period, the rate of penile cancer is as low as 1 case per one million person-years [53], whereas in Brazil where most men are uncircumcised, the rates are higher and penile cancer accounts for 2–5% of male cancers [54]. The low ASR of

penile cancer estimated in this study may be due to high prevalence of neonatal circumcision in Nigeria. Our findings of low incidence of penile cancer are similar to reports from other Sub-Saharan African countries [25].

The prevalence of HIV infection in sub-Saharan Africa has been linked to several HPV attributable cancers. Several studies in Nigeria have found an association between cervical cancer and HIV [47,55]. A registry linkage study in Nigeria reported a twofold higher risk of cervical cancer in people living with HIV/AIDS [31]. A recent systematic review and meta-analysis revealed an excess risk of anal cancer among men who have sex with men (MSM), particularly among those who were HIV positive [56]. Other HPV attributable cancers such as oropharyngeal cancers have also been linked with HIV infection [37]. More effective HIV/AIDS control interventions in developing countries may reduce the incidence of HPV attributable cancers particularly cervical cancer [27].

Our study has several important limitations. Studies of the prevalence of HPV infection in Africa are few, often have small sample sizes and lacked methodological rigor. Therefore, the prevalence measured may not be entirely representative of the population. In this study, we mostly used prevalence estimates derived from meta-analyses and provided a range of values for the attributable fractions in a bid to obtain more representative results. Secondly, this data was from only two of the six PBCR in Nigeria that had data for the period under study and this may limit the generalizability of our results. Furthermore, we cannot rule out the possibility of problems with completeness and representativeness of the cancer registration data based on the two catchment populations. However our sensitivity analyses showed that the ASR of cervical cancer in our study of 28.3 per 100,000 is very similar to the national estimate for Nigeria (29 per 100,000) as reported in GLOBOCAN 2012 [57].

5. Conclusion

This is the first study to provide information on the incidence of HPV associated and HPV attributable cancers in Nigeria. The estimate of HPV attributable cancers in our study is substantial and approximately 90% of these cancers would be prevented if HPV infection in this population is prevented through screening and prophylactic vaccination. Our findings would inform public health policy on the potential impact of HPV prevention and for examining future trends in HPV attributable cancers in Nigeria.

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Fig. 1.
Total cancers and total HPV associated cancers reported by gender, in two regions in Nigeria from 2012–2014.

Table 1

Previous HPV Prevalence studies in African populations.

Cancer Site	ICD-O Code	Regional ^a prevalence of HPV in cancers (African populations)	Studies in African populations (Sample size) [Source]	PAF estimates used in this study% [Source]
Cervix	C.53	83%–99%	Nigeria (192), Ghana (167), South Africa (300) [58] Nigeria (75) [59]	100 [11]
Vulva	C.51	100%	Botswana (35) [60]	40 [12]
Vagina	C.52	–	None	40–70 [21,12]
Anus	C.21	62%	Nigeria, Mali, Senegal (13) [13]	88–90 [21,13]
Oropharynx	C.01, C.09–C.10	19%	Ghana (78) [24]	12–46 [15,21]
Penis	C.60	65%–68%	Uganda (17) [23], Kenya (22) [22]	48 [14]

^aRegional estimates are presented for countries in West Africa where available, or other African countries.

Table 2

Total number of cancer cases and number of HPV associated cancers in 2012–2014 by cancer registry site.

Sex	All cancers (2012–2014)	Total HPV associated cancers	Number and percentages of HPV associated cancers					
			Cervix (%)	Vulva (%)	Vagina (%)	Anus (%)	Oropharynx (%)	Penis (%)
Female	2709 (100)	450 (16.6)	392 (14.5)	25 (1)	8 (0.3)	17 (0.6)	8 (0.3)	–
Female	1627 (100)	38 (2.3)	–	–	–	21 (1.3)	15 (0.9)	2 (0.1)
	4336 (100)	488 (11.3)	392 (9)	25 (0.6)	8 (0.2)	38 (0.9)	23 (0.5)	2 (0.04)

Table 3
Age standardised incidence rates of HPV associated cancers and cancers attributable to HPV in two regions in Nigeria, 2012–2014.

Sex	Cancer Site	ICD-O Code	Total no of cancers	ASRHPV Associated cancers	Total no of cancers attributable to HPV	Population attributable Fraction (PAF) %	ASR HPV Attributable cancers
Female	Cervix	C.53	392	28.3	100	392	28.3
	Vulva	C.51	25	1.3	40	10	0.5
	Vagina	C.52	8	0.4	40–70	3–6	0.2–0.3
	Anus	C.21	17	0.7	88–90	15	0.6
	Oropharynx	C.01, C.09–C.10	8	0.5	12–46	1–4	0–0.3
Total Female			450	31.2	–	421–427	29.6–30.0
Male	Penis	C.60	2	0.1	40–48	1	0.05
	Anus	C.21	21	1.4	88–90	18	1.2
	Oropharynx	C.01, C.09–C.10	15	0.8	12–46	2–7	0.1–0.4
Total male			38	2.3		21–26	1.4–1.7
Total both sexes			488	33.5		442–453	31–31.7