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Cohort Profile

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Cohort Profile: African Collaborative Center for Microbiome and Genomics Research's (ACCME's) Human Papillomavirus (HPV) and Cervical Cancer Study

Sally N Adebamowo,[1,2,3]* Eileen O Dareng,[4] Ayotunde O Famooto,[5] Richard Offiong,[6] Olayinka Olaniyan,[7] Kayode Obende,[8] Amos Adebayo,[9] Sanni Ologun,[10] Bunmi Alabi,[11] Peter Achara,[12] Rasheed A Bakare,[13] Michael Odutola,[5] Oluwatoyosi Olawande,[5] James Okuma,[5] George Odonye,[5] Ruxton Adebiyi,[5] Patrick Dakum[14] and Clement A Adebamowo,[1,2,3,5,15]; ACCME Research Group as part of the H3Africa Consortium

[1]Department of Epidemiology and Public Health, [2]Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA, [3]Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, USA, [4]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK, [5]Office of Strategic Information and Research, Institute of Human Virology Nigeria, Abuja, Nigeria, [6]Department of Obstetrics and Gynecology, University of Abuja Teaching Hospital, [7]Department of Obstetrics and Gynecology, National Hospital Abuja, [8]Department of Obstetrics and Gynecology, Garki Hospital Abuja, [9]Department of Obstetrics and Gynecology, Asokoro District Hospital, [10]Department of Obstetrics and Gynecology, Kubwa General Hospital Abuja, [11]Department of Obstetrics and Gynecology, Wuse General Hospital, Abuja, Nigeria, [12]Department of Obstetrics and Gynecology, Federal Medical Center, Keffi, Nigeria, [13]Department of Microbiology, University College Hospital, University of Ibadan, Ibadan, Nigeria, [14]Office of the Chief Executive Officer, Institute of Human Virology Nigeria, Abuja, Nigeria and [15]Institute of Human Virology, University of Maryland, Baltimore, MD, USA

*Corresponding author. Department of Epidemiology and Public Health, and University of Maryland Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, 660 West Redwood Street, Howard Hall, Room 119, Baltimore, MD 21201, USA. E-mail: sadebamowo@som.umaryland.edu

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Why was the cohort set up?

Globally, cervical cancer is the fourth most common cancer among women, with an estimated 528 000 new cases in 2012.[1] Although it remains a significant public health problem worldwide, the burden of cervical cancer falls disproportionately on low-resource countries. In the USA, the incidence rate of cervical cancer was 6.6 per 100 000 in 2012,[1] compared with 23.0 per 100 000 in Nigeria[2] which had about half the population of the USA in 2012.

Persistent high-risk human papillomavirus (hrHPV) infection of the cervix is a necessary cause of cervical cancer.[3,4] About 80% of sexually active individuals become

infected with at least one genital hrHPV in their lifetime. Most of the infections are cleared, but about 10% become persistent infections.[5–7] The mechanism by which some individuals are able to remain uninfected while some clear the infection and others remain persistently infected, remains unclear. Of the women with persistent hrHPV infection, only ~ 12% go on to develop cervical intraepithelial neoplasia (CIN)[2,3] and cervical cancer.[8] Therefore, several co-factors are required to support the cervical carcinogenesis induced by persistent hrHPV infection.[7,9]

Data from Western series suggest that HPV types 16 and 18 account for most of the cases of cervical cancer in those environments.[4] However, there have been few longitudinal studies of hrHPV infections and their association with cervical cancer in much of the rest of the world. Given the marked heterogeneity of types and prevalence of multiple hrHPV infection in many parts of the developing world, variation in ability of different hrHPV types to establish persistent infection and concerns about the coverage of existing vaccines, longitudinal studies of large numbers of women in the general population in different regions of the world, with information on HPV types and risk factors, are critical to bridging the knowledge gaps, especially in African populations where such studies are scarce.[10–14]

The aetiology of cervical cancer is multifactorial. It is clear that environmental risk factors such as smoking, age at first sexual intercourse, age at first full-term pregnancy, high parity and use of oral contraceptives which have been implicated in persistent hrHPV infection, do not completely explain the association between hrHPV infection and cervical cancer, and several studies have identified a role for genetics and heritability in its aetiology.[15–23] These studies suggest that genetic factors contribute to the risk of persistent hrHPV infection and progression to cervical cancer. A recent review of 15 studies on heritability of cervical cancer risk suggested that having a first-degree relative with cervical cancer increases an individual's risk by 1- or 2-fold.[24] Other reviews concluded that there is a potential role for genetic factors in cervical cancer *in situ* and estimated the heritability to be between 11% and 15%.[25–27] Nevertheless, there have been few studies of genetic risks of the different components of the pathway to cervical carcinogenesis among all populations, particularly in Africans.

An important yet understudied aspect of HPV carcinogenesis is the role of innate immunity and emerging knowledge about the vaginal microbiome, and the role that these play in cervical carcinogenesis.[28–34] Vaginal microbiota may affect the risk of persistent hrHPV infection through rich, complex, dynamic and individual-specific microbial interaction with the host such as through signalling of host cells that affect inflammatory, immunological, and host-defence functions.[35,36] Specific types of vaginal microbiota may sculpt the cervical cytokines in ways that influence the persistence of HPV infection or breach the incipient latency of the persistent hrHPV infection state and drive it towards induction of malignancy in the cervix.[35] Furthermore, health behaviours, including intravaginal health practice, number of sexual partners and other factors, may affect the types of vaginal microbiota and their association with risk of persistent hrHPV infection. There have been few studies of the vaginal microbiota[37,38] and the interaction between the vaginal microbiota and cervical cytokines and their association with persistent hrHPV infection.[27,28]

The design of the African Collaborative Center for Microbiome and Genomics Research (ACCME) HPV and Cervical Cancer Cohort Study enables us to study environmental, microbiomic, genetic and epigenetic factors associated with persistent hrHPV infection, in order to improve knowledge of the mechanism of HPV carcinogenesis and discover biomarkers of persistent hrHPV infection and cervical cancer. We evaluate the epidemiological determinants of persistent infection, and the genetic and epigenetic changes in hrHPV as well as in somatic cervical cells and their association with persistent hrHPV infection and CIN2+. We evaluate the epidemiological determinants of patterns of cervical cytokines and their association with persistent hrHPV infection. We identify the community state types and stability of the vaginal microbiota, and their association with persistent hrHPV infection. We conduct genome-wide association studies (GWAS) to identify the genetic variants associated with the risk of persistent hrHPV infection and CIN2+.

The ACCME cohort is located in Nigeria. Ethical approval to conduct this study was obtained from the National Health Research Ethics Committee in Nigeria. All study participants were informed about the study and were requested to consent before participation. The informed consent is reiterated at different study visits and new consent is obtained for specific components of the research project. An ethics and regulatory affairs coordinator conducts regular audits of the informed consent process and evaluates the understanding of the informed consent among randomly selected study participants. This study is funded by the National Institutes of Health.

Who is in the cohort?

There are 36 states, six geopolitical zones and a Federal Capital Territory in Nigeria. Our study is located in Abuja, the main municipality in the Federal Capital Territory, which is located in the centre of the country. In general, the socio-demographic characteristics of women in Abuja,

North Central Nigeria, were similar to those of women in the South East, South South, and South West zones in 2013, but not the North East or North West which are more rural and the women there are less likely to be educated or employed.[39] We randomly selected seven out of 42 districts in Abuja for our study. The populations served by these study sites varied from urban city dwellers to semi-rural to rural people living on farmlands and villages. In each district, we employed extensive community engagement strategies, to create awareness of the study and ensure that a representative sample of the target population was enrolled. These strategies included: focus group discussions and surveys to identify cultural issues, literacy levels and local language; town hall meetings and community forums to gain input from the general public; participatory evaluation; and partnerships with community stakeholders to create alliances and ownership and build trust. We also created awareness of the study through the use of: mass media including radio and television talk shows; social media including Twitter and Facebook; interactions with key opinion leaders; and engagement of religious leaders, women's advocacy groups, corporate organizations, the Nigerian Federal Ministry of Health and community members.

In this study, we identified women who were at least 18 years old, had had sexual intercourse and had no previous history of cervical abnormalities, cervical cancer or total abdominal hysterectomy, by area sampling in Abuja. Potential participants were offered HIV testing with voluntary counselling. Those who were HIV-positive were not eligible to participate in the cohort and were referred to free HIV treatment programmes. Enrolment into the cohort began in February 2014 in Abuja, Central Nigeria.

How often is follow-up?

Data are collected during the initial visit and at 6, 12, 18 and 24 months. Research nurses collect epidemiological data using our tablet computer-assisted survey instruments (TaCASI) directly into a secure web database application—the Research Electronic Data Capture (REDCap) platform hosted at the Institute of Human Virology (IHVN).[43] Paper copies of the study forms are available to serve as backup for data collection. Detailed contact information (address and phone numbers) are collected from all participants. Follow-up visits are scheduled at appropriate times and reminders are sent by text messages, e-mails and phone calls. Where participants cannot be reached by phone, home visits are conducted.

What is being measured?

The data collection tools were piloted in a study of 1000 women with similar characteristics as the participants of the ACCME study. In order to compute socioeconomic status (SES) in a low-resource environment where income data are sparse, we generated wealth index data as previously described.[44] In summary, we used principal components analysis (PCA) with varimax rotation to compute factor scores based on the sum of the ownership of household items weighted by their factor loading. We sorted the data on the first principal component which had the highest eigen value, and divided all respondents into three categories based on its value. Participants with the lowest 40% were categorized as low SES, the middle 40% were categorized as middle SES and the top 20% were categorized as high SES. The validity and reproducibility of the wealth index has been examined in previous studies and it correlates well with other measures of wealth in environments without reliable expenditure data.[44]

We adapted tools for the measurement of alcohol intake, cigarette smoking, tobacco use, sexual and reproductive health and medical and drug history from the PhenX toolkit version of 20 September 2013, version 5.6.[45] We obtained self-report of occurrence of diseases such as cancer, diabetes, myocardial infarction and stroke. We modified the Harvard School of Public Health's Nurses' Health Study II physical activity questionnaire to collect data on physical activity and we used the Nigerian food frequency questionnaire that we had previously developed to collect information on dietary intake. Members of the ACCME research group have used these tools for previous research in Africa.[46–48] We asked participants about their sexual activities in the past 24 h including history of sexual intercourse (vaginal, anal, oral), use of contraceptives, sex toys and lubricants, and vaginal symptoms. Given the sensitive nature of some questions, especially those on sexual history, we ensured the mode and placement of the questions were appropriate, the interviewers were trained to be culturally and morally sensitive and each interview was conducted in a relaxed, private setting, sufficiently so to encourage accurate responses.

Three blood pressure (BP) measurements are taken at least 1 min apart in accordance with the American Heart Association recommendations,[49] using the automated OMRON® BP760 (HEM-7220-Z) with patients in a sitting position, not earlier than 15 min after participant arrival at the study site. Standing height, body weight and waist and hip circumferences were measured in accordance with the World Health Organization (WHO) Multinational Monitoring of Trends in Cardiovascular Disease (MONICA) project.[50] Pelvic examinations were

performed on all participants and data on any significant findings in the lower abdomen, the vulva/perineum, vagina, cervix and adnexa were collected as described.[51,52] We performed bivalve speculum examination and measured the vaginal pH using pH paper (pHydrion®, Micro Essentials Laboratories, Brooklyn, NY) and compared colour change of the pH paper with the manufacturer-provided colour charts.[53,54] All research nurses passed a colour perception test before performing the pH tests. The data collected by questionnaires and during the Clinical Evaluation, Sample Evaluation and Testing schedule are outlined in Supplementary Table 1 (available as Supplementary data at *IJE* online).

Biological samples including blood and mid-vaginal and ectocervical cell samples are collected at baseline and during follow-up visits. The blood samples are separated into plasma, serum, buffy coat, red blood cells and clot. All biological samples are stored at -80 °C at the ACCME Laboratories, IHVN, Abuja, Nigeria. Germline, somatic and viral DNAs are extracted using MagNa Pure LC 2.0® and Qiagen Qiacube HT robotic nucleic acid isolation and purification platforms. Germline DNA is quantitated using NanoDrop 8000 UV-Vis spectrophotometer at wavelengths of 260 and 280 nm, after which working dilutions to the 5–10 ng of DNA required per reaction are created.

Cervical exfoliated samples are analysed for any HPV and hrHPV using SPF_{10} PCR-DEIA-$LiPA_{25}$, version 1, according to manufacturer's instructions. Samples of cervical cytokines are collected and stored immediately in ice coolers and transported to the laboratory for storage. Cervical cytokines are measured using polystyrene non-magnetic bead-based multiplex assay according to manufacturer's instructions (Bio-Rad® Bio-Plex 200 System®, Hercules, CA). The vaginal microbial species composition and abundance will be determined as described by Forney *et al.*[30] The V1-V3 hypervariable regions of the 16S rRNA genes will be amplified using an optimized primer set 27F and 533R as recommended by the Human Microbiome Project (HMP) [http://www.hmpdacc.org]. Colposcopy and biopsy will be done for all individuals with persistent hrHPV infection and clinical features of a cervical lesion suspected to be CIN2+ and for matching controls. Biopsy samples are handled according to the TCGA [http://cancergenome.nih.gov)] standard operating procedure. Spot urine samples are collected and tested for glucose, ketones, specific gravity, blood, pH, protein, nitrites and leukocytes with Multistix® 10 SG reagent strip; the rest are stored in the laboratory at -80 °C. Women with cervical cancer are biopsied and referred for appropriate treatment. We store fresh frozen samples and paraffin embedded samples of the cervical biopsy and collect minimal data from these women; they are not enrolled in the prospective cohort.

Quality assurance and control

Data

Tablet computer-assisted survey instruments (TaCASI) have proved versatile in survey research that incorporates sensitive questions like those on sexual behaviour.[55–57] We use real-time data entry into secure RedCap databases with in-built logic and error checks, which enables data managers to review data and follow-up on missing values and outliers with site research associates promptly.[11,12,55–59]

Laboratory

Two independent pathologists who are blinded to the HPV status of the participants report on the histological diagnoses. Quality assurance (QA) and quality control (QC) of HPV genotyping is done in collaboration with DDL diagnostic laboratory. Human genomics QA/QC is done in collaboration with the Center for Research on Genomics and Global Health, at the National Human Genome Research Institute. We store digital colposcopy images on a private cloud server for secondary review.

What has been found?

The focus of this project so far has been on establishing the study population and obtaining baseline data on known and potential risk factors of hrHPV infection and CIN2+, which will be used for epidemiological and genomic studies. Some early results are presented here.

From commencement of enrolment in February 2014 to July 2016, 11 500 women had been enrolled in the ACCME cohort. The women in this cohort have homogeneous contraceptive, sexual and reproductive characteristics and health status compared with similarly aged HIV-negative women, in the general population.[40–42] Many of the women enrolled were in their third or fourth decade of life, the mean age [standard deviation (SD)] of the participants was 39 (10) years. Most of the participants were married (77%; 8832/11 500), monogamous and live with their spouses (86%; 7556/8832). Many participants have had some university education (45%; 5152/11 500) and have professional jobs (36%; 4175/11 500). Selected socio-demographic characteristics of the study participants at baseline are shown in Table 1. To date we have tested the baseline samples of all the study participants for HPV using DEIA, and observed that 42% (4773/11 500) tested positive (Table 2). Similar tests for HPV have been done in 5349 participants at the 12 months follow-up visit, and we observed that 21% (1107/5349) of these women had persistent HPV infections. About 16% of the study participants have had oral sex and < 1% have had anal sex

Table 1. Selected baseline socio-demographic characteristics of women in the ACCME Cohort, *n* (%)

Characteristics	Total	Rural	Semi-rural	Urban
	n = 11500	*n* = 1380	*n* = 5336	*n* = 4784
Age, years[a]	38.8 (9.6)	38.4 (9.9)	37.8 (9.7)	40.1 (9.2)
Age categories, years				
18–29	2093 (18.2)	304 (22.0)	1180 (22.1)	609 (12.7)
30–39	4105 (35.7)	462 (33.5)	1926 (36.1)	1717 (36.0)
40–49	3530 (30.7)	398 (28.8)	1494 (28.0)	1638 (34.2)
50–59	1576 (13.7)	186 (13.5)	656 (12.3)	734 (15.3)
≥ 60	196 (1.7)	30 (2.2)	80 (1.5)	86 (1.8)
Tribe				
Hausa	862 (7.5)	79 (5.7)	598 (11.2)	185 (3.8)
Ibo	2531 (22.0)	195 (14.1)	875 (16.4)	1461 (20.5)
Yoruba	1322 (11.5)	59 (4.3)	464 (8.7)	799 (16.7)
Other tribes	6785 (59.0)	1047 (75.9)	3399 (63.7)	2339 (50.0)
Religion				
Atheist	23 (0.2)	2 (0.1)	11 (0.2)	10 (0.2)
Christian	9545 (83.0)	1208 (87.5)	4173 (78.2)	4164 (87.0)
Eckankar	2 (0.02)	0 (0.0)	0 (0.0)	2 (0.04)
Judaism	2 (0.02)	0 (0.0)	1 (0.01)	1 (0.02)
Muslim	1920 (16.7)	168 (12.2)	1147 (21.5)	605 (12.7)
Traditional	8 (0.07)	2 (0.1)	4 (0.1)	2 (0.04)
Marital status				
Cohabiting	23 (0.2)	8 (0.6)	11 (0.2)	4 (0.1)
Divorced/separated	310 (2.7)	33 (2.4)	112 (2.1)	165 (3.4)
Married	8832 (76.8)	1070 (77.5)	4204 (78.8)	3558 (74.4)
Single	1668 (14.5)	148 (10.7)	710 (13.3)	810 (17.0)
Widowed	667 (5.8)	121 (8.8)	299 (5.6)	247 (5.1)
Marital arrangement				
Monogamous (live separately)	386 (4.4)	56 (5.2)	131 (3.1)	199 (5.5)
Monogamous (live together)	7556 (85.6)	913 (84.4)	3529 (85.3)	3114 (86.6)
Polygamous (all live together)	628 (7.1)	84 (7.8)	380 (8.9)	164 (4.6)
Polygamous (live separately)	262 (2.9)	28 (2.6)	114 (2.7)	120 (3.3)
Education				
No formal schooling	1127 (9.8)	251 (18.2)	779 (14.6)	97 (2.0)
Primary	1069 (9.3)	277 (20.1)	598 (11.2)	194 (4.0)
Secondary	2507 (21.8)	486 (35.2)	1409 (26.4)	612 (12.8)
University	5152 (44.8)	309 (22.4)	2065 (38.7)	2778 (58.1)
Postgraduate	1645 (14.3)	57 (4.1)	485 (9.1)	1103 (23.1)
Occupation				
Professional	4175 (36.3)	208 (15.1)	1484 (27.8)	2483 (51.9)
Self-employed	3634 (31.6)	567 (41.1)	1920 (36.0)	1147 (24.0)
Manual	678 (5.9)	195 (14.1)	368 (6.9)	115 (2.4)
Skilled manual	897 (7.8)	149 (10.8)	507 (9.5)	241 (5.0)
Student	747 (6.5)	70 (5.1)	438 (8.2)	239 (5.0)
Unemployed	1369 (11.9)	191 (13.8)	619 (11.6)	559 (11.7)
Socioeconomic status				
Low	4600 (40.0)	927 (67.2)	2759 (51.7)	914 (19.1)
Middle	4715 (41.0)	373 (27.0)	1969 (36.9)	2373 (49.6)
High	2185 (19.0)	80 (5.8)	608 (11.4)	1497 (31.3)

[a]Mean (standard deviation).

(Table 3). Most participants thought anal sex was unacceptable for health (57%), religious (53%) and/or cultural (26%) reasons (multiple responses allowed). Some of the participants reported a history of physician-diagnosed hypertension (15%), diabetes (2%), hypercholesterolaemia (4%) or heart disease (0.3%) (Table 4). We found the mean (SD) vaginal pH was 5.2 (0.5); it was similar among HPV-positive and HPV-negative women. Selected

Table 2. Prevalence (%) of HPV infection among women in the ACCME cohort

HPV status	Any HPV[a]	Persistently DEIA HPV-positive	
		Low-risk HPV[b]	High-risk HPV[+]
HPV-positive at baseline	4773 (41.5)	1718 (36.0)	3050 (63.9)
HPV-positive at follow-up visit[c]	2305 (43.1)	521 (22.6)	1784 (77.4)
Persistent HPV-positive	1107 (20.7)	139 (12.6)	598 (54.0)

[a]Based on DEIA.
[b]Results based on LiPA.
[c]Follow-up visit at 12 months after baseline, current total $n = 5349$.

Table 3. Some baseline sexual and reproductive history of women in the ACCME cohort

Characteristics	Total	HPV-negative	HPV-positive
	$n = 11500$	$n = 6727$	$n = 4773$
		Mean (standard deviation)	
Age at menarche	14 (2)	14 (2)	14 (2)
Age at menopause	44 (9)	44 (9)	43 (9)
Age at first vaginal sexual intercourse	20 (4)	21 (4)	20 (4)
Age at first oral sexual intercourse	26 (6)	27 (6)	26 (6)
Age at first anal sexual intercourse	27 (7)	27 (7)	26 (7)
Number of lifetime sexual partners			
Vaginal	2.6 (2.6)	2.7 (2.6)	2.8 (2.7)
Oral	1.8 (1.7)	1.6 (1.5)	1.8 (1.8)
Anal	1.3 (1.2)	1.0 (0.6)	1.3 (1.2)
		n (%)	
Types of sexual experience[a]			
Vaginal	11500 (100.0)	6727 (100.0)	4773 (100.0)
Oral	1832 (15.9)	1016 (15.1)	816 (17.1)
Anal	69 (0.6)	42 (0.6)	27 (0.6)
First type of sexual experience			
Vaginal	9574 (98.3)	5605 (98.4)	3969 (98.1)
Oral	154 (1.6)	8 (1.5)	3 (1.8)
Anal	11 (0.1)	82 (0.1)	72 (0.1)
Oral sex type[a]			
Fellatio	964 (58.2)	545 (59.3)	419 (56.8)
Cunnilingus	689 (41.6)	371 (40.4)	318 (43.1)
Anallingus	4 (0.2)	3 (0.3)	1 (0.1)
Anal sex type[a]			
Receptive	195 (94.4)	109 (55.9)	86 (44.1)
Insertive (using objects e.g. sex toys)	1 (0.5)	0 (0.0)	1 (100.0)
Both	9 (5.1)	6 (66.7)	3 (33.3)
Sexual type preferred			
None	75 (0.8)	52 (0.9)	23 (0.6)
Vaginal	9363 (97.3)	5484 (97.2)	3879 (96.9)
Oral	14 (2.0)	9 (1.7)	5 (2.4)
Anal	196 (0.2)	99 (0.2)	97 (0.1)
Usual frequency of sexual intercourse			
Vaginal			
$<$ 1/month	3186 (32.5)	1826 (32.0)	1342 (33.2)
1–3/month	1825 (18.7)	1010 (17.7)	815 (20.2)
1/week	2339 (24.0)	1410 (24.7)	929 (23.0)
2–4/week	2075 (21.3)	1254 (22.0)	821 (20.3)
$\geq$ 5/week	335 (3.5)	202 (3.6)	133 (3.3)

(Continued)

Table 3. Continued

Characteristics	Total	HPV-negative	HPV-positive
	$n = 11500$	$n = 6727$	$n = 4773$
Oral			
< 1/month	9208 (95.1)	5392 (95.0)	3816 (95.1)
1–3/month	233 (2.4)	125 (2.2)	108 (2.7)
1/week	101 (1.0)	65 (1.2)	36 (0.9)
2–4/week	105 (1.1)	65 (1.1)	40 (1.0)
≥ 5/week	41 (0.4)	27 (0.5)	14 (0.3)
Anal			
< 1/month	9635 (99.6)	5643 (99.6)	3992 (99.6)
1–3/month	25 (0.2)	12 (0.2)	13 (0.3)
1/week	6 (0.05)	3 (0.05)	3 (0.06)
2–4/week	8 (0.07)	7 (0.1)	1 (0.02)
≥ 5/week	4 (0.03)	3 (0.05)	1 (0.02)
Usual gender of sexual partners			
Only males, never females	9546 (99.4)	5578 (99.3)	3968 (99.2)
Mostly males, rarely females	54 (0.5)	28 (0.6)	24 (0.7)
Only females, never males	10 (0.1)	5 (0.1)	5 (0.1)
Mostly females, rarely males	7 (1.0)	6 (0.1)	1 (0.1)
Menopausal status			
Premenopausal	8049 (82.7)	4704 (82.7)	3345 (82.8)
Postmenopausal	1678 (17.3)	985 (17.3)	693 (17.2)
Ever been pregnant			
Yes	8698 (89.1)	5163 (90.4)	3535 (87.3)
No	1061 (10.9)	545 (9.6)	516 (12.7)

[a]Multiple responses allowed. HPV results are based on DEIA tests at baseline only. Given the sensitive nature of the sexual and reproducibility history questions, some women did not respond. Therefore the total does not sum up to 11 500.

Table 4. Baseline history of selected physician-diagnosed medical conditions among women in the ACCME cohort, *n* (%)

Disease	Mean age at diagnosis (years)	Total (%)	Rural (%)	Semi-rural (%)	Urban (%)
		$n = 11500$	$n = 1380$	$n = 5336$	$n = 4784$
Hypertension					
Yes	40 (8)	1702 (14.8)	187 (13.5)	630 (11.8)	885 (18.5)
No	–	9798 (85.2)	1193 (86.5)	4706 (88.2)	3899 (81.5)
Diabetes					
Yes	43 (8)	219 (1.9)	21 (1.5)	69 (1.3)	129 (2.7)
No	–	11281 (98.1)	1359 (98.5)	5267 (98.7)	4655 (97.3)
Hypercholesterolaemia					
Yes	43 (8)	552 (4.1)	108 (7.8)	133 (2.5)	311 (6.5)
No	–	10948 (95.2)	1272 (92.2)	5203 (97.5)	4473 (93.5)
Rheumatic fever					
Yes	39 (10)	58 (0.5)	23 (1.7)	21 (0.4)	14 (0.3)
No	–	11442 (99.5)	1357 (98.3)	5315 (99.6)	4770 (99.7)
Heart disease					
Yes	40 (10)	35 (0.3)	0 (0.0)	11 (0.2)	24 (0.5)
No	–	11465 (99.7)	1380 (99.8)	5325 (99.8)	4760 (99.5)
TIA/stroke					
Yes	42 (9)	35 (0.3)	5 (0.4)	16 (0.3)	14 (0.3)
No	–	11465 (99.7)	1375 (99.6)	5320 (99.7)	4770 (99.7)
Kidney disease					
Yes	45 (9)	46 (0.4)	6 (0.4)	11 (0.2)	29 (0.6)
No		11454 (99.6)	1374 (99.6)	5325 (99.8)	4755 (99.4)
Cancer					
Yes	41 (10)	23 (0.2)	7 (0.5)	6 (1.1)	10 (1.2)
No	–	11477 (99.8)	1373 (99.5)	5330 (99.9)	4774 (99.8)

Table 5. Selected baseline gynaecological characteristics of women in the ACCME Cohort, *n* (%)

Gynaecological characteristics	Total	HPV-negative	HPV-positive
	n = 11500	*n* = 6727	*n* = 4773
Vaginal pH[a]	5.2 (0.5)	5.2 (0.5)	5.2 (0.6)
Ectopy observed			
Yes	1368 (11.9)	809 (12.0)	559 (11.7)
No	10132 (88.1)	5918 (88.0)	4214 (88.3)
Transformation zone			
< 25%	3324 (28.9)	1978 (29.4)	1346 (28.2)
25–50%	4310 (37.5)	2382 (35.4)	1928 (40.4)
51–75%	2901 (25.2)	1823 (27.1)	1078 (22.6)
> 75%	965 (8.4)	544 (8.1)	421 (8.8)
Squamo-columnar junction			
Fully observed	8245 (71.7)	4877 (72.5)	3368 (71.1)
Partially observed	2369 (20.6)	1406 (20.9)	963 (20.1)
Not observed	886 (7.7)	444 (6.6)	422 (8.8)
Cervical friability[b]			
None	10568 (91.9)	6168 (91.7)	4400 (92.2)
Mild	839 (7.3)	511 (7.6)	328 (6.9)
Moderate	93 (0.8)	48 (0.7)	45 (0.9)

HPV status based on DNA enzyme immunoassay (DEIA) test.
[a]Mean (standard deviation).
[b]Cervical friability: mild, discrete spot of blood on swab; moderate, pink discolouration, swab soaked.

gynaecological characteristics of the study participants at baseline are shown in Table 5. Our results on sexual health and behaviour provide important data for studies of associations between these characteristics and HPV-associated cancers including cervical, head and neck, and anal cancers, and identifies attitudes and beliefs which may contribute to the social epidemiological risk for other non-communicable diseases (NCD). The study attrition rate is ~ 20%.

Training and capacity development

The ACCME project includes a training programme in epidemiology, molecular biology, data management and analysis. Several pre- and postdoctoral trainees are currently engaged in the project and are taking the lead in several analyses and publications. Students and faculty members from Nigerian and US universities and research institutes have also used the resources of the project for their own research projects.

Future plans?

We will contribute DNA samples from our study participants to the H3Africa Biorepositories according to the H3Africa guidelines. We are participating in the development of the H3Africa Consortium Genome Analysis Array chip in collaboration with other H3Africa projects and Illumina Inc. The resultant chip will be highly informative for genomics research in African populations. We plan to replicate our genomics findings in other African cohorts. The combination of somatic and germline mutation analyses in our study enhances opportunities for gene discovery, understanding of gene functions, new clinical insights and integrative analysis of cervical cancer. Our research will also characterize the epidemiology of HPV infection in Nigeria before widespread deployment of HPV vaccination. We intend to maintain and expand this valuable cohort to include male partners of the participants and to study other NCDs in future.

What are the main strengths and weaknesses?

The ACCME cohort incorporates a large number of repeated measurements of a wide range of exposures. There are also strong data and laboratory QA/QC procedures in collaboration with local and international researchers incorporated into the project, thereby ensuring high quality of the data. An ethics and regulatory compliance officer independently monitors research activities at clinical sites and generates reports for the Study leadership for action. Close collaboration with the NIH-funded West African Bioethics Training Program [http://bioethicscenter.net)] ensures ongoing training in research ethics, good clinical and laboratory practices, and responsible conduct of research. We implement extensive community engagement efforts that include: community rallies; regular meetings with research participants; circulation of study newsletters that provide updates about study

progress and challenges; and motivational and health education messages through e-mails, radio, TV and newspapers. The study maintains a webpage, a Facebook page and an active Twitter account. Study participants are able to contact the research staff and leadership via phone applications, including Blackberry messenger and WhatsApp.

A major limitation of longitudinal studies is loss to follow-up. This can be particularly challenging in low-resource environments where participants have poor history of follow-up even in clinical care. To improve participant retention in the cohort, we deployed several strategies including extensive use of mobile health-based interventions such as automated phone applications that are used to send health tips and visit reminders to participants before their scheduled appointment, regularly. Thus, we have achieved a participant retention rate of ~80%.

Problems associated with conducting research in resource-limited settings that may affect ACCME include poor infrastructure, inadequate power supply, challenges with conduct of research in low-literacy environments and lack of trained personnel. To address these, we: purchased state of the art laboratory equipment with service agreements for genomic analyses; set up a three-level power backup system with multiple power generators, inverters and batteries for the laboratory; develop appropriate health education materials; train and re-train all research staff; and implement schemes for motivation of staff through regular research meetings and opportunities to attend international meetings, implementation of mentored research projects and generation of appropriate health education materials. All of these challenges have contributed to much higher cost for implementation of this research than anticipated. Nonetheless, we collaborate with renowned international institutions in the USA, UK and The Netherlands for ongoing staff training and support.

Can I get hold of the data? Where can I find out more?

Further information is available at [http://h3africa.org/]. Documentation for the ACCME cohort including the questionnaires, information sent to the participants and detailed information about the research, is available at [http://h3accme.com/. We also welcome specific queries and proposals for collaboration, which should be directed to the scientific director[(sadebamowo@som.umaryland.edu] and the principal investigator [cadebamowo@som.umaryland.edu] of ACCME.

Supplementary Data

Supplementary data are available at *IJE* online.

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