RISK FACTORS FOR HPV INFECTION/PERSISTENCE, PREMALIGNANT CERVICAL LESIONS & CERVICAL CANCER

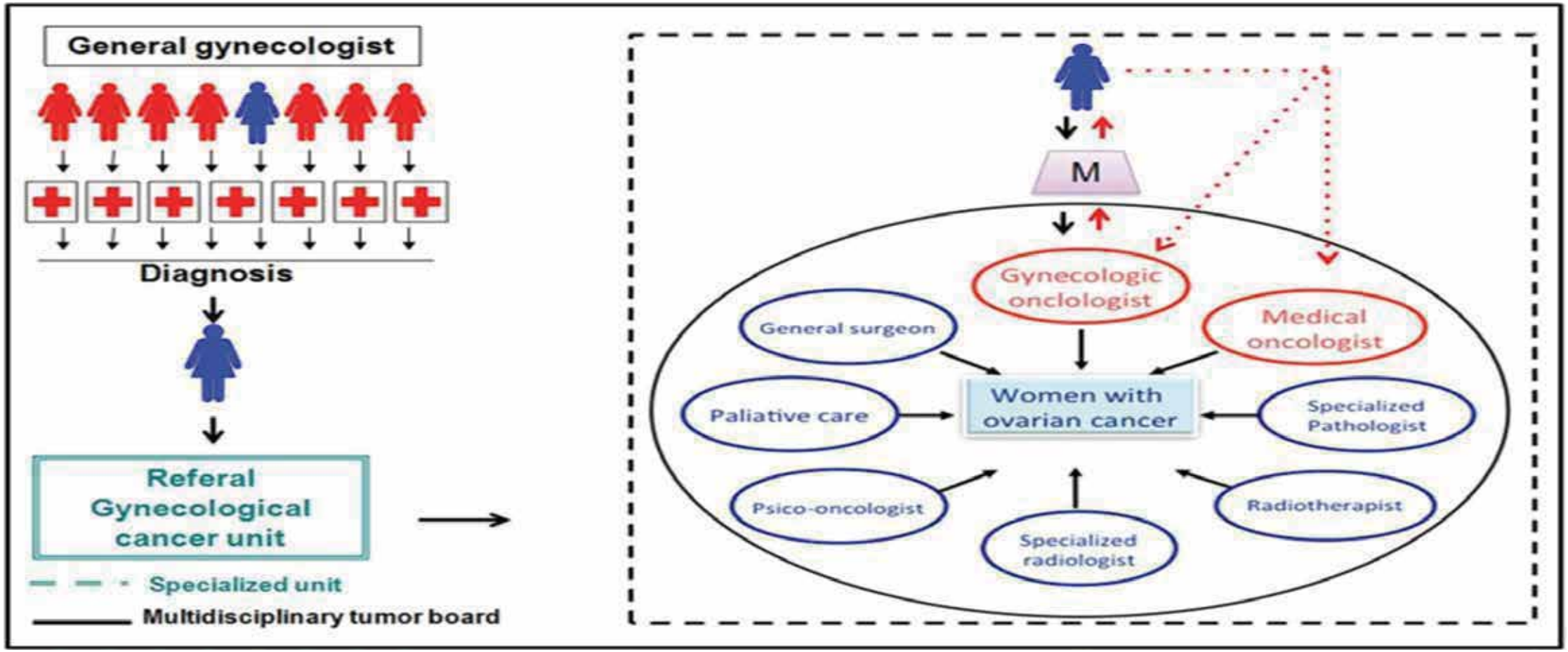
DR OTHINIEL MUSANA

GYNAE-ONCOLOGIST

FAQS 1: WHAT IS A GYNAE-ONCOLOGIST?

1. Gynaecologic oncologists are medical doctors with specialized knowledge to diagnose and treat cancer of the female reproductive system (Cervix, Ovary, Endometrial, Vulval and Vaginal Cancers).
2. Working in this field requires specialized training (surgery on reproductive organs, radiation therapy and chemotherapy).
3. Also perform medical procedures on non-reproductive organs affected by gynecologic cancer treatment such as the gastrointestinal and urinary tracts
4. Surgical Assistance to General Gynaecologists and Obstetricians in major complex benign surgeries and laparoscopic surgeries
5. There is a major difference in surgical and oncological (cancer related treatment) outcomes for patients managed by Gynae-oncologists vs general gynaecologists

WHAT MAKES A GYNAE-ONCOLOGY SERVICE?



FAQ 2: WHY THIS SERIES ON CERVICAL CANCER TO OPEN BHF CPD?

Context

- WHO 2020 Global Strategy towards the Elimination of Cervical Cancer.
- The first elimination strategy for a cancer in WHO's history
- Set measurable targets by 2030 (90-70-90 strategy)

1. 90% of girls should be fully vaccinated with HPV vaccine by 15 years of age
2. 70% of women should be screened using a high-performance test by age 35, and again by age 45
3. 90% of those identified with cervical disease should receive appropriate treatment
    a. 90% of women screening positive treated for pre-cancerous lesions
    b. 90% of invasive cancer cases managed.

FAQ 3: WHY ARE YOU FOCUSING ON CERVICAL CANCER YET THE HOT CAKE IS MATERNAL DEATHS AS A COUNTRY?

	Globocan 2020 Cervical cancer deaths	WHO report 2019 Cervical cancer deaths	Maternal deaths (AHSPR 2022/2023)
Reported Deaths	4,607	4,400	1,276 (IMMR)
5 year prevalence (all ages)	12,864		
Cumulative risk of cervical cancer, ages 0-74 (2020)		6.0%	
Cervical cancer mortality-to-incidence ratio (2020)		0.66	

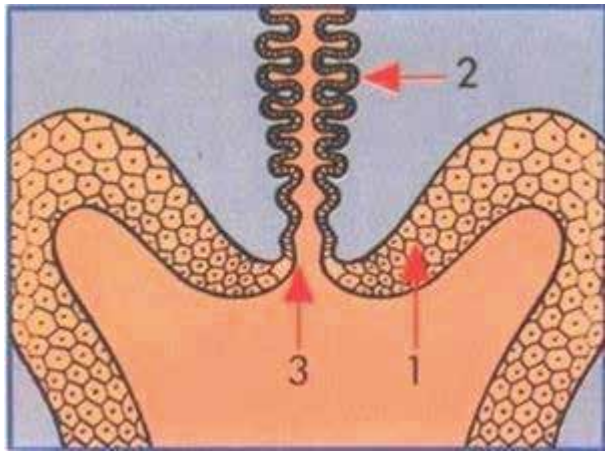
FAQ 4: WHAT IS A RISK FACTOR?

- A Risk Factor for Cervical cancer is any condition, behavior, or other characteristic that is known to increase the chances of an individual (female) developing a Premalignant Cervical disease or ultimately Cervical cancer.
- Some of these risk factors for cervical cancer maybe
  1. Modifiable Risk factors
  2. Non modifiable Risk factors
- Cervical Cancer Risk factors can be;
  1. Individual
  2. within the family, Within the community, or As a result of the institutions that surround the individual

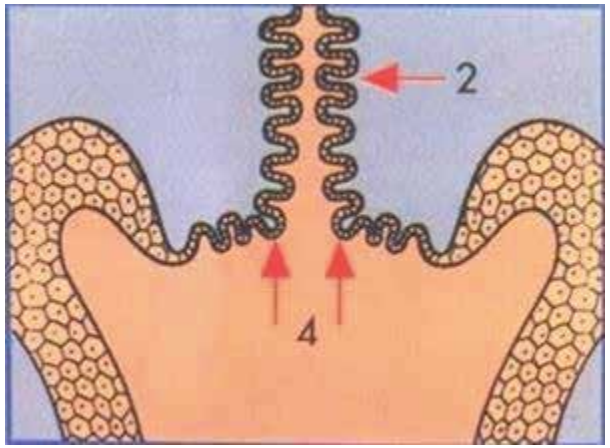
FAQ 5: WHAT IS THE CAUSE OF CERVICAL CANCER?

- Infection with High Risk HPV (HR-HPV) is the known cause of cervical cancer (found in > 99% of all Cervical cancer samples)
- Over 40 strains or subtypes of HR-HPV exist (most common are types 16 & 18 that cause 70% of all cervical cancers, vaccines contain these two subtypes)
- Infection with multiple HR-HPV is possible (evidence from local studies)
- HR-HPV is necessary but not sufficient to cause cervical cancer
  a. A female must have HR-HPV in her cervical cells in order to get cervical cancer
  b. Infection with HR-HPV alone will not lead to cervical cancer; there must be another risk factor that works with the HR-HPV to cause the cervical cancer
- HPV is an epitheliotropic (infects Skin and Mucosal surfaces)

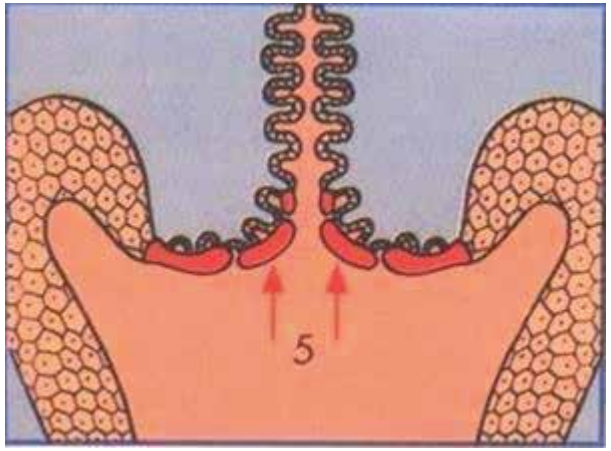
CHANGES IN THE CERVIX IN FEMALES (EFFECTS OF ESTROGEN)



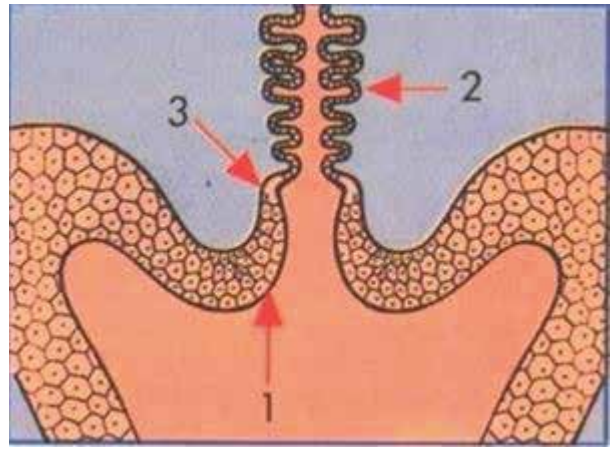
Squamocolumnar junction prior to puberty.



Eversion of the endocervical epithelium at puberty and first pregnancy



Metaplastic change of endocervical epithelium in the transformation zone



Relocation of SCJ in the endocervical canal after the menopause

NON SEXUAL TRANSMISSION OF HR-HPV

KEY MESSAGE: VERTICAL TRANSMISSION (MATERNAL TO CHILD TRANSMISSION) EXISTS AND MAY REQUIRE EMTCT APPROACH IN PREGNANCY AND REINFORCES NEED FOR EARLY VACCINATION

High-Risk Types of Human Papillomavirus (HPV) DNA in Oral and Genital Mucosa of Infants during Their First 3 Years of Life: Experience from the Finnish HPV Family Study

Marjut A. M. Rintala,[1] Seija E. Grénman,[1] Marja E. Järvenkylä,[1,2] Kari J. Syrjänen,[2] and Stina M. Syrjänen[2,3]

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Background. This study is aimed to clarify data on the acquisition, persistence, and clearance of high-risk types of human papillomavirus (HPV) DNA from the mucosa and the determinants of persistent mucosal HPV infection in infants.

Methods. Oral and genital scrapings from 324 infants were collected at birth, 3 days after delivery, and 1, 2, 6, 12, 24, and 36 months after delivery and tested for the presence of HPV DNA by nested polymerase chain reaction and hybridization with 12 high-risk HPV oligoprobes. HPV status and demographic data for parents were analyzed.

Results. During the follow-up period (median duration, 26.2 months), HPV DNA was found to be present in 12%–21% of oral scrape samples and in 4%–15% of genital scrape samples obtained from the infants. Oral HPV infection was acquired by 42% of children, cleared by 11%, and persisted in 10% of the infants, whereas 37% were never infected. The corresponding figures for genital HPV infection were 36%, 14%, 1.5%, and 47%. Kaplan-Meier analysis revealed that both the cumulative incidence of infection and clearance of HPV were parallel in oral and genital sites. Persistent oral HPV infection in the child was significantly associated with persistent oral HPV infection in the mother at month 36 of follow-up, hand warts in the mother, young age at onset of sexual activity for the mother, and the mother's use of oral contraception, as well as with the father's oral HPV status at 24 months. Persistent genital HPV infection in the infant was predicted by if the mother had started smoking at 18–21 years of age and by a history of genital warts.

Conclusions. Persistent carriage of high-risk HPV types was detected in oral and genital mucosa specimens obtained from 10% and 1.5% of the infants during their first 26 months of life. The rates of acquisition and clearance of HPV were similar in oral and genital mucosa.

Rate of vertical transmission of human papillomavirus from mothers to infants: Relationship between infection rate and mode of delivery

Hyun Park[1†], Si Won Lee[2†], In Ho Lee[2], Hyun Mee Ryu[2], A Reum Cho[3], Young Soon Kang[4], Sung Ran Hong[5], Sung Soon Kim[6], Seok Ju Seong[7], Son Moon Shin[8] and Tae Jin Kim[2*]

Abstract

Background: In contrast to consistent epidemiologic evidence of the role of sexual transmission of human papillomavirus (HPV) in adults, various routes may be related to HPV infection in infants. We have assessed the extent of HPV infection during the perinatal period, and the relationship between mode of delivery and vertical transmission.

Results: A total of 291 pregnant women over 36 weeks of gestation were enrolled with informed consent. Exfoliative cells were collected from maternal cervix and neonatal buccal mucosa. HPV infection and genotypes were determined with an HPV DNA chip, which can recognise 24 types. The HPV-positive neonates were re-evaluated 6 months after birth to identify the presence of persistent infection. HPV DNA was detected in 18.9 % (55/291) of pregnant women and 3.4 % (10/291) of neonates. Maternal infection was associated with abnormal cytology ($p = 0.007$) and primiparity ($p = 0.015$). The infected neonates were all born to HPV-positive mothers. The rate of vertical transmission was estimated at 18.2 % (10/55) which was positively correlated with maternal multiple HPV infection ($p = 0.003$) and vaginal delivery ($p = 0.050$), but not with labour duration and premature rupture of membranes. The rate of concordance of genotype was 100 % in mother-neonate pairs with vertical transmission. The neonatal HPV DNAs found at birth were all cleared at 6 months after delivery.

Conclusions: Vertical transmission of HPV DNA from HPV infected mother to the neonate increased when the infant was delivered through an infected cervix. However, the absence of persistent infection in infants at 6 months after delivery may suggest temporary inoculation rather than true vertical infection.

NON SEXUAL HR-HPV TRANSMISSION

NOT ALL HR-HPV IS SEXUALLY TRANSMITTED AND AS SUCH COMMON IN VIRGINS I.E. NON COITAL TRANSMISSION

Detection of human papillomavirus DNA on the fingers of patients with genital warts

C Sonnex, S Strauss, J J Gray

Objective: To determine whether patients with genital warts carry human papillomavirus (HPV) DNA on their fingers.
Methods: 14 men and eight women with genital warts had cytobrush samples taken from genital lesions, finger tips, and tips of finger nails. Samples were examined for the presence of HPV DNA by the polymerase chain reaction.
Results: HPV DNA was detected in all female genital samples and in 13/14 male genital samples. HPV DNA was detected in the finger brush samples of three women and nine men. The same HPV type was identified in genital and hand samples in one woman and five men.
Conclusion: This study has identified hand carriage of genital HPV types in patients with genital warts. Although sexual intercourse is considered the usual mode of transmitting genital HPV infection, our findings raise the possibility of transmission by finger-genital contact.
(*Sex Transm Inf* 1999;75:317–319)

Detection of Genital HPV Types in Fingertip Samples from Newly Sexually Active Female University Students

Rachel L. Winer[1], James P. Hughes[2], Qinghua Feng[3], Long Fu Xi[1,3], Stephen Cherne[3], Sandra O'Reilly[1], Nancy B. Kiviat[3], and Laura A. Koutsky[1]

Abstract

Background: Little is known about detection of genital human papilloma virus (HPV) types in women's fingertips. The study objectives were to determine the presence of genital HPV types in fingertip samples and the agreement between fingertip and genital samples for detecting HPV.

Methods: At triannual visits, genital and fingertip samples were collected from female university students and tested for 37 HPV genotypes by PCR-based assay. Type-specific concordance between paired fingertip and genital samples was evaluated using κ statistics for percent positive agreement ($\kappa+$). Paired samples with type-specific concordant fingertip and genital results were selected for variant characterization.

Results: A total of 357 fingertip samples were collected from 128 women. HPV prevalence in fingertip samples was 14.3%. Although percent positive agreement between fingertips and genitals for detecting type-specific HPV was low (17.8%; $\kappa+ = 0.17$; 95% confidence interval, 0.10-0.25), 60.4% of type-specific HPV detected in the fingertips was detected in a concurrent genital sample. All but one of 28 paired concordant samples were positive for the same type-specific variant in the fingertip and genital sample. Redetection of HPV types at the subsequent visit was more common in genital samples (73.3%) than in fingertip samples (14.5%; $P < 0.001$).

Conclusions: Detection of genital HPV types in the fingertips was not uncommon. Although impossible to distinguish between deposition of DNA from the genitals to the fingertips and true fingertip infection, the rarity of repeat detection in the fingertips suggests that deposition is more common.

Impact: Finger-genital transmission is plausible but unlikely to be a significant source of genital HPV infection. *Cancer Epidemiol Biomarkers Prev; 19(7); 1682–5. ©2010 AACR.*

High Frequency of Human Papillomavirus Detection in the Vagina Before First Vaginal Intercourse Among Females Enrolled in a Longitudinal Cohort Study

Marcia L. Shew,[1] Bree Weaver,[1,2] Wanzhu Tu,[3] Yan Tong,[3] J. Dennis Fortenberry,[1] and Darron R. Brown[2,4]

Background. Genital human papillomavirus (HPV) infection is believed to be primarily sexually transmitted. Few studies have documented the detection of HPV in the vagina before first vaginal intercourse.

Methods. We used a longitudinally followed cohort of adolescent females without prior vaginal intercourse to examine the frequency of detection of vaginal HPV and the association between first reported HPV detection and noncoital sexual behaviors.

Results. HPV was detected in 45.5% of subjects (10 of 22) before first vaginal sex. Seven of these 10 subjects reported noncoital behaviors that, in part, might have explained genital transmission.

Conclusions. HPV can be detected in the vagina before first sexual intercourse, highlighting the need for early vaccination.

Table 1. Demographic Characteristics of and Human Papillomavirus (HPV) Types Found in Adolescent Females Before First Vaginal Sex

Variable	Swab Samples Positive for HPV, No. ≥1 (n = 10)	≥2 (n = 7)	Days Between First and Second Positive Swab Sample, Median (IQR)
Demographic characteristic			
Age, y, mean ± SD	14.9 ± 1.2	14.9 ± 1.1	…
African American race	10 (100)	7 (100)	…
Age at first vaginal sex, y, mean ± SD	17.2 ± 1.3	16.7 ± 0.8	…
Age at first HPV detection, y, mean ± SD	16.6 ± 1.6	16.2 ± 0.8	…
HPV type detected			
Any	29	19	273 (1200)
High risk			
Overall[a]	16	9	273 (360)
IARC-defined carcinogen[b]	10	5	231 (444)
Low risk[c]	13	5	347 (1379)
6, 11, 16, and/or 18	3	2	1180 (1323)
16 and 18	1	1	1841

HIV AND CERVICAL CANCER

KEY MESSAGE: HIV ASSOCIATED IMMUNOSUPPRESSION HIV REACTIVATES HR-HPV IN CAUSATION OF CERVICAL CANCER, HIV IS A **GROUP I** CARCINOGEN WRT CERVICAL CANCER

Human Papillomavirus Infections in Nonsexually Active Perinatally HIV Infected Children

Anna-Barbara Moscicki, MD,[1] Ana Puga, MD,[2] Sepideh Farhat, MSc,[1] and Yifei Ma, MSc[1]

Abstract

Although human papillomavirus (HPV) infections are common in HIV-infected adults, little is known about children. Our objective was to examine the prevalence of and risks for HPV of the oral mucosal and external genital areas in nonsexually active (NSA) perinatally (P) HIV+ children and compare with HIV-exposed but uninfected (HEU) children. A convenience sample attending a pediatric clinic were enrolled. Samples for HPV were obtained from the oral and anogenital areas and tested for one of 37 HPV types. The mean age of the 48 PHIV+ children was 14.3 ± 3.9 years vs. 6.2 ± 4.8 for the 52 HEU ($p < 0.001$). Of the 23 PHIV+ girls, 30.4% had anogenital and 17% had oral HPV, and of the 27 HEU girls, 2 (7.4%) anogenital and 0 had oral HPV. Of the boys, 4/23 (17.4%) and 1/25 (4%) PHIV+ had anogenital and oral HPV, respectively, and 3/24 (12.5%) and 1/25 (4%) HEU had anogenital and oral HPV, respectively. Rates of HPV did not differ by age among the PHIV+, whereas older HEU were more likely to have HPV than younger HEU ($p = 0.07$). This large age gap precluded statistical comparison by HIV status. The presence of HPV in NSA PHIV+ children may have implications regarding HPV vaccination efficacy.

Persistence of Human Papillomavirus Infection in HIV-Infected and -Uninfected Adolescent Girls: Risk Factors and Differences, by Phylogenetic Type

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Background. High rates of persistence of human papillomavirus (HPV) infection have been reported for adult women with human immunodeficiency virus (HIV) infection. Although most women are first infected with HPV during adolescence, persistence of specific HPV types has not been carefully examined among HIV-infected adolescents. The objective of this study was to examine the rates of and risk factors for persistence of HPV types among HIV-infected and -uninfected adolescent girls.

Methods. This is a prospective cohort study of female adolescents, aged 13–18 years, participating in the Reaching for Excellence in Adolescent Care and Health project, a national study of HIV-infected and -uninfected adolescents. The main outcome measured was type-specific loss of initial HPV DNA detected. Loss of HPV DNA was defined for the following categories of HPV DNA types: low risk, which included types 6, 11, 42, 44, 54, 40, 13, 32, 62, 72, 2, 57, and 55; and high risk, which included types 16-like (16, 31, 33, 35, 52, 58, and 67), 18-like (18, 39, 45, 59, 68, 70, 26, 69, and 51), and 56-like (56, 53, and 66).

Results. Prevalent or incident HPV infection was detected in 334 girls. When type-specific loss of HPV was examined, HIV-uninfected girls had a shorter mean time to loss of initial infection than did HIV-infected girls (403 days vs. 689 days, respectively; $P < .0001$). By means of multivariate analysis, CD4 immunosuppression and the presence of multiple HPV-type subgroups were found to be associated with persistence of HPV.

Conclusion. Since persistence of high-risk HPV types has been strongly linked with the development of invasive cancer, the prolonged persistence of HPV observed among HIV-infected adolescents who are relatively healthy underscores the importance of prevention of HPV infection in this group.

Effect of Human Immunodeficiency Virus Infection on Human Papillomavirus Clearance Among Women in Senegal, West Africa

Zhuochen Li,[1] Rachel L. Winer,[1] Selly Ba,[2] Marie Pierre Sy,[2] John Lin,[1,3] Qinghua Feng,[3] Geoffrey S. Gottlieb,[4,5] Papa Salif Sow,[2] Nancy B. Kiviat,[3] and Stephen E. Hawes[1,5,6]

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Background. Persistent infection with high-risk human papillomavirus (HPV) is associated with development of invasive cervical cancer.

Methods. Longitudinal data was collected from 174 Senegalese women. We employed marginal Cox proportional hazards models to examine the effect of human immunodeficiency virus (HIV) status (HIV positive vs HIV negative) and HIV type (HIV-1 vs HIV-2 vs dual HIV-1/HIV-2) on clearance of type-specific HPV infection. Analyses were stratified by incident versus prevalent HPV infection.

Results. Incident HPV infections in HIV-positive women were less likely to clear than those in HIV-negative women (adjusted hazard ratio [HR] = 0.60; 95% confidence interval [CI], .38–.94). Among HIV-positive women, HIV-2–infected women and HIV-1/2 dually infected women were more likely to clear HPV incident infections than HIV-1–infected women (HR = 1.66; 95% CI, .95–2.92 and HR = 2.17; 95% CI, 1.12–4.22, respectively). Incident HPV infections in HIV-positive women with CD4 cell count ≤500 cells/μL were less likely to clear than those in HIV-positive women with CD4 cell count >500 cells/μL (HR = 0.65; 95% CI, .42–1.01). No significant associations were observed for prevalent HPV infections.

Conclusions. HIV infection reduced the likelihood of clearance of incident HPV infection. Furthermore, among HIV-positive women, low CD4 cell count and dual HIV infection were each associated with reduced likelihood of clearance.

Keywords. human immunodeficiency virus; HIV; HIV-2; HPV; clearance; human papillomavirus; women.

SEXUAL ACTIVITY/BEHAVIOR

KEY MESSAGE: SEXUAL BEHAVIOUR INFLUENCES RISK OF HR-HPV INFECTION, PERSISTENCE AND CLEARANCE

Prevalence of vaginal HPV infection among adolescent and early adult girls in Jos, North-Central Nigeria

Nanma T. Cosmas[1], Lohya Nimzing[1,2], Daniel Egah[1,3], Ayo Famooto[4], Sally N. Adebamowo[5] and Clement A. Adebamowo[4,5*]

Abstract

Purpose: Knowledge of the prevalence of HPV infection among adolescent and early adult girls is essential to determining the best age for the introduction of HPV vaccine, monitoring vaccine efficacy, and giving insight into determinants of persistent high-risk HPV infection, a necessary cause of cervical cancer. Yet, there have been limited studies of HPV infection among adolescent and early adult girls in low-and-middle-income countries.

Methods: In this cross-sectional study, we randomly selected 205 girls, aged 9–20 years, from 10 schools in central Nigeria. We obtained informed consent and assent, collected data, and trained participants to self-collect vaginal samples using swab stick. We genotyped HPV using SPF_{10}-DEIA/$LiPA_{25}$ and analyzed data using Stata 14®.

Results: The mean (SD) age of the girls was 14.9 (2.3) years. We found HPV in 13.2% of vaginal swabs. The earliest age at which anyHPV and hrHPV infections were detected was 10 and 12 years respectively. The prevalence of any HPV peaked at 16 and 17 years, hrHPV at 16 years, lrHPV at 17 and 18 years and multiple hrHPV 18 years of age. The prevalence of hrHPV infection was 1.5% among the 9–12 years age group, 2.9% among 13–16 years and 3.4% among 17–20 years old. The commonest hrHPV types detected were 52 (3.9%), 18 (1.5%) and 51 (2.4%). The most common lrHPV types was 6 (2.9%).

Conclusion: The prevalence of HPV infection in these urbanized young girls in Nigeria is high and commences after 9 years of age. HPV vaccination in this population should start at 9 years of age or younger to prevent the establishment of persistent HPV infection.

The Role of Sexual Behavior and Human Papillomavirus Persistence in Predicting Repeated Infections with New Human Papillomavirus Types

Anna-Barbara Moscicki[1], Yifei Ma[1], Janet Jonte[1], Susanna Miller-Benningfield[1], Evelyn Hanson[1], Julie Jay[1], Cheryl Godwin de Medina[1], Sepideh Farhat[1], Lisa Clayton[1], and Stephen Shiboski[2]

Abstract

Background: Although human papillomavirus (HPV) infections are common in young women, the rate of and risk for repeated new infections are not well documented. We examined the rate of and risks for new HPV detection in young women.

Methods: We used data from an ongoing study of HPV, initiated in 1990. Sexually active women ages 12 to 22 years were eligible. Interviews on behaviors and HPV testing were done at 4-month intervals; sexually transmitted infection (STI) testing was annual or if symptomatic. Starting with first HPV detection, time to the next (second) visit (event) with detection of new HPV types, and then the second event to time to third event was calculated. Risks were determined using Cox proportional hazard model.

Results: Sixty-nine percent of 1,125 women had a second event, and of those with a second event, 63% had a third event by 3 years, respectively. Women with HPV persistence from initial visit to second event [hazard ratio (HR) = 4.51 (3.78-5.37)], an STI [HR = 1.47 (1.00-2.17)], bacterial vaginosis [HR = 1.60 (1.07-2.39)], and number of new sex partners [HR = 1.10 (1.05-1.15 per partner/mo)] were independent associations for HPV. Risks for third event were similar.

Conclusion: This study documents the repeated nature of HPV infections in young women and their association with sexual risk behaviors.

Impact: This finding underscores the lack of clinical utility of HPV testing in young women. Further studies are needed to examine host factors that lead to HPV acquisition and persistence. *Cancer Epidemiol Biomarkers Prev; 19(8); 2055–65. ©2010 AACR.*

Prospective follow-up of 2,065 young unscreened women to study human papillomavirus incidence and clearance

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Human papillomavirus (HPV) is a necessary factor in the development of cervical intraepithelial neoplasia and cervical cancer. However, HPV is also a very common sexually transmitted virus and many women clear their infection. To study HPV incidence and clearance, 2,065 women, aged 18–29 years, were followed for 12 months and were asked to provide a self-collected cervico-vaginal sample and fill-out a questionnaire every 3 months. For HPV DNA detection, the SPF_{10}-DEIA $LiPA_{25}$ system was used. Incidence rates of any-type high-risk HPV and low-risk HPV were 17.0 per 1,000-person months, and 14.3 per 1,000-person months, respectively. HPV types 16, 52, 51 and 31 had the highest type-specific incidence rates. HPV incidence was increased in singles, and women having a new relationship. A higher number of lifetime sex partners, and a higher frequency of sexual contacts in the past 3 months was associated with an increased HPV incidence. The overall clearance of the newly detected type-specific high-risk HPV infections and low-risk HPV infections was 61.2% and 69.0%, respectively. Having a sexual relationship compared to being single, and a higher sexual age both positively influenced the clearance of any-type high-risk HPV. Among the women infected with HPV 16, the women who had a co-infection had a lower proportion of clearance of HPV 16. In conclusion, in this young Dutch study population, HPV incidence rates are not related to age and comparable to other western countries. Clearance was only independently related to factors associated with sexual behavior, either past or current.

COMBINED ORAL CONTRACEPTIVES

COCS ARE CLASSIFIED AS **A GROUP 1 CARCINOGEN** FOR HUMANS (WHO/IARC MONOGRAPH 2019)

WHAT IS THE EVIDENCE ON ORAL CONTRACEPTIVE PILLS?

- Cogliano V, Grosse Y, and Baan R, et al (2005) Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment Lancet Oncol 6(8) 552–553 https://doi.org/10.1016/S1470-2045(05)70273-4 PMID: 16094770
  a. List COCs a Group 1 carcinogen for Cervical cancer (i.e. Carcinogenic to humans alongside HIV, Tobacco)
  b. Risk increased for women using the pill for more than 5 years; risk reduces with cessation of use
- COCs have other benefits like prevention of Endometrial and Ovarian cancers
- Long-term COC users must be advised to do regular cervical cancer screening

List of classifications by cancer sites with *sufficient* or *limited evidence* in humans, *IARC Monographs* Volumes 1–135[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Uterine cervix	Diethylstilbestrol (exposure in utero) Estrogen–progestogen oral contraceptives (combined) Human immunodeficiency virus type 1 (infection with) Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 Tobacco smoking	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, and 82

(2006), Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. Int. J. Cancer, 119: 1108-1124. https://doi.org/10.1002/ijc.21953

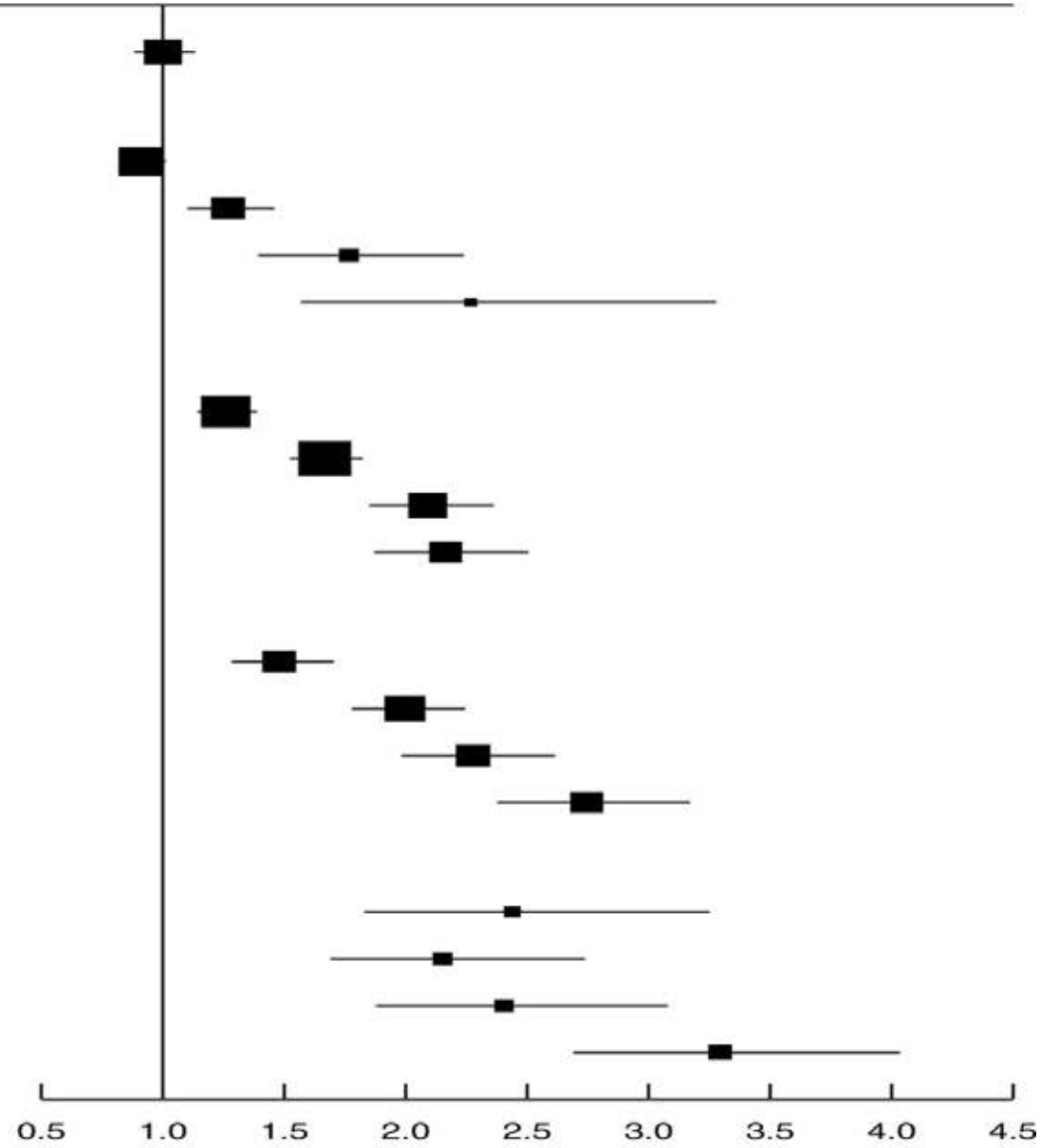
PARITY AND AGE AT FIRST TERM PREGNANCY ON CERVICAL CANCER RISK

KEY MESSAGE: THE HIGHER THE NUMBER OF TERM PREGNANCIES AND THE EARLIER THE AGE OF FIRST TERM PREGNANCY, THE HIGHER THE RISK OF CC

Age at first FTP (years)	Cases/ Controls	RR[1]	RR[2] (95% FCI)	Relative Risk & 95% FCI	Cases/ Controls	RR[2]	RR[3] (95% FCI)	Relative Risk & 95% FCI
Nulliparous	660/2837	1.00	1.00 (0.88 - 1.13)					
30+	390/1733	0.71	0.70 (0.60 - 0.81)		390/1733	1.00	1.00 (0.84 - 1.20)	
29	121/537	0.73	0.85 (0.67 - 1.08)		121/537	1.23	1.17 (0.89 - 1.53)	
28	177/594	1.02	1.18 (0.96 - 1.46)		177/594	1.72	1.71 (1.33 - 2.19)	
27	197/785	0.81	0.94 (0.77 - 1.14)		197/785	1.37	1.27 (1.02 - 1.58)	
26	336/969	1.19	1.42 (1.22 - 1.67)		336/969	2.03	1.77 (1.47 - 2.14)	
25	361/1183	1.10	1.24 (1.06 - 1.45)		361/1183	1.79	1.67 (1.38 - 2.01)	
24	410/1377	1.08	1.26 (1.09 - 1.45)		410/1377	1.83	1.53 (1.30 - 1.81)	
23	597/1559	1.44	1.62 (1.43 - 1.84)		597/1559	2.38	2.05 (1.77 - 2.38)	
22	680/1821	1.44	1.42 (1.26 - 1.60)		680/1821	2.08	1.70 (1.48 - 1.95)	
21	793/2021	1.59	1.49 (1.33 - 1.66)		793/2021	2.19	1.84 (1.61 - 2.11)	
20	1064/2182	1.93	1.73 (1.57 - 1.92)		1064/2182	2.55	2.07 (1.84 - 2.34)	
19	1040/2103	2.08	1.79 (1.61 - 1.99)		1040/2103	2.63	2.16 (1.89 - 2.46)	
18	1002/1856	2.25	1.94 (1.73 - 2.18)		1002/1856	2.86	2.27 (1.96 - 2.63)	
17	824/1370	2.63	2.37 (2.07 - 2.73)		824/1370	3.55	2.67 (2.22 - 3.20)	
16	591/848	3.08	2.57 (2.16 - 3.05)		591/848	3.80	2.91 (2.32 - 3.64)	
<16	516/658	3.25	2.62 (2.16 - 3.17)		516/658	3.81	2.59 (2.01 - 3.33)	
Linear trend test: χ^2_1 = 173.4; p<0.001				0.0 1.0 2.0 3.0 4.0	Linear trend test: χ^2_1 = 58.8; p<0.001			0.0 1.0 2.0 3.0 4.0

[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on number of full term pregnancies.*

Number of FTPs	Cases/ Controls	RR[1]	RR[2] (95% FCI)
Nulliparous	660/2837	1.00	1.00 (0.88 - 1.13)
Age at first FTP: 25+ years			
1-2	903/3705	0.81	0.91 (0.82 - 1.01)
3-4	448/1554	1.13	1.27 (1.10 - 1.46)
5-6	156/397	1.50	1.77 (1.39 - 2.24)
7+	75/145	2.33	2.27 (1.57 - 3.28)
Age at first FTP: 20-24 years			
1-2	1097/3422	1.27	1.26 (1.14 - 1.39)
3-4	1201/3064	1.65	1.67 (1.52 - 1.82)
5-6	681/1402	2.14	2.09 (1.85 - 2.36)
7+	565/1072	2.26	2.16 (1.87 - 2.50)
Age at first FTP: 17-19 years			
1-2	581/1405	1.97	1.48 (1.28 - 1.70)
3-4	877/1666	2.36	2.00 (1.78 - 2.24)
5-6	626/1077	2.67	2.28 (1.98 - 2.61)
7+	782/1181	2.92	2.74 (2.38 - 3.17)
Age at first FTP: <17 years			
1-2	162/273	3.42	2.44 (1.83 - 3.25)
3-4	237/381	3.07	2.15 (1.69 - 2.74)
5-6	237/327	3.37	2.40 (1.88 - 3.08)
7+	471/525	3.76	3.29 (2.69 - 4.03)



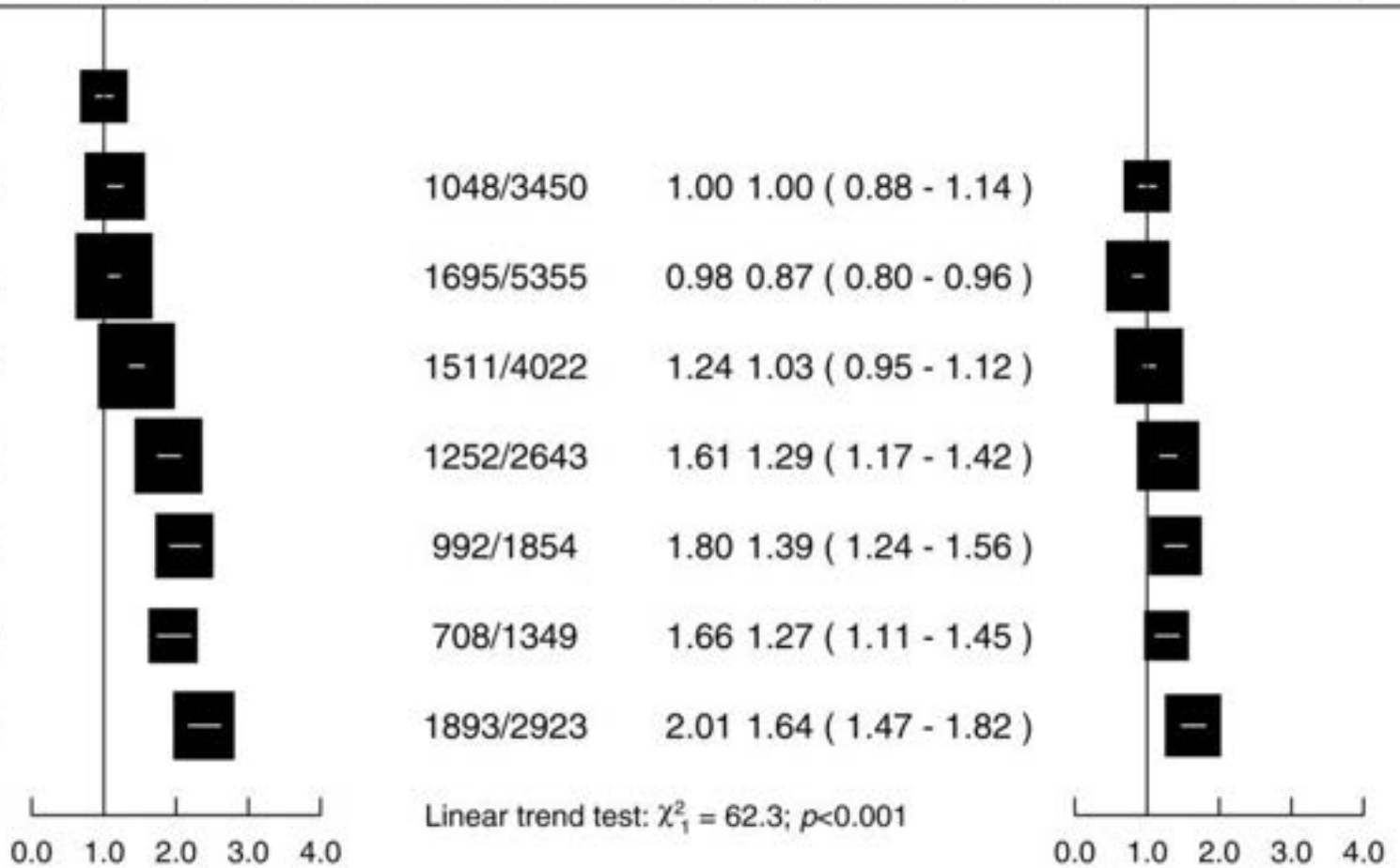
[1] *Conditioned on age and study or study centre.*

[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*

Number of FTPs	Cases/ Controls	RR^1	RR^2 (95% FCI)	Cases/ Controls	RR^2	RR^3 (95% FCI)
Nulliparous	660/2837	1.00	1.00 (0.88 - 1.13)			
1	1051/3474	1.24	1.15 (1.05 - 1.27)	1048/3450	1.00	1.00 (0.88 - 1.14)
2	1701/5392	1.18	1.14 (1.06 - 1.23)	1695/5355	0.98	0.87 (0.80 - 0.96)
3	1513/4060	1.61	1.45 (1.35 - 1.57)	1511/4022	1.24	1.03 (0.95 - 1.12)
4	1260/2682	2.15	1.90 (1.74 - 2.07)	1252/2643	1.61	1.29 (1.17 - 1.42)
5	999/1874	2.55	2.11 (1.91 - 2.34)	992/1854	1.80	1.39 (1.24 - 1.56)
6	712/1376	2.43	1.96 (1.74 - 2.21)	708/1349	1.66	1.27 (1.11 - 1.45)
7+	1916/3021	2.98	2.39 (2.17 - 2.62)	1893/2923	2.01	1.64 (1.47 - 1.82)

Linear trend test: $\chi^2_1 = 178.5$; $p<0.001$

Linear trend test: $\chi^2_1 = 62.3$; $p<0.001$



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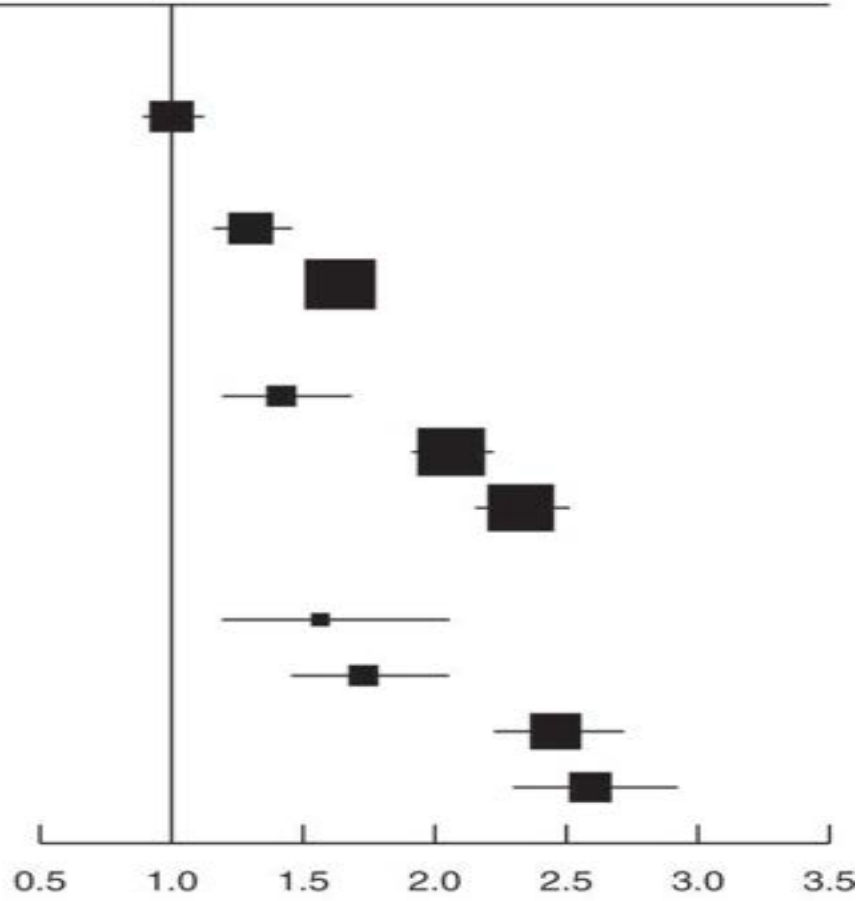
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on age at first full term pregnancy.*

Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies

Age at 1st FTP(years)	Cases/ Controls	RR[1]	RR[2] (95% FCI)
Age at first intercourse: 25+			
25+	577/2625	1.00	1.00 (0.89 - 1.12)
Age at first intercourse: 20-24			
25+	587/2090	1.33	1.30 (1.16 - 1.46)
20-24	1637/4730	1.90	1.64 (1.53 - 1.76)
Age at first intercourse: 17-19			
25+	296/789	2.00	1.42 (1.19 - 1.68)
20-24	1513/3484	2.56	2.06 (1.91 - 2.23)
17-19	1676/3300	3.05	2.33 (2.15 - 2.51)
Age at first intercourse: <17			
25+	122/297	2.10	1.57 (1.19 - 2.06)
20-24	394/746	3.02	1.73 (1.45 - 2.05)
17-19	1190/2029	3.76	2.46 (2.22 - 2.72)
<17	1107/1506	4.51	2.59 (2.30 - 2.92)



[1] *Conditioned on age and study or study centre.*

[2] *As in [1], and conditioned on lifetime number of sexual partners and number of full term pregnancies.*

Intl Journal of Cancer, Volume: 119, Issue: 5, Pages: 1108-1124, First published: 05 June 2006, DOI: (10.1002/ijc.21953)

STIS (CHLAMYDIA) AND CERVICAL CANCER

KEY MESSAGE: CHLAMYDIA IS IMPLICATED IN DNA DAMAGE RESPONSE (**DDR**) DISRUPTION & ALTERATION OF THE CELL MEDIATED IMMUNITY (**CMI**)

2021; 12(16): 4891-4900. doi: 10.7150/jca.58582

Review

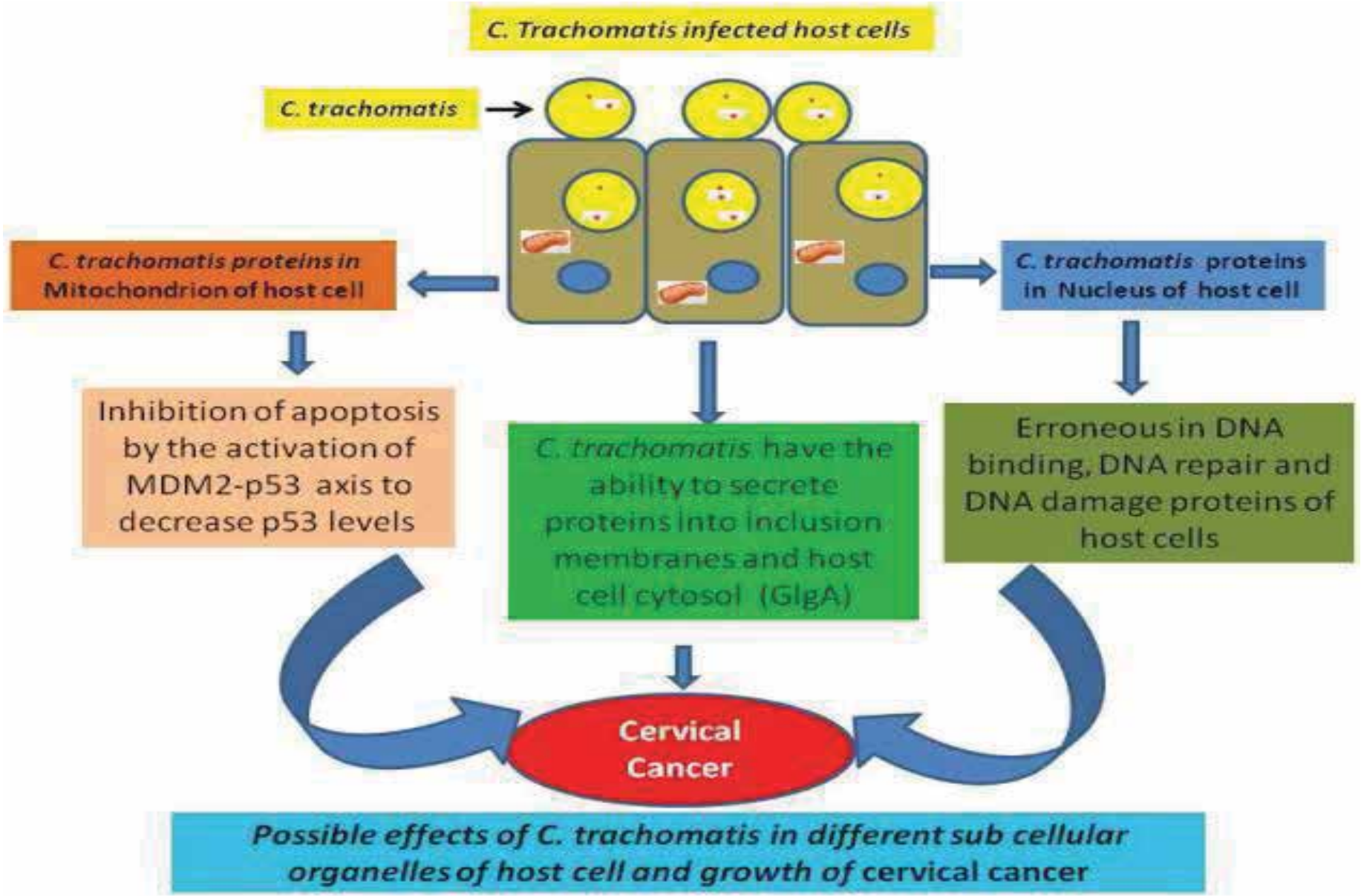
Chlamydia Trachomatis Infection: Their potential implication in the Etiology of Cervical Cancer

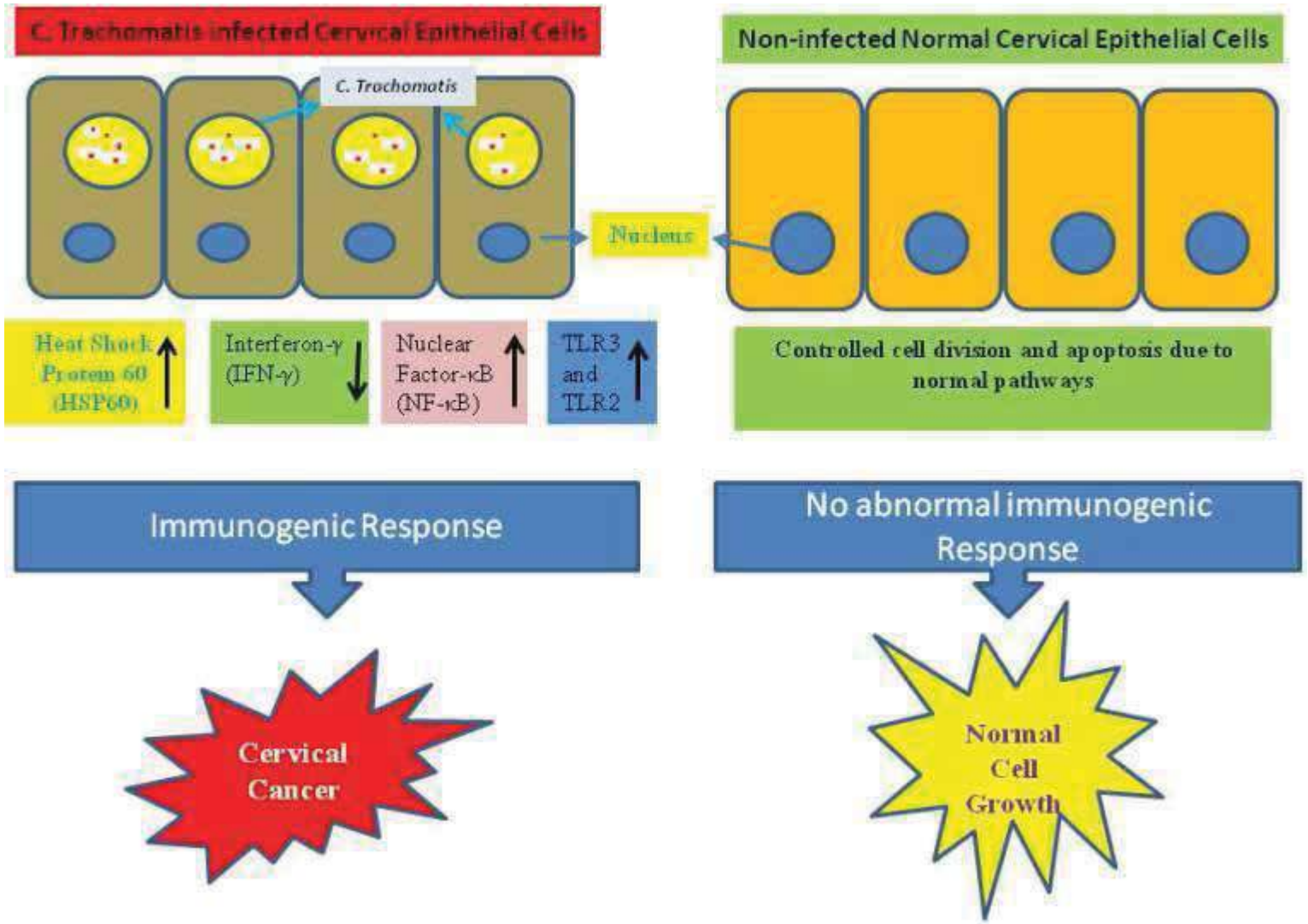
Xingju Yang[1], Anam Siddique[2], Abdul Arif Khan[3], Qian Wang[4], Abdul Malik[5], Arif Tasleem Jan[6], Hassan Ahmed Rudayni[7], Anis Ahmad Chaudhary[7], Shahanavaj Khan[2,5,8]

Abstract

Pathogenic bacterial strains can alter the normal function of cells and induce different levels of inflammatory responses that are connected to the development of different diseases, such as tuberculosis, diarrhea, cancer etc. *Chlamydia trachomatis* (*C. trachomatis*) is an intracellular obligate gram-negative bacterium which has been connected with the cervical cancer etiology. Nevertheless, establishment of causality and the underlying mechanisms of carcinogenesis of cervical cancer associated with *C. trachomatis* remain unclear. Studies reveal the existence of *C. trachomatis* in cervical cancer patients. The DNA repair pathways including mismatch repair, nucleotide excision, and base excision are vital in the abatement of accumulated mutations that can direct to the process of carcinogenesis. *C. trachomatis* recruits DDR proteins away from sites of DNA damage and, in this way, impedes the DDR. Therefore, by disturbing host cell-cycle control, chromatin and DDR repair, *C. trachomatis* makes a situation favorable for malignant transformation. Inflammation originated due to infection directs over production of reactive oxygen species (ROS) and consequent oxidative DNA damage. This review may aid our current understanding of the etiology of cervical cancer in *C. trachomatis*-infected patients.

Key words: bacteria; *C. trachomatis;* infection; *C. trachomatis* proteins; cervical cancer; etiology


C. Trachomatis infected host cells
C. trachomatis
C. trachomatis proteins in Mitochondrion of host cell
C. trachomatis proteins in Nucleus of host cell
Inhibition of apoptosis by the activation of MDM2-p53 axis to decrease p53 levels
C. trachomatis have the ability to secrete proteins into inclusion membranes and host cell cytosol (GlgA)
Erroneous in DNA binding, DNA repair and DNA damage proteins of host cells
Cervical Cancer
Possible effects of C. trachomatis in different sub cellular organelles of host cell and growth of cervical cancer



C. trachomatis infection reduces cell-mediated immunity, and the generation of free radicals. These alterations cause damages to DNA and impair the function of DNA repair which may increase the genetic instability

TOBACCO SMOKING

TOBACCO SMOKING

Review Article

Smoking and Cervical Cancer

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Cervical cancer (CC) is the third most common cancer in women worldwide; however, CC is a preventable disease, and much effort should be done to prevent it. Persistence of high-risk HPV infection is the strongest epidemiologic risk factor for CC, however it is not sufficient for development of the disease it cofactors should be present. In 2004; IARC listed cervical cancer among those causally related to smoking. Smoking interferes with incidence and prevalence of HPV infection and is associated with cervical intraepithelial neoplasia and invasive CC. Multiple factors seem to intervene on cervical carcinogenesis related with tobacco, especially by direct local carcinogenic effect and local immunosuppression. Smoking addition is also closely related with other confounding factors, like unfavorable psychosocial events, systemic immunity, contraception, and nutrition, which got difficult epidemiologic evaluation of smoking role on cervical carcinogenesis. Smoking habits should be taken in account in clinical practice and in research concerning CC.

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High-resolution disease maps for cancer control in low-resource settings: A spatial analysis of cervical cancer incidence in Kampala, Uganda

INSTITUTIONAL FACTORS

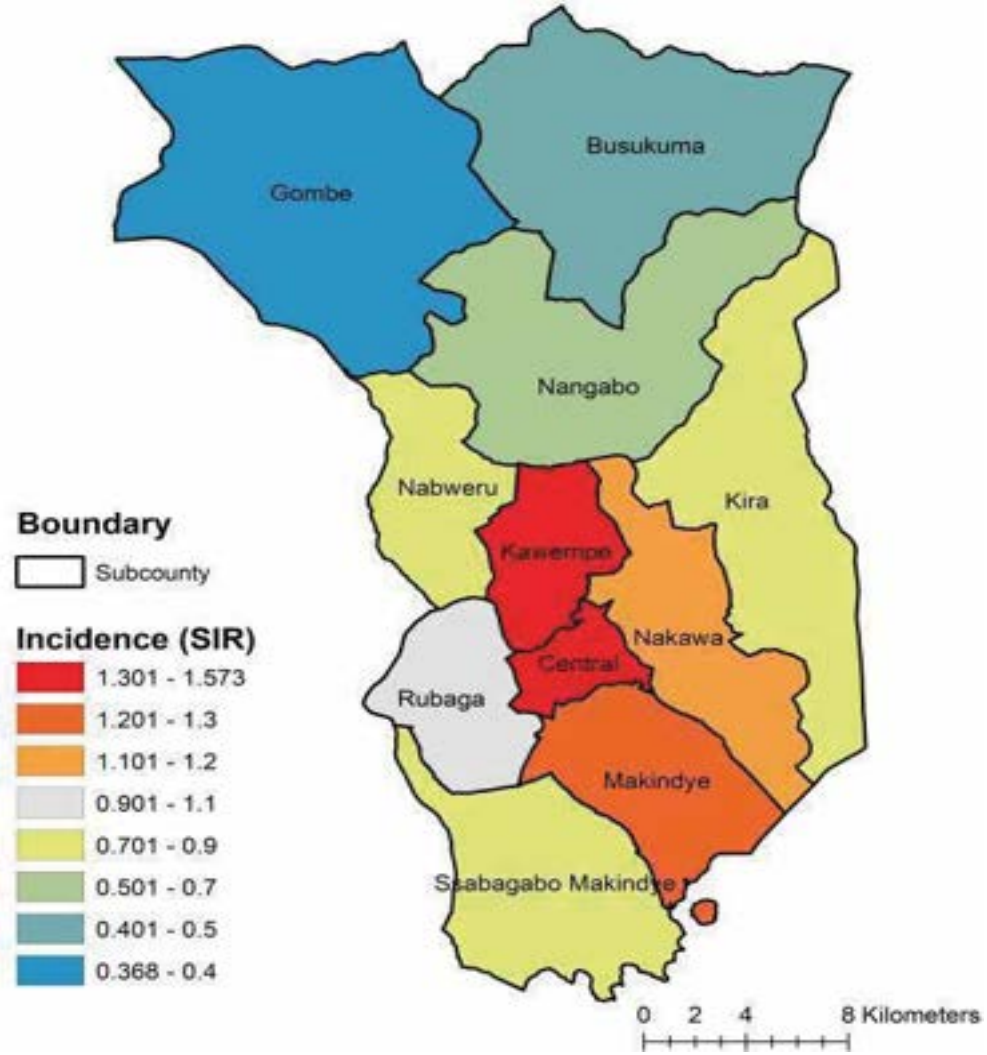
THE CASE IN KAMPALA AS AN EXAMPLE

Background The global burden of cervical cancer is concentrated in low-and middle-income countries (LMICs), with the greatest burden in Africa. Targeting limited resources to populations with the greatest need to maximize impact is essential. The objectives of this study were to geocode cervical cancer data from a population-based cancer registry in Kampala, Uganda, to create high-resolution disease maps for cervical cancer prevention and control planning, and to share lessons learned to optimize efforts in other low-resource settings.

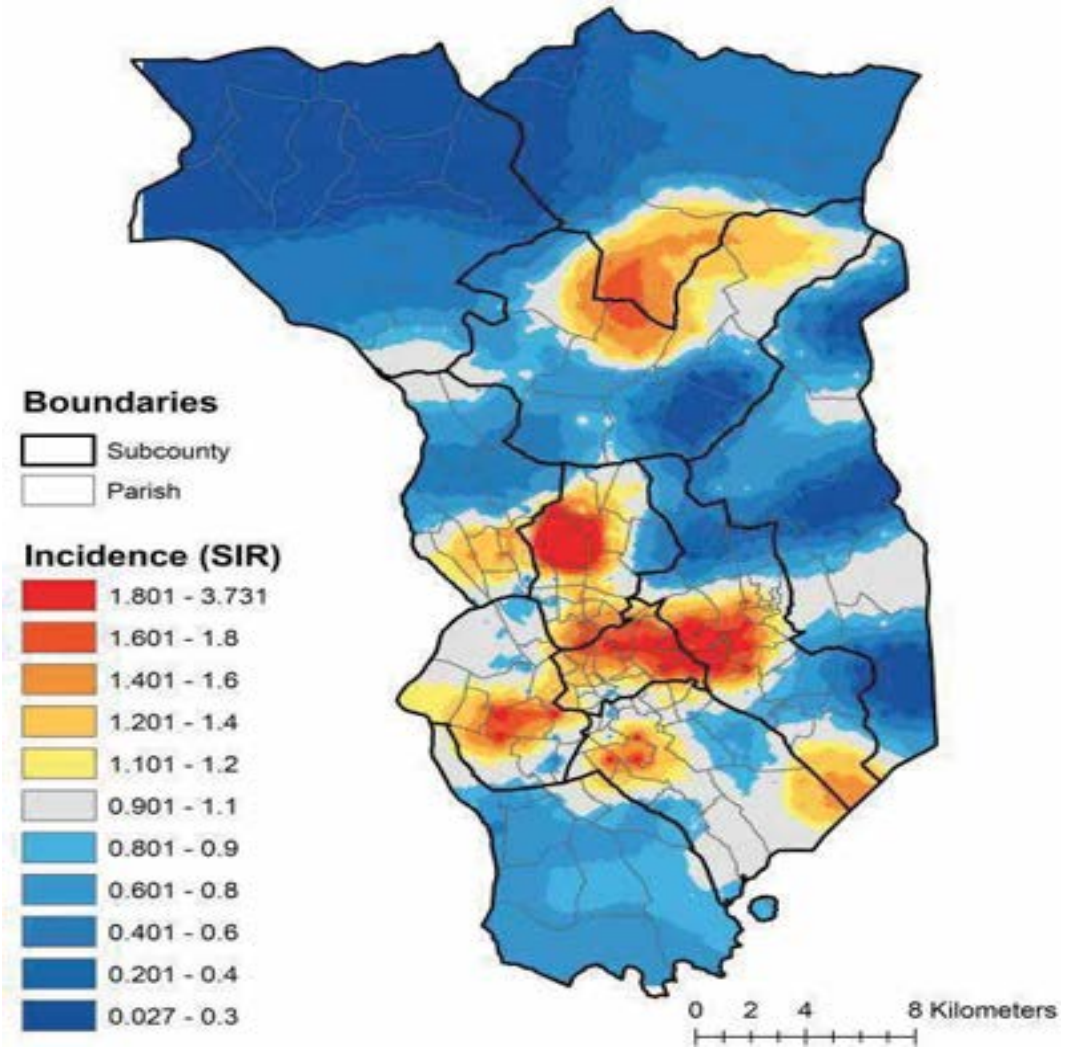
Methods Kampala Cancer Registry records for cervical cancer diagnoses between 2008 and 2015 were updated to include geographies of residence at diagnosis. Population data by age and sex for 2014 was obtained from the Uganda Bureau of Statistics. Indirectly age-standardized incidence ratios were calculated for sub-counties and estimated continuously across the study area using parish level data.

Results Overall, among 1873 records, 89.6% included a valid sub-county and 89.2% included a valid parish name. Maps revealed specific areas of high cervical cancer incidence in the region, with significant variation within sub-counties, highlighting the importance of high-resolution spatial detail.

Conclusions Population-based cancer registry data and geospatial mapping can be used in low-resource settings to support cancer prevention and control efforts, and to create the potential for research examining geographic factors that influence cancer outcomes. It is essential to support LMIC cancer registries to maximize the benefits of limited cancer control resources.



Cervical Cancer Incidence by Subcounty, Kampala Cancer Registry Catchment Area, Uganda, 2008-2015



Cervical cancer incidence across the KCR Catchment area, spatially filtered using parish level data, 2008-2015.

WHAT NEXT?