The Association Between Female Hormonal Contraceptive Use and HPV Prevalence in Female Participants, Rakai, Uganda

by

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Abstract:

A cross-sectional analysis that included 1378 HIV-uninfected female participants aged 15-49 was conducted to investigate the association between hormonal contraceptive use and high-risk human papilloma virus (HR-HPV) prevalence in Rakai, Uganda. Hormonal contraception (HC) use consisted of injectable DMPA (n=126), oral contraception (n=25) and implants (n=3) in this study.

The analysis was stratified by age into two groups 15 to 29 and 30 to 49 years, because HR-HPV in the older women was most relevant to the risk of cervical neoplasia. The overall prevalence rate of infection with HR-HPV decreased with older age for both the HC users (exposure group) and non-pregnant and non-HC users (reference group).

The results showed that the use of hormonal contraceptive was not associated with increased prevalence rate of HR-HPV after controlling for other covariates including age, number of sexual partners in the previous year, condom use in previous year, educational level and current pregnancy or breastfeeding status. (Crude prevalence risk ratio (PRR)=1.064, P-value=0.57). After adjusting for other covariates in the log-binomial model, the association between HC use and the risk of infection with HR-HPV was not statistically significant for the two age groups. Female participants aged 15 to 29 had an adjusted PRR=1.043, P-

value=0.73 and participants aged 30 to 49 had an adjusted PRR=1.059 with P-value=0.83.

Conclusion: Hormonal contraceptive use by female participants was not significantly associated with increased prevalence of infection with HR-HPV and the effect of interaction between HC use and age on the risk of infection with HR-HPV is not statistically significant.

More research is needed to examine the effect of HC use on HPV incidence and persistence.

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Best,

Yang

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1.Introduction:

Infection with human papillomavirus (HPV) is prevalent among individuals who are sexually active in developing countries.[1] Moreover, developing countries contribute to more than 85% of the HPV disease burden in the world. [2] HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 are considered to be the primary high-risk (oncogenic) types of HPV (HR-HPV denotes high risk HPV) and genotypes 6, 11, 26, 40, 42, 43, 53, 54, 55, 61, 67, 70, 71 72, 73, 81 82, 83, 84, and 108 are considered to be low-risk (non-oncogenic) types of HPV. High-risk genotypes of HPV cause cervical, vulval and anal cancer among women and penile and anal cancers among men.[3]

There are over 490,000 cases and 250,000 deaths from cervical cancer each year worldwide, which makes cervical cancer the second most common female cancer in the world. [4] Cervical cancer in eastern Africa has the highest incidence and mortality rate from cancer. In 2008, the estimated age standardized rates (ASR) mortality and incidence rates of cervical cancer are 25.3 deaths/1000 people and 34.5 new cases/1000 person years, respectively in eastern Africa.[2] A meta-analysis conducted in 2007 summarized the prevalence of HR-HPV of different regions in the world, in which Eastern Africa had both the highest crude and adjusted HPV prevalence.[1] Approximately 20 million women in sub-

Saharan Africa use hormonal contraceptives with 55% of them using injectable DMPA and hormonal contraceptive use is becoming more prevalent in eastern Africa. [5] Long duration of hormonal contraceptive (HC) use is associated with increased risk of diagnosis of cervical cancer in several case-control studies[6] and infection of HR-HPV is a necessary but not sufficient cause of most cervical cancers. [7] Therefore, the association between hormonal contraceptive use and infection with HR-HPV is of considerable importance because infection with HR-HPV in hormonal contraceptive users could increase cervical cancer risk. However, the conclusions of studies investigating the associations between hormonal contraceptive use and risk of infection with HR-HPV are not consistent. Some studies reported weak associations and some reported strong associations. The adjustments for other risk factors such as age, condom use and number of sexual partners were also limited for some studies. [8] Moreover, the findings of some studies investigating the association between oral contraceptive use and risk of infection with HR-HPV[8] [9]may not be generalized to eastern Africa area where the major type of hormonal contraceptive used in eastern Africa is injectable DMPA.

Therefore, this cross-sectional study was conducted to assess the association between the female HC use (including injectable DMPA,

implants and oral contraception) and the risk of infection with HR-HPV in female participants in Rakai, Uganda. Results of this cross-sectional analysis could provide preliminary information of the association between HR-HPV positivity among women in eastern Africa and hormonal contraceptive use.

2.Methods:

2.1.Data collection process and selection criteria:

Two clinical trials enrolled male participants and their female partners were conducted in Rakai, Uganda from 2003 to 2006 to assess the effectiveness of male circumcision for the prevention of HIV infection in men and transmission of HIV to their female partners. Another objective of these two studies was to assess the effectiveness of male circumcision for prevention of other sexually transmitted infections including HR-HPV in men and transmission of HR-HPV to their female partners.[10 11]

The goal of this cross-sectional analysis was to investigate the association between female hormonal contraception use and the risk of prevalent infection with HR-HPV in female participants, utilizing the baseline data collected from the two clinical trials of male circumcision mentioned above.

During the enrollment process of these trials, female partners of the male participants who were married or in long-term consensual unions were invited to participate the study after providing written informed consent. The consent forms informed women of the potential risks, benefits and the procedures of the clinical trials and that participation

totally voluntary. [11]

During the enrollment visit, female participants were interviewed by fieldworkers to record information about their socio-demographic characteristics, pregnancy or breastfeeding status, history of condom use by herself or male partners in the last 12 months, history of alcohol use before last sex, number of sexual partners in the last 12 months, current use of family-planning methods including HC use and symptoms of genital-tract infections (genital ulcer disease, vaginal discharge, and dysuria). Female participants were also asked to provide self-collected vaginal swabs for HPV detection and the HPV genotyping was done with the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN, USA).[11]

2.2.HPV detection and HIV testing

Vaginal swabs were stored in specimen transport medium at -80^0 C (Digene Corporation, Gaithersburg, MD, USA). Only vaginal swabs with β-globin gene or viral DNA or both were included in this analysis. HPV genotyping used the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN, USA). The high-risk genotypes of HPV were genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. HIV status was determined by two separate ELISAs tests, and discordant ELISA results

were confirmed by HIV-1 western blot. [11]

2.3.Study design:

This cross-sectional analysis utilized the baseline data of HIV-uninfected female participants collected by the two clinical trials. The infection with HR-HPV was defined as at least one type of HR-HPV.

Female participants who were HIV positive at baseline were excluded from the data analysis since HIV infection is strongly associated with higher rates of infection and persistence of HR-HPV.[12]

Family planning methods in this study included oral contraceptives, injectable DMPA, implants, male condoms, spermicides, and intrauterine devices (IUD). The exposure to HC was defined as self-reported current use of one of the three contraceptive methods: Oral contraceptive, injectable DMPA and implant.[5] All women currently using HCs, used one of the three HC methods listed above. Among female participants who were currently pregnant or breastfeeding, none reported current use of HCs, and pregnancy status of female participants was treated as a separate category in the analysis.

2.4.Statistical analysis:

The enrollment socio-demographic characteristics, sexual behaviors and symptoms of STI for female participants were tabulated to assess the overall relevant information of female participants users.

The differences in characteristics between HC users and non-HC users were assessed by two-sided χ^2 test or Fisher's exact test. If the distribution of characteristics was statistically different with a P-value<0.05, multivariate analysis adjusting for that factor was used to account for potential confounding.

It is well established that HR-HPV age-specific prevalence is U shaped, higher in the young, decreasing with age and gradually increasing when women become older.[13] In addition, we wanted to assess whether there is an interaction between HC use and age on the risk of infection with HR-HPV. Therefore, female participants were stratified into 15 to 29 and 30 to 49 age groups age groups.

The prevalence rate ratios of infection with HR-HPV associated with HC users relative to non-pregnant, non-HC users (reference group), stratified by age, were tabulated to assess the interaction between HC use and age on risk of infection with HR-HPV. Pregnant female participants were excluded from the reference group. The 95% CIs and p-values of

prevalence risk ratios were obtained by unconditional maximum likelihood and Wald test respectively.

Unadjusted and adjusted prevalence risk ratios of infection with HR-HPV and their corresponding 95% confidence intervals associated with HC users relative to non-HC users were estimated by fitting log-binomial model.[14] Log-binomial models are usually employed when estimating prevalence risk ratios in cohort studies or clinical trials. Covariates included in the multivariate log-binomial model were age, educational levels, number of sexual partners in the last 12 months, condom use by either the female participant or male partners in the last 12 months and current self-report of HC use. Educational level and number of sexual partners in previous year were included in the multivariate analysis since they were risk factors for infection with HR-HPV in other studies.[1516] The use of condoms in the last 12 months was also adjusted in the model because condom use could potentially lower the risk of HR-HPV.

A sensitivity analysis was conducted to estimate the relative risk of infection with HR-HPV associated with HC users relative to non-pregnant and non HC-users by further excluding female participants who used condoms in the last 12 months and having more than one sexual partners in the previous year to test if the results were robust.

The statistical analysis was performed using R and STATA version 13. R package “epitools” and “glm” function associated with multivariate log-binomial model were used in the analysis.

3.Results：

There were 1378 HIV-uninfected women in this analysis. At enrollment, the proportion of vaginal swabs with amplifiable cellular DNA was 99.56% (1372/1378). The prevalence rate of infection with HR-HPV was 36.52% (501/1372).

The socio-demographic characteristics of female participants are summarized in Table 1. There were 1029 (74.64%) female participants aged 15 to 29 and 349 (25.33%) female participants aged 30 to 49. The majority of female participants 1320 (95.8%) had one sexual partner in the prior year and 57 (4.2%) female participants reported more than one sexual partner in the previous year. Non-use of condoms in the previous year was reported by 1135 (82.44%) female participants or their male partners, and 242 (17.56%) female participants or their male partners used condoms in the previous year. The percent of female participants reported current use of HC method was 154 (11.2%) and 1224 (88.8%) did not use HCs. The number of female participants who were currently pregnant or breastfeeding was 305 (22.13%).

Table 1: Socio-Demographic Characteristics for Female Participants

Characteristics	Female Characteristics (N=1378) Number (%)
Age	
15-29	1029(74.67%)
30-49	349(25.33%)
Marital Status	
Polygamous union	24(1.75%)
Monogamous	1353(98.25%)
Number of sex partner in previous year	
1	1320(95.8%)
>1	57(4.2%)
Alcohol drinking before sex	
Never	917(66.54%)
Sometimes/Inconsistent	461(33.46%)
Condom use in previous year	
Used condom in previous year	242(17.56%)
Not used condom in previous year	1135(82.44%)
Religion	
None	5(0.36%)
Catholic	839 (60.89%)
Muslim	48(3.48%)
Protestant	380(27.58%)
Pentecostal	106(7.69%)
Educational levels	
None/Primary	1198(87.25%)
Secondary/Post Secondary	175(12.75%)
Current report of HC use	
Using any of the HC method	154(11.2%)
Not using HC method	1224 (88.8%)
Different types of HC method	
Pills & Norplant	28(2.03%)
Injection	126(9.1%)

Pregnant or breastfeeding	
Currently pregnant or breastfeeding	305(22.13%)
Currently Not pregnant or breastfeeding	1073(77.87%)
Self reported STI symptoms previous year	
Genital ulcer disease	193(14.01%)
Urethral or Vaginal discharge	648(47.02%)
Dysuria	275(19.96%)

***Condom use in previous year refers to either female participants use or male partners use**

The socio-demographic characteristics of HC users and Non HC-users and comparisons of the differences between the two groups are summarized in Table 2. Most of the socio-demographic characteristics were comparable except educational levels in which HC users tend to have higher educational level compared with non-HC users (P-value=0.00013). Therefore, educational level was adjusted in the multivariate analysis in case it is associated with different risk of infection with HR-HPV.

Table 2. Socio-demographic characteristics for HC users and Non-HC users

Characteristics	HC user (N=154) Number (%)	Non HC user (N=1224) Number (%)	$\chi 2$ test or Fisher's exact test P-values
Age			
15-29	110(71.43%)	919(75.08%)	0.38
30-49	44(28.57%)	305(24.92%)	
Marital Status			
Polygamous union	5(3.25%)	19(1.55%)	0.18
Monogamous	149(96.75%)	1204(98.45%)	
Number of Sex partners in previous year			
1	147(95.45%)	1173(95.83%)	0.96
>1	7(4.55%)	50(4.17%)	
Alcohol use before sex			
Never	99(64.29%)	818(66.83%)	0.59
Sometimes/Inconsistent	55(35.71%)	406(33.17%)	
Religion			
Catholic	99(64.29%)	740(60.71%)	0.62
Muslim/Other	5(3.25%)	43(3.53%)	
Protestant/CoU	42(27.27%)	338(27.73%)	
Saved/Pentecostal	8(5.19%)	98(8.04%)	
Educational level			
None/ primary	119(77.27%)	1079(88.15%)	<0.001
Secondary/ post secondary	35(22.73%)	140(11.44%)	
Condom use in previous year			
Not use	126(81.82%)	1009(82.43%)	0.92
USE	28(18.18%)	214(17.48%)	

***Condom use in previous year refers to either female participants use or male partners use condom in previous year**

Table 3 summarizes the crude prevalence risk ratios with their P-values. The crude prevalence risk ratios for female participants aged 30 to 49 is less than 1 with P-value=0.002 which is consistent with the general finding that older women have lower prevalence of HR-HPV infection. The number of sexual partners in previous year was a risk factor for infection with HR-HPV with P-value<0.0001. The use of condom was shown to be a risk factor with crude PRR 1.218 (P-value=0.02) because women who used condoms in the last 12 months tend to have more sexual partners in the last 12 months (14.3%=34/238) compared with women who didn't use condom in the last 12 months (2%=23/1133). The pregnancy or breastfeeding status was not associated with the prevalence of infection with HR-HPV, which is consistent with results of several cohort studies.[17 18] We did not observe a significant association between HC use and prevalence of infection with HR-HPV (crude PRR=1.064, P-value=0.57)

Table 3. Crude Prevalence Risk Ratios for each covariate by fitting Univariate Model

Covariates	Number of HPV/N	Crude PRR	95% CI	P-values
Age				
15-29	400/1026(38.99%)			
30-49	101/346(29.19%)	0.75	[0.62, 0.90]	0.002
Education levels				
None/ primary	431/1192(36.16%)			
Secondary or higher	69/175(39.43%)	1.09	[0.90, 1.32]	0.38
Number of sex partner in previous year				
1	466/1314(35.46%)	1.68	[1.34, 2.10]	<0.001
>1	34/57(59.65%)			
Condom use in previous year				
Used	398/1133(35.15%)	1.22	[1.03, 1.44]	0.02
Non-use	102/238(42.86%)			
HC use				
Non-HC users	424/1219(36.26%)	1.06	[0.86, 1.32]	0.57
HC users	59/153(38.56%)			
Pregnancy Status				
Yes	382/1069(35.73%)			
No	119/303(39.27%)	1.10	[0.94, 1.29]	0.25

- **The 95% CI of each covariate was obtained by taking exponentiate of the 95% Wald's confidence interval.**

In Table 4, the prevalence risk ratios of infection with HR-HPV associated with HC users relative to non-pregnant and non-HC users (reference group in Table 4) stratified by four age groups were tabulated to further explore the relationship between age and HC use. This showed the prevalence of HR-HPV for both the exposure group and the reference group decreased with age until age 35 and increased in the age interval 36 to 49 years, which is consistent with the literature. [13] The estimated prevalence risk ratios of infection with HR-HPV were all above one and peaked during the middle age groups. Figure 1 illustrates the same results

of Table 4 using scatterplot to visualize the trend.

Table 4. Prevalence Risk Ratios of Infection with HR-HPV Associated with HC users relative to non-pregnant and non-HC users

Age Group	Number of HR-HPV/ (%)		95% CI of PRR	P-Values
[15,24)	HC use	22/51(43.14%)	1.05(0.75,1.47)	0.28
	Reference group	176/428(41.12%)		
[25,29]	HC use	23/59(38.98%)	1.19(0.83,1.72)	0.34
	Reference group	80/245(32.65%)		
[30,35]	HC use	10/33(30.30%)	1.30(0.71, 2.36)	0.40
	Reference group	32/137(23.36%)		
[36,49]	HC use	4/10(40%)	1.21(0.54, 2.71)	0.64
	Reference group	35/106(33.02%)		

- **The 95% CI of each age group was obtained by taking exponentiate of the 95% Wald's confidence interval.**
- **The reference group in Table 4 refers to female participants who were non-HC users and not pregnant or breastfeeding.**

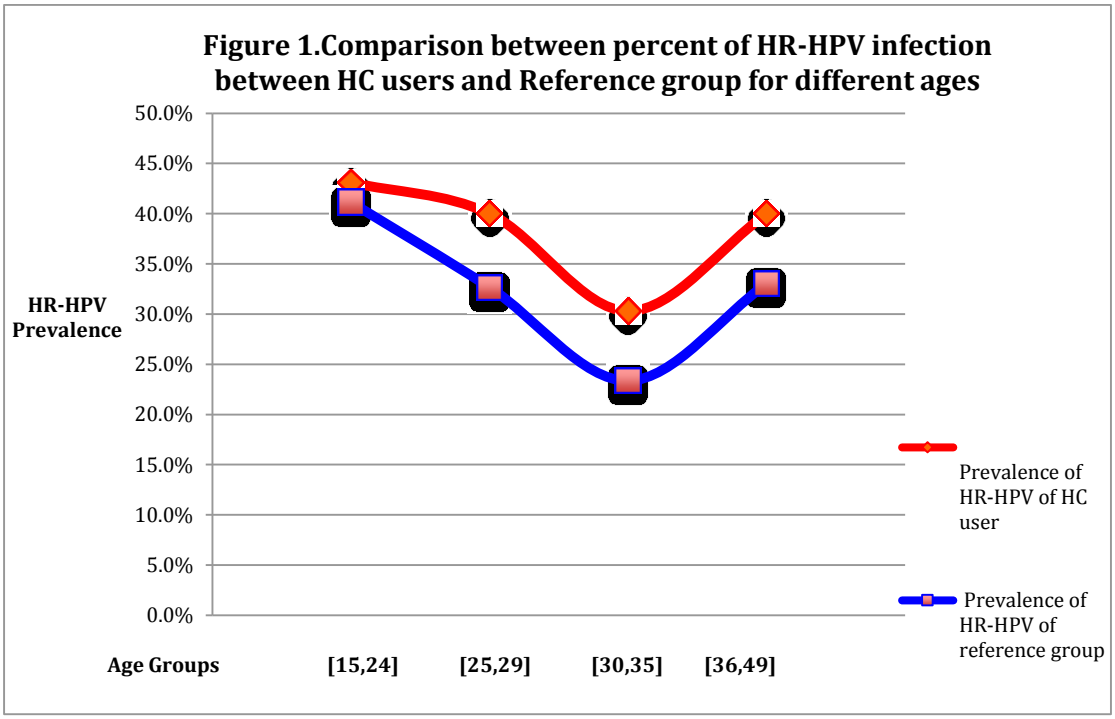

Table 5 summarizes the prevalence risk ratios of infection with HR-HPV associated with HC-users relative to non-pregnant and non-HC users stratified by two age groups. Female participants aged 15 to 24 and 25 to 29 were combined together since the prevalence of HR-HPV for HC users were similar in these two groups and female participants aged 30 to 35 and 36 to 49 were combined together since there were relatively few people in these two age groups. The estimates of risk ratios for two age groups were both higher than 1.

Table 5. Prevalence Risk Ratios of infection with HR-HPV associated with HC users relative to non-pregnant and non-HC users

Age Group	Number of HR-HPV/ (%)		95% CI of PRR	P-Values
[15,29]	HC use	45/110(40.91%)	1.08(0.84 1.37)	0.56
	Reference group	256/673(38.04%)		
[30,49]	HC use	14/43(32.55%)	1 .18(0 .73 1.9)	0.49
	Reference group	67/243(27.55%)		

- **The 95% CI of each age group was obtained by taking exponentiate of the 95% Wald's confidence interval.**
- **The reference group in Table 5 refers to female participants who were non-HC users and not pregnant or breastfeeding.**

Table 6 summarizes the adjusted prevalence risk ratios and associated 95% confidence intervals as well as p-values for each of the covariates in the multivariate log-binomial model. After adjusting for other covariates including age, educational level, use of condom in the previous year, number of sexual partners in the previous year and current status of pregnancy or breastfeeding, association between HC use and the

risk of infection with HR-HPV was not statistically significant. In addition, the interaction between age and HC use on the effect of infection with HR-HPV was also shown to be statistically insignificant. Female participants who aged 30 to 49 have prevalence risk ratio 0.758 with P-value=0.005 indicating that the risk of infection with HR-HPV for older female participants is less than younger women. The number of sexual partners in the previous has relative risk 1.565 with P-value<0.0001 showing that being sexually active is an important risk factor of getting infection with HR-HPV

Table 6. Adjusted Prevalence Risk Ratios of infection with HR-HPV for Covariates in Multivariate Log-binomial model

Covariates and Interaction term	Adjusted PRR	95% CI of Adjusted PRR	Adjusted PRR P-values
Women aged 30 to 49	0.76	[0.62 0.92]	0.01
Education level is Secondary or higher	1.03	[0.84 0.25]	0.78
Number of sexual partners>1 in Previous Year	1.57	[1.22 2.01]	<0.0001
Used condom in Previous Year	1.08	[0.90 1.30]	0.40
Current Pregnant	1.08	[0.92 1.27]	0.35
Age group 15 to 29: HC user to non-HC user	1.04	[0.82 1.33]	0.73
Age group 30 to 49: HC user to non-HC user	1.11	[0.70 1.75]	0.67

- **The multivariate log-binomial model fitted in this analysis is**

$$\log(\frac{\pi(x)}{1-\pi(x)}) = \beta_0 + \beta_1 \square HC + \beta_2 \square age + \beta_3 \square condom + \beta_4 \square s\exp + \beta_5 \square edu + \beta_5 \square preg + \beta_6 \square age \square HC$$

- **Covariates HC=1 represents self-report of current hormonal contraceptive method. Age has two categories and reference level is women aged 15 to 29. Condom=1 represents the using of condom use in the last 12 months. Sexp=1 represents whether the number of sexual partners in the last 12 months is more than one. Edu=1 represents female participants received secondary or post secondary education. Preg=1 represents female participants are currently pregnant. Age*HC represents the interaction term between Hormonal Contraceptive Method and Age.**

- **The 95% CI of each covariate was obtained by taking exponentiate of the 95% Wald's confidence interval.**

Table 7 summarized the results of sensitivity analysis after excluding female participants who used condom and having more than one sexual partners in the previous year from both the HC use group and reference group. We can see the results of Table 6 did not differ much from Table 4 implying that the result is robust.

Table 7.Sensitivity Analysis: Prevalence risk ratios of infection with HR-HPV associated with HC users relative to reference group*

Age Group	Number of HR-HPV/N (%)		95% CI of PRR	P-values
[15,29]	HC use*	40/89(44.94%)	1.28 (0.99 1.66)	0.06
	Reference group*	187/536(34.89%)		
[30,49]	HC use *	11/35(31.43%)	1.30 (0.75 2.24)	0.35
	Reference group*	49/202(24.26%)		

- **The 95% CI of each age group was obtained by taking exponentiate of the 95% Wald's confidence interval.**
- **The HC user* refer to female participants who were currently using HC method and didn't use condom in the previous year and had only one sex partner in previous year.**
- **The reference group* in table 7 refers to female participants who were non-HC users and non-pregnant or breastfeeding, didn't use condom in the previous year and had only one sex partner in previous year.**

4.Discussion:

The results suggest that there was no statistically significant association between hormonal contraceptive use and the prevalence of infection with HR-HPV for female participants. The number of sexual partners in the last 12 months is an important risk factor of infection with HR-HPV and female participants aged 30 to 49 have lower risk of infection with HR-HPV compared with women aged 15 to 29.

Hormonal contraceptive use was shown not to be a risk factor for infection with HR-HPV among female participants in Rakai, Uganda. There are three hypotheses about the mechanisms of how hormonal contraceptives make women more likely to develop cervical cancers: 1) HC use could increase the risk of cervical cancer by increasing the acquisition of HR-HPV 2) HC use could modify the host immune responses to HR-HPV so that HR-HPV becomes more persistent 3) HC use could increase the risk of development of pre-cancerous lesions.[6] As mentioned before, this cross-sectional analysis could not investigate any of the three hypotheses, but could provide information on the necessity of conducting studies to explore whether HC use might increase the acquisition or persistence of HR-HPV or both.

There are limitations to this research. Firstly, this was a cross

sectional analysis focusing on the HR-HPV prevalence of female participants at baseline which was primarily a descriptive analysis. The casual effect between hormonal contraceptive use and the prevalence of HR-HPV could not be assessed. Secondly, all the female participants in this study were either married or in a long-term consensual relationship. Therefore, we couldn't generalize the results of this research to unmarried or non-consensual relationships. Thirdly, we only recorded current reports of HC-use therefore the effect of duration of HC use on the prevalence of HR-HPV were not assessed. Fourthly, the sample size of hormonal contraceptive users aged 30 to 49 is small in this study yielding limited power to detect an effect between hormonal contraceptive and prevalence of infection with HR-HPV.

In conclusion, we did not observe an association between HC use and HR-HPV in this Ugandan study.

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Profile

Master of Science Student studying biostatistics with concentration on **Survival Analysis and Causal Inference**. Public health researcher with strong abilities and knowledge on drawing inferences from quantitative data, performing data management and conducting data analysis through multiple statistical packages. Experienced in application of mathematical and statistical models in real problems. Fluent in English and native in Chinese.

Education

Master of Science (SCM) in Biostatistics **Sep.2013—-May. 2015(expected)**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
GPA: 3.61

Relevant courses work:

4 terms of Methods in Biostatistics, Principle of Epidemiology
4 terms of Essentials of Probability and Statistical Inference
Survival analysis I, Survival analysis II
Analysis of Longitudinal Data, Bayesian Method in Statistics
Statistical Programming Packages (R, SAS, STATA), Causal Inference in Medicine and Public Health

Bachelor of Arts in Finance **Sep.2008----Aug.2012**
Michigan State University, East Lansing. MI
Dean's list: 3 semesters

Relevant coursework in mathematics: Calculus I, Calculus II, Multivariable Calculus, Linear Algebra, Advanced Linear Algebra, Analysis, Abstract Algebra