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Malaria and Cervical Cancer Risk from HPV in Kampala, Uganda

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Introduction

When it was clear that the Burkitt's-Lymphoma, prototype for many African tumours, was attributable to an oncogenic virus, the EBV, and to Falciparum Malaria (FM), [1-5] an extension of these findings was mandatory. Many years back in an epidemiological study assessing human papilloma viruses we postulated therefore that cosmopolitan malaria is a causal factor in cancer of the uterine cervix (CC) [6]. Supported generously by Karolinska Institutet in Stockholm, the ugandan counterpart in our study group worked extensively on HIV and, as others, found no association [7]. Unexpectedly, sera were left over from a large number of women, more than enough to investigate in a further case-control design regarding malaria, endemic in Kampala, the capital city of Uganda.

Results

Composition of the study (Table 1). 104 cases and 217 controls entered the study between September 2004 and October 2006 in Mulago Hospital, Kampala. Squamous types (SCC) were much more frequent than Adenocarcinomas (AC). HPV includes HPV's of 28 types, in particular those of high risk, namely 16, 18 and 45. It is important to note that the values for the characteristics of cases and controls are rather similar. Randomization, a prerequisite of a case-control study, was therefore preserved in the group of subjects remaining over with sera.

Single CC- risks of FM and HPV (Table 2). The OR's are high and statistically significant for HPV.

For FM they are low and almost significant according to antibody levels measured by ELISA-method (BIO-RAD). Using histology, non-significant changes occur. For SCC there is a little rise.

The risks of AC decrease markedly: FM alone is without risk, the OR for HPV is lowered by 50%.

Stepwise rise in risk of HPV according to antibody level of FM (Table 3) - Such assessments are popular to strengthen associations. From FM no additions are seen at the first two levels L0- and L4-. The cut off for FM was therefore chosen to be level L8-. The risks of 5.52 and 5.88 are close to the risk for HPV alone which is 5.51 (not shown). In the other two levels L8- und L12+ the increase is much more marked, namely from 5.88 to 32.70 and then the biggest jump to 64.77 being the highest risk estimate overall in our calculations. For the respective levels of FM-antibodies confidence limits are wide and always overlapping.

However, a linear trend connects these results (p<0-01). Statistical significance cannot be dismissed. Obviously, there

Table 1: Characteristics of subjects in the former HIV- and in the present malaria- study.

	Cases n=316	Controls n=314	Cases n=104	Controls n=217
Squamous cell carcinoma	83.9(265)	- - -	84.6(88)	- - -
Adenocarcinoma *	13.3(42)	- - -	15.4(16)	- - -
HPV pos. (%)	222/239(92.9)	95/309 (30.7)	92/104 (88.5)	76/217(35.0)
Mean age (SD)	46.1(11.3)	41.0 (12.4)	45.9(11.5)	41.6(12.7)
Age sex (SD)	18.4(13.9)	20.2 (17.3)	18.6(13.6)	19.4(15.2)
Parity mean (SD)	6.9(5.8)	4.8(4.0)	6.5(3.4)	5.2(3.9)

*5 additional cases showed mixed and 4 other histology.

Table 2: Odds Ratio (OR) estimates with 95% Confidence Interval (CI) for Malaria- and HPV- infections and cervical cancer, and number of cases and control women.

Infection	OR1	95% CI	Cases	Controls
Malaria	1.53	0.93 - 2.52	68, 36	112, 105
HPV	13.77	7.07 - 26.82	92, 12	76, 141
Squamous cell carcinoma				
Malaria	1.67	0.98 - 2.86	59, 29	112,105
HPV	15.82	7.50 - 33.37	79, 9	76, 141
Adeno-carcinoma				
Malaria	1.09	0.34 - 3.44	9, 7	112, 105
HPV	7.74	2.13 - 28.13	13, 3	76, 141

[1] age adjusted odds ratio.

Table 3: Stepwise combined risks (OR) of cervical cancer for HPV-infection with rising antibody levels of malaria irrespective of HIV-infection [1].

Antibody level	L0-	L4-	L8-	L12+
No. of subjects				
- HIV pos. or neg.	8, 14, 3, 26	19, 23, 6, 48	31, 21, 2, 40	34, 18, 1, 34
Age-adjusted OR				
- HIV pos. or neg.	5.52	5.88	32.7	64.77
95% CI				
- HIV pos. or neg.	1.15-26.59	2.04-16.95	6.94-153.99	8.15-514.71

[1] extended Mantel-Haenszel chi-square for linear trend = 6.72, p-value (1 degree of freedom) <0.01.

Table 4: Risks for FM controlled for HPV among all cases of cervical cancer.

Infection	OR1	95% CI	Cases	Controls
HPV+				
Mal +				
HPV+				
Mal -	2.28	1.34 - 3.89	65 27	39 37
HPV-				
Mal+				
HPV-				
Mal -	0.31	0.10 - 0.96	3 9	73 68

Always relative to a risk of 1.0 in the lower category Mal-HPV- and Mal-HPV+. Cut off level for malaria is 8. [1] Age-adjusted odds ratio; 95% CI.

is synergism between HPV and FM when the virus meets the plasmodia.

Risk of FM controlling for HPV-infection (Table 4). The opposite constellation is also of interest. When FM is second in the infection after the virus, the combined CC- risk is only 2.28, lower than 5.51 for HPV. With no virus infection the risk of FM alone is with 0.31 even inverted.

Accounting for FM-infection, there is antagonism between HPV and FM.

Conclusion

The high synergistic risks for FM and HPV are applicable to real life. The example are young girls living in endemic areas. A long lasting Infection with FM takes place early in childhood and the HPV-infection is acquired in puberty with the onset of sexual activities. The antagonism of FM and HPV occurs much less frequently in ladies afflicted with FM being second after the HPV- infection, e.g. in tourists or in migrants into Uganda from areas free of malaria in Rwanda. An unanswerable rather intricate question remains. Which interactions can be observed in CC negative for HPV?.

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