THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 9

RESEARCH ARTICLE

Cervical Cancer Risk in East and Central Africa from Interaction with Falciparum Malaria

Prof. Michael Odida[1], Prof. Thomas Löscher[2], Prof. Helga Rehder[3], Prof. Jürgen Freers[4], Priv.-Doz. Dr. Med. Rolf Schmauz[5*]

[1]Department of Pathology, Faculty of Medicine, Gulu University, P.O.B. 166, Gulu, Uganda.
[2]Deceased. Department of Infectious and Tropical Medicine, Ludwig-Maximilians-University Munich, Germany
[3]Institute of Medical Genetics, Medical University Vienna, Austria.
[4]em., Faculty of Medicine, Makerere University Kampala, Uganda, MB.Ch.B (hons.).M.Med.M.Sc.
[5]Corresponding author, Darmklinik Exter, Detmolder Str. 264, 32602 Vlotho, FRG' M.S.Epi (Harv).

[*]sesee@t-online.de

OPEN ACCESS

PUBLISHED
30 September 2025

CITATION
Odida, M., Löscher, T., Rehder, H., Freers, J., Schmauz, R., 2025. Cervical Cancer Risk in East and Central Africa from Interaction with Falciparum Malaria. Medical Research Archives, [online] 13(9). https://doi.org/10.18103/mra.v13i9.6855

DOI
https://doi.org/10.18103/mra.v13i9.6855

ISSN
2375-1924

ABSTRACT

From material available from a prior case- control study conducted in Kampala, Uganda cervical cancer risks were assessed in detail for falciparum malaria alone and in combination with HPV. Single cervical cancer risks from falciparum malaria, controlled or uncontrolled for HPV, were always very low. Significant interaction was observed between falciparum malaria and HPV. When the odds ratio was used to measure interaction, in particular synergy, a significant correlation coefficient resulted for HPV and falciparum malaria among cases, but not among controls. Among HIV-negatives stepwise regression with rising level of antibodies against falciparum showed a range of risks from 5.92 up to a synergistic value of 75.15. In sequential analyses risks controlled for HPV and falciparum malaria, respectively, showed each alone for falciparum malaria an inverse estimate of 0.47 and for HPV a decreased positive value of 7.05. When falciparum malaria meets HPV or vice versa, respectively, the range between antagonistic and synergistic values remains rather large. It amounts to 2.31 - 34.94. The antagonistic interaction of falciparum malaria with HIV noted in the literature and put up as hypothesis needs further assessment. Falciparum malaria may prevent HIV-associated cervical cancer. A small significant decrease in risk observed in Rwanda could not be attributed to antiretroviral therapy in spite of almost complete coverage. As alternative may serve FM. According to official statements prevalence of malaria, formerly very low, is on the increase.

Introduction

The idea of an association between malaria and cancer is very old. Cancer was a disease of civilization and malaria offered protection. Later when occasional biopsies were sent overseas, there were enough cases of overt malignancy to disprove these early conclusions from Africa[1].

Several decades ago in a case-control study in Kampala, Uganda, providing risks for the association between human papilloma viruses (HPV) and cervical cancer (CC), contributions from falciparum malaria (FM) were postulated[2]. The next step was to demonstrate in Uganda geographical correlations between the tumour, namely squamous cell carcinomas of high grade malignancy, and malarial endemicity[3]. Later on, when a random sample was left over with serological specimen from a large case-control study on human immunodeficiency virus (HIV) and HPV, a similar smaller study was initiated to assess the behaviour of FM towards CC risks from HPV. The sample for HIV proved to be incomplete. Instead a review of the literature is offered for the assumption what FM may do to CC risks from HIV. Short communications have already been published[4,5,6]. What follows now are detailed analyses of single and paired risks to strengthen associations and to unravel interactions. This procedure will allow to predict when infection with FM carries a high, a low or no potential at all for cervical neoplasia.

Material and Methods

Between September 2004 and December 2006 a large case-control study was conducted in Mulago Hospital, Kampala, Uganda[4]. The aim was to assess interactions between HIV and HPV. 316 cases and 314 controls were recruited. Controls were taken from visitors attending the patient. From this large HIV- study sera remained over for further use from 104 cases and 217 controls.

In the present FM-study each case had little more than two controls. FM-antibodies against mero- and sporozoites were assayed using the ELISA method (BIO- RAD). HIV was measured by the rapid test recommended by the Health authority. The results were taken from the HIV-study[4]. All cases had a biopsy.

The Stata-programme was used to compute age-adjusted odds ratios (OR) and confidence intervals (CI) of 95% (Tables 1-3) or 90% (Table 4)[7]. When observations are small, it is only little less powerful than Fisher's exact test. It works in a very similar way even with only one subject in one of the cells of the fourfold table. With the extended Mantel-Haenszel chi square test for linear trend stepwise regression of the odds ratio (OR) between malaria and HPV was examined (Table 3). Interactions were tested with correlations. The coefficients were obtained from OR's of the two infections among cases and among controls (Table 4)[8].

Table 1. - Characteristics of subjects in the former HPV-, HIV- and in the present FM- study[1]

	Cases	Controls	Cases	Controls
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)
HIV pos. (%)	55/293 (18.8)	54/308 (17.5)	13/104 (12.5)	41/217(18.9)
Parity mean(SD)	6.9 (5.8)	4.8 (4.0)	6.5 (3.4)	5.2 (3.9)
HPV pos. (%)	222/239 (92.9)	95/309 (30.7)	92/104 (88.5)	76/217 (35.0)

[1]data from (6)

Table 2. – Odds ratios (OR)[1] and number of observations for FM- and HPV-infections[2] according to all cases of CC, to cell type and grade of malignancy

Infection Histology	LCI	OR	UCI	Cases +	Cases -	C'trls +	C'trls -
FM							
CC	0.93	1.53	2.53	68	36		
SCC	0.98	1.67	2.86	59	29		
LG	0.64	1.36	2.88	25	14	113	106
HG	0.99	1.94	3.83	34	15		
ACC	0.34	1.09	3.44	9	7		
HPV							
CC	7.19	14.00	24.81	92	12		
SCC	7.62	16.07	33.88	79	9		
LG	5.39	15.77	46.16	35	4	76	143
HG	6.23	16.40	43.17	44	5		
ACC	2.13	7.74	28.13	13	3		

[1] age-adjusted OR with 95% lower and upper confidence interval (LCI, UCI).
[2] Cut-off level for FM is 8. - For abbreviations see text. - Controls are for FM
[3]and HPV, respectively, over all listed risk estimates.

Table 3. - Stepwise regression of risks between HPV and levels of FM-AB among cases and controls irrespective of HIV-infection and among HIV-negatives

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
- HIV negative	7, 10, 3, 21	13, 16, 6, 40	30, 14, 1, 35	30, 16, 1, 29
Age-adjusted OR				
- HIV pos. or neg.	5.52	5.88	32.70	64.77
- HIV negative	5.92	5.16	75.15	54.26
95% CI				
- HIV pos. or neg.	1.15-26.59	2.04-16.95	6.94-153.99	8.15-514.71
- HIV negative	1.10-31.99	1.65-16.06	9.32-605.95	6.74-436.95

[2]extended Mantel-Haenszel chi square for linear trend = 6.72 or 4.55, respectively. P-value (1 degree of freedom) (<0.01 or <0.03). [1]Incomplete information. Some HIV-infected cases were lost and thus are not listed (Table 1).

Table 4. – Assessment of a correlation between the infections FM and HPV among cases* and controls

Cases			LCI	OR	UCI	LC	OR	UCI	Ctrls.		
	HPV+	HPV-							HPV+	HPV-	
FM+	65	27							39	37	FM+
FM-	3	9	2.27	7.22	23.03	0.61	0.98	1.57	73	68	FM-

*squamous cases of CC only. For abbreviations see text.

Results

Randomisation and composition of the sample. – Subjects were taken out from the body of data of the large HIV-study. Randomisation was not lost through this procedure. Comparison of frequencies of their characteristics showed similar distributions (Table 1). The same holds for histological types of CC. Squamous cell carcinomas (SCC) predominated, adenocarcinomas (AC) occurred but rarely; 86% and 14% (246, 39) and 85% and 15% (88, 16), respectively. The notable exception were dissimilar proportions of HIV-infections with serology among cases of 18.8% and 12.5%, respectively. Their loss is not obvious and may invalidate stepwise regression analysis between HPV and level of FM-AB covering HIV-positives and negatives, but not for HIV negatives (Table 3). For this reason the whole chapter on FM, HIV and CC was left out. Risks with and without inclusion of interactions with FM were not assessed. Instead published reports were scrutinised for prevalence of FM and CC risks from HIV[9].

Histology was provided by one of us (MO). High grade malignancy predominated slightly in both cell types; the proportions were the same, each with 56% (49, 9). For HPV results were also taken from the orginal study. HPV includes 28 types of the HPV, in particular the viruses of high risk, namely 16, 18 and 45. 88.5% and 35.0% of cases and controls were positive, respectively.[6]

In Kampala during the collection of the data for the HIV-study in the years 2004-6 FM-AB against sporo- and merozoites are present in almost the whole population. All subjects in the study showed AB. Only four, two cases and two controls, were under level one. At FM-AB level four, 93 out of 104 cases (89.4%) and 180 out of 217 controls (82.9 %) were positive. At a cut off level of 8 68 out of 104 cases (65.4%) were positive for FM and 112 out of 217 controls (51.6 %). This level was chosen for the analyses to ensure a sizeable number of observations. For cut off level 8 and above the designation was malaria positive or severe malaria (M+), below this cut off level it was negative or little malaria (M-).

Odds ratios for FM and HPV. - We measured the risks for FM and HPV and called these single risks. (Table 2). In addition to the overall term CC the cases were broken down in common histological entities, namely squamous cell carcinomas (SCC), adenocarcinomas (AC) and low grade and high grade malignancy (LG, HG). The estimates are always much lower for FM than for HPV. In both groups the rare AC show the lowest risks; as the cases were few, distinction between LG and HG was not attempted. The highest OR's of 1.94 and 16.4 for FM and HPV, respectively, were seen in the category SCCHG. The values of 1.67 and 1.94 are of borderline statistical significance. Larger number of cases or applying lower CI's of 90 % would secure for FM statistically an association with subgroups of CC, namely SCC and SCCHG.

Stepwise rise in risk (Table 3). - Such assessments are popular to strengthen associations. A linear trend is statistically obvious both at the $p<0.01$ or at the $p<0.03$ level indicating a synergistic dose-response relationship between CC risk from HPV and level of FM-antibodies. The steps L0- and L4- include cases with very low and low AB levels. Cases without FM-AB-levels were not found. The risks from the pair HPV/FM show a marked rise in two steps from L4- to L12+ irrespective of the status of HIV. For HIV-negatives it levels off with a value lower at L12+ than at L8-which peaks with 75.15. The confidence limits overlap widely, but in the assessment of a linear trend statistical significance is reached. The jump from L4- to L8- is six- or even 15-fold. Synergistic interaction is obvious. CC risks from HPV and FM alone are considerably lower and for FM not different from zero (Table 5).

Table 5. –Sequence of risks for FM among HPV-non-infected and HPV-infected and vice versa. Squamous cell carcinoma only (88 cases)*

Set of Infections	No. of observations		LCI	OR	UCI	LCI	OR	UCI	No. of observations		Set of infections
HPV+ FM+	56	39							56	39	FM+ HPV+
HPV- FM-	6	68	7.46	**16.27**	35.50	7.46	**16.27**	35.50	6	68	FM- HPV-
HPV+ FM+	56	39							56	39	FM+ HPV+
HPV+ FM-	23	37	1.33	**2.31**	4.03	12.50	**34.94**	97.67	3	73	FM+ HPV-
HPV- FM+	3	73							23	37	FM- HPV+
HPV- FM-	6	68	0.14	**0.47**	1.54	3.09	**7.05**	16.08	6	68	FM- HPV-

*cut-off level for malaria is 8; OR with 90% CI. – For abbreviations see text. Point estimates are in bold.

Interactions between FM and HPV (Table 4). - Whether the single risks for FM and HPVare independent from each other, was tested with correlations among cases and controls (Table 3). In the combination FM and HPV the high OR's of 7.22 and only 0.98 among cases and controls, respectively, are statistically significantly different. The upper CI of 1.57 does not overlap with the lower CI of 2.27. Between the two infections these point estimates therefore indicate interaction.

Sequence of infections by FM and HPV (Table 5). - An ideal tool to reveal hidden interactions. From these two infections result six different combinations. To show convincingly presence of bias inherent in single risks subjects with only FM- or HPV-infection are needed for the estimate of CC risk attributable to a single agent. Such a value is the OR of 0.47 with 90% CI 0.14-1.54 thus including 1, a value showing a risk of zero. FM-infection alone is not a risk for CC. In other CC risk estimates accounting for FM introduces marked changes. The single unpaired risk from HPV is 14.00, but 100% lower is the single risk of 7.05 from HPV after controlling for infection with FM (Tables 2, 5). A further remarkable combination occurs when HPV meets FM. A high risk is attained, namely the synergistic risk of 34.94 (Table 5).

Discussion

Through interactions with HPV FM has been shown to be an important CC risk factor in subsaharian Africa. Single uncontrolled risks do conceal this property. All of them are low and only some of borderline significance. Wouldn't it be prefferable to call such uncontrolled measures summary risks?

A valuable finding is the sequence of infections with HPV. When FM occurred as first or second infection, a low antagonistic or a high synergetic risk resulted, respectively. FM alone did not produce CC. The risk of 0.47 is inverted. When FM meets HPV there is antagonistic interaction with a risk of 2.47. The second highest risk value observed in the FM-study, namely 34.94 (95% CI 12.5 - 97.7), was seen in the synergistic pair HPV/FM. The highest risk, also synergistic, was noted in the regression analysis for HPV at FM-AB level 8. It reached 75.15 with the largest 95% CI (9.32-605.95).

The sequential analyses may mirror pathways CC takes in the population. Very young children are infected by the plasmodia and develop chronic FM. When as young ladies later in life infection with HPV supervenes, the highest synergetic risk ensues attributable to the pair HPV/FM. By contrast, among female migrants from malaria-free highlands of Rwanda into areas western Uganda where FM prevails or tourists from western countries carrying only HPV, attacks by FM are antagonistic and thus beneficial. The difference to HPV alone is of borderline statistical significance and may be real.

Another CC-risk factor is the infection with HIV common in many parts of the world.[7] Rates of

prevalence of FM are reported from East and Central Africa as well as case-control studies for HIV-associated cancer[11-16]. Such studies including in addition FM are not yet available. However, as a first step an inverse geographical correlations was observed in Central and East Africa. CC risks from HIV were high in Rwanda, intermediate in Tanzania and zero in the metropolitean area of Kampala while the prevalence of FM showed the opposite trend. These observations allow the hypothesis of an antagonistic action against HIV- associated CC. FM may prevent this type of cervical cancer. A remarkable argument is that three zero risks from HIV observed in Kampala between the years 1984-1998 cannot be attributed to ART. This specific treatment was started only in the early 2000's after the first three studies on CC risks from HIV had been completed[2,15,16].

A candidate to lower the incidence of HIV associated CC is antiretroviral therapy (ART). Final positive decision is pending. Two surveys from Rwanda during the years 2012-6 and 2007-18 report a decline in CC risk from 5.9 to 2.3, 95% CI (3.8 – 9.2 and 2.0-2.7, respectively) showing statistical significance.[13, 17] However, the second study underscores the fact that in an area of high ART coverage a broad spectrum of cancer in the country may be attributable to HIV. In addition, the decrease in CC risk from HIV observed in Rwanda almost a decade ago may well be attributable to the prevalence of FM. However, reports are highly variable. A last official statement underlines that prevalence of FM, many years ago very low in the country, is on the increase[13,18].

Patterns of diseases are subject to permanent change. The question to answer is inasmuch these findings obtained in the past are applicable to present times. No doubt, urban settings, i.e. the capital city Kampala, have a generally low burden[10]. The validity of interactive FM is not lost for individuals afflicted and for many parts of the globe where increased prevalence persists. What happens if planned vaccination programmes are put into practice? If there is no vaccination against HPV CC risks from HPV may decrease, but according to the hypothesis of prevention from FM CC attributable to HIV-infection could go up.

The web of causation of cervical cancer attributable to FM is complex. Interactions need assessment for multiple infections including HIV and recently vaginal microbiota[19], breakdowns for detailed histology and secondary or associated disorders such as idiopathic tropical splenomegaly and sickle cell disease, respectively. Considering the incomplete availability of data it is more than adequate that experts of IARC and WHO convened to determine state of the science and future directions for research on HIV and cancer[20]. The inclusion of FM in these concerted efforts would seem to be very worthwile or even mandatory.

Conflict of Interest Statement:

None.

Funding Statement:

German Academic Exchange Service to MO.

Acknowledgements:

In memoriam of Alfred Gropp, Professor of Pathology at the University of Lübeck, academic teacher of HR and RS.

References:

1. von Hansemann, D. Über das Vorkommen von Geschwülsten in den Tropen. Z. Krebsforsch. 1914; 14: 39-45.

2. Schmauz R, Okong P, de Villiers EM, Dennin R, Brade L, Lwanga SK, Owor R. Multiple infections in cases of cervical and cancer from a high incidence area in tropical Africa. Int J Cancer 1989; 43: 805-9.

3. Odida M, Schmauz R, Lwanga SK. Grade of malignancy of cervical cancer in regions of Uganda with varying malarial endemicity. Int J Cancer 2002; 99: 737–41.

4. Odida M, Sandin S, Mirembe F, Kleter B, Quint W, Weiderpass E. HPV types, HIV and invasive cervical carcinoma risk in Kampala, Uganda: a case-control study in Uganda. Infect Agent Cancer. 2011; 6(1):8

5. Odida M, Löscher T, Rehder H, Schmauz R. Malaria and cervical cancer risk from HPV in Kampala, Uganda. Epidemiol Public Health. 2024; 2(2): 1040.

6. Odida M, Rehder H, Larsen CH, Freers J, Schmauz R. Falciparum Malaria prevents HIV-associated Cervical Cancer in East and Central Africa (Hypothesis). Med Res Archives. 2025; 13(5) (2025). DOI: https://doi.org/10.18103/mra.v13i5.6499

7. Stata: Statistical software for science. Google https://www.stata.

8. Miettinen OS. Lecture Notes, Harvard School of Public Health, 1972.

9. Stelzle D, Tanaka LF, Lee KK, Khalil AI, Baussano I, Shah ASV, McAllister DA, Gottlieb SL, Klug SJ, Winkler AS, Bray F, Baggaley R, Clifford GM, Broutet N, Dhalal S. Estimates of the global burden of cervical cancer associated with HIV. The Lancet Global Health, 16.11.2020 – DOI:10.1016/s2214-109X(20)30509-X.

10. Prevalence of falciparum malaria in Kampala of today (Google, accessed August, 23rd, 2025)

11. Rwanda Malaria Profile (Google, accessed July, 13th, 2024).

12. Tanzania Malaria Map (Google, accessed July, 13th, 2024).

13. MpungaT, Znaor A, Uwizeye FR, Uwase A, Munyanshongore C, Franceschi S, Clifford GM., *et al.* A case–control study of HIV- infection and cancer in the era of antiretroviral therapy in Rwanda. Int J Cancer 2018; 143:1348-55.

14. Kahesa C, Mwaiselage J, Wabinga HR, Ngoma T, Kalyango JN, Karamagi CA. Association between invasive cancer of the cervix and HIV-1 infection in Tanzania: the need for dual screening. BMC Public Health 2008; 8:262.

15. Sekirime WK, Gray R. HIV Infection among Uganda Women with Cervical Cancer: a Retrospective Study. Gynecol Obstet Invest 2007; 63:222-8.

16. Newton R, Ziegler J, Beral V, Mbidde E, Carpenter L, Wabinga H, Mbulaiteye S, Appleby P, Reeves G, Jaffe H. A case-control study of human immunodeficiency virus infection and cancer in adults and children residing in Kampala, Uganda. Int J Cancer 2001; 92: 622-7.

17. Dusingize J.C, Murenzi G, Muhoza B, Buzinge L, Remera E, Uwinkindi F, Hagenimana M, Rwibasira G, Nsanzimana S, Castle P, Anastos K, Clifford G.M. Cancer risk among people living with Human Immunodeficiency Virus (HIV) in Rwanda from 2007 to 2018. Int J Cancer 2024;12:2149.

18. Mpunga Tharcisse (Google, accessed August, 23rd, 2025).

19. Javadi K, Ferdosi-Shahandashti, Rajabnia M, Khaledi M. Vaginal microbiota and gynaecological cancers: a complex and evolving relationship. Infect Agent Cancer. 2024;19(27).

20. Engels E.A, Shiels M.S, Barnabas R.V, Bohlius J, Brennan P, Castilho J, Chanock S.J, Clarke M.A, Coghill A.E, Combes J.D, Dryden-Peterson S, D'Souza G, Gopal S, Jaquet A, Lurain K, Makinson A, Martin J, Muchengeti M, Newton R, Okuku F, Orem J, Palefsky J.M, Ramaswami R, Robbins H.A, Sigel K, Silver S, Suneja G, Yarchoan R, Clifford G.M. State of the science and future directions for research on HIV and cancer: summary of a joint workshop sponsored by IARC and NCI. Int J Cancer. 2024;154(4):596-606. DOI:10.1002/ijc.34727

