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# GRADE OF MALIGNANCY OF CERVICAL CANCER IN REGIONS OF UGANDA WITH VARYING MALARIAL ENDEMICITY

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**As in a prior study on malignant lymphomas, 3 and 6 areas of Uganda showing low and high malarial endemicity, respectively, were selected for analysis and the data retrieved from the Kampala Cancer Registry, which in the 1960s and 1970s collected cases of cancer through a widely used free biopsy service from the whole country. Overall incidence rates were derived from 924 cases from the 12-year period 1964–1975. For reasons of economy, grade of tumour was determined only in cases pertaining to the 6-year period 1968–1973. Of 457 cases, 304 could be reviewed histologically. Only the group of squamous cell carcinomas (84.9%, 258 cases) was large enough for subsequent geographic analysis. High incidence rates of CC were found in areas with high malarial endemicity, whereas low incidence rates occurred where malaria was either frequent or rare. A correlate to malarial infection was the proportion of high-grade carcinomas irrespective of the overall incidence of CC. With high prevalence of malaria and high CPRs of 35–74%, the relative share of high-grade cancer amounted to 50–67%. Where malaria was rare with low CPRs of 8–11%, these values were lower and varied only from 25–39% with a similar range of 14%. Geographic agreement between malarial endemicity and the PI of high-grade cancer was high in the 9 study areas and only slightly lower than for BL, for which the association with malaria is beyond doubt. Compared to areas with little malaria, the RR for the incidence of high-grade carcinomas in areas with severe malaria was increased. The value was 2.04 with a 95% confidence interval of 1.37–3.04. Attributable to secondary immunodeficiency, lifelong exposure to malaria may result in excess frequency of high-grade malignant tumours not only in the group of malignant lymphomas but also in CC.**


**Key words:** *cervical cancer; tropical Africa; malaria; immunodeficiency; malignancy grade*

Geographic pathology is a useful tool to arrive at hypotheses in aetiologic research of diseases. In Uganda, a small country with marked variation in climate, ethnic composition and disease patterns, material for study of the geographic distribution of malignant tumours is available from the KCR[1] for the 12-year period 1964–1975. The opportunity is unique since such countrywide cancer surveys have not been conducted in any other region of tropical Africa. A notable contribution is the observation of an association between malaria and BL[2] and the other groups of aggressive or high-grade Hodgkin's and non-Hodgkin's lymphomas.[3,4] Incidence was higher in areas of high compared to areas of low malarial endemicity due to an excess frequency of cases of aggressive or high-grade malignancy.

Sexually transmitted infections are common in Uganda,[5,6] as presumably in many parts of tropical Africa. Data on their geographic distribution in up-country areas are lacking. In Kampala, a prior study on the sexually transmitted disease CC had shown, in addition to HPVs, an association with multiple concurrent genital infections.[7] Serum titers to viral and bacterial agents, namely, herpes simplex virus 1 and/or 2, cytomegalovirus, Epstein-Barr virus and *Chlamydia trachomatis,* were very common, very high and much higher than reported in studies from Western countries; but HIV infection was much more frequent among controls (27.8%) than among cases (6.2%). The conclusion was that secondary immunodeficiency attributable to chronic malaria may also affect local cervical immunity.

In Uganda, the incidence of CC did not follow the geographic distribution of malarial endemicity. Areas of low incidence can be found in regions with either marked or little malaria.[8] Nonetheless, the majority of cases collected from all over the country showed undifferentiated or high-grade carcinoma.[6] In this particular group of tumours, malaria therefore may still play a role. From 2 regions which show low and high malarial endemicity and comprise 3 and 6 areas, respectively, we have reviewed the histology of cases of CC. For squamous cell carcinomas, which were by far the most common type of CC, we then determined how many cases were of high-grade malignancy and plotted these proportions within the 2 study areas. The overall incidence of CC and of BL was used as a control. In addition, the RR of developing high-grade cervical cancer of the squamous cell type in areas of high malarial endemicity is estimated.

## MATERIAL AND METHODS

During the 12-year period 1964–1975, the Department of Pathology of Makerere University provided a histopathology service for the whole of Uganda.[1] The number of biopsies registered during this period averaged almost 10,000 per year. All malignant neoplasms identified by the service were recorded in the KCR. Cases filed as CC (ICD code 171[9]) were retrieved from the registry. The area of residence of the case was taken from the biopsy request form. Cases without this information were assigned to the area in which the reporting hospital was located. For economic reasons, histologic review of cases of CC was limited to the 6-year period 1968–1973. Hematoxylin and eosin sections were recut and reviewed jointly with knowledge of clinical data but without information on the geographic origin of the case. Classification and grading of cervical squamous cell carcinomas were the same as previously described.[10] Low-grade tumours were those showing remarkably little atypia and good stratification. In high-grade tumours, there were marked nuclear pleomorphism, often large nuclei, a single prominent large eccentric nucleolus or multiple nucleoli and little or no stratification. When comparing this classification with the scheme formerly used in Kampala,[6] the cate-

*Abbreviations:* ASR, age-standardised rate; BL, Burkitt's lymphoma; CC, cervical cancer; CPR, crude parasite rate; CR, crude rate; HPV, human papillomavirus; KCR, Kampala Cancer Registry; PI, proportional incidence; RR, relative risk.

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gories of undifferentiated and high-grade squamous cell carcinoma are almost the same. The difference is only that a group of cases showing small cells with a uniform basaloid or transitional appearance, which in the present classification would be of low- or of high-grade malignancy depending on nuclear pleomorphism, was formerly included as undifferentiated. There were 50 (19.4%) such cases in our study, of which 26 (52.0%) were of high-grade malignancy.

The proportional or relative incidence of high-grade squamous cell carcinoma is given by the percentage of the number of high-grade cases out of the total. To reduce distortions attributable to ascertainment, the overall incidence of CC was obtained from a large sample of cases pertaining to the 12-year period 1964–1975. These cases were not reviewed histologically and, thus, include in addition to squamous cell carcinomas other much less common histologic types of CC. A CR and an ASR were computed using the female population in 1969,[11] the standard world population and the direct method of age standardisation.[12] Rates for BL were derived from the survey on malignant lymphomas,[3] pertain to the 8-year period 1966–1973, include both females and males and are specific for the age group 0–14 years. Outside this age range, cases of BL are extremely rare.

The division of Uganda follows the administrative boundaries determined in 1967.[11] The study areas selected were at that time districts and are the same as in previous reports on malaria and malignant lymphomas.[3,4] Medical services were of comparable standard throughout, particularly in the distribution of hospitals.[13] The region showing severe malarial endemicity comprises 6 former districts in the north and east (West Nile, Acholi, Lango, Teso, Bukedi and Busoga), areas in which the rate of infection is graded as predominantly holo- and hyperendemic. The region with little malaria includes the former districts of Kigezi, Ankole and Toro in the southwest and west. Malarial infection rates vary from malaria-free or hypoendemic to a number of areas showing mesoendemic malaria to 1 area in Toro, the Semliki Valley, where endemicity is similar to that of the northern region (Fig. 1). For each area, CPRs comprising all age groups of the population are listed. These had been determined in malaria surveys carried out in 1966–1967 among schoolchildren and the general population of all of Uganda except Buganda, including the areas of Masaka, Mubende and West and East Mengo (Fig. 1).[14] The sample size varied in the areas between 1,782 and 49,809 people examined. From each person, a thick and a thin blood smear were taken on the same slide and analysed at a central laboratory for schizonts of *Plasmodium falciparum, P. malariae, P. ovale* and *P. vivax* and for gametocytes.[15] More than 80% of malarial infections in Uganda are caused by *P. falciparum* and about 15% by *P. malariae.* Only a very small proportion can be attributed to *P. ovale* and *P. vivax.*[14–16]

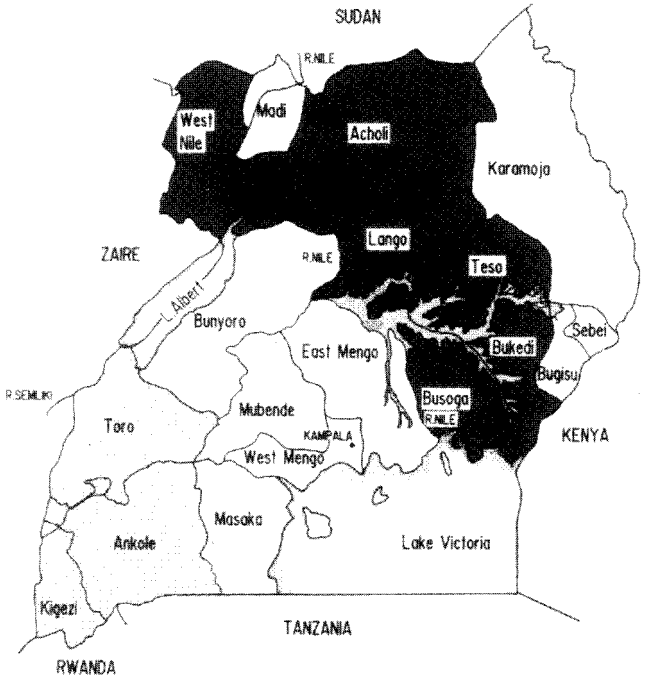


**FIGURE 1** – Map of Uganda with administrative borders showing the 2 regions differing in malarial endemicity and the 18 districts at the time of the 1969 census. Dark areas, holo- and hyperendemic regions (malaria +++); light areas, mesoendemic areas and less (malaria ±). The endemicity of malaria is taken from Kafuko *et al.*[15] (Reprinted from Schmauz *et al.*[3])

## RESULTS

### *Composition of study material*

In the 12-year period 1964–1975, 924 cases of CC were recorded from the 2 regions at the KCR. In the 6-year period 1968–1973, registration amounted to almost half of this value, *i.e.,* 457 cases. Tissue in paraffin blocks was available in 371 cases, but in 67 cases the quality of the tissue was poor. Further exclusions were the histologic groups with a small number of cases. There were 13 and 4 cases showing adenocarcinomas or mixed carcinomas with both squamous and glandular elements, respectively, and 29 unclassifiable cases. Only the group of squamous cell carcinomas (84.9%, 258 cases) was large enough for divisions according to geography and grade of malignancy.

### *Excess frequency of high-grade squamous cell carcinomas in endemic areas*

There were 132 (51%) high-grade squamous tumours and 126 (49%) low-grade tumours. The proportion of cases of high-grade malignancy differed markedly between the 2 regions, being higher in areas with severe malaria (Fig. 3). In the latter areas, 58.8% of cases of squamous cell carcinoma were of high-grade malignancy, while in areas with little malaria this relative frequency was only 28.8% (Table I).

In the analysis by smaller geographic units, the yearly incidence of CC showed a range of CR or ASR varying from 1.2 to 6.4 and from 1.9 to 9.4/100,000, respectively. Low rates were found in the areas of Ankole, West Nile, Kigezi and Bukedi; moderately high rates in Toro and Lango; and high rates in Teso, Busoga and Acholi. The overall incidence of CC shows agreement with malarial endemicity only when the incidence is high. The areas of Acholi, Busoga and Teso show high cancer rates and belong to the region with high endemicity. In the region of low endemicity, high incidence rates were not observed. However, discrepancies were noted when the incidence was moderately high or low. Rates of these orders can be found in both regions with little and severe malaria, namely, in the areas of Toro and Lango and of Kigezi or Ankole and West Nile or Bukedi.

A correlate to malarial endemicity is the PI of high-grade cervical squamous cell carcinoma. Where malaria is rare, the percentages range between 25.0% and 38.5% only. By contrast, in areas of high endemicity, the values are always higher, varying between 50.0% and 66.7% (Table I). These differences point to a high association between malaria and the relative incidence of high-grade CC of the squamous cell type ($\chi^2 = 16.59$ with 1 d.f., $p < 0.001$). In the low- and high-endemicity regions, however, there was no significant variation in the PI of these high-grade tumours ($\chi^2 = 0.80$ with 2 d.f., $p = 0.671$, and $\chi^2 = 1.66$ with 5 d.f., $p = 0.894$, respectively).

### *Geographic correlation between malaria and the PI of high-grade squamous cell cervical carcinoma*

Further evidence can be added to the relationship with malaria from multiple geographic comparisons. The strength of the correlation was measured and compared with the values obtained for all histologic types of CC and for BL. Table II shows, for the 9 areas

**TABLE I** – INCIDENCE OF CC DURING THE YEARS 1964–1975 IN REGIONS OF UGANDA WITH VARYING MATERIAL ENDEMICITY BY AREA AND PI OF HIGH-GRADE SQAMOUS CELL CARCINOMA DURING THE PERIOD 1968–1973

| Area | CR | ASR | PI | | |
|---|---|---|---|---|---|
| | | | % | Cases | |
| | | | | High-grade | Total |
| Region with malaria ± | | | | | |
| Toro | 2.61 | 3.09 | 25.0 | 7 | 28 |
| Kigezi | 1.69 | 2.96 | 28.0 | 7 | 25 |
| Ankole | 1.20 | 1.88 | 38.5 | 5 | 13 |
| Total | 1.72 | 2.72 | 28.8 | 19 | 66 |
| Region with malaria +++ | | | | | |
| West Nile | 1.42 | 1.99 | 60.0 | 9 | 15 |
| Acholi | 6.42 | 9.38 | 60.0 | 18 | 30 |
| Lango | 2.68 | 4.33 | 52.6 | 10 | 19 |
| Teso | 3.09 | 3.36 | 66.7 | 18 | 27 |
| Bukedi | 1.88 | 2.70 | 50.0 | 10 | 20 |
| Busoga | 4.56 | 5.87 | 59.3 | 48 | 81 |
| Total | 3.36 | 4.71 | 58.9 | 113 | 192 |

**TABLE II** – INCIDENCE OF CC DURING THE YEARS 1964–1975, PI OF HIGH-GRADE SQUAMOUS CELL CERVICAL CARCINOMA DURING THE PERIOD 1968–1973 AND AGE-SPECIFIC INCIDENCE OF BL DURING THE YEARS 1966–1973 IN COMPARISON TO THE CPR (%) OF MALARIA DURING THE YEARS 1966–1967 IN REGIONS OF UGANDA WITH VARYING MATERIAL ENDEMICITY BY AREA

| Area | CR | ASR | PI[1] | BL[2] | CPR |
|---|---|---|---|---|---|
| Region with malaria ± | | | | | |
| Ankole | 1.20 | 1.88 | 38.5 | 0.28 | 7.9 |
| Kigezi | 1.69 | 2.96 | 28.0 | 0.14 | 8.1 |
| Toro | 2.61 | 3.09 | 25.0 | 0.89 | 10.6 |
| Region with malaria +++ | | | | | |
| Busoga | 4.56 | 5.87 | 59.3 | 0.71 | 35.9 |
| Lango | 2.68 | 4.33 | 52.6 | 3.65 | 49.3 |
| Bukedi | 1.88 | 2.70 | 50.0 | 0.77 | 66.3 |
| Teso | 3.09 | 3.36 | 66.7 | 2.28 | 71.3 |
| Acholi | 6.42 | 9.38 | 60.0 | 3.78 | 72.4 |
| West Nile | 1.42 | 1.99 | 60.0 | 5.14 | 74.1 |

[1]Cases of squamous cell carcinomas of high-grade malignancy/all cases of squamous cell carcinoma.–[2]Yearly age-specific incidence rate for the age group 0–14 years/100,000.

**TABLE III** – CORRELATION COEFFICIENTS BETWEEN THE CPR THE ASR AND CR OF CC, THE PI OF HIGH-GRADE SQUAMOUS CELL CERVICAL CANCER AND THE AGE-SPECIFIC INCIDENCE RATE OF BL IN 9 SELECTED AREAS OF UGANDA[1]

| Type of tumour and Rate | *n* | *R* | *P* |
|---|---|---|---|
| CC | | | |
| ASR | 924 | 0.27 | n.s. |
| CR | 924 | 0.37 | n.s. |
| PI | 132/258 | 0.82 | <0.02 |
| BL | 366 | 0.87 | <0.01 |

[1]*n*, number of cases observed in the 9 areas; *R*, Spearman's coefficient of rank correlation; n.s., not significant.

studied, the CPR of malaria, the CR and ASR of CC, the PI of high-grade squamous cell CC and the incidence rate of BL. The areas are ranked according to the degree of malaria prevalence, as indicated by the CPR. Table III shows the rank correlation coefficients between the CPR and the different rates for CC and BL. There is no significant codistribution with the incidence of CC whether calculated as CR or as ASR. However, the distributions of the PI of high-grade squamous cell CC and the CPR were highly correlated ($R = 0.82$, $p < 0.02$). The geographic association between BL and malaria, which is beyond doubt[2,3,17] and shows in the same 9 study areas only a slightly higher correlation coefficient and significance level ($R = 0.87$, $p < 0.01$), corroborates the importance of the finding of a geographic correlation with malaria for high-grade CC of the squamous cell type.

*RR of high-grade squamous cell CC in areas of high malarial endemicity*

From a 4-fold table derived from Table I, the RR of developing high-grade rather than low-grade CC in areas of high-grade malarial endemicity when an area of low endemicity forms the basis of the comparison can be estimated. In the region with severe malaria, 113 and 79 cases were of high and low grade, respectively. With little malaria, the corresponding values were 19 and 47. The RR is 2.04 with a 95% confidence interval of 3.04–1.37. Thus, between the 2 study regions (Fig. 3), there is a 2-fold difference in the relative incidence of high-grade cancer.

## DISCUSSION

The use of geographic distribution together with histologic parameters supported an association between malaria and a particular type of CC, squamous cell carcinoma of high-grade malignancy. Adenocarcinomas, adenosquamous carcinomas and other less common histologic variants of CC could not be studied because the sample of such cases was too small. Cancer of the uterine cervix can be viewed as a sexually transmitted disease, and the risk of cancer at this site is determined by sexual lifestyle. Malaria is holoendemic in the area, but the known high standard of sexual hygiene among the population of West Nile is believed to be the reason why both penile cancer and CC are rare.[18] There was no way of determining to what extent malarial infection may account for the variations in incidence of CC according to grade of malignancy since information on the distribution of covariables, namely completeness of ascertainment and known factors of cervical carcinogenesis, was not available for the 9 study areas. The association with malaria is therefore not related to incidence but only to the relative share of high-grade squamous cell carcinomas in the overall incidence of CC of this type. Where malaria is prevalent with high endemicity, it varies between one-half and two-thirds and is about twice as high as in areas where malaria is rare (Tables I, II). Compared to areas with little malaria, the RR for

the relative incidence of high-grade carcinomas is 2-fold higher in areas with severe malaria.

Cases of CC were undoubtedly underreported in our survey. In some regions of Uganda, the yearly incidence may be as high as 30 or 40 per 100,000.[19] Compared to the rates obtained in the present survey (Tables I, II), this would indicate that very many cases remained undiagnosed. Even marked regional variations in ascertainment would not affect the comparisons since we used only proportional rates. Ugandan patients tend to come to hospital late in the course of CC. For example, even among women in the capital city of Kampala, where medical services are better developed than in up-country areas, 68% of cases were in stages III and IV.[7] A laboratory of cytology is in operation in Kampala.[20] In up-country areas, cytology screening programs do not exist, and the early stages of the disease are not noted since the site is deep. A long-held assumption was that patients with late-stage tumours show longer delays in presentation than those in early stages, but according to Symonds *et al.,*[21] the related parameter is tumour biology as expressed by proliferation rates. Differences in stage, and thus also tumour grade at presentation, cannot be ascribed therefore to delays in hospital attendance. An uneven distribution of aetiologic factors, *e.g.,* sexual lifestyle or number and intensity of genital infections, could have produced the relationship between malarial endemicity and tumour grade, particularly when comparisons are few. In our study, which includes observations from 9 areas, it is unlikely that variations in tumour grade attributable to sexual lifestyle resulted in a correlation with malarial infection.

Secondary immunodeficiency attributable to parasitic diseases is certainly a neglected aspect of cervical carcinogenesis in tropical countries,[7] but it appears that the distribution of diseases of this type other than malaria[13] does not explain the geographic findings of our study. Trypanosomiasis is spreading in recent years,[22] but during the time of our study it was too rare in Uganda to affect rates of tumour grade. Only 50 cases per year were observed in restricted areas, namely, Bukedi, Busoga and West Nile. In Kala Azar, namely visceral leishmaniasis and onchocerciasis are candidates, but they either were not recorded at all or were uncommon, respectively. In schistosomiasis, both systemic immunosuppression and local action must be considered. A relationship to lymphoreticular tumours has been postulated in Egypt and Nigeria.[23,24] Although views are divergent,[25] eggs infesting the cervix may increase the risk of cancer at this site. The trematodes are common in Uganda, particularly the species *Schistosoma mansoni,* and are much more prevalent in the study area with marked malaria. However, in Uganda, an addition to the burden of cancer at any site can be ruled out[26] and, in the present study material (tissues from cervical cancer biopsies), schistosomal eggs were not found.

Finally, a classic objection against a geographic correlation is that it may be the result of a relationship through a third variable. For example, while the geographic associations delineated in Uganda between condylomata acuminata and cancer of the vulva, vagina, cervix and penis pointed to common underlying viral agents,[8,27] later shown to be HPVs, it was clear at the same time that these concomitant frequencies could have reflected merely patterns of sexual promiscuity prevailing in the population. For the association between malaria and CC no such a variable is apparent.

The incidence rates of CC were given as a CR and an ASR. With Ugandan cases, both methods of computation have disadvantages. It is difficult to say which approach is superior in assigning rank orders to the 9 areas. The results are not markedly different, and it appears justifiable therefore to derive the PI from observed numbers of cases rather than from an ASR. When the rank orders are compared between the CR and ASR, 4 areas, Kigezi, Lango, Bukedi and Teso, differ by 1 place and the remaining 5 do not change (Tables I, II). The shortcoming of the CR is that it does not account for the age distribution of the population. However, the bias introduced is small. In the 9 areas, the proportion of females over 65 years old varies between 2.3% and 4.2%.[11] The problem with age standardisation is that information on age had not always been obtained. The proportion of such cases varies considerably between the 9 areas, showing a range between 6.2% and 25.0%. Nonetheless, since cases of unknown age were included in the age-specific rates according to the distribution of cases with known age, these differences may lead only to small distortions.

Breakdown of the immune system is the mechanism through which malaria may affect carcinogenesis. In children, T cell–mediated immunity is suppressed during acute attacks of the plasmodia.[28] The reason for these changes in the T-cell compartment appears to be the malarial pigment hemozoin. When taken up by macrophages, the antigen-processing and immunomodulatory functions are reduced.[29] Under such circumstances, latent and chronic viral infections, *e.g.,* herpes viruses, are activated[28,30–32] and BL develops. In the adult population in which CC occurs, chronic malaria prevails with different long-term reactions to the plasmodia.[33] An important general aspect is that immunity is lowered when there is severe malaria attributable to anaemia, which is common, particularly in pregnancy. A specific pathway was suggested to be the excessive synthesis of malaria-specific IgE and related T-cell dysfunction, which might increase the susceptibility to cancer.[34] Infection by HPVs is a key variable in cervical carcinogenesis.[35] It is conceivable that among immunodeficient women suffering from chronic malaria, these agents may more frequently produce tumours of high-grade malignancy.

The idea of an association between malaria and cancer is very old. In the early days of modern medicine, the belief was widespread that due to a protective effect from malaria cancer was extremely rare in tropical Africa. With the expansion of Western health services, including shipment of occasional biopsies to Europe, it was realised that cancer was not uncommon. No striking geographic differences in tumour patterns were detected, and the assumption of a beneficial action of malaria on the incidence of malignant tumours was no longer tenable (reviewed by von Hansemann[36]). The turning point came when a childhood tumour, very common in tropical Africa and even today still known as BL, was related to malaria.[2,37] In Kenya and later in Uganda and other countries, the highest frequencies could be observed in holoendemic areas. There are now again strong geographic indications to include in addition to BL other high-grade virus-associated malignant tumours arising in the lymphatic system and on the cervix uteri. A number of virus-associated cancers are common both in tropical Africa and in a variety of disorders associated with impairment of the immune system.[38] Perhaps further extensions of the association could come from studies directed at such tumours, in particular cancer of the liver and Kaposi's sarcoma.

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