Polymorphism of MMP1 and MMP3 promoter regions and HR-HPV infection in women from Burkina Faso and Côte d’Ivoire

Abstract: The single nucleotide polymorphism (SNP) of the promoter region of MMP-1 (at 1607 bp) and MMP-3 (at 1171 bp) create Ets binding sites. Correlations between these SNPs and sensitivity to several biological processes such as metastasis and recurrence of cancer have been reported in several studies.

In this case-control study, we looked for these SNPs in women infected with or not with high-risk human papillomaviruses (HR-HPV). The frequency, distribution and correlation of these SNPs with the presence or absence of HR-HPV infection were evaluated.

Genotypes 1G1G, 1G2G and 2G2G for MMP1 and genotypes 5A5A, 5A6A, 6A6A for MMP3 were found in our study population. In general, we noted that the 1G (40.8%) and 2G (64.8%) alleles were more frequent in non-infected women and infected women, respectively, and more specifically this difference was significant in women from Côte d’Ivoire.

These results, although yet to be reaffirmed with assays for quantifying the mRNA of these genes, suggest that the SNP of the MMP-1 promoter could promote infection with HR-HPV.

Keywords: High-risk HPV; Cervix cancer; mRNA expression; MMPs polymorphism.

Introduction

Cervix cancer is one of the most common female cancers in women worldwide, with more than 570,000 new cases and more than 311,000 deaths each year [1]. It ranks second in terms of incidence and mortality behind breast cancer in context of low Human Development Index (HDI). Developing countries have the greatest cases of the disease due to insufficient screening and surveillance [2].

High-risk Human Papillomavirus (HR-HPV) is implicated in 99.7% of cervical carcinomas [3]. HPVs infect skin and mucosal epithelial cells of the anogenital tract using several mechanisms, such as the attachment of the virus to several types of molecules in the extracellular matrix and its internalization by endocytosis. Laminins 5 (LN5) and Heparan sulphate proteoglycans (HSPG) are examples of the extracellular matrix (ECM) molecules which are used
in the process of internalization of HPV [4, 5]. The state or homeostasis of ECM is determined by proteins such as metalloproteins (MMPs) which are enzymes capable of degrading or activating some of its components. Thus, the molecular mechanisms underlying HPV infection or non-infection can be enhanced by simple nucleotide polymorphisms (SNPs) in the regulatory areas of genes coding for these MMPs capable of interacting with ECM.

Type 1 matrix metalloproteinases (collagenase-1 or MMP1) and type 3 metalloproteinases (stromelysine or MMP3) are two genes located on the long arm of chromosome 11 [6] and code for two enzymes degrading certain components of the ECM. MMP-1 plays a major role in the breakdown of collagen type I, while MMP-3 acts on collagens type II, III and IV [7], but also promote the activation of other members of the MMP family [8]. A SNP insertion of a guanine (G) at position -1607 /-1608 in the promoter creates a binding site for the transcription factors of the Ets family, one of the largest families of transcription factors from the ETS family bind to DNA with a central GGA (A/T) sequence. This SNP has been associated with upregulation of MMP-1 transcription and possibly increases the activity of this enzyme [9, 10]. The insertion of adenosine (A) into the promoter of the MMP-3 gene, at position -1612 /-1617 upstream of the start of transcription, creates a polymoramic series of six adenosines (allele 6A), while the wild type variant has five adenosines (allele 5A). The presence of the 6A allele allows the binding of the ZBP-89 repressor which downregulates the expression of the MMP-3 gene [11-13]. We hypothesized that changes in the metabolism of the ECM caused by polymorphisms in the MMP genes may help promote HR-HPV infection. Genotyping studies of HR-HPV implicated in cervical cancer have been carried out in Côte d’Ivoire and Burkina Faso; without addressing the genetic factors that would be associated with this infection and its fate. The distribution and frequency of HPV genotypes found in cervical lesions in these two countries are different from those known worldwide; this suggests an involvement of the genetic factors of the host. The objective of this study was to determine the associations between SNPs at positions 1607 and 1617 in MMP1 and MMP3 genes, respectively, and HR-HPV infection in Côte d’Ivoire, the collection was made in the cities of Abidjan, Yamoussoukro and Bouaké, respectively at the Yopougon University Hospital Center, at the Catholic Hospital Saint Joseph Moscati and in the Bouaké University Hospital Center. These are the three main urban centers of the country from North to South through the center. In Burkina Faso, the Yalgado Ouedraogo and Sourou Sanou University Hospital Centers in Ouagadougou and Bobo Dioulasso respectively served as collection sites; these are the two main urban centers in the country (Burkina Faso), one in the center and the other in the South.

**Inclusion criteria:** for the collection of swabs, all women who were sexually active and who gave their free and informed consent to screening during the study period were included, however those (women or girls) who were virgins, pregnant, having undergone a total hysterectomy and not assenting were not admitted to the study.

**DNA extraction, HR-HPV detection and MMP genotyping**

**DNA extraction:** Total DNA was extracted with the “Rida Xtract” kit, from R-biopharm, according to the protocol provided by the manufacturer.

**Detection of HR-HPV:** real-time multiplex PCR was performed using the “HPV genotypes 14 Real-TM Quant” kit from Sacace Biotechnologies Srl, Italy, using the SaCycler-96 Real Time PCR v.7.3 from “Sacace Biotechnologie. This kit can detect of 14 high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56,58, 59, 66 and 68).

**Characterization of the MMP1 and MMP3 genotypes:** the characterization of the polymorphism of MMP1 and MMP3 genes was carried out using standard PCR. The Restriction Fragment Length Polymorphism (PCR-RFLP) method was used for genotyping the MMP1 gene using the technique described by Nishioka et al. [14]. The reaction mixture consisted of: AmpliTaq Gold 360 Master Mix (12.5 µl), Primer (1 µl for each primer) in table 1, sterilized water (5.5 µl). For each sample, 5 µl of DNA was added to 15 µl of the PCR mix. The amplification was performed according to the following program: Initial activation at 95°C (15 min); 35 cycles of 95°C (30 s), 58°C 95°C (30 s), 58°C (30 s) and 72°C (30 s) and a final extension to 72°C (7 min). After amplification, the PCR products were digested for 24 hours with the restriction enzyme Alul (ThermoFisher), which recognizes the AG ^ CT sites and cuts better at 37°C in a Tango buffer. The digestion mix per sample was composed as follows: Alul digestion enzyme

**Methodology**

**Study site and population:** the study population consisted of 952 endocervical cell samples (collected by swabs). The swabs were collected in two countries in West Africa, namely Ivory Cost (IC) and Burkina Faso (BFA).
Genotyping of the polymorphism of the MMP3 gene was performed using the technique of detection of the specific allele (AS-PCR or Allele Specific-Polymerase Chain Reaction) described by Morosova et al. [15]. AS-PCR is a technique which uses two pairs of specific primers to amplify each of the alleles and whose amplicons are different in size. The PCR mix consisted of the following components: DNA polymerase (0.5 µl), Buffer B (10 µl), MgCl2 (10 µl), Primer (1.5 µl/primer) in table 1, dNTP mix (1 µl) and H2O (70.5 µl). Finally, 5 µl of DNA was added to 95 µl of the PCR mix previously distributed in the wells of the PCR plate. The standard PCR schedule was performed according to the following chronology: initial activation at 95°C for 15 minutes; 35 cycles composed of DNA denaturation at 94°C for 30s, an hybridization of 54°C for 30s and an extension of 72°C for 30s; and a final extension of 72°C for 7 minutes. PCR products (MMP3) or products of enzymatic digestion (MMP1) were evaluated after 30 min electrophoresis under 120V in a 1.5% agarose gel under ethidium bromide staining and visualized in an ultraviolet transilluminator.

Data analysis

Standard statistical software for the social sciences (SPSS) version 21 was used for the analysis and interpretation of the data. The results were considered statistically significant if p ≤ 0.05 by using the Fisher Exact test. The Odd Ratio (OR) and 95% confidence intervals (CI) were calculated to estimate the association between MMP1 and MMP3 genes frequencies and HPV infection using Epi Info 7.2.2.16

Ethical approval: This research involved human subjects and has complied with all national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the ethics committee for health research in Burkina Faso (Deliberation: N° 2018-01-012) and also with the agreement of the managers of the collection sites.

Informed consent: Informed consent has been obtained from all individuals included in this study

Results

HR-HPV genotyping results

Sociodemographic and behavioral characteristics of women

Among 952 women included in the study, dysplasias was found in 15.02% (143/952), 18.5% (176/952) and 11.9% (113/952) of women respectively with IVA, IVL and IVA / IVL.
Genotyping results from fourteen HR-HPVs showed that 38.1% (363/952) of women in the study population were infected with at least one genotype. The results of genotyping and those of dysplasias showed that 44% (160/363), 27.8% (101/363) and 26.7% (97/363) of women with dysplasias, diagnose respectively by IVL, IVA and IVL / IVA were infected with HR-HPV.

All the fourteen (14) HR-HPV genotypes sought in our study have been identified in the participating women. Taking into account multiple infections, 531 HR-HPV were found in 363 infected women. The first five most common HPV-HR genotypes found in these infected women were HPV68 (12.6%), HPV52 (10.9%), HPV56 (10.5%), HPV 56 (9.6%), HPV 31 (8.8%), HPV45 (8.3%) (Figure 1). HPV18 (5.5%), HPV16 (1.7%) and HPV33 (1%) were the least commonly found genotypes. The twelve genotypes, excluding 16 and 18 were found in 95.6% (347/363) while HPV16 and HPV18 were found in only 10.5% (38/363) of infected women (Figure 1).

**Genotypic and allelic frequency of polymorphisms 1G-1607-2G and 5A-1171-6A in MMP1 and MMP3 respectively**

Two hundred and forty-five (245) swabs of women from Côte d’Ivoire and Burkina Faso were used for these MMPs gene genotyping. These women were divided into two groups, those infected with HR-HPV (group of cases) and those uninfected (control group). Eighty-six (86) of these women, including 32 infected and 54 uninfected, came from Côte d’Ivoire and 159 women, including 61 infected and 98 uninfected, from Burkina Faso.

The characterization of the polymorphism of the MMP1 gene due to the deletion/insertion of a guanine (1G/2G) at position 1607 in the promoter of the MMP1 gene gave three genotypes including 1G1G, 2G2G and 1G2G. Homozygote 2G2G (44.91%) was the most common genotype in this population. In addition, of the two alleles (1G and 2G) of the polymorphism studied, the 2G allele was predominant with 61% (Table 2).

The characterization of the polymorphism in the promoter of the MMP3 gene also gave three genotypes, namely 5A5A, 6A6A and 5A6A. The heterozygote 5A6A (44.91%) was the most common genotype in this population. In addition, of the two alleles (1G and 2G) of the polymorphism studied, the 2G allele was predominant with 61% (Table 2). The characterization of the polymorphism in the promoter of the MMP3 gene also gave three genotypes, namely 5A5A, 6A6A and 5A6A. The heterozygote 5A6A (44.91%) was the most common genotype in this population. In addition, of the two alleles (1G and 2G) of the polymorphism studied, the 2G allele was predominant with 61% (Table 2).
Distribution of genotypic and allelic frequencies of 1G-1607-2G and 5A-1171-6A polymorphisms respectively in MMP1 and MMP3 according to cases and controls.

The allelic frequency distribution of 1G and 2G of MMP1–1607 was 40.8% and 59.2%, respectively, in controls (HR-HPV negative), compared to 35.5% and 64.5% in cases (HR-HPV positive), resulting in an increase in the frequency of the 2G allele of the MMP1 gene (OR 0.77 to 95%) observed in cases (HPV positive) (Table 3). The distribution of genotypic frequencies in controls and cases showed that the two groups were in Hardy Weinberg equilibrium (p = 0.61 and p = 0.45 respectively). The distribution of these genotypes gave 25.7% (1G/1G), 30.2% (1G/2G) and 44.1% (2G/2G) in the controls, while in the cases there were 17.2% (1G/1G), 36.6% (1G/2G) and 46.2% (2G/2G). The frequency of the homozygous variant (2G/2G) and the heterozygote (1G2G) was found to be slightly higher in the cases compared to the controls (Table 3).

Alleles 5A and 6A of the MMP3–1171 gene had a frequency of 50.6% and 49.4% respectively in the controls, compared to 44.6% and 55.4% in HPV positive women, which shows an increased frequency of the 6A allele in infected women (Table 3). The frequencies of the three MMP3 genotypes in the controls were 15.1% (5A/5A), 71.1% (5A/6A) and 13.8% (6A/6A) whereas in the positive HPV, the frequencies were 8.6% (5A/5A), 72% (5A/6A) and 19.4 (6A/6A) (Table 3). The frequency of the heterozygous variant (5A/6A) was found to be equal in the two groups. Also, the homozygous variants 5A5A and 6A6A had a slightly high frequency in the control group and in the case group, respectively. For the distribution of the polymorphism of the MMP3 gene, the two groups (control and case) were in Hardy Weinberg equilibrium (p = 0.562922; p = 0.393167 respectively) (Table 3).

In general, the trend in genotypic frequencies was approximately identical for each country, as summarized in Figure 3. The distribution of the genotypes of the MMP1 and MMP3 genes according to the country showed an absence of the homozygous 5A5A genotypes in Ivorian women infected with HR-HPV. For certain groups, a deviation from the Hardy-Weinberg equilibrium was observed: these are the groups of Ivorian women infected

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**Table 2**: Genotypic frequency of MMP1 and MMP3 in the general population.

| Gene    | Genotypes | N (%) | Alleles     | N (%) |
|---------|------------|-------|-------------|-------|
| MMP1   | 1G1G       | 55(22.4%) | 1G          | 190(39%) |
|         | 1G2G       | 80(32.7%) | 2G          | 300(61%) |
|         | 2G2G       | 110(44.9%) |             |       |
| MMP3   | 5A5A       | 31(12.7%) | 5A          | 237(48%) |
|         | 5A6A       | 175(71.4%) | 6A          | 214(52%) |
|         | 6A6A       | 39(15.91%) |             |       |

**Table 3**: Frequency of allelic and genotypic distribution of the polymorphism of the MMP1 and MMP3 genes in women infected or not infected with HPV.

| Genes     | HPV – n (%) | HPV + n (%) | OR (95% IC) | P value |
|-----------|-------------|-------------|-------------|---------|
| MMP1 Genotypes |            |             |             |         |
| 1G1G       | 39 (25.7)   | 16 (17.2)   | 1.00 (ref)  |         |
| 1G2G       | 46 (30.2)   | 34 (36.6)   | 1.8 (0.86-3.74) | 0.07 |
| 2G2G       | 67 (44.1)   | 43 (46.2)   | 1.56 (0.77-3.13) | 0.13 |
| HWE*       | 0.610793    | 0.453497    |             |         |
| MMP1 Alleles |           |             |             |         |
| 1G         | 124 (40.8)  | 66 (35.5)   | 1.00 (ref)  |         |
| 2G         | 180 (59.2)  | 120 (64.5)  | 1.25 (0.85-1.02) | 0.14 |
| MMP3 Genotypes |           |             |             |         |
| 5A5A       | 23 (15.1)   | 8 (8.6)     | 1.00 (ref)  |         |
| 5A6A       | 108 (71.1)  | 67 (72)     | 1.78 (0.75-4.2) | 0.12 |
| 6A6A       | 21 (13.8)   | 18 (19.4)   | 2.46 (0.88-6.84) | 0.06 |
| HWE*       | 0.562922    | 0.393167    |             |         |
| MMP3 Alleles |           |             |             |         |
| 5A         | 154(50.6)   | 83(44.6)    | 1.00 (ref)  |         |
| 6A         | 150(49.4)   | 103(55.4)   | 1.27 (0.88-1.83) | 0.11 |

* Hardy-Weinberg equilibrium, if p <0.05 - not compatible with HWE
with HR-HPV for the polymorphism of MMP3, 5A-1171-6A (p = 0.046) and the group of Burkinabe women infected with HR-HPV for the polymorphism of MMP1 1G -1607 2G (p = 0.046).

Analysis of alleles according to country of origin showed that alleles 5A and 6A had approximately the same frequencies in women from both countries, whether they were infected or not. The 1G allele had a significantly higher frequency in uninfected women (0.43) than in infected women (0.17) in Côte d’Ivoire (p = 0.0004) (Table 4). In Burkinabe women the 1G allele had a frequency of 0.45 and 0.40 respectively in infected and non-infected women. In Ivory Coast, the 2G allele had a higher frequency in infected women (0.83 and 0.57 respectively); in BFA the frequency of the same allele was lower in infected women than in uninfected women (0.55 and 0.60 respectively) (Table 4).

Alleles 5A and 6A had a significantly high frequency respectively in uninfected and infected women in Ivorian women (p = 0.016). However, these alleles (5A and 6A) had an equal frequency in the group of cases and controls in Burkinabe women.

The evaluation of the combined effect of the polymorphism of the MMP1 and MMP3 genes on HPV infection showed that the frequency of the 1G2G/5A6A and 2G2G/5A6A hybrids had a high frequency in both groups but also that their frequency is more high in the group of infected women than the group of uninfected women (Table 5). Women with the 1G1G/5A5A genotype had a slightly lower frequency in infected women than in those without infection; the one with the genotype 2G2G/6A6A had a higher frequency in infected women than in those without infection.
The HR-HPV found in women in our population were divided into two groups, namely the group consisting of HPV16 and 18 and the group of HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The distribution of the genotypes of the polymorphism of each of the two genes as a function of the two groups of HR-HPV did not show any significant difference (Table 6).

### Discussion

Uteri cervix cancer is the leading female cancer and the leading cause of cancer death among women in most countries in West Africa, despite its long latency period. This primacy of cervical cancer is favored by several socio-demographic factors and the inadequacy of an efficient health system [16, 17]. Primary prevention of cervical cancer is essentially based on healthy lifestyles and vaccination against HPV which remains a very important means of combating this disease. However, to increase the effectiveness of such a program, it is essential to understand not only the distribution and prevalence of HR-HPV within the population but also to research the genetics factors that would influence the infection and the occurrence of this sickness. Knowing these factors is important as much as it will help to improve cancer prevention and treatment.

Among infected women in this study, the first five most frequent HPV-HR genotypes found were in decreasing order HPV68, HPV52, HPV66, HPV56, HPV31 and HPV45; HPV16 and HPV18 were the least prevalent genotypes. These results are clearly different from those predicted by the International Agency for Research on Cancer (IARC), according to which genotypes 16 and 18 are found in approximately 70% of cervical infections with respectively 53% and 15% of frequency [18]. Several studies that investigated the distribution and frequency of HPV genotypes in Africa have already noted differences from that observed around the world; these same studies have also shown that in Africa this situation vary according to the country [19]. Studies in Malawi and Gabon found high frequencies of HPV16 and 18 similar to those predicted by IARC [20, 21] while other similar studies, in others countries have shown a very low frequency of genotypes 16 and 18 at the expense of other genotypes [22, 23].

Despite the strong impact of HR-HPV E6/E7 oncoproteins on cell homeostasis, this is not enough to explain the occurrence of cervical infection and cancer. Therefore, further alterations in the cell as well as in its microenvironment are necessary for the establishment and progression of the tumor. These alterations may relate, for example, to the modification of the extracellular matrix (ECM). The frequency and distribution of HR-HPV genotypes, different according to the zones, would be determined by the polymorphism of metalloproteinases such as MMP1 and MMP3 which are proteinases acting on the ECM. The search for polymorphisms of these two genes made it possible to find three genotypes for each of the two genes: **MMP1** (1G1G, 1G2G, 2G2G) and **MMP3** (5A5A, 5A6A, 6A6A). The analysis of these genotypes

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**Table 5:** Evaluation of the combined effect of polymorphisms of the MMP1 and MMP3 genes on HPV infection.

| MMP1 | HPV Negatives (N=152) | HPV Positives (N=93) |
|------|-----------------------|----------------------|
|      | 1G1G N(%)             | 1G1G N(%)            |
| MMP3 | 1G2G N(%)             | 1G2G N(%)            |
| 5A5A | 2G2G N(%)             | 2G2G N(%)            |
| 0.0% | 00% (3.3%)            | 09% (5.9%)           |
| 5A6A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/5A5A | 05 (3.3%) | 01 (2.2%) |
| 5A6A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/5A6A | 09 (5.9%) | 03 (3.2%) |
| 6A6A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/6A6A | 08 (5.3%) | 05 (5.4%) |
|      | 1G2G N(%)             | 1G2G N(%)            |
| 1G1G | 2G2G N(%)             | 2G2G N(%)            |
| 0.0% | 00% (3.3%)            | 03 (3.2%)           |
| 5A5A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/5A5A | 09 (5.9%) | 03 (3.2%) |
| 5A6A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/5A6A | 11 (11.8%) | 26 (27.95%) |
| 6A6A | 2G2G N(%)             | 2G2G N(%)            |
| 1G1G/6A6A | 13 (8.6%) | 30 (32.3%) |

**Table 6:** The combined effect of polymorphisms of the MMP1 and MMP3 genes on the HR-HPV genotype.

| MMP1 and MMP3 genotypes | HPV16/HPV18 Others HR-HPV | p-value |
|-------------------------|---------------------------|---------|
| 1G1G                    | 3                         | 16      | Ref (1) |
| 1G2G                    | 6                         | 32      | 0.63    |
| 2G2G                    | 3                         | 42      | 0.24    |
| 5A5A                    | 1                         | 8       | Ref (1) |
| 5A6A                    | 9                         | 65      | 0.7     |
| 6A6A                    | 2                         | 17      | 0.7     |

*HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 et 68
did not show a significant difference between the 5A and 6A alleles of MMP3 in infected and uninfected women. However, the frequency of the 1G allele was very high in the group of uninfected women and that of the high 2G allele in the group of women infected with HPV without being statistically significant (p= 0.14). Thus, one could suspect a specific protective role of this variant of MMP-1 in HPV infection through local remodeling of the extracellular matrix. Several studies have already associated a low frequency of the 1G1G genotype and/or the 1G allele with rapid tumor growth [15]. As for the 2G allele, its frequency was high in infected women. Consequently, these women carrying the 2G allele seem to constitute a high risk group for cervical lesions. Authors who have worked on a Chinese population have revealed a high incidence of adenomyosis in homozygotes for the 2G allele [24]. In addition, other studies have also revealed the predominance of the 2G allele in breast cancer compared to controls, with a 2 times higher risk for breast cancer [25] and in the invasive nature of lung cancer and endometrial cancer [26].

By analyzing the distribution of the polymorphism according to the country, the frequency of the 2G and 6A alleles in infected Ivorian women was significantly high (p = 0.0004; p = 0.016).

The action of MMPs could be conceived through certain cellular receptors allowing the attachment of HR-HPV, when it enters the host cell. One of the mechanisms described is the ability of HPVs to bind to certain components of the ECM (such as LN5, syndecan), which then act as receptors for viruses. Indeed, a strong expression of MMPs has been associated with a strong expression of syndecan-1 and syndecan-2 in several biological processes [28, 29]. However, the 2G alleles is associated with high levels of expression of MMP1 and consequently a high expression of LN5 which would promote the attachment of HPV and its internalization in the host cell. There are some biological events involving certain MMPs and/or their mutation in the infectious pathology of viruses, in particular HR-HPV. These are new perspectives that will allow us to investigate the direct interaction between these molecules and the polymorphisms of MMPs.

Conclusion

Our study is a pioneer in the research of genetic factors linked to HR-HPV infection in Burkina Faso and Côte d’Ivoire. Thus, the results obtained are fairly preliminary and these genetic associations should be confirmed in other much larger female populations. In conclusion, we can suggest an association between the port of the 2G-1607 MMP-1 allele and infection with HR-HPV and this variant of the promoter of the MMP-1 gene can be considered as a potential genetic marker of a HR-HPV infection.

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