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PREDICTIVE PLASMA BIOMARKERS FOR CARCINOMA OF CERVIX

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ABSTRACT

Cervical cancer is twelfth most common and the second deadliest cancer in women. About 80% of which occurs in developing countries, where the disease is also the leading cause of cancer-related death among women. Out of which, 20% of all cervical cancers occur in India with 75% of advanced stages. Thus carcinoma of the uterine cervix is the commonest malignancy to affect the female population in India. The main objective of the present study is to find any association between cervical cancer and biochemical genetic markers like Plasma proteins - Haptoglobin [HP] and Group specific component [GC] systems. In the present study, 150 cases (females) presenting Cervical cancer and same number of age and sex matched healthy controls were included. The plasma protein markers HP and GC systems were typed using standard acrylamide gel electrophoresis. The statistical significance of differences between patients and controls were tested. Analysis of the data was carried out using Epi Info 5 software. Pooled odds ratios and relative risk were calculated by the random-effects method. Multifactor Dimensionality Reduction (MDR) analysis was performed using MDR software (v. 3.0.2). The results revealed that the inter group heterogeneity was found to be a significant value, when observed between cervical cancer patients and controls in HP and GC systems. Test of association of HP gene polymorphism showed a highly significant association in dominant model with cervical cancer. A significant association between GC gene polymorphism and cervical carcinoma was observed in homozygote and heterozygote comparison and in recessive model. The risk estimates for all combinations is <1, which indicates that (HP and GC) are protective variants and are associated with a lower risk of developing cervical cancer. In conclusion, we identified Haptoglobin and Group Specific Component in plasma as potential biomarkers related to carcinoma of cervix.

KEYWORDS: Genetic Polymorphisms, Biomarkers, Association, Haptoglobin, Group Specific Component.

INTRODUCTION

A number of genetic polymorphisms exist in human beings, which manifest variable susceptibilities towards pathogenesis and aetiology of a particular disease. Some genetic markers might be serving some hidden important biological functions for understanding the biological significance of polymorphisms in man. Special attention is being diverted towards the relationship between the genetic markers and human diseases. A biochemical marker will influence disease susceptibility which implies that some product related to gene determining biochemical trait or possibly the product of some closely linked genes take part in the complex mechanism influencing diseases. Biochemical genetic markers are of considerable importance in disease association studies. Global analysis of plasma proteins (plasma proteomics) in relevant clinical samples is a key approach for the detection of molecules that may be differentially expressed with disease, and as such are of utility as bio-markers for the early detection of disease.

Cancer is a complex disease involving multiple genetic and environmental risk factors. To clarify the contribution of genetic factors and decipher the relationship between genes, environment, and cancer, association studies are generating much genetic information. This has often taken the form of studying single nucleotide polymorphisms in different genes. Analyzing such data is challenging, and raises the issues of multiple comparisons and potential false-positive associations. [1] Cervical cancer (CxCa) is the second leading cause of cancer-related deaths after breast cancer, for women between 20 and 39 years old. [2] Infection by the human papillomavirus (HPV) is considered as the central risk factor for CxCa.[3] However, it is unlikely to be the sole cause for developing cancer. Ongoing research investigates the role of specific genetic and environmental factors in determining HPV persistence and subsequent progression of the disease.[4] In this context, genetic association studies constitute a significant scientific approach that may lead to a more comprehensive and holistic insight on the origin of complex diseases, such as CxCa.[5] Genetic association studies aim to detect association between one or more genetic variants (for example, polymorphisms) and a trait, which might be some quantitative characteristic, a discrete attribute, or a disease.[6]

The existence of genetically determined polymorphisms of plasma proteins has led to a number of investigations into the possible correlations between these genetic markers and human diseases. We report here the polymorphism data of two genetic markers namely, Haptoglobin (HP) and Group Specific Component (GC) systems in cervical cancer patients. The main objective of the present study is to determine whether these two genetic markers are predictors of cervical cancer.

MATERIAL AND METHODS

In this study, 150 cervical cancer patients were enrolled for plasma protein analysis. 150 members of age and sex matched healthy individuals with no known history of any disease were taken as controls. The study was ethically approved for collecting blood samples from the human subjects by the local [Andhra University] ethics committee. Blood samples were collected from local cancer hospitals, Visakhapatnam, the North Coastal region of Andhra Pradesh, South India. Samples were collected in sterile vials containing 15% EDTA as an anticoagulant from both cancer patients and controls. The plasma was separated and DNA was isolated and stored at -20°C until use. The plasma protein markers - Group specific component (GC) were typed by acrylamide gel electrophoresis [7] and Haptoglobin (HP) as described by Clark.[8]

STATISTICAL ANALYSIS

Analysis of the data was carried out using Epi Info (v.5). In addition, the gene frequencies were estimated by using maximum likelihood methods[9] and goodness of fit between the observed and expected phenotype frequencies were tested.[10] Genotype frequencies were checked for deviation from Hardy–Weinberg equilibrium and were not significantly different from those predicted. Odds ratios and 95% confidence interval (95% CI) were calculated to assess the strength of the relationship between different phenotypes of the two genetic polymorphisms HP and GC with cervical cancer. Pooled odds ratios and relative risk were calculated by the random-effects method.[11] For odds ratio, confidence interval was calculated. The significance level was 5%.

Multifactor Dimensionality Reduction (MDR) analysis was performed using MDR software (v. 3.0.2) to study case-control data, gene-gene interactions and gene-environment interactions.[12,13] Best models with possible combinations of the polymorphisms were considered based on 10-fold cross validation and maximum testing accuracy. Once MDR identifies the best combination of factors, the final step is to determine which multifactor

levels (genotypes) are high risk and which are at low risk using the entire data set. This final evaluation is conducted with a threshold ratio that is determined by the ratio of the number of affected individuals divided by the number of unaffected individuals in the data.

RESULTS

The results of the two genetic markers namely, Haptoglobin (HP) and Group Specific Component (GC) systems in cervical cancer patients and controls were summarized.

HAPTOGLOBINS

Distribution of phenotypes and allele frequencies of genetic marker Haptoglobin was shown in **Table 1**. The frequency of HP*1 and HP*2 alleles in patients are 11% and 89% and in controls it was 20% and 80% respectively. The disease group showed predominant occurrence of HP 2-2 phenotype. The Chi-square test for homogeneity was found to be non-significant ($\chi2 = 0.1716$; df = 1, $0.70>p>0.50$) in controls and in cervical cancer patients ($\chi2 = 0.5669$; df = 1, $0.50>p>0.30$). The inter group heterogeneity was also found to be ($\chi^2 = 8.3050$; df = 2; $0.05>p>0.01$), a significant value when observed between cervical cancer patients and controls.

Association between different combinatory forms of alleles is estimated. Test of association of HP phenotypes with the disease condition compared to the control group, the odds ratio and relative risks are shown in **Table 2.** No significant association between HP gene polymorphism and cervical carcinoma was observed in the homozygote comparison (1-1 vs 2-2: RR = 0.17, OR = 0.16, 95%CI = 0.01-1.48, $\chi2 = 3.44$, p = 0.0637), heterozygote comparison (1-1 vs 2-1: RR = 0.33, OR = 0.31, 95%CI = 0.01-2.93, $\chi2 = 1.24$, p = 0.2659), recessive model (1-1 vs 2-1/2-2: RR = 0.20, OR = 0.19, 95%CI = 0.01-1.74, $\chi2 = 2.72$, p = 0.0990) and allele contrast (1 vs 2: RR = 0.55, OR = 0.49, 95%CI = 0.21-1.17, $\chi2 = 3.09$, p = 0.0787), while high significance was found in dominant model (1-1/2-1 vs 2-2: RR=0.61, OR = 0.50, 95%CI = 0.29-0.86, $\chi2 = 7.14$, p = 0.0075).

In dominant model of inheritance, the odds ratio for individuals with 1-1/2-1 phenotype to develop the disease under study for carriers of allele 1 is 0.50. Since this OR is lower than 1, the allele 1 is a protective factor for cervical cancer. The odds of 2-2 individuals to develop cervical cancer, is 1/0.50 = 2 times higher than those of patients. In recessive model of inheritance, the individuals with 1-1 phenotype are 1-0.19 = 0.81 times less likely, with respect to odds, to get cervical cancer or they have 81% lower odds to get cervical cancer.

The Relative risk of haptoglobins for all combinations is <1, which indicates that (HP) is a protective variant and is associated with a lower risk of developing cervical cancer. Having a protective genetic variant can actually decrease the likelihood that you will develop a disease. When a person who has two copies of this protective variant (1-1) is compared to a person that has no copies of the protective variant (2-2), the individual with two copies of protective genetic variant is 83% less likely (relative risk =0.17) to develop cervical cancer.

Table1: Analysis of association between Haptoglobin (HP) polymorphism and risk for cervical carcinoma

System	Genotype	Cervical Cancer Patients		Controls	
		Observed	Expected	Observed	Expected
HP	1-1	01.00	01.90	05.00	05.80
	2-1	32.00	30.10	49.00	47.40
	2-2	117.00	117.90	96.00	96.80
	Total	150.00	150.00	150.00	150.00
Chi-square (χ^2)		χ^2= 0.5669^{NS} (0.50>p>0.30)		χ^2=0.1716^{NS} (0.70>p>0.50)	
HPAlleles 1 2		0.1100 ± 0.0181 0.8900 ± 0.0181		0.2000 ± 0.0231 0.8000 ± 0.0231	
Intergroup Heterogeneity		χ^2= 8.3050* (0.05>p>0.01)			

***p<0.05, **p<0.01, ***p<0.001, NS Non-significant**

Table 2: Test of Association, Relative Risk, Odds Ratio and 95% Confidence Interval estimates of Haptoglobin (HP) genotypes in disease and control groups

Haptoglobin (HP)	Genotype combinations	Disease and Control groups				
		RR	OR	95%CI	χ^2 value	p- value
Homozygote Comparison	1-1 vs 2-2	0.17	0.16	0.01-1.48	3.44	0.0637
Heterozygote Comparison	1-1 vs 2-1	0.33	0.31	0.01-2.93	1.24	0.2659
Dominant Model	1-1/2-1 vs 2-2	0.61	0.50	0.29-0.86	7.14**	0.0075
Recessive Model	1-1 vs 2-1/2-2	0.20	0.19	0.01-1.74	2.72	0.0990
Allele contrast	1 vs 2	0.55	0.49	0.21-1.17	3.09	0.0787

***p<0.05, **p<0.01, ***p<0.001, NS Non-significant**

Table 3: Comparative table of Haptoglobin and cancer Gynecological tumors

Neoplasia	Sn	Author	Year	Country	Case/ Ctrl (N)	Conclusions
Breast cancer	1	Tsamantains[14]	1980	Greece	109	Overrepresentation of HP1 allele
	2	Kaur[15]	1984	India	50/50	Overrepresentation of HP1 allele
	3	Bartel[16]	1985	Germany	246	Overrepresentation of HP1 allele
	4	Awadallah[20]	2004	Jordan	200/129	Higher frequency of HP1 allele
	5	Atoum[20]	2004	Jordan	42/86	Higher frequency of HP1& 2 alleles
	6	Hudson[17]	1982	USA	-	No association
	7	Gast[18]	2008	USA	371	No association
	8	Ibrahim[19]	2012	Sudan	56/39	No association
Ovarian Cancer	1	Dobryszyck & Wavas[21]	1983	Polland	114/132	Associated HP1 allele
	2	Fröhlander &Stendah[22]	1988	Sweden	182	Associated HP*2-1 phenotype
	3	Ibrahim[19]	2012	Sudan	24/39	No association
Cervical Cancer	1	Present Study	2015	India	150/150	HP*2 alleles as the most represented
	2	Larkin[25]	1967	USA	256/430	HP*2 alleles as the most represented
	2	Milunicova[23]	1969	Checoslovakia	85/170	HP1 allele carriers are at risk
	3	Bartel[24]	1985	Germany	256/430	HP1 allele carriers are at risk
	5	Mahmud[26]	2007	Canada	307/358	In HPV positive women, risk for HP1-1 is higher CIN III
	7	Quaye[27]	2009	Ghana	60/120	Decreased risk for HP*2-2 individuals
	6	Bicho[28]	2011	Portugal	196/396	In ICC women the risk for HP1-1 carriers is greater.
	8	Ibrahim[19]	2012	Sudan	22/39	No association

Table 3 depicts that comparative table of Haptoglobin and cancer gynecological tumors. Geographic differences have been reported regarding the influence of the HP alleles in cancer risk. HP 1-1 is over represented in patients with breast cancer in three earlier studies[14,15,16] while no such association was found between HP phenotypes and susceptibility to breast cancer in three other studies.[17,18,19] Whereas, Awadallah and Atoum[20] concluded that the distribution of the HP phenotype in breast cancer patients depended on the family history, the HP*1 and HP*2 allele frequencies being higher in patients with familial and non-familial breast cancer, respectively. The HP*1 gene is over represented in ovarian carcinoma,[21] and an association has been reported between the HP 2-1 phenotype and a family history of ovarian carcinoma.[22] Milunicova[23] and Bartel[24] indicated that HP*1 allele carriers were at

risk of cervical cancer development. In opposition our study and Larkin reported that the HP*2 allele as the most represented in their cervical cancer cases.[23,24,25]

GROUP SPECIFIC COMPONENT

Distribution of phenotypes and allele frequencies of genetic marker Group specific component (GC) was shown in **Table 4**. The frequency of GC*1 and GC*2 alleles in patients are 57% and 43% and in controls it was 68% and 32% respectively. The disease group showed predominant occurrence of homozygous 2-1 phenotype. The Chi-square test for homogeneity was found to be non-significant ($\chi 2 = 0.0577$; df = 1, 0.90>p>0.80) in controls and was significant in cervical cancer patients ($\chi 2 = 4.2044$; df = 1, 0.05>p>0.01). The inter group heterogeneity was also found to be ($\chi^2 = 11.1740$; df = 2; 0.01>p>0.001), a significant value when observed between cervical cancer patients and controls.

Association between different combinatory forms of alleles is estimated. Test of association of HP phenotypes with the disease condition compared to the control group, the odds ratio and relative risks are shown in **Table 5**. No significant association between GC gene polymorphism and cervical carcinoma was observed in the dominant model (1-1/2-1 vs 2-2: RR=0.96, OR = 0.69, 95%CI = 0.33-1.45, $\chi 2 = 1.08$, p = 0.2976) and allele contrast (1 vs 2: RR = 0.84, OR = 0.62, 95%CI = 0.34-1.16, $\chi 2 = 2.58$, p = 0.1081), while significance was found in homozygote comparison (1-1 vs 2-2: RR = 0.81, OR = 0.44, 95%CI = 0.19-0.98, $\chi 2 = 4.82$, p = 0.0281), heterozygote comparison (1-1 vs 2-1: RR = 0.63, OR = 0.45, 95%CI = 0.26-0.76, $\chi 2 = 10.09$, p = 0.0014), recessive model (1-1vs 2-1/2-2: RR = 0.60, OR = 0.44, 95%CI = 1.36-3.74, $\chi 2 = 11.17$, p = 0.0008).

In dominant model of inheritance, the odds ratio for individuals with 1-1/2-1 phenotype to develop the disease under study for carriers of allele 1 is 0.69. Since this OR is lower than 1, the allele 1 is a protective factor for cervical cancer. The odds of 2-2 individuals to develop cervical cancer, is 1/0.69 = 1.4 times higher than those of patients. In recessive model of inheritance, the individuals with 1-1 phenotype are 1-0.44 = 0.56 times less likely, with respect to odds, to get cervical cancer or they have 56% lower odds to get cervical cancer.

The Relative risk of Group specific component for all combinations is <1, which indicates that (GC) is a protective variant and is associated with a lower risk of developing cervical cancer. Having a protective genetic variant can actually decrease the likelihood that you will develop a disease. When a person who has two copies of this protective variant (1-1) is

compared to a person that has no copies of the protective variant (2-2), the individual with two copies of protective genetic variant is 19% less likely (relative risk =0.81) to develop cervical cancer.

Table 4: Analysis of association between Group Specific Component (GC) polymorphism and risk for cervical carcinoma

System	Genotype	Cervical Cancer Patients		Controls	
		Observed	Expected	Observed	Expected
GC	1-1	42.00	40.30	70.00	69.40
	2-1	86.00	61.30	64.00	65.30
	2-2	22.00	23.30	16.00	15.40
	Total	150.00	150.00	150.00	150.00
Chi-square (χ^2)		χ^2= 4.2044* (0.05>p>0.01)		χ^2=0.0577^{NS} (0.90>p>0.80)	
GC Alleles 1 2		0.5700 ± 0.0313 0.4300 ± 0.0313		0.6800 ± 0.0269 0.3200 ± 0.0269	
Intergroup Heterogeneity		χ^2= 11.1740** (0.01>p>0.001)			

***p<0.05, **p<0.01, ***p<0.001, NS Non-significant**

Table 5: Test of Association, Relative Risk, Odds Ratio and 95% Confidence Interval estimates of Group Specific Component (GC) genotypes in disease and control groups

Group Specific Component (GC)	Genotype combinations	Disease and Control groups				
		RR	OR	95%CI	χ^2 value	p- value
Homozygote Comparison	1-1 vs 2-2	0.81	0.44	0.19-0.98	4.82*	0.0281
Heterozygote Comparison	1-1 vs 2-1	0.63	0.45	0.26-0.76	10.09***	0.0014
Dominant Model	1-1/2-1 vs 2-2	0.96	0.69	0.33-1.45	1.08	0.2976
Recessive Model	1-1 vs 2-1/2-2	0.60	0.44	0.27-0.74	11.17***	0.0008
Allele contrast	1 vs 2	0.84	0.62	0.34-1.16	2.58	0.1081

***p<0.05, **p<0.01, ***p<0.001, NS Non-significant**

MDR ANALYSIS

MDR software was used to analyze the interaction of the 2 factors that may affect the cervical cancer, and the results were detailed in **Tables 6** and **7**. We found that the cross-validation (CV) consistency of the two-factor model (HP and GC) was maximal (10/10), and the accuracy of the test samples was the highest (0.5933). Permutation testing was used to perform a hypothesis test and evaluate its statistical significance. Thus, the two-factor interaction model was the best model, which shows that there was an interaction between the two genetic markers (p<0.001). The 2-way model is found to be significant. **Table 7** summarizes the two locus phenotype combinations associated with high risk and with low risk, along with the corresponding distribution of cases and of controls, for each multi locus

genotype combination. The cell is labelled as either high risk if the case–control ratio reaches or exceeds a predetermined threshold (for example, ≥1) and low risk if it does not reach this threshold (Graphs 1 & 2). The interaction information analysis revealed a strong synergism between the two markers HP and GC, contributing to cervical cancer.

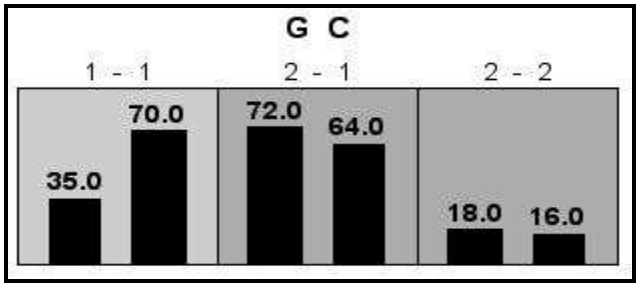
Table 6: Results of MDR analysis on genetic factors

No. of loci	Polymorphism Model	Testing Accuracy	CVC	Prediction error (%)
1	GC	0.5933	10/10	40.67**
2	HP, GC	0.5933	10/10	40.67**

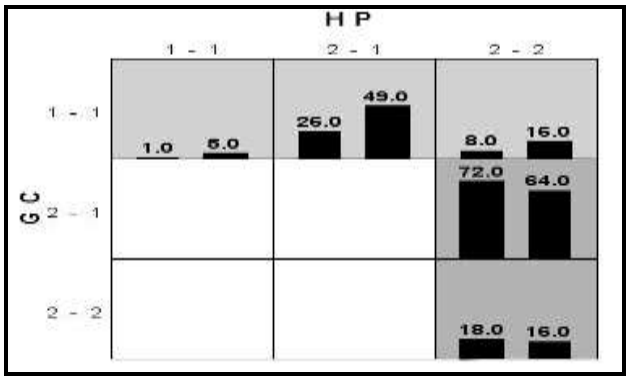
**P≤0.01 based on 1000 permutations.

Table 7: Distribution of high-risk and low-risk genotypes in the best two locus model

Pattern	Multilocus–genotype combinations		Number of		Case/control ratio	Association with cardiomyopathy
	HP	GC	cases	controls		
1	1-1	1-1	1	5	0.2	Low-risk
2	2-1	1-1	26	49	0.5306	Low-risk
3	2-2	1-1	8	16	0.5	Low-risk
4	2-2	2-1	72	64	1.125	High-risk
5	2-2	2-2	18	16	1.125	High-risk

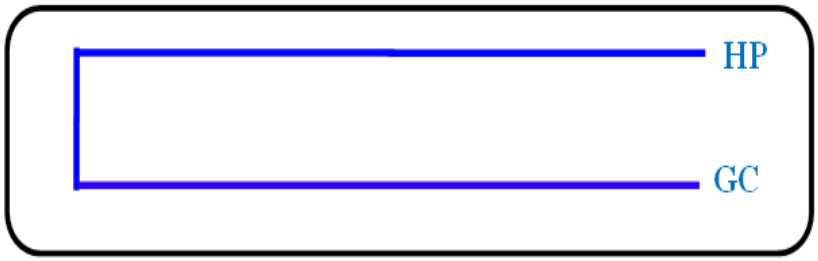


Graph 1: An MDR Analysis of the one-factor GC- Interaction Model of Ca-Cx



Graph 2: An MDR Analysis of the Two-factors (HP, GC) - Interaction Model of Ca-Cx

In the cell in the figure, the left bands represent the disease case, and the right bands represent the control case. High-risk combinations are depicted as darkly shaded cells, low-risk combinations as lightly shaded cells.



Graph 3: A Tree Diagram of the Interactions among two factors (HP and GC) for Ca-Cx, as analyzed by MDR

The dendrogram (Graph 3) depicts the location of longitudinal connecting bars indicating the strength of the dependence: Blue bars represent stronger associations.

DISCUSSION

Smithies[29] identified the presence of a genetic polymorphism in the HP gene. Haptoglobin is a hemoglobin-binding protein expressed by a genetic polymorphism as three major phenotypes: 1-1, 2-1 and 2-2. Free HB from lysed erythrocytes is eliminated by glomerular filtration, and this can cause renal damage. HP reduces the loss of HB and iron because the HP-HB complex is not filtered through the glomeruli[30-33] 1 g of the HP 1-1 protein contains more αβ-subunits than 1 g of HP 2-1 or HP 2-2 protein, giving the HP 1-1 protein the ability to bind more hemoglobin than the other two HP types.[30] Due to the smaller size of the HP 1-1 protein, it is more effective in sieving into environments where the HP 2-2 protein might be restricted, thereby offering superior protection against hemoglobin in these environments.[30] The HP 1 protein is more efficient in preventing oxidation by hemoglobin and in preventing heme release from the HP-HB complex.[34,35]

The association of haptoglobin phenotypes with different clinical conditions has become of great interest to researchers. HP 1-1 is a much better antioxidant than HP 2-2.[36] On the other hand, HP 2-2 is more angiogenic than other phenotypes.[37,38] There is marked variation in the frequency of HP genes with geographic region.[39,40] The HP*2 allele originated in India and propagated around the world as a result of intense genetic pressure, gradually replacing the hegemony of the HP*1 allele. This suggests that the HP*2 allele may have a selective advantage over the HP*1 allele.[40] The frequency of the HP*1 allele increases from Southeast Asia to Europe and Africa and from Asia to America, by way of Alaska. The equilibrium of the HP*1/HP*2 polymorphism is broadly constant throughout the world. In India, the frequency of HP*2 allele is high at the population level (84%) which is in consistent with our HP*2 allele frequency (89%).

Several functional differences between haptoglobin phenotypes have been demonstrated that appear to have important biological and clinical sequences. Haptoglobin polymorphism is associated with the prevalence and clinical evolution of many inflammatory diseases, including infections, atherosclerosis and autoimmune disorders.[41] The HP concentration in humans is generally stable but changes with age. Haptoglobin levels may be affected by the HP phenotype, with circulating concentrations in the following order HP1-1 > HP 2-1 > HP 2-2.[30,42]

The strong genetic pressure favoring the 2-2 phenotype suggests an important role of haptoglobin in human pathology. Cervical neoplasia is a good model that illustrates haptoglobin and its polymorphism influence in the several steps of its natural history interacting with oncogenic and non-oncogenic HPV (Human Papillomavirus) and other co-factors such as sexual steroid hormones and smoking habits.[43,44] Larkin demonstrated in 1967 that, in cervical cancer patients, the frequency of HP 2-2 is higher compared to normal controls. Our results were consistent with this study. Moreover, a decrease in HP 2-1 phenotypes among cases with benign and malignant neoplasm of the cervix and cervical carcinomas was reported in our study. There was a significant association when observed between cervical cancer patients and controls. Whereas, it was demonstrated that HP*1 allele carriers are at risk for cervical cancer by Milunicova[23] and Bartel.[24] There was no association found between HP phenotypes and susceptibility to different female's gynecological cancers in Sudan.[19]

HP has been found to be produced at a high level in the tumor tissue.[45] Probably the most important biological function of HP consists in the host defence responses to infection and inflammation, acting as a natural antagonist for receptor-ligand activation of the immune system. Therefore, HP immune modulatory effects and HP levels should be investigated to be used as a marker to assess the susceptibility to different types of cancer, and to assess the success of treatment and the recurrence of the disease. Also, Base-line data on HP phenotypes and levels in relation to different ethnic groups is important information to monitor the malignant diseases. Further investigations on a larger number of females with cervical cancer are needed to confirm the present findings. Furthermore, HP phenotypes and levels in each cancer type for each susceptible organ, in familial and non-familial types of cancer need to be fully investigated in large scales.

Vitamin D-binding protein, also known as GC-globulin (group-specific component), is a protein that in humans is encoded by the GC gene.[46] Human group-specific component (GC) is the major vitamin D-binding protein in plasma.[47] It binds to vitamin D and its plasma metabolites and transports them to target tissues (Entrez gene). As GC protein-derived macrophage activating factor, it is a Macrophage Activating Factor (MAF) that has been tested for use as a cancer treatment that would activate macrophages against cancer cells.[48]

Vitamin D metabolites exert significant antineoplastic activity in preclinical models. Vitamin D activity and role has been especially investigated for prostate, breast, colorectal, and skin cancer.[48-50] Vitamin D may also play a role in the genetic predisposition to cancer development. A low vitamin D activity is associated with an increased cancer risk and a more aggressive tumor growth, while high activity of this pathway induces anti-tumoral effects. In particular, serum circulating levels of 25(OH) D levels <20 ng/ml seems to expose to the risk of developing mammary and colorectal cancer. About 200 different SNPs of VDR have been described. There are indications that GC 1-1 may be associated with Psoriasis and less probably with Carcinoma of the uterus, Neurodermatitis, Diabetes mellitus and Rheumatoid Arthritis. But in our study, the disease group showed predominant occurrence of homozygous 2-2 phenotype and there was a significant association observed between cervical cancer patients and controls. Therefore, vitamin D has a prominent role in natural tumorocidal activity of immune system as an initial precursor. However, data available now are often contradictory and it is still not possible to achieve any conclusion about the correlation between VDR genotype and cancer occurrence.

CONCLUSIONS

In conclusion, we identified Haptoglobin and Group Specific Component in plasma as potential biomarkers related to carcinoma of cervix. However, diverse geographic regions, with very different distribution of alleles, various genetic variation backgrounds and above all, having different environments that interact with genomes to give highly variable phenotypes, may explain controversial results. Therefore, further functional studies of these proteins will provide more information on their roles in the development and progression of cervical cancer.

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DISCLOSURE OF INTEREST

The authors have no conflicts of interest to declare.

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