Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 8143 - 8147
Received 16 February 2021; Accepted 08 March 2021.

Polymorphism of *CYP1A1* Gene and the variation in rs4646903, rs1048943 that occurs of Cervical Cancer in Iraq

Rawaa Abdul-Ameer Abdul-Jabbar[1], Ghanyia Jasim Shanyoor[2]

[1]Biology Department, College of Science, Mustansiriyah University, Baghdad, Iraq.

E-mail: rawaaattar@uomustansiriyah.edu.iq

[2]Biology Department, College of Science, Mustansiriyah University, Baghdad, Iraq.

ABSTRACT

Background: Cervical cancer is a type of cancer which occurs due to the abnormality in the cervix cells. **Objective**: this study aimed to inspect the relationship between cervical cancer risk and the polymorphism of CYP1A1 gene. **Materials and Methods**: 80 females were selected in this study (40 patients with cervical cancer, and 40 normal considered as control group), the age mean was 40±15.2 for the patients and 39±14.9 for control group, this study was achieved in Alwayia Hospital for Gynecology and Obstetrics, Baghdad for the period (December, 2019 to April, 2020). SNP polymorphism and the risk of cervical cancer were investigated in both individuals. SNP-SNP was analyzed by the means of GMDR (Generalized Multifactor Dimensionality Reduction). **Results**: the OR (95%CI), and the odds intended to were carried out to find the relation between rs1048943 and rs4646903 such as GG or AG of rs1048943, and CC or TC OF rs4646903 genotypes which the researchers expect to have main risk for cervical cancer, and then the results were compared with AA, and TT, and it was found that the combination of rs104893 and rs4646903 will give a validation of 100/100, while the accuracy of test was 0.5989, and the p-value was 0.0105. **Conclusions**: there is association between cervical cancer and the variant genotypes, and there is opportunity of interference that CC or TC subjects, and GG or AG that belongs to rs4646903 and rs108943 respectively.

KEYWORDS

Polymorphism, CYP1A1, rs104893, rs4646903, Cervical Cancer, Iraq.

Introduction

Cancer is the most dangerous diagnosis in human and cervical cancer considered as one the cancer that happened due to the abnormality in the cervix cells, precisely in the uterus which affects the lower division attached and joined with vagina (Vijaylakshmi, J. *et al.*, 2017; Hoidy, W.H . *et al.*, 2019; Jemal A, *et al*., 2011). Different infections and strain can contaminate this part of female's body, and Human Papilloma Virus (HPV) can consider as the most familiar one that may cause cancer in cervical, and mostly the HPV virus transferred through skin-skin rubbing (friction contact), or sexually, which play the main role in infection (Ferlay J, *et al*., 2010). However, when human infected with HPV viral, the immune system spontaneously respond to avoid the consequences and stop the progression of harming, yet the virus may remain for months and sometimes for years which may eventually cause cancer (Wright, C.M. *et al.*, 2010; Wang X, *et al.*, 2019; Iida H., *et al*., 2009).

CYP1A1 gene polymorphism is the most significant threat and risks that cause the interaction and linking between rs1048943 and rs4646903 which increases the risk of cervical cancer due to the functional and efficient changes that occurs in the enzyme which could cause cancer (Sengupta, D. *et al.*, 2018; Chen D., *et al.*, 2015).

This study was carried out find the association of CYP1A1 gene polymorphism and the interaction and linking between rs1048943 and rs4646903.

Materials and Methods

The current study was carried on Alwayia Hospital for Gynecology and Obstetrics, Baghdad for the period (December, 2019 to April, 2020), the study was carried out on 80 individuals, 40 of them were considered as control group (they were healthy, and they do not shows any symptoms of cervical cancer, and no changes in genotype or disorders), while the other 40 patients were subjected to different tests according to Rotterdam consensus criteria.

The SNPs tag in CYP1A1 was chosen as an important factor, the test was carried out in accordance with 1000 Genomes Project protocol (https://www.coriell.org) and Rotterdam 2004 (Rotterdam EA, 2004). The genomic DNA was achieved according to methods carried out by Lei et al., 2005, and the method explained by Cai et al.,

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 8143 - 8147
Received 16 February 2021; Accepted 08 March 2021.

2013 (Cai L., *et al.*,2013) . The clinical tests were carried out as considered by Li et al, 2017 (Li S, *et al.*, 2017).

Extraction and Genotyping to Genomic of DNA

The selection of CYP1A1 gene and the SNPs was achieved in accordance to a certain rules, as: MFA (Minor Allele Frequency), and Its relation with cervical cancer. Two SNPs of CYP1A1 were chosen in this research: rs1048943, and rs4646903, the Genomic DNA was extracted from individuals (patients and control) in accordance to the method explained by Lou and his coworkers in 2007 (Lou XY., *et al.*, 2007), and by Li and his coworkers in 2016 (Li S., *et al.*, 2016). The genotype sequence of both genotypes (rs1048943, and rs4646903) was listed in table 1.

Table 1. Probe sequence description for 2 SNPs (according Taqman Fluorescence)

Chromosome	SNP	Sequence	Allele	Consequence
15:74720644	rs1048943	5'-CAAGCGGAAGTGTATCGGTGAGACC[A/C/G/T]TTGCCCGCTGGGAGGTCTTTCTCTT-3;	A/G	Missense
15:74719300	rs4646903	5'- TTGTTTCACTGTAACCTCCACCTCC[A/C/T]GGGCTCACACGATTCTCCCACCTCA-3'	T/C	Downstream variant 500B

Statistical Analysis

The standard deviation (SD) and the mean for the variables, as well as the percentages were compared and calculated. All the data were analyzed and statistically studied using SPSS package version 25.0 was used to carry out these analyses, as well as (http://bioinfo.iconcologia.net/SNPstats), and Hardy–Weinberg equilibrium (HWE).

Results

The regression was achieved logistically and relation between cervical cancer and SNP was carried out by adding a model like age, and smoking as well with WC and BMI with other factors as shown in table 2 according to Lou and his coworkers in 2007 (Lou XY, *et al.*, 2007).

Table 2. General characteristics of the study groups (both patients and control)

Variables	Control group (n=40)	Patients (40)	*P*-Value
Age (years)	40±15.2	39±14.9	0.207
BMI (kg/m^2)	25.7±5.9	23.8±6.1	<0.001
WC (cm)	86.5±9.1	84.2±8.9	0.003
HDL (mmol/l)	1.26±0.31	1.29±0.29	0.002
TC(mmol/l)	4.9±1.3	4.8±1.1	0.024
FPG(mmol/l)	6.3±2.5	6.1±2.1	0.269
TG(mmol/l)	1.9±0.7	1.8±0.8	0.112

To find and achieve the OR (95%CI), and the rations of the odds intended to find the relation between rs1048943 and rs4646903 and their effect on the risk of cervical cancer a certain tests and analysis were carried out like GG or AG of 1048943, and CC or TC OF rs4646903 genotypes that have main risk for cervical cancer, and then compare them with AA, and TT. Tables 3, and the relationship and the interaction, it was found that the combination of rs104893 and rs4646903 will give a validation of 100/100, while the accuracy of test was 0.5989,

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 8143 - 8147
Received 16 February 2021; Accepted 08 March 2021.

and the p-value was 0.0105.

Table 4 shows the interference of the risk of cervical cancer and the 2 genes (rs1048943 rs4646903 interactions).

Table 3. Frequencies of allele genotype of 2 SNPs between control group and cervical cancer

SNPs	**Frequency %**					
	Allele	Patients (n=40)	Control (n=40)	95% Cl	*P*-Value	H-W test (control group)
rs4646903	C	19(26.9)	13(21.1)	---	0.003	---
	T	62(72.5)	64(78.2)	---	---	---
	TT	21(52.5)	24(0.60)	1.00	0.008	0.327
	TC	16(40.0)	14((35.0)	1.81-1.17	---	---
	CC	5(8.0)	2(5)	1.23-2.34	---	---
	CC+TC	19(47.5)	15(37.5)	---	---	---
rs1048943	G	11(27.5)	9(22.5)	---	0.271	---
	A	60(73.8)	62(76.9)	---	---	---
	AA	1.0022(55.0)	23(57.5)	1.00	0.529	0.371
	GG	3(7.5)	2(5.0)	0.84-1.52	---	---
	AG	16(40.0)	14(35.0)	0.89-1.37	---	---
	AG+GG	17(42.5)	16(40.0)	(0.88-1.38)	0.304	----

Table 4. Interface linking of the risk of cervical cancer, and the rs4646903 and rs1048943 genes

rs108943	**Rs4646903**	**OR (95%CI)**	***P*-value**
AA	TT	1.00	---
GG or AG	TT	(084-11.52)1.05	0.123
AA	CC or TC	(1.23-2.34)1.19	0.020
GG or AG	CC or TC	(0.88-1.38)2.01	<0.001

Discussion

This research is a first work to study and report the relation between polymorphism of CYP1A1 gene and the risk of cervical cancer in Iraqi women. It was found that there is an important association that occurs in rs4646903 genotypes which increased the risk of cervical cancer due to the mutant in the genotypes (Omiecinski CJ. *et al.*, 1990; He XF., *et al.*, 2014).

The CYP1A1 gene was chosen because this gene belong to the family of CYP gene (Zou JG et al., 2014). which considered as a tissue that referred to extra hepatic that has responsibility of a certain substrates called (endogenous) as well cancer, in addition to its responsibility as a detoxification to a lot of carcinogens by the formation of a certain compound (intermediates), and destroy the DNA. This indicates the association between genotypes (CYP1A1) and different types of cancers such as, prostate, lung, ovarian, pancreatic, breast as well as cervical cancer, these types of cancer were studied and evaluated by many researchers and in different countries, but a very little of them studied the relationship of the cervical cancer with CYP1A1 (Ozturk T, *et al.*, 2011; Li H, *et al.*, 2012; Liu G, *et al.*, 2000; Naif, HN, *et al.*, 2018).

In 2014 Abbas and his coworkers (Abbas M, *et al.*, 2014) shows that the existence of G and C allele in rs1048943 and rs4646903 respectively, could be an indication for the cervical cancer, this can be related to the variant polymorphism of CYP1A1 which affect its enzyme.

In this study, the focus was on the effect of interference of many CYP1A1's SNPs on the cervical cancer, and it was found that CC or TC subjects, and GG or AG that belongs to rs4646903 and rs108943 respectively, are the main risk in cervical cancer, while AA, and TT doesn't have a significance. Also it was found that carcinogens process needs many steps (multistep) and many factors (multifactor), and during this process a lot of biological pathways and alternations in genes will involved because the cancer is considered as a very complex disease that has association with many genes in combination with the environment.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 8143 - 8147
Received 16 February 2021; Accepted 08 March 2021.

Conclusion

- It was found that there is an important association between cervical cancer and the variant genotypes.
- There is a possibility of interference that CC or TC subjects, and GG or AG that belongs to rs4646903 and rs108943 respectively.

References

[1] Jain, V., Ratre, Y.K., Amle, D., Mishra, P.K., & Patra, P.K. (2017). Polymorphism of CYP1A1 gene variants rs4646903 and rs1048943 relation to the incidence of cervical cancer in Chhattisgarh. *Environmental toxicology and pharmacology*, *52*, 188-192. https://doi.org/10.1016/j.etap.2017.04.009

[2] Hoidy, W.H., Jaber, F.A., & Al-Askiry, M.A. (2019). Association of CYP1A1 rs1048943 Polymorphism with Prostate Cancer in Iraqi Men Patients. *Asian Pacific journal of cancer prevention: APJCP*, *20*(12), 3839-3842. https://doi.org/10.31557/APJCP.2019.20.12.3839

[3] Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: a cancer journal for clinicians*, *61*(2), 69-90.

[4] Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C., & Parkin, D.M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer*, *127*(12), 2893-2917.

[5] Wright, C.M., Larsen, J.E., Colosimo, M.L., Barr, J.J., Chen, L., McLachlan, R.E., & Fong, K.M. (2010). Genetic association study of CYP1A1 polymorphisms identifies risk haplotypes in nonsmall cell lung cancer. *European Respiratory Journal*, *35*(1), 152-159. https://doi.org/10.1183/09031936.00120808

[6] Wang, X. E., Li, W., Song, W., Xu, L., Zhang, L., Feng, X., & Meng, H. (2019). Association of CYP 1A1 rs1048943 variant with aggressive periodontitis and its interaction with hyperlipidemia on the periodontal status. *Journal of periodontal research*, *54*(5), 546-554. https://doi.org/10.1111/jre.12658

[7] Iida, H., Kumar, J.V., Kopycka-Kedzierawski, D.T., & Billings, R.J. (2009). Effect of tobacco smoke on the oral health of US women of childbearing age. *Journal of public health dentistry*, *69*(4), 231-241.

[8] Sengupta, D., Guha, U., Mitra, S., Ghosh, S., Bhattacharjee, S., & Sengupta, M. (2018). Meta-analysis of polymorphic variants conferring genetic risk to cervical cancer in Indian women supports CYP1A1 as an important associated locus. *Asian Pacific journal of cancer prevention: APJCP*, *19*(8), 2071-2081. https://doi.org/10.22034/APJCP.2018.19.8.2071

[9] Chen, D., & Gyllensten, U. (2015). Lessons and implications from association studies and post-GWAS analyses of cervical cancer. *Trends in Genetics*, *31*(1), 41-54.

[10] https://www.coriell.org/1/NHGRI/Collections/1000-Genomes-Collections/1000-Genomes-Project?gclid=CjwKCAjw_sn8BRBrEiwAnUGJDjfy-EgAh6gXQLtIPRs_mSxc-s0NdsJXaNDq0YNdowxvYSnmP8JR9RoC5pIQAvD_BwE

[11] Rotterdam EA-SPCWG (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility*, 81(1), 19–25.

[12] Cai, L., Deng, S.L., Liang, L., Pan, H., Zhou, J., Wang, M.Y., & He, L. (2013). Identification of genetic associations of SP110/MYBBP1A/RELA with pulmonary tuberculosis in the Chinese Han population. *Human genetics*, *132*(3), 265-273.

[13] Li, S., Zhao, L., & Wan, X. H. (2017). A missense variant rs4645843 in TNF-α gene is a risk factor of polycystic ovary syndrome in the Uygur population. *The Tohoku journal of experimental medicine*, *243*(2), 95-100.

[14] Lou, X.Y., Chen, G.B., Yan, L., Ma, J.Z., Zhu, J., Elston, R.C., & Li, M.D. (2007). A generalized combinatorial approach for detecting gene-by-gene and gene-by-environment interactions with application to nicotine dependence. *The American Journal of Human Genetics*, *80*(6), 1125-1137.

[15] Li, S., Li, G., Kong, F., Liu, Z., Li, N., Li, Y., & Guo, X. (2016). The Association of CYP 1A1 Gene with Cervical Cancer and Additional SNP–SNP Interaction in Chinese Women. *Journal of clinical*

laboratory analysis, *30*(6), 1220-1225.

[16] Omiecinski, C.J., Redlich, C.A., & Costa, P. (1990). Induction and developmental expression of cytochrome P450IA1 messenger RNA in rat and human tissues: detection by the polymerase chain reaction. *Cancer Research, 50*(14), 4315-4321.

[17] He, X.F., Wei, W., Liu, Z.Z., Shen, X.L., Yang, X.B., Wang, S.L., & Xie, D.L. (2014). Association between the CYP1A1 T3801C polymorphism and risk of cancer: Evidence from 268 case–control studies. *Gene, 534*(2), 324-344.

[18] Zou, J.G., Ma, Y.T., Xie, X., Yang, Y.N., Pan, S., Adi, D., & Chen, B.D. (2014). The association between CYP1A1 genetic polymorphisms and coronary artery disease in the Uygur and Han of China. *Lipids in health and disease*, *13*(1), 1-12. https://doi.org/10.1186/1476-511X-13-145

[19] Öztürk, T., Kahraman, Ö.T., Toptaş, B., Kisakesen, H.I., Cakalir, C., Verim, L., & Isbir, T. (2011). The effect of CYP1A1 and GSTM1 gene polymorphisms in bladder cancer development in a Turkish population. *In vivo*, *25*(4), 663-668.

[20] Li, H., Xiao, D., Hu, L., & He, T. (2012). Association of CYP1A1 polymorphisms with prostate cancer risk: an updated meta-analysis. *Molecular biology reports*, *39*(12), 10273-10284.

[21] Liu, G., Ghadirian, P., Vesprini, D., Hamel, N., Paradis, A.J., Lal, G., & Foulkes, W.D. (2000). Polymorphisms in GSTM1, GSTT1 and CYP1A1 and risk of pancreatic adenocarcinoma. *British journal of cancer*, *82*(10), 1646-1649.

[22] Naif, H.M., Al-Obaide, M.A., Hassani, H.H., Hamdan, A.S., & Kalaf, Z.S. (2018). Association of cytochrome CYP1A1 gene polymorphisms and tobacco smoking with the risk of breast cancer in women from Iraq. *Frontiers in public health*, *6*, 96. https://doi.org/10.3389/fpubh.2018.00096

[23] Abbas, M., Srivastava, K., Imran, M., & Banerjee, M. (2014). Association of CYP1A1 gene variants rs4646903 (T> C) and rs1048943 (A> G) with cervical cancer in a North Indian population. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *176*, 68-74.