Complex Interplay of CYP1A$_1$ Genetic Polymorphism on Colorectal Cancer Susceptibility

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ABSTRACT

*Colorectal cancer (CRC) is one of the most common malignancies in developed countries. It occurs via an interaction between an individual genetic background and environmental parameters such as dietary factors. A number of studies have suggested that dietary procarcinogens, such as heterocyclic amines, N-nitroso compounds and polycyclic aromatic hydrocarbons, might be related to the carcinogenesis of CRC. The carcinogens that cause the development of CRC enter the body as procarcinogens via transporters and are activated to carcinogens or eliminated by various enzymes. These toxicokinetic-related proteins are also controlled by our genetic background (e.g. by genetic polymorphisms).**Aim of work**: To analyze the common genetic polymorphisms in the genes for the metabolic enzymes* CYP1A$_1$ *in an attempt to elucidate the association between these polymorphisms and sporadic cases of colorectal carcinoma among Egyptian patients. **Subjects and Methods**: This is a prospective controlled study where we investigated the association between polymorphism of cytochrome P4501A$_1$ (m2) and colorectal cancer using PCR-RFLPS. Over a period of twenty one months, the present study included forty patients with colorectal carcinoma diagnosed by histopathological examination of tumor biopsy and not on chemotherapy or radiotherapy. Twenty healthy subjects, matched for age and sex were included as a control group. For all subjects, peripheral blood samples were assayed for genetic polymorphism of CYP1A$_1$.**Results:** Our results showed that a statistically significant association existed between CYP1A$_1$ variant genotype (p=0.015 and the odds ratio OR=0.105 with the 95% confidence interval 0.028-0.390) and colorectal cancer. **Conclusion:** The studied polymorphism may be associated with the risk of development of colorectal carcinoma in Egyptian patients however, large scale studies are essential to confirm that association.*

Keywords: Colorectal cancer, CYP1A$_1$, genetic polymorphism

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in both men and women in industrialized countries. In 2000, CRC accounted for 9.4% of the world's new cancers, with 945,000 cases diagnosed and 7.9% of the world's cancer deaths, with 492,000 deaths. In 2008, CRC represented 8.9% of all cancers with lung and breast cancers

having higher incidence (14.5% and 10.8%, respectively)[1, 2]

CRC is more prevalent in North America, Argentina, Australia, New Zealand and parts of Europe, and for this reason it is commonly regarded as a western lifestyle disease. [3]

CRC is one of the most common malignant neoplasms in Egypt, representing 6.5% of cancers and tends to occur in younger Egyptians with no specific predilection to age. However, 29% of the tumors occurred in patients under 30 years and 26% of patients were aged 60 years. The median age of all patients with CRC was 48 years which is younger than that in developed countries. [4,5]

It is widely accepted that colorectal carcinogenesis is a multistep process involving the inactivation of a variety of tumor-suppressor and DNA-repair genes and simultaneous activation of certain oncogenes.[6]

Cancer risk resulting from human exposure to exogenous chemicals (xenobiotics), like polycyclic aromatic hydrocarbons (PAH), which are ubiquitous environmental, dietary, and tobacco carcinogens may vary according to the ability to clear the xenobiotics from the body[1, 2, 6]

Polymorphisms in the genes that encode enzymes involved in the metabolism of PAHs (xenobiotic-metabolizing enzymes), such as the cytochrome P450 group (CYP) and the glutathione-S-transferase group (GST), result in varying activity levels of these enzymes, which can then influence xenobiotic clearance. The metabolism of PAHs involves both activation (phase I) and clearance (phase II) reactions by these enzymes.

During activation, reactive intermediates are formed that can bind to DNA and result in adducts that cause mutations if not repaired, thereby initiating carcinogenesis. [7]

It is likely that the expression and activity levels of the xenobiotic-metabolizing enzymes determine the relative level of activation and detoxification of carcinogens. These levels are important because increased levels of activation, decreased detoxification or both may increase colorectal cancer incidence. [8]

The cytochrome P450 family is a large and diverse group of enzymes. The function of most CYP enzymes is to catalyze the oxidation of organic substances. The substrates of CYP enzymes include metabolic intermediates such as lipids, steroidal hormones, as well as xenobiotic substances such as drugs. [9, 10]

Genes encoding CYP enzymes and the enzymes themselves are designated with the abbreviation CYP, followed by an Arabic numeral indicating the gene family (e.g. CYP1, CYP3), a capital letter A,B,C indicating the subfamily (e.g. CYP1A, CYP3A) and another numeral for the individual gene/isoenzyme/isoform (e.g. $CYP1A_1$. $CYP3A_4$). [11]

These enzymes are variably distributed in tissues, but are mainly present in the liver, the main organ involved in drug and toxin removal, but a remarkable amount is also found in the small intestine. CYP is present in the microsomal part of the cytoplasm. [12]

Cytochrome P450 $CYP1A_1$ is one of the three members of the CYP1 family, which is found mainly in extrahepatic tissues and participates in

the metabolism of a vast number of xenobiotics, as well as a small number of endogenous substrates. Among the different reactions catalyzed by $CYP1A_1$, hydroxylation at a vacant position of an aromatic ring is considered to be the hallmark for the reactive conversion products that can cause oncogenic mutations in experimental animals and humans. [13]

The $CYP1A_1$ gene, located on chromosome 15, band 15q 22-24, comprises seven exons and six introns and spans 5810 base pairs. In humans, $CYP1A_1$ is under regulatory control of the aryl hydrocarbon receptor, a transcription factor that regulates gene expression. [14]

$CYP1A_1$ expression is mediated through a specific cytosolic receptor, the aryl hydrocarbon receptor or AhR. The transcription of $CYP1A_1$ is inhibited by the AhR-related factor aryl hydrocarbon receptor repressor or AhRR, which localizes in the nucleus in the form of a dimeric protein. [15, 16]

Regarding $CYP1A_1$ polymorphism, several mutations in the gene have been described. The four principal sequence variants are a thymine to cytosine substitution at the 3' end of the gene (mutation 1) that gives rise to a Mspl restriction enzyme site, an adenine to guanine substitution (mutation 2), resulting in a IIe-462 Val exchange in the heme binding region of exon 7, an African American-specific thymine to cytosine substitution (mutation 3) in intron 7, and cytosine to adenine variant (mutation 4) resulting in a threonine 461 aspargine amino acid change in the heme-binding site of the enzyme. [17,18]

METHODOLOGY

Sixty subjects were chosen over a 21 month period (1st February 2009- 31st October 2010) from the Department of General Surgery at Cairo University Hospital

Subjects were divided into 2 groups:

- Group 1 included forty patients newly diagnosed with CRC (22 males and 18 females). The mean age was 48.5 ± 11.57years (range from 17-70 years). Sixteen patients were smokers (40%) and only two patients gave a positive family history of colorectal cancer.

- Group 2 included twenty apparently healthy individuals to serve as controls (12 males and 8 females). The mean age was 48.85 ± 12.5years (range from 18-65 years). Eight persons were smokers and none gave a positive family history of colorectal cancer.

All patients were subjected to full history taking and complete clinical examination. In Group 1 patients, radiological assessment including pelvi-abdominal scanning, chest radiography, abdominal sonography, sigmoidoscopy and colonoscopy as well as biopsy and histopathological examination were done.

From each participant in the study, 9 ml of venous blood were drawn and divided into 6ml of blood dispensed into 2 sterile EDTA vacutainer tubes and mixed properly (one for DNA extraction was done without delay, the other for CBC), and the other 3ml of blood were dispensed into sterile plain vacutainer tubes, centrifuged for 10 minutes at

3000rpm, and the separated serum was used for tumor marker evaluation and routine chemistry analysis.

All sixty subjects underwent laboratory investigations including CBC, kidney and liver functions, tumor markers (CEA and CA 19-9), genetic analysis of $CYP1A_1$ gene polymorphism for detection of $CYP1A_1$ A4887G (m2) using PCR-RFLP.

Genomic DNA extraction from peripheral blood leucocytes was done using Qiagen GmbH (Hoffman La Roche AG Max-Volmer-Strabe 4-40724-Hilden-Germany). The analysis of C.T transversion at position 4887 in exon 7 of $CYP1A_1$, which results in the replacement of Thr by Asn at residue 461 in the heme binding region of the enzyme, was performed using PCR-RFLP as described by **Cascorbi and co-workers** [19]. Extracted DNA samples were amplified using M2F, 5⁻ CTGTCTCCCTCTGGTTACAGGAAGC and M2R, 5'⁻ TTCCACCCGTTGCAGCAGGATA GCC primers PCR was performed for 40 cycles with denaturing at $95^{o}C$ for 1 min, annealing at $56^{o}C$ for 1 min and extension at $72^{o}C$ for 1 min. The PCR products were then digested with Bsa1 enzyme (New England-Bio Labs Catalog No. 18006327799) at $37^{o}C$ overnight, then subjected to electrophoresis in ethidium-bromide-stained 3% agarose gel and visualized by ultraviolet light transillumination to detect m2 mutation.

Statistical analysis: All our data were statistically described in terms of range, mean standard deviation (+/- SD), frequencies and related frequencies when appropriate.

Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square test was performed. Exact test was used when the expected frequency is less than 5. Multivariate logistic regression analysis was done to rest the effect of all important factors on the occurrence of CRC in the study sample. A probability value (p value) less than 0.05 was considered statistically significant.

RESULTS

In the current study both groups were age and sex matched (p›0.05) and no significant difference in smoking could be detected (p=0.22). Concerning the site of the carcinoma, we detected a higher prevalence of distal tumors in the sigmoid colon and rectum (57.5%). The main presenting symptom in our patients was bleeding per rectum (37.5%), diarrhea (25%), abdominal pain (22.5%), and constipation (15%).

On comparing the levels of the tumor markers CEA and CA 19-9 between cases and controls, a statistically significant difference was detected between the two groups (p=0.042 and 0.0264), respectively.

Biopsies from our patients revealed adenocarcinoma in 87.5% (35/40), mucinous adenocarcinoma in 7.5 % (3/40) and signet cell ring adenocarcinoma in 5% (2/40)of cases.

The *BSA I* RFLP analysis for $CYP1A_1$ polymorphism revealed three genotypes; IIe/IIe; homozygous for the presence of the cut site

(homozygous wild-type allele) with two bands at 150 bp and 65 bp, IIe/Val heterozygous (heterozygous genotype) for the presence of the cut site with three bands at 204 bp, 150 bp and 65 bp and Val/Val homozygous (homozygous rare mutant allele) type for the absence of the cut site with an undigested band at 204 bp (Figure 1)

In $CYP1A_1$ gene polymorphism, the cases included 5/40 (12.5%) with $CYP1A_1$ (m2) mutation compared to 1/20 (5%) in the control group. A statistically significant difference was detected on comparing the incidence of $CYP1A_1$ mutation between the two groups; p=0.015 and the odds ratio OR= 0.105 with the 95% confidence interval (C.I)(0.028-0.390). (Table 1)

No statistically significant differences were found between the incidence of $CYP1A_1$ mutation and the age of patients (p=0.296), smoking (p=0.051), site of the tumor whether proximal or distal tumors (p=0.904). (Tables 2, 3, and 4)

On investigating the association between $CYP1A_1$ mutation and sex of CRC patients, it was found that 5/5 (100%) of patients with the mutation were males, while none of the patients having the mutation was a female. This difference was statistically significant; p= 0.031. (Table 5)

All five patients with the $CYP1A_1$ mutation had adenocarcinoma; two patients were 55 years old, while the other three patients were 42, 50 and 59 years old. Two tumors were found in the rectum, while the other three tumors were detected in the cecum, descending colon, and sigmoid colon. High levels of CEA (above 5ng/ml) were detected in three patients (60%), whereas elevated levels of CA 19-9 (above 40 U/ml) were found in four patients (80%).

The association between $CYP1A_1$ polymorphism and the pathological type of malignancy showed no statistical significance; p=0.665, in which 100% of patients with variant genotype had adenocarcinoma and none had mucinous or signet ring cell adenocarcinoma. (Table 6)
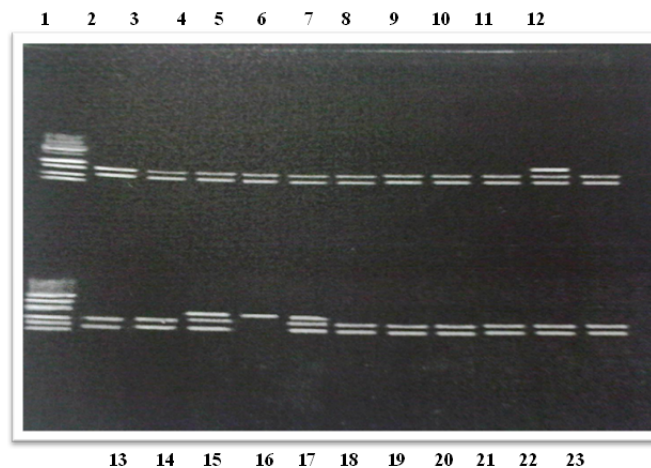
Figure (1): gel electrophoresis showing the CYP1A₁m2 mutation gene polymorphism after BsrDI digestion.

- Lane 1: DNA marker
- Lanes 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 18, 19, 20, 21, 22 and 23: are homozygous wild types (IIe/IIE) (two bands at 150 bp and 65 bp)
- Lanes 11, 15, 17: are heterozygous for the mutation (IIe/Val), (three bands at 204 bp, 150 bp, and 65 bp)
- Lane 16: homozygous for the mutation (Val/Val) (one band at 204 bp)

Table (1): Frequency of CYP1A₁ genotypes among the two groups

		Cases (n=40)	Controls (n=20)	P
		Number (%)		
CYP1A₁ Genotypes	**IIe/IIe**	35 (87.5%)	19 (95%)	0.015 (S)
	IIe/Val	4 (10%)	1 (5%)	
	Val/Val	1 (2.5%)	0 (0%)	
	Gene polymorphism	5 (12.5%)	1 (5%)	

Table (2): Frequency of CYP1A₁ Genotypes according to the ages in cases

	CYP1A₁ Genotypes		p
	Wild type (n=35)	Variant (n=5)	
	Number (%)		0.296
Age ≤ 50	19 (54.3%)	2 (40%)	
Age > 50	16 (45.7%)	3 (60%)	

Table (3): Frequency of CYP1A$_1$ Genotypes according to smoking

	CYP1A$_1$ Genotypes		P
	Wild type (n=35)	Variant (n=5)	
	Number (%)		0.051
Negative	23 (65.7%)	1 (20%)	
Positive	12 (34.3%)	4 (80%)	

Table (4): Frequency of CYP1A$_1$ Genotypes according to the site of malignancy

	CYP1A$_1$ Genotypes		P
	Wild type (n=35)	Variant (n=5)	
	Number (%)		0.904
Proximal	15 (42.9%)	2 (40%)	(NS)
Distal	20 (57.1%)	3 (60%)	

Table (5): Frequency of CYP1A$_1$ genotypes among both sexes

	CYP1A$_1$ Genotypes		P
	Wild Number (%)	Variant (n=5)	
	Type (n=35)		0.031 (S)
Males	17 (48.6%)	5 (100%)	
Females	18 (51.4%)	0 (0%)	

Table (6): Frequency of CYP1A$_1$ genotypes according to the pathological type of the tumor

	CYP1A$_1$ Genotypes		P
	Wild type (n=35)	Variant (n=5)	
	Number (%)		
Adenocarcinoma	30 (85.7%)	5 (100%)	0.665 (NS)
Mucinous Adenocarcinoma	3 (8.6%)	0 (0%)	
Signet cell ring carcinoma	2 (5.7%)	0 (0%)	

DISCUSSION

Colorectal carcinoma diagnosis is often made at a too late stage inducing a poor prognosis, emphasizing the need for prevention and early diagnostic tools. Metabolic enzymes, including phase I and phase II enzymes, are involved in activation and detoxification of xenobiotics, which play an important role in the pathogenesis of colorectal cancer. Cytochrome P450, including family 1, subfamily A, polypeptide 1 (CYP1A$_1$), is one of the phase I enzymes, metabolizing a large number of endogenous and exogenous substances, such as polycyclic aromatic hydrocarbons, heterocyclic amines, aromatic amines, and N-nitrosamines. Thus, CYP1A$_1$ plays an important role in human susceptibility to colorectal cancer due to various exogenous factors.[20, 21, 22]

CONCLUSION

In conclusion, CYP1A$_1$ Ile462Val polymorphism may contribute to colorectal cancer risk, however, further study is needed with a large-scale case-control sample to validate the identified risk in our current study. In addition, potential gene-gene and gene-environment interactions should be taken into account when the relation between CYP1A$_1$ Ile462Val polymorphism and colorectal cancer risk is further evaluated.

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تأثير تعدد الأشكال الوراثية لـ سى واى بى ١أ،على حدوث الإصابة بسرطان القولون والمستقيم

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سرطان القولون والمستقيم هو احد الأورام الجينية الأكثر شيوعا فى مصر ويمثل ٦.٥% من حالات السرطان وغالبا مايحدث فى الشباب المصريين مع عدم الميل إلى سن معينة ، وفي هذا البحث وجد أن ٢٩% من المرضى كانت اعمارعم اقلمن ٣٠ عاما و ٢٦% من المرضى اقل من ٦٠ عاما ومتوسط العمر لهؤلاءالمرضى ٤٥ عاما ولكن هذا المتوسط أقل من ذلك فى البلدان المتقدمة.

سرطان القولون والمستقيم هوعملية متعددة الخطوات التى تنطوى على تعطيل مجموعة متنوعة من الجينات الكابته للورم ، والتى تصلح الحمض النووى وتبطل عمل الجينات المسرطنة. تعدد أشكال الجينات التى تشارك فى عملية التمثيل الغذائى مثل مجموعة الـ سى واى بى ٤٥٠ بى ، واس ترانسفيريزالجلوتاثيون. واختلاف مستويات نشاط هذه الأنزيمات يؤدى إلى عدم إصلاح الطفرات الجينية فى الحامض النووى ويؤدى إلى الشروع فى التسرطن.

الجين سى واى بى ١أ، يقع على الكروموزوم ١٥ وتمتد قاعدته إلى ٥٨١٠ نيوكلتيد ويوجد به العديد من الطفرات منها الطفرة ٢ والتى ندرسها فى البحث وقد أجريت هذه الدراسة لتقييم وجود ارتباط محتمل بين تعدد الأشكال لأنزيم الـ سى واى بى ١أ، وهى الطفرة ٢ وبين خطر الأصابة بسرطان القولون والمستقيم فى المرضى المصريين.

شملت هذه الدراسة ٦٠شخصا على مدى ٢١ شهر ما بين ١ فبراير ٢٠٠٩ إلى ٣١ أكتوبر ٢٠١٠ تم تقسيمهم إلى مجموعتين المجموعة أ تشمل ٤٠ مريضا بسرطان القولون والمستقيم بمستشفى قصر العينى جامعة القاهرة ، والمجموعة ب تشمل ٢٠ فرداً من الأصحاء [المجموعة الضابطة]. أخذ التاريخ المرضى الكامل والفحص الأكلينيكي الكامل بعد عمل الغحص الاشعاعى للصدر والبطن والموجات فوق الصوتية لجميع المشاركين فى البحث وأجريت لهم فحوصات معملية شملت صورة الدم الكاملة ووظائف الكلى والكبد ودلالات أورام وتحليل الجينات الوراثية لتعدد الأشكال لـ سى واى بى ١أ١ للكشف عن الطفرة ٢ لأستخدام بى سى ار ريفلب.

وأظهرت النتائج وجود أرتباط ذات دلالة أحصائية بين تعدد الأشكال الوراثية لـ سى واى بى ١أ، وحدوث سرطان القولون والمستقيم فى المرضى المصريين مما يجعله عامل خطر محتمل لحدوث المرض.