Complex interplay of CYP1A1 Genetic Polymorphism on Colorectal Cancer Susceptibility

Thesis

Submitted In Partial Fulfillment for the Requirements of the Master Degree in Clinical & Chemical Pathology

BY

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2010

Acknowledgments

First of all, I thank God for his blessings and aid.

I would like to express my deepest gratitude and special thanks to Dr ***Nancy Mohamed El Gendy,*** *Assistant Professor of Clinical and Chemical Pathology, Faculty of Medicine – Cairo University. It is an honor to work under her guidance. I am greatly thankful for her enlightening supervision, continuous support, precious advice and the valuable time she offered me.*

I am also grateful to ***Dr. Mariam Halim Yacoub,*** *Lecturer of Clinical and Chemical Pathology Faculty of Medicine – Cairo University, for her supervision throughout this work.*

My special thanks to ***Dr Engy Mohamed El Khatib,*** *Lecturer of Clinical and Chemical Pathology Faculty of Medicine – Cairo University, for her great help and support in finishing this work.*

Finally no words can express my feeling to my family for their patience and help.

Abstract

Colorectal cancer is caused by both genetic and environmental factors. We investigated the association between polymorphism of cytochrome P4501A1 (m2) and colorectal cancer in 40 cases and 20 controls using PCR-RFLP. Our results showed that a statistically significant association existed between CYP1A1 variant genotype ($p=0.015$ and the odds ratio OR $=0.105$ with the 95% confidence interval 0.028- 0.390) and colorectal cancer.

Key words

- Colorectal cancer
- CYP1A1

CONTENTS

LIST OF ABBREVIATIONS

AHH: Aryl hydrocarbon

AJCC: American Joint Committee on Cancer

APC: Adenomatous Polyposis Coli

ARNT: Ah receptor nuclear translocator

ASO: Allele Specific Oligonucleotide

bp: Base pair

CA19-9: Carbohydrate antigen 19-9

CBC: Complete blood count.

CEA: Carcinoembryonic antigen

CIN: Chromosomal instability

GST: glutathione S transferase

CRC: Colorectal Cancer

CYP: Cytocrome P450

DNA: Deoxyribonucleic acid

EDTA: Ethylenediaminetetraacetic acid

ER: Endoplasmic reticulum

FAD: Flavin adenine dinucleotide

FAP: Familial adenomatosis polyposis

FMN: Flavin mononucleotide

FOBT: Fecal occult blood test

HNPCC: Hereditary Non Polyposis Colorectal Cancer

HRT: Hormone Replacement Therapy

IBD: Inflammatory bowel disease

Ile: Isoleucine

MSI: Microsatellite instability

NADH: Reduced Nicotinamide adenine dinucleotide

NADPH: Reduced Nicotinamide adenine dinucleotide phosphate

PAHs: Polycyclic aromatic hydrocarbons

PCR: Polymerase chain reaction

RFLP: Restriction Fragment Length Polymorphism

Taq: Thermus aquaticus

TNM: Tumor Node Metastasis

TP53: Tumor protein P53

Val: Valine

XMEs: Xenobiotic metabolizing enzyme

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in both men and woman in industrialized countries. Most colorectal cancer are sporadic, but a significant proportion (5-6%) has a clear genetic background. It is now 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 **(Christian et al., 2005).**

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.

Polymorphisms in the genes that encode enzymes involved in the metabolism of PAHs (xenobiotic-metabolizing enzymes), such as the cytochrome *P*450 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 detoxification (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 **(Nebert et al., 2006).**

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 **(Yoshida et al., 2007).**

Advances in molecular biology have allowed detection of many allelic variants of several drug metabolizing enzymes so that individuals with the susceptible genotypes can be determined easily **(Kiyohara, 2000).**

The analysis of CYP1A1 gene polymorphism can be performed by RFLP analysis of PCR- amplified DNA **(Masson et al., 2005),** as well as PCR allele specific oligonucleotide hybridization assays **(Maja et al., 2002).**

Aim of the Work

The aim of work is to use genotyping approach to examine the relationship between genetic polymorphism in CYP1A1 and the susceptibility to colorectal cancer.

COLORECTAL CANCER

A neoplasm is a disease that is characterized by excessive and uncontrolled growth and spread of structurally and biologically abnormally differentiated cells that can originate from any tissues of the body. Malignant neoplasms, including cancer, resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their cellular/structural form and function **(Jemal et al., 2008).**

Epidemiology

Worldwide, colorectal cancer is the most commun form of cancer. In 2000, colorectal cancer accounted for 9.4% of the world's new cancer, with 945.000 cases diagnosed, and 7.9% of the world's cancer death, with 492.000 deaths **(Parkin, 2001).**

Colorectal cancer is ranked the third in both genders for all malignant diseases, in 2008 representing 8.9% of all cancers with only lung and breast cancers having higher incidence **(Jemal et al., 2008).**

CRC is more prevalent in North America, Argentina, Australia, New Zealand and part of Europe, Japan and Israel, and for this reason, is commonly regarded as the a western life style disease. However, although the incidence and mortality are higher in countries with a western life style, the global incidence is rising and the majority of the word's case of colorectal cancer occur

outside of countries in which traditional western life style are dominant **(Jemal et al., 2007).**

In western countries, CRC has its peak incidence in the 6 th and 7th decades of life and a mean age of 63 years at time of diagnosis with only 1 to 6% of colorectal cancer occurring in patients younger than 40 years of age (1% in Sweden 2% in England and 5.4% in New Zealand) **(Isbister et al., 1990).**

In developing countries, economic development and the adoption of earlier western life style have lead to an increased CRC incidence similar to that of developed countries more then two decades ago **(Ries et al., 2008).**

In Egypt; the community is showing shift toward the western type of life regarding food habits. Both high-fiber diets (cereals, vegetables, and fruits) and low-fiber high protein diets (meat and fatty food) are commonly consumed **(Khafagy et al., 2000).**

Colorectal neoplasia is one of the most common malignancies in Egypt. It represents 6.5% of cancer in Egypt **(El-Bolkainy et al., 2005).** It was found that CRC tends to occur at younger age in Egyptians and the disease had no predilection to a specific age group however 29% of the tumors occurred in patients under 30 years and 26% of patients were aged above 60 years. The median age of all patients with colorectal cancer was 45 years which is younger than that in developed countries **(Khafagy et al., 2000).**

The difference in the age distribution between the Egyptian population and western communities can be partially explained by

the younger age of Egyptian population, in which 65% are younger than 30 years of age **(1998census)** and may be also due to chemical carcinogens such as organochlorines, organic solvents (e.g. benzene) and polycyclic aromatic hydrocarbons (PAH).

Colorectal cancer affects men and women almost equally **(Albamo et al., 2007).** Among all racial group in the United States, African Americans have the highest sporadic CRC incidence and mortality rate **(Kauh et al., 2007).**

Etiology

Nowadays it is well recognized that a complex interaction between individual genetic features and environmental factors, especially diets, is involved in the etiology of CRC **(Ries et al., 2008).**

I-Environmental factors

The worldwide incidence and mortality of the disease suggest a co-existence of environmental causes of great impact, and studies on migrant populations suggest that the risk for CRC is influenced by environmental exposure **(Waitzberg et al., 2002).**

1-Diet

Bowel cancer incidence is generally higher in populations with westernised'diets and these populations also tend to have a higher proportion of overweight and obese people and lower levels of exercise.