Relationship between Metabolic Enzymes Polymorphisms and Colorectal Cancer

Thesis

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BY

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Abstract

Colorectal cancer is caused by both genetic and environmental factors. We investigated the association between polymorphism of cytochrome P4501A1 (m1) and glutathione-S-transferase M1and colorectal cancer in 40 cases and 20 controls using PCR for GSTM1 and PCR-RFLP for CYP1A1 (m1) polymorphism detection. Our results showed that no statistically significant association existed between GSTM1 null genotype (OR=0.658, 95%CI= (0.217-1.997) or CYP1A1 (m1) genotype (OR=0.333, 95% CI= (0.078-1.416) and colorectal cancer.

Key words

- Colorectal cancer
- GSTM1
- CYP1A1

RECOMMENDATIONS

From the present work we recommend the following:

1- Large scale studies will be required to confirm weak associations and to establish relationships between cancer risk and different metabolic genotypes.

2- Further increasing the number of studied polymorphisms, and determining their combined effects in increasing the risk of developing colorectal cancer.

3- Studies of interaction between traditional epidemiological risk factors and exposure to dietary or other environmental carcinogens and metabolic enzyme polymorphisms may help in exploring mechanisms, identifying susceptible population or individuals and making practical use of study results to develop preventive strategies beneficial to human health.

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CONTENTS

LIST OF ABBREVIATIONS

AA: Acetaldehyde.
Ah: Aryl hydrocarbon.
AHH: aryl hydrocarbon hydroxylase.
AJCC: American Joint Committee on Cancer.
APC: Adenomatous Polyposis Coli.
ARNT: Ah receptor nuclear translocator.
ASO: Allele Specific Oligonucleotide.
BaPDE: benzo[*a*]pyrene diol epoxides
bp: Base pair
CA 19-9: Carbohydrate antigen 19-9.
CBC: Complete blood count.
CEA: carcinoembryonic antigen.
cGST: cytosolic glutathione S transferase.
CIN: Chromosomal instability.
CRC: Colorectal cancer.
CT: Computed tomography.
CTC: Computed tomography colonography.
CYP: Cytochrome P 450
dATP: deoxy adenine triphosphate
DCC: Deleted in colorectal cancer
dCTP: deoxy cytosine triphosphate
ddNTPs: didcoxynucleotides triphosphate
DNA: Deoxyribonucleic acid
dNTPs: deoxy nucleoside triphosphate
dTTP: deoxy thiamine triphosphate
EDTA: Ethylenediaminetetraacetic acid.
ER: endoplasmic reticulum.
FAD: Flavin adenine dinucleotide
FAP: Familial adenomatosis polyposis
FMN: Flavin mononucleotide
FOBT: Fecal occult blood test
FRET: Fluorescence resonance energy transfer
GSEC: Genetic Susceptibility to Environmental Carcinogens
GSH: Glutathione
GST: Glutathione S-transferase
GSTA: GST Alpha

GSTK: Kappa GST
GSTM: GST MU
GSTO: GST Omega
GSTP1: GST Pi
GSTT: GST Theta
HCAs: Heterocyclic amines.
HNPCC: Hereditary Nonpolyposis Colorectal Cancer.
HRT: Hormone Replacement Therapy
IBD: Inflammatory bowel disease
Ile: Isoleucine
IUAC: International Union Against Cancer.
kDa: Kilo Dalton
MAPEG: Membrane associated proteins involved in eicosanoid and glutathione metabolism
MMR: Mismatch repair
MRP: Multidrug resistance-associated protein.
MSI: Microsatellite instability
Msp1: Moraxella species
NADH: Reduced Nicotinamide adenine dinucleotide
NADPH: Reduced Nicotinamide adenine dinucleotide phosphate
NAT*:* *N*-acetyltransferases
NOCs: N-nitroso compounds
NSAIDs: Nonsteroidal anti-inflammatory Drugs
PAHs: polycyclic aromatic hydrocarbons
PCR: polymerase chain reaction
PET: Positron emission tomography
PhIP: 2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine .
RFLP: Restriction Fragment Length Polymorphism
ROS: reactive oxygen species
rpm: round per minute
Taq: Thermus aquaticus
TNM: Tumor Node Metastasis
TP53: tumor protein P53
Val: Valine
XMEs: xenobiotic metabolizing enzymes

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Introduction

Colorectal carcinoma (CRC) is one of the most frequent causes of cancer death in industrialized countries for both men and women **(Boyle and Ferlay, 2005)**

Colorectal cancer is considered to be a multifactorial disease, in which multiple exposures to endogenous factors and dietary carcinogens interact with individual genetic background in a complex manner resulting in modulation of the risk **(Ishibe et al., 2002)**.

Metabolic activation of carcinogens is carried out by phase I enzymes. In contrast, phase Π enzymes contribute to the detoxification of substance activated during phase I. The equilibrium between phase I and phase Π activities is critical in the host response to xenobiotics **(Sinnet et al., 2000).**

The cytochrome p450 (CYP) enzymes are of critical importance for the metabolism of carcinogens such as polycyclic aromatic hydrocarbons, and CYP1A1 plays a key role in their metabolic activation. In addition, the glutathione s transferases play an important role in the detoxification of carcinogens to reduced glutathione **(Yoshida et al., 2007)**

Most of the human metabolizing enzymes are genetically polymorphic, and these polymorphisms may affect the enzyme activity or inducibility (**Kiss et al., 2000).**Genetic polymorphisms in CYP1A1 and GSTM1 may play an interactive role in the risk for 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)**. Gene polymorphisms of GSTM1 can be detected by using end point PCR or Real-Time PCR **(Wittwer et al., 2004)** as well as high-throughput Allele-Specific GSTM1 Detection**(Barnette et al., 2004).**

Aim of the Work

The aim of this work is to investigate the association between metabolic enzymes polymorphisms, namely, CYP 1A1 and GSTM1 and the risk of colorectal cancer.

COLORECTAL CANCER

Epidemiology

Incidence

Colorectal cancer (CRC) is a major health problem in industrialized countries, it 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).**

Colon and rectum cancers accounted for about 1 million new cases in 2002. Survival estimates at 5 years are 65% in North America, 54% in Western Europe, 34% in Eastern Europe, and 30% in India **(Parkin, 2005).**

However, in developing counties, economic development and the adoption of earlier Western life-styles have led to an increased CRC incidence similar to that of developed countries more than two decades ago **(Ries et al., 2008).**

In Egypt colorectal cancer is one of the most common malignant neoplasms .It represents 6.5% of cancers in Egypt **(EL-Bolkainy et al 2005).**

In Egypt; the community is showing shift toward the Western type of life regarding food habits. Food consumption is very heterogeneous; 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)**.

Age is a major risk factor for sporadic CRC. It is a rare diagnosis before the age of 40, the incidence begins to increase significantly

between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter **(Dennis and Finlay, 2009).**

In a study performed by **Abou-Zeid et al., (2002)** it was found that colorectal cancer tends to occur at younger age in Egyptians. In their study they performed a seven-year review of all colorectal adenocarcinoma patients who presented to the Department of Surgery, Ain Shams University. Data from three other major hospitals throughout the country were retrieved and compared with Ain Shams data. They found that the disease had no predilection to a specific age group however thirty-eight percent of the tumors occurred in patients aged less than 40 years, and only 15 percent of patients were aged above 60 years. They reported that the high prevalence in young people can neither be explained on a hereditary basis nor can it be attributed to bilharziasis. Patients usually show an advanced stage of the disease at presentation and a higher incidence of treatment failure caused by a delay in the diagnosis and a more aggressive pattern of the disease**.**

Contrary to the common belief that the disease affects mainly men, it is the almost only major malignancy that affects men and women almost equally (ratio: 1.2:1) **(Bond, 2000; McLoed et al., 2000).**