Genetic Predisposition of Colorectal Carcinoma and Screening Program for High Risk Group Population

Essay

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By

Mohamed Moustafa Tawfik
M. B., B. Ch.

Supervised by

Prof. Dr. Mohamed Ragheb
Professor of General Surgery
Faculty of Medicine
Ain Shams University

Dr. Abd-Elwahab Ezzat
Lecturer of General Surgery
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
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﴿بسم الله الرحمن الرحيم﴾

﴿وقل رب زدنى علما﴾

صدق الله العظيم

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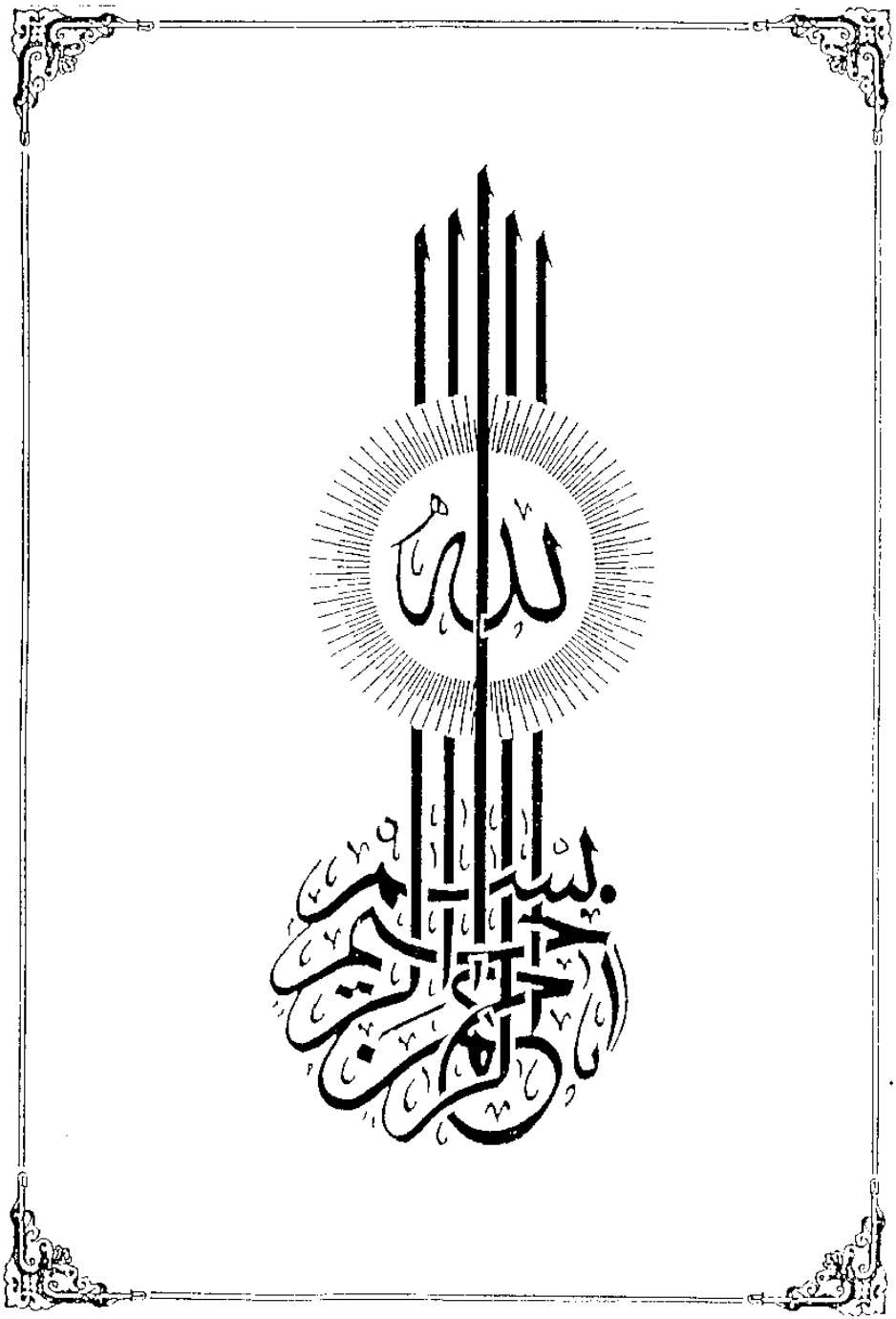

For my mother which gave me
her love & life

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Contents

Introduction

The incidence of Colorectal Cancer is increasing rapidly after age of 40 in the general population, doubling every five years until age of 60.

Dealing with Colorectal Cancer needs to detect more patients with localized disease. In asymptomatic patients with localized disease the survival rate is as high as 90%.

The aetiology of Colorectal Cancer is not entirely clear but substantial epidemiologic and experimental information obtained over the last two decades have given some insight into various potential causative factors.

Aim of the Work

The aim of this essay is to present update comprehensive review of genetic predisposing factors and high risk group, Oncogenes, suppressor genes and allele losses in Colorectal Cancer helping in early diagnosis.

Epidemiology, Aetiology and presentatoin of Colorectal carcinoma

Epidemiology:

Carcinoma of the large bowel occur with great variation in frequency in different parts of the world.

The disease is particulary prevelant. In developed countries a notable exception being Japan which though a very industrialized nation has only a moderate incidence of colon cancer. This variation in incidence are related not so much, to racial charachteristic as to environmental influnces ***(Goligher, 1984).***

Epidemiology - population studies:

Large bowel cancer is common in North America western Europe and Australia but relatively rare in Africa, Asia and the Andean Countries of South America ***(Gerhardsson, 1990).***

The colorectal cancer is greater in urban areas than in rural areas. Greater among the Jewish population than among other population and greater among whites, than among blacks ***(Zinkin, 1983).***

The physical environments includes those factors determined by location and which are shared of necessity by all members of a community (e.g. air pollution, rainfall, climate, drinking water) whereas the cultural

environment is determined by the individual and may be shared by few members of the same community (e.g., diet, smoking, and use of drugs., personal hygene habits, sexual habits ***(McDermott et al., 1980).***

Epidemiology - high risk states:

A number of diseases have been demonstrated to carry on above - average risk of colorectal Carcinogensis the principale are though to predispose to cancer and include the genetically determined predisposition, colorectal adenomas and chronic inflammatory disease of the colorectum.

In addition a number of disease states associated with an increaed risk of colorectal cancer (including cholecystectomy and polya partial gastrectomy) may not necessarily preidispose to malignancy ***(Boulis W. et al., 1984).***

The age specific incidence of the disease in the United States appears to rise steadily from the second to the ninth decades. Men have proportionally more rectal cancer than women but both sexes are relatively equally represented ***(Cohen et al., 1989).***

Epidemiology - Metabolic studies:

There have been many attempts to identify putative carcinogenes or tumor promoters in faeces, and negative results have been obtained for cholesterol metabolites, tryptophan metabolites. N-nitroso compounds,

phenolic compounds and dietary carcinogens. Bruce and his colleagues (1977) have described a family of faecal mutagens which have been identified as olyenyl ethers. Although a number of studies have suggested a correlation between faecal mutagen activity and colorectal cancer risk in population, others have shown no relation. The results of the prospective study described by Bruce et al., (1979), will be valuable indicators of the importance of these mutagens. There is now a large body of evidence incriminating bile acids in colorectal carcinogenesis and this subject has been reviewed in detail recently. The majority of studies have been of the total faecal bile acids and although most types of study show a clear relationship, the failure of a number of the case - control studies to confirm this correlation suggested that further refinement of this hypothesis relating bile acids to colorectal carcinogenesis is needed. Recent studies by Owen et al., (83, 84, 85) Suggest that the ratio of lithocholic to deoxycholic acid may be a better risk factor than the total bile acid concentration ***(West et al., 1989).***

Aetiology

At present very little is known about the process of intiation in colon cancer. A vival etiology is possible, given the growing interest in oncogenes and earlier studies showing cytomegalovirus in colon carcinoma tissue other possibilites include various protein metabolites such as ammonia, volatile phenols or tryptophan and N-nitrose compounds. However much more is known about the promotion in colon carcinogenesis ***(Haskell et al., 1990).***

Numerous studies suggest that it is multifactorial. Heridetiary factors have been implicated in some patients, but the overwhelming majority of cases, appear to be related to extragenetic factors ***(Goldberg et al., 1989).***

It is strongly suggested that cancer of the large bowel is associated with environmental factors of which those related to diet appears to be the most important ***(Hill , 1985).***

Two major theories of dietary etiology. Predominate, but neither theory fully explains the available data the first theory relates to dietary fibers and the second to dietary fat ***(Hill , 1985).***

1. Dietary sugar:

A suggested mechanism is that with elevated consumption of refined carbohydrate there will be higher cells turnover rates favoring carcinogensis ***(Weisburger, 1991).***

The elevated consumption of refined carbohydrate has been noted as a possible etiologic factor in some population with a high incidence of colon cancer ***(Bresalier et al., 1985).***

2. Dietary fat:

Persons on a typical western diet (high in meat and fat) excrete about three times as much bile acids and neutral sterols in the feces as do vegetarians. Also a high fat diet changes the composition of the intstinal flora, with increased numbers of clostridial (especially C. paraputrificum and C bulyricum) and Bacteroides organisms that are known to chemically alter primary bile acids and sterols. These cholesterol bile acids metabolites are throught to be carcinogenic ***(Bristol et al., 1985).***

There is now a large body of evidence incriminating bile acids in colorectal carcinogeneses. A recent study suggests that the ratio of lithocholic to deoxycholic acid may be a better risk factor than the total bile acid concentration ***(Leveson & Vowder, 1986).***

A correlation between the intake of animal fat and large bowel cancer has been made in several studies and is currently the most widely accepted association between diet and cancer ***(McMichael et al., 1985).***

3. Dietary calcium:

Dietary calcium decreases the risk of colon cancer ***(Arbman et al., 1992).*** Probably by modulating the promoting effect of bile acids. The exact mechanism may be complex. Ranging from a simple elimenation of bile acids as water insoulble calcium soaps to a subtler molecular inhibition of promotion by calcium salts at the cellular membran level. ***(Weisburger, 1991).***

4. Dietary fiber:

It is postulated that a high - fiber diet may decrease the colonic transit time and thus decrease the contact time of carcinogensis with the large bowel mucosa ***(Goldberg et al., 1989).***

Also a high fiber diet results in increase bulk of the stools that in turn dilute the concentration of carcinogens ***(Haskell et al., 1990).***

These factors may explain how a high fiber diet could lower the incidence of large bowel carcinoma. For colon cancer separatly a high intake of calcium and cereal fibers is associated with a reduced risk ratio. For rectal

cancer a high intake of total fiber and cereal fiber with reduced risk ratio ***(Potter et al., 1986)***.

5. Alcohol intake:

It was found that there is a two fold increase in cancer risk for daily alcohol drinkers this is applied particulary to rectal cancer ***(Arbman et al., 1992).***

Such alcohol use increase cell cycling in the rectal mucos a possible mechanism of increase carcenogensis ***(Arbman et al., 1992).***

6. Fecal pH.

Epidemiologic studies from south Africa and the U.S.A. reveal a high incidence of colon cancer in subject with a higher stool pH ***(cohen et al., 1989)***

At the lower pH, bile and fatty acids are more in the non ionised form with lessened absorption and less potential to damage mucosa and consequantly lower risk of colon cancer ***(weisburger 1991).***

7. Normal bile Acids:

Directly, related to the intake of fat, population that consume more fat, have more bile acid secreation and an associated increase incidence of colonic cancer. Removing the gall bladder result in high levels of bile acids in the ceacum, ascending colon and may associated with great frequency of right-sided colon cancer ***(Turnbull et al., 1981).***

Presentation of colorectal carcinoma:

The early carcinoma is an asymptomatic process. The common symptomes are relatively late manifestation of the disease. Also the symptomatology of colorectal carcinoma when it occurs is similar to other non-malignant colorectal lesions. Accordingly the patient will not seek for medical advice early, making early diagnosis difficult.

There are two main ways in which patients with colorectal carcinoma may present to the surgeon:

1. As non urgent cases with insideously developing chronic symptomes chiefly affecting bowel function or general health.

2. As emergency with acute intestinal obstruction or with perforation of the colon and peritonitis. There was a study carried out on 1644 patints with colorectal carcinomas found that 75.2% had been non urgent cases 18% as emergencies with acute intestinal obstruction and 6.8% as emergencies with peritonitis from intestinal perforation ***(Goligher, 1984).***