COLORECTAL CANCER IN PATIENTS 30 YEARS OLD AND YOUNGER

Thesis

Submitted by

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<tr>
<td>ANP</td>
<td>Autonomic nerve preservation</td>
</tr>
<tr>
<td>APC</td>
<td>Adenomatous polyposis coli tumor suppressor gene</td>
</tr>
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<td>APR</td>
<td>Abdominoperineal resection</td>
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<tr>
<td>ASA</td>
<td>Aspirin</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CCRTH</td>
<td>Concomitant Chemo-radiation therapy</td>
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<tr>
<td>CD</td>
<td>Crohn’s disease</td>
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<td>CEA</td>
<td>Carcinoembryonic Antigen</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
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<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
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<tr>
<td>CTC</td>
<td>CT Colonography</td>
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<td>CTH</td>
<td>Chemotherapy</td>
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<tr>
<td>FAP</td>
<td>Familial adenomatous polyposis</td>
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<td>FIT</td>
<td>Fecal immunochemical techniques</td>
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<td>FOBT</td>
<td>Fecal occult blood test</td>
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<tr>
<td>HCAs</td>
<td>Heterocyclic Amines</td>
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<tr>
<td>HNPCC</td>
<td>Hereditary non polyposis colon cancer</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>LAR</td>
<td>Low anterior resection</td>
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<td>NSAID</td>
<td>Non steroidal anti-inflammatory drugs</td>
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<td>PJS</td>
<td>Peutz–Jegher’s syndrome</td>
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<tr>
<td>PSC</td>
<td>primary sclerosing cholangitis</td>
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<tr>
<td>RR</td>
<td>Risk Reduction</td>
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<td>RTH</td>
<td>Radiotherapy</td>
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<tr>
<td>TEM</td>
<td>Transanal endoscopic microsurgery</td>
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<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
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<tr>
<td>TRUS</td>
<td>Transrectal ultrasonography</td>
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<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Key Words

Colon – Rectum – Colorectal – Cancer

Young age – 30 years
Introduction
INTRODUCTION

Colorectal cancer (CRC) is generally thought of as a disease of elderly. Recent studies on age distribution of this disease clearly delineated the rising incidence of colorectal cancer in young age all over the world with about (7%) of this disease occurring in patients younger than 40 years and about (1.5%) increase in its incidence rate every year despite the noted decrease of the incidence rate in all age groups.\textsuperscript{1,2,3}

Previous studies from Egypt reported a much higher incidence of CRC in young age with about (35%) of this disease occurring in patients younger than 40 years which is 5 times higher than the average incidence rate all over the world. It was also reported that most of the cases were sporadic with no inheritance pattern, or relation to special exposures related to the occupation or the residence of the patients.\textsuperscript{272}

In agreement to the western literature, most of the cases of CRC in young age in Egypt present with more advanced stages and carries an aggressive behavior regarding the histopathological cell types and grades with poor survival rates.\textsuperscript{286}
Aim of the study
Aim of the Study

To study colorectal cancer in patients 30 years old and younger who presented to the National Cancer Institute from the beginning of 2008 till the end of 2010, with special reference to the demographic distribution, possible risk factors, clinical presentation, investigations and methods of diagnosis, pathological patterns, stage at initial presentation, and treatment modalities.
Review of Literature
1. Epidemiology of Colorectal Cancer

1.1 Incidence and mortality

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide (excluding non-melanoma skin cancer) representing (9.8%) from all malignant tumors, preceded by lung cancer (12.7%) and Breast cancer (10.9%). Almost (60%) of the cases occur in developed regions. The incidence rates vary 10 fold in both sexes worldwide, the highest rates being estimated in Australia, New Zealand and Western Europe, the lowest in Africa (except Southern Africa) and South-Central Asia. Incidence rates are substantially higher in men than in women (overall sex ratio 1.4:1). About (608000) deaths from colorectal cancer are estimated in 2008 worldwide, accounting for (8%) of all cancer deaths, making it the fourth most common cause of death from cancer.

The percentage of CRC in the young population (<40 years) relative to the total number of colorectal cancer patients ranged from (0.4%) to as high as (35.6%), with average incidence rate of (7%). No statistically significant difference was found in gender distribution in young patients with CRC.

The incidence rate of colorectal cancer in young patients (<40 years) in USA was found to be rising over the past 25 years despite the decrease in the incidence rate for all age groups.

1.2 Etiology and risk factors of colorectal cancer

Possible risk factors of CRC include increasing age (more than [90%] of cases occur in people aged 50 years or older), previous colonic polyps or previous CRC, family history of CRC, Inflammatory bowel disease (the risk increases with duration of illness [2% at 10 years, 18% by 30 years], and severity and extent
of inflammation)\textsuperscript{10,10,11,12}, and environmental factors (e.g., red meat, high-fat diet, inadequate intake of fiber, obesity, sedentary lifestyle, diabetes mellitus, smoking, and high consumption of alcohol).\textsuperscript{13}

1.2.1 Factors associated with an increased risk of colorectal cancer

**Excessive alcohol use**

Several cohort and case control studies suggest a modest-to-strong positive relationship between alcohol consumption and large bowel cancers.\textsuperscript{14,15,16,17}

**Cigarette smoking**

A comprehensive systematic review and meta-analysis of prospective studies examining the relationship between cigarette smoking and CRC incidence and mortality were conducted; findings provided strong evidence that smoking is associated with an increased risk of CRC, which was observed consistently in analysis of current and past smokers. Factors associated with increased risk include; daily cigarette consumption, duration of smoking, packs per years and age of initiation. Higher risk was found for rectal cancer than for colon cancer across all smoking variables.\textsuperscript{18}

**Obesity**

At least three large cohort studies have found an association between obesity and CRC incidence & mortality.\textsuperscript{19,20,21} The Nurses’ Health Study found that women with a body mass index (BMI) of more than 29, compared with women with a BMI of less than 21, had an adjusted risk reduction (RR) for CRC incidence of 1.45 (95% CI).\textsuperscript{19} Another prospective cohort study found that men and women with a BMI of 30 to 34.9 had an adjusted RR for CRC mortality (compared with people with a BMI of 18.5–24.9) of 1.47 (95% CI), with a statistically significant dose-response effect, these effects were similar in men and women.\textsuperscript{21}
1.2.2 Factors associated with a decreased risk of colorectal cancer

Physical activity

A sedentary lifestyle has been associated in some but not all studies with an increased risk of CRC. Numerous studies examined the relationship between physical activity and colon cancer risk, they showed an inverse relationship between level of physical activity and colon cancer incidence.

Coffee Consumption

A meta-analysis of several case control studies on coffee consumption and colorectal cancer risk found that the risk of colorectal cancer for regular coffee drinkers was approximately (17%) lower than for non/occasional drinkers. The protection was about (30%) for the highest coffee drinkers and (6%) for an increase in consumption of one cup of coffee/day. The inverse association was stronger for colon than for rectal cancer.

Aspirin

A systematic review of 46 observational studies of Aspirin (ASA) and CRC found a reduction in the incidence of CRC with daily use of Aspirin.

Non-steroidal anti-inflammatory drugs

A large cohort study (301,240 people with 3,894 colorectal cancer cases) found an association between daily or weekly non-steroidal anti-inflammatory drug (NSAID) use and reduced 10-year incidence of proximal and distal, but not rectal, colorectal cancer, with a hazard ratio (HR) of 0.67 (95% CI) for daily use for colon cancer.
1.2.3 Role of Diet in Colorectal Cancer

Dietary intake has been implemented as both a causative and preventive agent in the etiology of colorectal cancer, a number of dietary components have been implicated as possible factors in the development or protection against CRC. In the final summary of the WCR/AICR (World Cancer Research Fund/American Institute for Cancer Research), the strongest evidence shows that red meat and processed meat and substantial consumption of alcoholic drinks are causes of this cancer. Foods containing dietary fiber, and also garlic, milk, and calcium, probably protect against this cancer. There is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, fish, foods containing vitamin D, and selenium and foods containing it protect against colorectal cancer, and that foods containing iron, cheese, foods containing animal fats, and foods containing sugars are causes of this cancer.13

Total Caloric intake

Total caloric intake was found to be one of the important risk factors of CRC. A direct relationship was found between the incidence of CRC and the number of calories consumed per day.30

Meat as a risk factor

In a large prospective study of meat consumption and colorectal cancer risk, both red and processed meat intakes were positively associated with colorectal cancer and these associations could be related to heme iron, nitrate, and the Heterocyclic Amines (HCAs) MeIQx and DiMeIQx formed in meats cooked at high temperatures. In contrast to red meat, white meat is not associated with an elevated risk of colorectal cancer; one of the main differences between red and white meat is
the iron content. These findings are in agreement with a recent and large summary of the epidemiologic literature.

**Dietary fat**

The recent WCRF/AIRC report studied five cohort studies and came with the conclusion that “There is a limited amount of fairly consistent evidence suggesting that consumption of foods containing animal fat is a cause of colorectal cancer”.

A meta-analysis of animal fat intake and colorectal cancer reviewing six prospective cohort studies with comprehensive dietary assessments, contributing 1070 cases of colorectal cancer and ≈ 1.5 million person-years of follow-up, showed no consistent evidence of a positive association between consumption of animal fat and colorectal cancer. Specifically, the study found no association between the highest animal fat intake category and colorectal cancer. Furthermore, none of the subgroup analyses (ie. sex, anatomic tumor site, and study design) indicated positive patterns of associations. On the other hand an old study performed by Willett et al. showed a monotonic pattern of intake-response, i.e. an increasing risk of colon cancer with increasing categories of animal fat consumption.

**Plant Foods**

The recent WCRF/AIRC report found a dose response effect of dietary fiber intake on colorectal cancer risk in a meta-analysis of existing cohort studies (Risk Reduction [RR] per 10 g/d = 0.90, 95% CI = 0.84 to 0.97). These findings strengthen existing evidence that supports recommendations to increase dietary fiber intake in populations to reduce colorectal cancer incidence. plausible mechanisms whereby dietary fiber may influence colorectal cancer risk, including reduction in colonic transit time, dilution of gut contents, alteration of bile
acid metabolism, and fermentation of fiber by the colonic micro-flora resulting in production of short-chain fatty acids that stimulate apoptosis.  

**Dairy Product and colorectal cancer**

The recent WCRF/AIRC report found that milk intake probably protects against colorectal cancer, but there was limited suggestive evidence that intake of cheese increases risk. Because there also was evidence that high calcium and dairy intake increases prostate cancer risk, no recommendation was provided with regard to intakes of dairy products.

**Folate, Methionine and Selenium**

Several studies have shown that higher levels of dietary folic acid Methionine, and Selenium have been associated with lower risks of CRC. 

**1.2.4 Environmental pollution and CRC**

Exposures to both organic and metal dusts were significantly associated with rectal cancer in young men. Exposure to Organochlorine pesticides was found to contribute to human colorectal cancer development.

**1.3 Predisposing Factors of CRC in young patients**

Majority of CRC in young adults is sporadic, and reports suggest that only (16%) of patients have a documented predisposing factor (“Predisposing factors” were in general considered to be a personal history of inflammatory bowel disease, familial adenomatous polyposis, or hereditary non-polyposis colorectal cancer syndrome). Other articles included patients with a history of colon polyps or other primary cancers.
2. Pathology of CRC

2.1 Molecular Basis of Colorectal Cancer

The disease begins as a benign adenomatous polyp, which develops into an advanced adenoma with high grade dysplasia and then progresses to an invasive cancer. The clinical behavior of a colorectal cancer results from interactions at many levels (Fig.1). The challenges are to understand the molecular basis of individual susceptibility to colorectal cancer and to determine factors that initiate the development of the tumor, drive its progression, and determine its responsiveness or resistance to antitumor agents.

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**Fig.1 Multifactorial Colorectal Carcinogenesis.**

The molecular events that drive the initiation, promotion, and progression of colorectal cancer occur on many interrelated levels. This dynamic process involves interactions among environmental influences, germ-line factors dictating individual cancer susceptibility, and accumulated somatic changes in the colorectal epithelium.