INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer Worldwide ***(Siegel et al., 2013).*** In Egypt it ranks as the second cancer after breast cancer constituting 8.6% of all malignancies ***(Helal et al., 2015).*** Recent data from the United States revealed that the incidence of CRC showed an increase trend in the young age ***(Bailey et al., 2014).*** Studies from other low income, highly populated countries like Bangladesh ***(Ahmed et al., 2005),*** Iran ***(Fazeli et al., 2007),*** India ***(Gupta et al., 2010),***and Pakistan ***(Amini et al., 2013)*** reported similar findings.

In Egypt, a recent analysis performed at Ain-Shams University Hospitals found that CRC had a higher frequency during the period 2006-2010 as compared to the period 2001-2005 with decrease in the mean age of patients ***(Helal et al., 2015).*** These results agreed with those reported by ***(El-Hennawy et al., 2003).***

The reasons for this rising incidence of CRC in young age from different geographic areas in the world are not clear. The environmental and dietary factors as well as lack of screening in the young people have been suggested as potential risk factors ***(Bailey et al., 2014).***

Available data showed that CRC in the young patients has distinct clinical and pathological characteristics which are

different from CRC in older patients. Most important, it has more tendencies to be rectal and presented with advanced stage and high grade.

Although the pattern of CRC in the young age has been investigated in several areas of the world as Jordan ***(Al-Jaberi et al., 2003)***, Taiwan ***(Chiang et al., 2003),*** Iran ***(Fazeli et al., 2007),*** Israel ***(Shemesh-Bar et al., 2010),*** India ***(Gupta et al., 2010),*** Nigeria ***(Ibrahim et al., 2011)*** and USA ***(Bailey et al., 2014),*** no similar studies have been performed in Egypt, except that of **(*El-Hennawy et al., 2003)*** which consisted of 50 rectal cancers only. Amore recent epidemiologic study investigated the age distribution of CRC in Egyptian patients which recommended clinicopathologic evaluation of CRC in the young Egyptian patients ***(Veruttipong et al., 2012).***

AIM OF THE WORK

The purpose of the current study is to compare the clinicopathological features, p53 expression and survival outcomes in young patients with those in the older age group.

REVIEW OF LITERATURE

1. Epidemiology of Colorectal cancer

Colorectal cancer (CRC) is the third common cancer worldwide. Generally more than 1 million people get colorectal cancer every year in the world, that's reflecting the increase in deaths number about 490,000 in 1990 reaching to 715,000 deaths in 2010. It's being the fourth common cause of cancer death after lung, stomach and liver cancer. It is more common in developed than developing countries. According to data from the SEER *(The Surveillance, Epidemiology, and End Results),* incidence rates in 5 years (2005-2009) decreased in males by 0.6% per year and were stable in females. Recent rapid decline in colorectal cancer incidence rates have largely been attributed to increase in screening that can detect and allow the removal of precancerous polyps. Death rates continue to decrease for the CRC. Over the past two decades, death rates have decreased from their peak by more than 30% for CRC, this decrease in death rates for colorectal cancers largely reflects improvements in early detection and/or treatment ***(Lozano et al., 2012; Siegel et al., 2013).***

In Egypt, it ranks as the second cancer after breast cancer constituting 8.6% of all malignancies, and a recent analysis performed at Ain-Shams University Hospitals found that CRC had a higher frequency during the period 2006-2010 as

compared to the period 2001-2005 with decrease in the mean age of patients ***(Helal et al., 2015).***

Most CRCs occur predominantly in older patients, with an average age at diagnosis of approximately 60 to 70 years**.** Nonetheless, CRCs affect younger patients as well, with a rare incidence for patients younger than 40 years, so the incidence of CRC for the different ten year age groups increased from 1.22 patients per 100,000- population for the youngest age group (age ≤ 30 years) to 195.2 patients per 100,000 population for the oldest age group (age ≥ 80 years) ***(Chiang et al., 2003).***

CRC trends reflect patterns in older age groups, among whom the majority of cases occur, masking trends in young individuals. From 2009 to 2013, CRC incidence rates decreased by 4.6% per year in individuals 65 years of age and older and by 1.4% per year in individuals 50-64, but increased by 1.6% per year in adults younger than 50. Notably, the increase in young adults followed a decade of rapid declines during the late 1970s and early 1980s, Reasons for the rise in young age groups are unknown, but may reflect an increased sedentary lifestyle and a higher prevalence of obesity and/or unfavorable dietary patterns in children and young adults. CRC death rates in adults younger than 50 years of age increased by about 1% per year from 2005 to 2014 following decades of decline. This trend is in contrast to older age groups, among whom death rates are decreasing by about 1% per year in individuals 50-64

years of age and by 3% per year in those 65 and older ***(Andrews et al., 2017)***.

Rectal cancer Egyptian patients <40 years of age have more advanced disease at presentation and a higher incidence of treatment failure caused by both a delay in the diagnosis and a more aggressive pattern of the disease ***(El-Hennawy et al., 2003).***

CRC was more common in patients from urban (55%) than rural (45%) areas. This may reflect different etiologic patterns in this Egyptian population ***(Veruttipong et al., 2012)***.

2. Risk factors of colorectal cancer

There are many causes contributing to colorectal cancer varying from genetically to habitual causes as;

- ***Diet and lifestyle***

Meat consumption, smoking and alcohol consumption are risk factors and highly caloric food rich in animal fat combined with a sedentary lifestyle, also the people who have type 2 (adult onset) diabetes have an increased risk of CRC, through additional risk factors as; obesity and a sedentary lifestyle, this association remains even after accounting for physical activity, body mass index, and waist circumference, but some studies suggest that metformin (a drug- commonly used to lower blood glucose levels in diabetic patients) independently reduces CRC incidence ***(Andrews et al., 2017)***.

Vegetable anticarcinogens such as antioxidants and inducers of detoxifying enzymes, binding of luminal carcinogens, fiber fermentation to produce protective volatile fatty acids, and reduced contact time with colorectal epithelium due to faster transit may explain decrease a risk of CRC ***(Hamilton et al., 2006)***.

Most studies find that calcium consumption from dairy foods and/or supplements and higher blood levels of vitamin D are associated with a decreased risk of developing adenomas and CRC**.** On the contrary the folate intake consumed through diet or supplements is promoting growth of pre-existing tumors in potential way while inhibiting formation of new tumors in healthy tissue ***(Keum et al., 2015; Song et al., 2015)***.

Physical activity is strongly associated with a reduced risk of colon cancer, but not rectal cancer, the most physically active people have a 25% lower risk of developing both proximal and distal tumors than the least active people. Additionally, people who are more physically active before a CRC diagnosis are less likely to die from the disease than those who were less active, people who are the most sedentary (e.g., spend the most hours watching TV) have a 25% to 50% increased risk of colon cancer compared to those who are least sedentary ***(Boyle et al., 2012).***

- ***Heredity and medical history***

According to a family history of CRC most people increasing risk of CRC because of a medical or family history should begin CRC screening before age 50**,** Up to 30% of CRC patients have a family history of the disease, about 5% of which are due to an inherited genetic abnormality, the People with a first-degree relative (parent, sibling, or child) who has been diagnosed with CRC have 2 to 4 times the risk of developing the disease compared to people without this family history ***(Johns and Houlston, 2001; Patel and Ahnen, 2012).***

Many of CRC clustered in families is thought to be due to the interaction between lifestyle factors and the cumulative effect of relatively common genetic variations that increase disease risk**,** as opposed to rare hereditary syndromes that more strongly influence risk, these hereditary syndromes account for about 5% of all CRCs and are associated with specific gene mutations ***(Patel and Ahnen, 2012).***

The most common hereditary CRC syndrome is Lynch syndrome (formerly known as hereditary nonpolyposis CRC or HNPCC) which accounts for approximately 2% to 4% of all cases. Individuals with Lynch syndrome are also at increased risk for a wide variety of other cancers, including endometrial, ovarian, small intestine, and stomach, among people with Lynch syndrome, an estimated 18% of men and 19% of women will develop CRC by age 50, rising to 45% and 54%, respectively, by age 70 ***(Bonadona et al., 2011).***

Familial adenomatous polyposis (FAP) is the second most common predisposing genetic syndrome, accounting for fewer than 1% of all CRCs characterized by the development of hundreds to thousands of colorectal polyps beginning at 10-12 years of age, Without intervention, the lifetime risk of CRC approaches 100% by age 40 ***(Ricciardiello et al., 2016).***

- ***Chronic inflammation***

People who have chronic inflammatory bowel disease, a condition in which the colon is inflamed over a long period of time, have almost double the risk of developing CRC compared to people in the general population**,** the most common forms of inflammatory bowel disease are Ulcerative colitis and Crohn's disease, in which CRC risk increases with the extent, duration, and severity of disease, but has decreased over time, likely due to increased use of medications to control inflammation and screening surveillance to detect premalignant lesions ***(Castano-Milla et al., 2014).***

Ulcerative colitis (US) is an independent risk factor for the development of CRC, the incidence of CRC in patients with extensive UC was 5.4%. Patients with pancolitis are at high risk of CRC, left-sided colitis is moderate risk and proctitis and proctosigmoiditis are low risk, being similar to the non-UC population. CRC risk varied by age at initial diagnosis of UC; patients diagnosed at childhood (0-19 years old) had a relative risk of 43.8 followed by those diagnosed in young (20-39 years old) with a relative risk of 2.65 ***(Yashiro, 2014).***

- ***Modifying factors***

Non-steroidal anti-inflammatory drugs and some naturally compounds block the biochemical abnormalities in prostaglandin homeostasis in colorectal neoplasms. Some of these agents cause a dramatic involution of adenomas but their role in the chemoprevention of adenocarcinoma is less clear. Polymorphisms in key enzymes can alter other metabolic pathways that modify protective or injurious compounds, e.g. methylenetetrahydrofolate reductase, N acetyltransferases, glutathione- S-transferases, aldehyde dehydrogenase and cytochrome P-450, these polymorphisms may explain individual susceptibility or predisposition among populations with similar exposures ***(Hamilton et al., 2006)***.

3. Pathogenesis of Colorectal cancer

- ***Chromosomal instability***

Colorectal cancer is a disease originating from the epithelial lining of the colon or rectum of the Gastrointestinal tract, most frequently as a result of mutations in the signaling pathway that increase signaling activity. The loss of genomic stability can drive the development of colorectal cancer by facilitating the acquisition of multiple tumor-associated mutations. The Chromosomal instability is an efficient mechanism for causing the physical loss of a wild-type copy of a tumor-suppressor gene, such as APC, P53, and SMAD family member 4 (SMAD4), whose normal activities oppose the

malignant phenotype ***(diagram 1) (Markowitz and Bertagnolli, 2009; Abdul-Khalek et al., 2010)***.

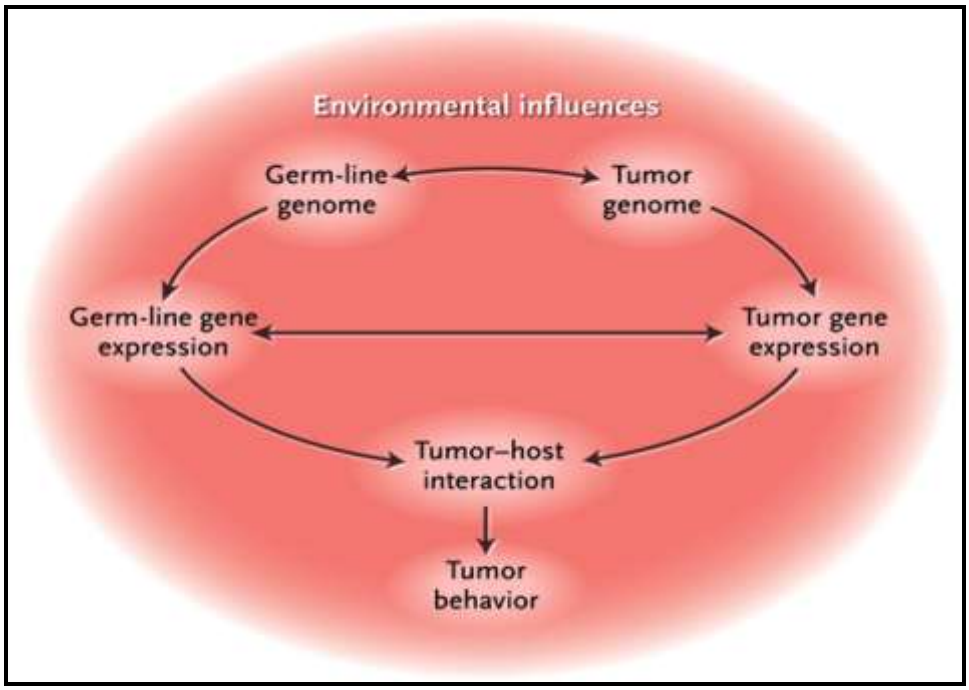

Diagram (1): Multifactorial Colorectal Carcinogenesis ***(Markowitz and Bertagnolli, 2009).***

- ***DNA repair defects***

In a subgroup of patients with colorectal cancer, there is inactivation of genes required for repair of base–base mismatches in DNA, collectively referred to as mismatch-repair genes ***(diagram 2).*** The inactivation can be **inherited**, as in hereditary non-polyposis colon cancer, also known as the Lynch syndrome, or **acquired**, as in tumors with methylation associated silencing of a gene that encodes a DNA mismatch-repair protein ***(Cleary et al., 2009)***.

In patients with HNPCC, germ-line defects in mismatch-repair genes (primarily MLH1 and MSH2) confer a lifetime risk of colorectal cancer of about 80%, with cancers evident by the age of 45 years, on average**,** the loss of mismatch-repair function in patients with HNPCC is due not only to the mutant germ-line mismatch-repair gene but also to somatic inactivation of the wild-type parental allele. Genomic instability arising from mismatch repair deficiency dramatically accelerates the development of cancer in patients with HNPCC. Germ-line mutations of another mismatch-repair gene, MSH6, attenuates the predisposition to familial cancer. Somatic inactivation of mismatch-repair genes occurs in approximately 15% of patients with non-familial colorectal cancer. In these patients, biallelic silencing of the promoter region of the MLH1 gene by promoter methylation inactivates mismatch repair ***(Lynch et al., 2008).***

The loss of mismatch-repair function is easy to recognize by the associated epiphenomenon of microsatellite instability, in which the inability to repair strand slippage within repetitive DNA sequence elements changes the size of the mononucleotide or dinucleotide repeats (microsatellites) that are scattered throughout the genome**.** Cancers characterized by mismatch-repair deficiency arise primarily in the proximal colon, and in sporadic cases, they are associated with older age and female sex**.** In mismatch-repair deficiency, tumor-suppressor genes, such as those encoding transforming growth

factor β (TGF-β) receptor type II (TGFBR2) and BCL2-associated X protein (BAX), which have functional regions that contain mononucleotide or dinucleotide repeat sequences, can be inactivated ***(Vogelstein and Kinzler, 2004; Hampel et al., 2005).***

An alternative route to colorectal cancer involves germ-line inactivation of a base excision repair gene, mutY homologue (MUTYH, also called MYH). The MYH protein excises from DNA the 8-oxoguanine product of oxidative damage to guanine**.** In persons who carry two inactive germ line MYH alleles, a polyposis phenotype develops, with a risk of colorectal cancer of nearly 100% by the age of 60 years. MYH associated polyposis is increasingly recognized. One third of all persons in whom 15 or more colorectal adenomas develop have MYH-associated polyposis ***(Kastrinos and Syngal, 2007).***

- ***Aberrant DNA methylation***

Epigenetic silencing of genes, mostly mediated by aberrant DNA methylation, is another mechanism of gene inactivation in patients with colorectal cancer. A methylated form of cytosine in which a methyl group is attached to carbon 5 (5-methylcytosine) defines a fifth DNA base, introduced by DNA methylases that modify cytosines within CpG dinucleotides. In the normal genome, cytosine methylation occurs in areas of repetitive DNA sequences outside of exons;

it is largely excluded from the CpG-rich "CpG islands" in the promoter regions of approximately half of all genes. By comparison, in the colorectal-cancer genome, there is a modest global depletion of cytosine methylation but considerable acquisition of aberrant methylation within certain promoter associated CpG islands. This can induce epigenetic silencing of gene expression. In sporadic colorectal cancer with microsatellite instability, somatic epigenetic silencing blocks the expression of MLH1 ***(Issa, 2004).***

Among the loci that can undergo aberrant methylation in colorectal cancer, a subgroup seems to become aberrantly methylated as a group, a phenomenon called the CpG island methylator phenotype (CIMP, or CIMP-high)**.**The molecular mechanism for CIMP remains unknown, but the phenomenon is reproducibly observed in about 15% of colorectal cancers and is present in nearly all such tumors with aberrant methylation of MLH1 ***(Toyota et al., 1999).***

- ***Mutational inactivation of tumor suppressor genes***

Colorectal cancers acquire many genetic changes, but certain signaling pathways are clearly singled out as key factors in tumor formation, One of these changes, the activation of the Wnt signaling pathway, is regarded as the initiating event in colorectal cancer, occurs when the oncoprotein β-catenin binds to nuclear partners (members of the T-cell factor–lymphocyte

enhancer factor family) to create a transcription factor that regulates genes involved in cellular activation**.** The *β*-catenin degradation complex controls levels of the *β*-catenin protein by proteolysis. A component of this complex, APC, not only degrades *β*-catenin but also inhibits its nuclear localization ***(Vogelstein and Kinzler, 2004)***.

The most common mutation in colorectal cancer inactivates the gene that encodes the APC protein. In the absence of functional APC, the brake on *β*-catenin-Wnt signaling is inappropriately and constitutively activated. Germ-line *APC* mutations give rise to familial adenomatous polyposis, an inherited cancer-predisposition syndrome in which more than 100 adenomatous polyps can develop; in carriers of the mutant gene, the risk of colorectal cancer by the age of 40 years is almost 100% ***(Lynch et al., 2008).***

The inactivation of the p53 pathway by mutation of TP53 is the second key genetic step in colorectal cancer In most tumors, the two TP53 alleles are inactivated, usually by a combination of a mis-sense mutation that inactivates the transcriptional activity of p53 and a 17p chromosomal deletion that eliminates the second TP53 allele**,** often this processes coincides with the transition of large adenomas into invasive carcinomas. The CRC with mismatch-repair defects, TP53 remains wild-type, though in these cancers the activity of the p53 pathway is probably attenuated by mutations in the BAX inducer of apoptosis ***(Vazquez et al., 2008).***