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**جـــامعـــة جيـجـــل محمد الصديق بن يحي**
**University of Mohamed Seddik Ben Yahia Jijel**

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**Theme**

# Analysis of the nutritional, epidemiological and pathological profiles in 34 cases of CRC in Jijel region

**Board of Examiners**

**Chairperson: Mrs CHERBAL Asma**

**Examiner: Mrs BENSAM Moufida**

**Supervisor: Mrs ABBES Arbia**

**Guest: Dr RECHRECHE Hocine**

**presented by:**

**BOUMALA Ilhem**

**BENALIA Selma**

**MENIA Mohamed**

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**Abbreviations List**

APC: Adenomatous polyposis coli

CIN: Chromosomal instability

CTNNB1: Catenin (Cadherin-Associated protein) Beta1

EGFR: Epidermal Growth Factor Receptor

EPIC: European Prospective Investigation Of Cancer and Nutrition

FAP: Familial Adenomatous Polyposis

FOBT: Fecal Occult Blood Test

HNPCC: Hereditary Non-Polyposis Colorectal Cancer

IARC: International Agency for Research on Cancer

IGF2: Insulin _Growth Factor

LOH: Loss of Heterozygosity

LS: Lynch Syndrome

MAPK: Mitogen _Activated Protein Kinase

MMR: DNA Mismatch Repair

MSI: Microsatellite instability

NCI: National Cancer Institute

NHS: National Health Service

NSAIDS: Nonsteroidal Anti-inflammatory drugs

RAS: Kirsten Rat Sarcoma Viral Oncogene Homolog

TNM: Tumor Node Metastases

VEGF: Vascular Endothelial Growth Factor

WHO: World Health Organization

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# Introduction

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Colorectal cancer (CRC) is an important public health problem throughout the world. It is the third most common cancer in men (Boyle et al., 2011), after prostate cancer and lung cancer (Fang et al., 2011) (663,000 cases in 2008: 10% of all cancer cases) and the second in women (Boyle et al., 2011) after breast cancer and lung cancer (Fang et al., 2011), (570,000 cases: 9.4% of all cancer cases) worldwide (Boyle et al., 2011). The World Health Organization (WHO) estimates an increase of 77% in the number of newly diagnosed cases of CRC and an increase of 80% in deaths from CRC by 2030 (Binefa et al., 2014).

The CRC rate varies among different regions. The rates were traditionally higher in the developed and industrial countries, whereas the less developed countries had lower rates. Nevertheless, CRC incidence is dramatically increasing in many developing countries such as in former eastern European communist bloc, eastern Asian regions, such as Hong Kong, Taiwan, urban China, Singapore, and Thailand as well as in western Asian, Iran, Saudi Arabia, Jordan, Yemen and Egypt (Bishehsari et al., 2014).

The role of environmental factors in this considerable increase have been highlighted by migration studies which have demonstrated a spectacular differences in colorectal between Native Africans (incidence < 5 per 100 000) and African Americans (incidence: 52 per 100 000). In one hand, western life style and dietary habits characterized by higher intake of meat, fat and total calories, along with increasing life expectancy and population growth may explain these discrepancies. On the other hand, preventative and therapeutic management of CRC is compromised by the development of greater tumor virulence possibly resulting from disparities in educational and insurance status, screening behavior, treatment patterns, social support, and access to and use of health care facilities (Sharma and O'Keefe, 2007).

Algeria is an example of real epidemiological transition. This transition is marked by a structural change in the epidemiological profile of the population. The demographic transition resulted in a gradual aging of the population importantly towards people over 60 years in the age pyramid. However, the transformation of the environment, an acute change in the individual and collective life (increased smoking, stress, sedentary lifestyle, urbanization) and life style change are the cause of emergence of non-communicable diseases, including cancer, which is often a multifactorial disease and its causes are difficult to study (Cherif et al., 2014).

The case-control studies are one of the epidemiological methods used to reveal the relationship between exposure to some environmental factors and the outcomes resulting, such as CRC. In these retrospective investigations, data about exposure to a risk factor or several risk factors is collected by interviewing the cases (a group known to have the outcome) and the controls (a group known to be free of the outcome) then comparing the frequency of the exposure between the tow (Lewallen and Courtright, 1989; Song and Chung, 2010).

Despite the number of such studies tackling the effect of diet on the occurrence of CRC, many discrepancies in the cumulative results have been registered to date. One way to reduce the effect of measurement error is to study different populations with diverse dietary practices, which increases the between-person variance in diet and enables the detection of modest diet-cancer associations (Van Duijnhoven et al., 2009).

The situation in Algeria is characterized by scarce data about the role of dietary regimen in the incidence of CRC and its potent possible implication in primary prevention of this health problem. In view of better understanding of CRC progression in Algeria, especially in the population of the Jijel region, the principal objectives of this work was to explore the relationships between lifestyle and the CRC profiles. The lifestyle indicators are obesity, overweight, and lack of exercise and/or physical activity, socioeconomic and cultural status and medical history and/or surgery. Also to study the diet impact on the CRC risks. Eating habits will be evaluated depending on the composition of meals and the distribution thereof in the day and the food frequency by food group.

# Part I. Bibliographical section

## I.1 General Introduction to CRC

### I.1.1 CRC epidemiology

CRC is one of the most cancer types leading of morbidity and mortality worldwide. In 2012, it was the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Almost 55% of the cases occur in more developed regions. There is wide geographical variation in incidence across the world and the geographical patterns are very similar in men and women. The incidence rates varies ten-fold in both sexes worldwide. The highest estimated rates being in Australia/New Zealand (ASR 44.8 and 32.2 per 100,000 in men and women respectively) and the lowest in Western Africa (4.5 and 3.8 per 100,000) (GLOBOCAN, 2012).

Mortality is lower (694,000 deaths, 8.5% of the total) with more deaths (52%) in the less developed regions of the world, reflecting a poorer survival in these regions. There is less variability in mortality rates worldwide (six-fold in men, four-fold in women), with the highest estimated mortality rates in both sexes in Central and Eastern Europe (20.3 per 100,000 for men, 11.7 per 100,000 for women), and the lowest in Western Africa (3.5 and 3.0, respectively) (GLOBOCAN, 2012).

In the last decades, Algeria has been in front of a medical transition where non-communicative diseases have become the most prevalence diseases with all the economic and social burdens resulting. Cancer is one of the health disabilities that constitute a huge challenge in both diagnosis and management (Cherif et al., 2014). Data about incidence of colorectal cancer in Algeria are divergent between different references. According to Cherif et al. (2014), the new CRC cases in Algeria during 2014 were 2687 among men, occupying the second place among all cancer types. The crude incidence rate is 13.5/ 100,000, while the standardized incidence rate is 16.3. The median age at diagnosis is 65 years. Between female, 2245 new CRCs cases were recorded. The CRC represent the second common cancer observed in women cancers. The crude incidence rate per 100,000 inhabitants is 11.2, corresponding to standardized incidence rates of 16.1. The median age at diagnosis is 56 years. In North Africa, we note the same incidence. The incidence remains low as compared to industrialized countries.

The numbers presented in the GLOBOCAN project by the International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO), for 2012 are lower with 1690 new cases in both of the sexes with the majority of which are ranged in the population aged below 65 old: 1179 males and 1155 females. For 2015, 1992 new cases are estimated between men and 1900 new cases between women. The aim of the project is to provide contemporary estimates of the incidence of, mortality and prevalence from major types of cancer, at national level. The GLOBOCAN gives an estimation of the variation expected in 2035. By analyzing the estimation given for some countries and regions around the word, it appears that a dramatically increase of incidence of colorectal cancer in Algeria will take place, 115.71 % (more than that for USA or Western Europe) (GLOBOCAN, 2012).

### I.1.2 Etiology of CRC

The known risk factors for CRC are as follows: a diet low in fruit and vegetables, excessive intake of red meat and saturated fat, alcohol intake, a sedentary lifestyle, tobacco and being overweight. However, the main risk factor is age. From 50 onwards, CRC is much more frequent, and the incidence increases exponentially with age (Binefa et al., 2014). Furthermore, rapid urbanization with environmental pollution, lifestyle alterations such as reduction in physical activity, may have also contributed to the rising incidence of CRC, although this alone does not explain its disproportionate rise in incidence in previously low incidence parts of the world (Deen et al., 2016).

### I.1.3 Anatomic Distribution, anatomopathology and TNM stadification of CRC

The large bowel can be separated into the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and the rectum. The parts of the colon up to the midtransversum are considered the right-sided or proximal colon, whereas the parts of the colon after the mid-transversum are considered the left-sided or distal colon (Haubrich, 1995).

It is believed that the vast majority of CRCs develop from benign precursor lesions, the so-called adenomatous polyps or adenomas, through a series of genetic changes over a long-time period (i.e. the adenoma–carcinoma sequence; Fig. 1). The CRC development may takes at least 10 years form a small adenoma to metastatic cancer (Bretthauer, 2011).

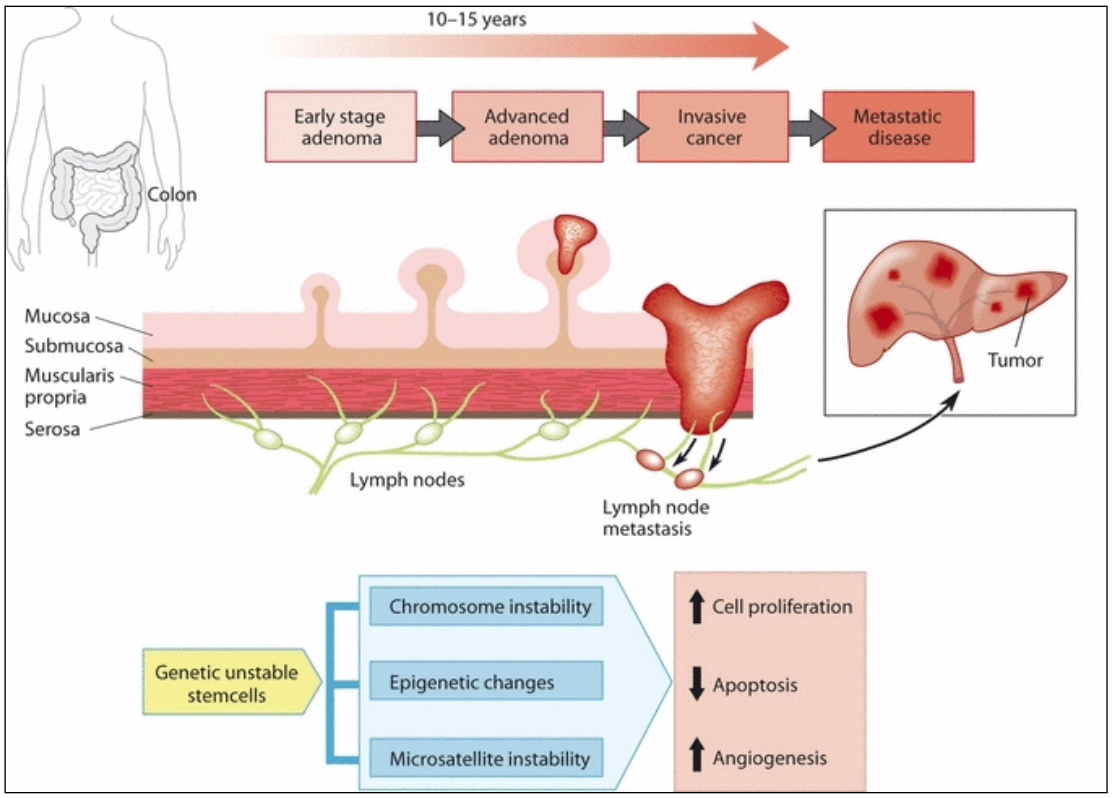


***Fig. 1. Development of CRC from normal mucosa to metastatic cancer (Bretthauer, 2011).***

The choice of the cancer therapy approach depends on three essential factors: the site of origin, the histological type (including grade) and the extent or stage of the cancer. Cancer staging is an important component, not only of patient care, but also of cancer research and control activities. The globally accepted method for describing the extent of cancer is the anatomically based TNM (tumour, node, metastases) staging system, which classifies the cancer as to its local, regional and distant extent. The TNM classification has become the accepted basis of cancer staging (Brierley, 2006).

In the TNM system classification (Table1), the designation T refers to the local extent of the untreated primary tumour at the time of diagnosis and initial work (Compton and greene.,2004), Tumour in T1, invades submucosa, T2: invades muscularis propria, T3 and T4 are more extensive, T3 indicates invasion through muscularis propria into subserosa or into nonperitonealised pericolic or perirectal tissues while T-4 invades adjacent organs (Fry et al., 2008) .The designation "N" refers to the status of the regional lymph nodes (Compton et al., 2004), N1: 1-3 positive nodes, N2:4 or more positive nodes. (Fry et al., 2008) and "M" refers to distant metastatic disease at this time (Compton and Greene, 2004) M1: Distant metastases present (Fry et al., 2008).

***Table 1. TNM Classification of CRC according to OMS (1997).***

| | | | |
|---|---|---|---|
| **Primary tumor (T)** | | | |
| TX | Primary tumor cannot be assessed | | |
| T0 | No evidence of primary tumor | | |
| Tis | Carcinoma in situ (intraductal tumor) | | |
| T1 | Solitary tumor without vascular invasion | | |
| T2a | Solitary tumor with vascular invasion | | |
| T2b | Multiple tumors, with or without vascular invasion | | |
| T3 | Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion | | |
| T4 | Tumor with periductal invasion | | |
| **Regional lymph nodes (N)** | | | |
| NX | Regional lymph nodes cannot be assessed | | |
| N0 | No regional lymph node metastasis | | |
| N1 | Regional lymph node metastasis present | | |
| **Distant metastasis (M)** | | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis | | |
| **Stage grouping** | | | |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| Stage IVA | T4 | N0 | M0 |
| | Any T | N1 | M0 |
| Stage IVB | Any T | Any N | M1 |

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

### I.1.4 CRC diagnosis

#### I.1.4.1 Colonoscopy

The colonoscopy is a procedure in which a long, flexible and narrow tube with a light and tiny camera on one end is used to look inside the rectum and colon. It allows direct inspection of the entire colonic mucosa, tissue biopsies and polyp removal throughout the colorectal in one single session. Furthermore, It's used as a follow-up intervention for individuals with positive results with another CRC screening tool (Garborg et al., 2013; Bretthauer, 2011).

Also, it's considered the gold standard of excellence for the diagnosis of colorectal pathologies, however it involve some limitation such as complications, cost and its lower acceptance by the population (because of the requirement of a specific diet and the intake of a bowel cleansing preparation, the fear of anesthesia and the exploration itself or shame **(**Binefa et al., 2014)

### I.1.4.2 Sigmoidoscopy

Flexible sigmoidoscopy is an endoscopic examination of the distal colon and rectum with a flexible endoscope: either a sigmoidoscope (60 cm long) or a colonoscope (130⁄160 cm long). Flexible sigmoidoscopy is performed after cleansing the distal colorectal using an enema, usually administered about 30–60 min before the examination. The procedure is restricted by the length of the endoscope, the extent of bowel cleansing and patient tolerance and is often regarded as successful if the rectum and sigmoid colon have been adequately examined. Flexible sigmoidoscopy is usually performed without sedation (Bretthauer, 2011).

### I.1.4.3 Fecal Occult Blood Test

Fecal occult blood test (FOBT) is a non-invasive, widespread CRC screening method. The guaiac Fecal Occult Blood Test **(**gFOBT) detects the presence of blood in feces through a chemical reaction dependent upon the heme peroxidase activity, It's an inexpensive test that can be mailed to patients. Annual or biennial gFOBT have shown to decrease CRC mortality rates by 15%-33%. In the Minnesota Colon Cancer Control Study, a 30-year follow-up of patients randomly assigned to annual/or biennial gFOBT usual care showed a 32% decrease in CRC mortality. Furthermore, mortality reduction was more pronounced in men compared to women (El Zoghbi and Cumming, 2016).

Another more powerful FOB test is the immunochemical test, sometimes called the iFOBt or the Faecal Immunochemical Test (FIT) which is specific only for human since globin present in the large bowel and is unaffected by diet. Immunochemical tests are commercially available and are used in screening programs in a variety of countries. They have not been tested in a randomised trial setting (Young et al., 2011).

## I.1.5. CRC Treatment

The survival of patients with CRC has increased constantly for many years due to superior surgical techniques, improved postoperative care, regular follow-up and an increased use of effective systemic therapy in the adjuvant and the palliative setting (Meyerhardt et al., 2005; Pfeiffer et al., 2007). All these advancements are important, but the establishment of multidisciplinary teams which facilitates the optimising of therapy choice for individual patients (Pfeiffer et al., 2007; Pfeiffer et al., 2009).

### I.1.5.1 Loco-regional non-metastatic CRC treatment

The cornerstone of treatment is surgical resection. For early-stage cancers, surgery alone may cure the disease. For colon cancer, the preferred procedure is a hemicolectomy (resection of either the right or the left colon) with wide (> 5 cm) margins of normal colon. A general surgeon can typically perform this procedure. Surgery for rectal cancer is much more complex. High-volume, specialized surgeons and centers have been associated with better outcomes: less likely to need an ostomy bag, lower rates of local recurrence, better overall survival (Michael and Zalcberg, 2008).

The availability of radiation therapy is most relevant for cancers of the rectum, as local recurrence is much more common than in colon cancer, because of the inability to obtain wide margins and the lack of a serosal barrier. Radiation therapy has improved local control for persons with stages II and III rectal cancer (Hoffe et al., 2010).

The patients with advanced CRC are treated with chemotherapy as palliative rather than curative intent. For over four decades, the fluorouracil has been the mainstay of treatment for advanced colorectal cancer. The folinic acid is intravenously given before fluorouracil to enhance the fluorouracil's cytotoxicity. Chemotherapy delays the occurrence or progression of symptoms by about six months and improves symptoms, weight gain, and functional performance in about 40% of patients. Palliative chemotherapy in advanced CRC should not be restricted by chronological age but by fitness and activity level (Young and Rhea, 2000).

### I.1.5.2 Metastatic CRC treatment

Systemic chemotherapy has been the main treatment modality for patients with metastatic colorectal cancer. Current cytotoxic agents are fluoropyrimidine-based regimens in combination with oxaliplatin or irinotecan. Recently, significant progress has been made in the management of metastatic CRC. These improvements are due in large part to the availability of new therapeutic agents targeting two major axes, epidermal growth factor receptor (EGFR) signalling and angiogenesis. The anti-EGFR agents cetuximab and panitumumab have demonstrated benefit in RAS (NRAS and KRAS) wild-type patients in first- and second-line treatment in combination with chemotherapy, as well as in chemorefractory patients. Similarly, clinical benefit derived from agents binding to circulating vascular endothelial growth factor (VEGF), a key determinant in the process of angiogenesis,

has been demonstrated. Moreover, the use of antiangiogenic treatments in conjunction with chemotherapy is standardized in metastatic CRC care (Verdaguer et al., 2016).

### I.2 CRC carcinogenesis Mechanisms

The CRC is a multistep process that results from the accumulation of genetic and epigenetic alterations triggering the adenoma-adenocarcinoma switch. It's characterized by molecular heterogeneity (Lao et al., 2012), and each tumor has a unique combination of genetic alterations. So, each CRC patient should be submitted to specific treatment planning (Goel and Boland 2012). The Fig.2 illustrates important molecular, genetic, and epigenetic changes with respect to disease progression (Tariq and Ghias, 2016).

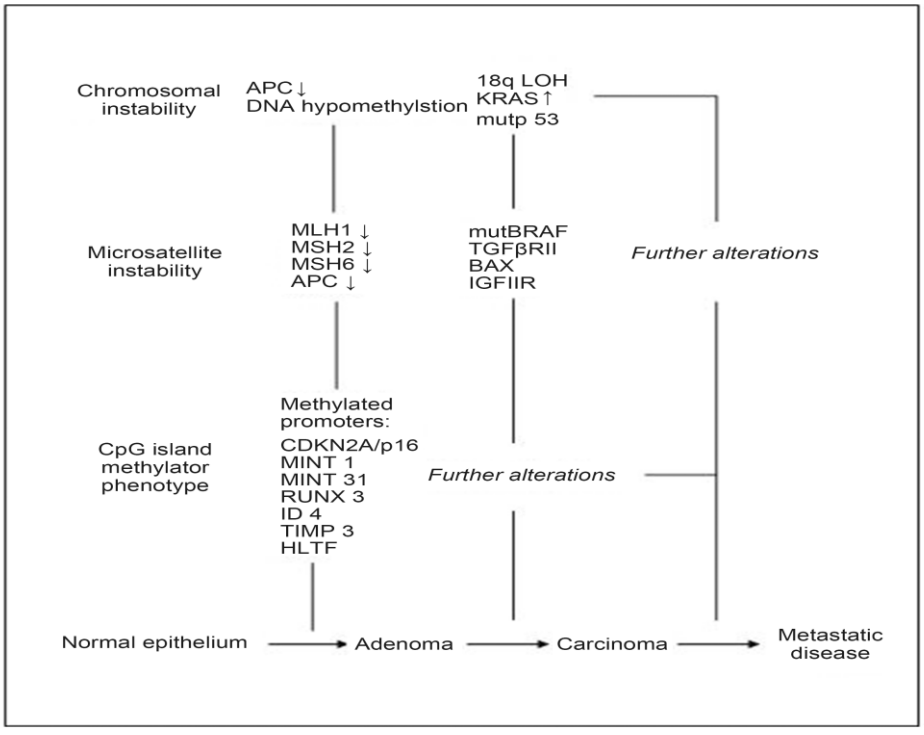


***Fig.2. Important molecular, genetic and epigenetic changes with respect to disease progression (Tariq and Ghias, 2016).***

### I.2.1Genomic instability

#### I.2.1.1 Chromosomal instability

The chromosomal instability (CIN) refers to genetic changes that include insertions, inversions, deletions and rearrangements at the chromosomal level (Hagland et al., 2013). Aneuploidy and heterozygosity loss (LOH) are the major players in CIN tumors, which not only constitute most of the sporadic tumors (85%) but also involve familial adenomatous polyposis (FAP) cases associated with germline mutations in the *APC* gene (Tariq and Ghias, 2016). Chromosome instability is caused mainly by failures in the mitotic process (e.g., in chromosome transmission, at the mitotic spindle checkpoint, in kinetochore-microtubule attachment dynamics) and/or in the mitotic apparatus (e.g., kinetochore, centrosome) that cause mitotic process failures (Fan et al., 2013). Genetic changes include the activation of proto-oncogenes such as KRAS and C-MYC and inactivation of the tumor suppressor genes, APC, and p53, and heterozygosity loss of the chromosome 18 long arms (Silla et al., 2014).

#### I.2.1.2 Microsatellite instability

MSI tumors, whose carcinogenetic pathway is also known as the "Mutator Phenotype pathway", represent 10%-15% of all CRCs. MSI is due to an inability of the DNA nucleotide mismatch repair (MMR) system to correct errors that often occur during DNA replication, which is controlled by several genes (including MLH1, MSH2, MSH6 and PMS2) and is characterized by the accumulation of single nucleotide mutations and alterations in the lengths of repetitive microsatellite nucleotide sequences. MSI tumors are characterized by a more frequent location in the right colon, increased mucin production, the presence of signet ring cells, and low-grade tumor differentiation (Silla et al., 2014).

In 1997, the National Cancer Institute held a workshop where a five-marker MSI panel was validated. This panel included two mononucleotide markers, namely BAT25 and BAT26, and three dinucleotide markers, namely D5S346, D2S123, and D17S250. Tumors with instability in $\geq$ 30% of markers are called MSI-high (MSI-H). Those with instability in <30% are called MSI-low (MSI-L), while those without MSI are called MSI stable (MSS). Mutations in MLH1, MSH2, MSH6, and PMS2 have been associated with a risk of developing LS (Tariq and Ghias, 2016).

MSI tumors are present in two CRC forms: hereditary forms such as lynch syndrome (LS), the molecular basis of which is a germline mutation in an MMR gene; and sporadic cases, in which MSI is due to hypermethylation of MLH1 (Silla et al., 2014).

The observation raises questions about the role of these DNA repair proteins and the homologs in the initiation and progression of colorectal cancer. To address these questions, mice with inactivating mutations in all of the known mutS and mutL homologs have been generated (i.e., Msh2, Msh3, Msh4, Msh5, Msh6, Mlh1, Pms1, and Pms2). Analyses of the mouse phenotypes revealed a role for some of the DNA mismatch-repair genes in lymphoma and GI tract carcinogenesis and in mammalian meiosis. Among the transgenic mutant mice, msh2, msh3, msh6, and mlh1 mice showed cancer development in the GI tract (Fan et al., 2013).

### I.2.2 Epigenetic instability

The epigenetic events that are relevant to cancer risk are believed to occur early in cancer development, thus may serve as potential "first hits" for tumorigenesis (Verma et al., 2014).

#### I.2.2.1 CpG island methylator phenotype

The CIMP pathway, which accounts for almost 40% of CRC, is characterized by promoter hypermethylation of various tumor suppressor genes, most importantly p16INK4a, MGMT and MLH1, SFRP2, and vimentin genes (Goel and Boland, 2012). CIMP-high tumors have a distinct clinical, pathologic, and molecular profile, such as association with proximal location in the colon, female sex, and poor differentiation. From the molecular point of view, they show a higher frequency of BRAF mutations, MSI and, albeit less often, P53 mutations (Silla et al., 2014).

Importantly, gene-silencing resulting from aberrant DNA methylation cooperates with other genetic mechanisms to alter the key molecular pathways critical in colorectal carcinogenesis (Sakai et al., 2014). First coined the term "CIMP" and defined the CpG island methylator phenotype as a subset of CRC. In contrast, the hypomethylation of CpG sites has been associated with the overexpression of oncogenes within cancer cells (Chong et al., 2016).Methylation of tumor suppressor genes silenced by hypermethylation and detectable in

the plasma or serum of patients with CRC has been shown to hold promise as a potential methodology for the CRC detection (Cassinotti et al., 2012).

On the other end, genetic instability could also be caused by global genomic hypomethylation. Studies have identified number of different genes hypomethylated in CRC, such as CARD 14, CCDC116, TIAM1, and MAEL, that can have a variety of effects on signaling, e.g., by nuclear factor-kappa B (NF-κB), or other cellular functions relevant to CRC carcinogenesis including, but not limited to, cell adhesion, cell cycle control, cell migration and differentiation (Bishehsari et al., 2014).

Hypomethylation refers to a marked global decrease in methylation on cytosine bases103–106 that is observed in hyperplastic and adenomatous polyps and carcinomas. Hypomethylation in the repetitive DNA sequences, such as in satellite regions, can lead to genomic instability. Furthermore, loss of imprinting or promoter demethylation could reactivate the retrotransposons. The demethylation of the long interspersed nuclear element promoter has been suggested as an early event. However, demethylation has also been observed in the normal colonic mucosa of the same patients. The loss of imprinting of insulin-like growth factor 2 (IGF2) is seen in almost 40% of CRC tumors, which leads to microsatellite instability in younger patients (Tariq and Ghias, 2016).

### I.2.2.2 Histones modifications

Indeed, the posttranslational modification state of the histones appears to regulate the chromatin state in a transcriptionally active (euchromatin) or transcriptionally repressed state (heterochromatin) through a “histone code.” This histone code is altered in cancer and correlated with aberrant methylation and the alteration of the tumor suppressor genes expression in cancer.

The best understood histone modifications in CRC are acetylation/deacetylation and methylation/demethylation of lysine and arginine residues within histone tails. It has been shown that while dimethylation and trimethylation of histone H3 lysine (H3K4me2/me3) and acetylation of H3/H4 (H3K9Ac and H4K9Ac) amino acids constitute transcriptionally active marks, transcriptionally inactive gene promoters are frequently characterized by

trimethylation of histone H3 lysine 9 and 27 (H3K9me3 and H3K27me3) residues. These bivalent histone modifications are mediated by transcriptional repressors, the polycomb group proteins that are instrumental in silencing a specific group of tumor suppressor genes in human cancers (Tannapfel et al., 2010).

#### I.2.2.3 MicroRNAs

Noncoding RNAs, particularly microRNAs (miRNAs or miRs), are mechanistically involved in controlling the expression of various cancer-associated genes, and their expression may be altered in cancer. Analogous to genes, miRNAs can act either as tumor suppressors (tsmiRs) by inhibiting the expression of oncogenes or as tumor promoters (oncomiRs) by suppressing the expression of target tumor suppressor gene (Slaby et al., 2009).

### I.2.3 Genetic CRC predisposition mechanisms

The two best-studied hereditary syndromes are familial adenomatous polyposis and hereditary CRC syndrome non-polyposis (HNPCC). The FAP is an autosomal-dominant colorectal cancer syndrome, caused by a germline mutation in the adenomatous polyposis coli (APC) gene, on chromosome 5q21. It is characterized by hundreds of adenomatous colorectal polyps; with an almost inevitable progression to CRC at an average age of 35 to 40 years. Associated features include upper gastrointestinal tract polyps (Galiatsatos et al., 2006). The HNPCC or the Lynch syndrome, accounts for 2-4% of all CRC cases. Although individuals with HNPCC are predisposed to several types of cancer, the lifetime risk of CRC is the highest (~75%). Colon cancers and polyps arise in LS patients at a younger age than in the general population with sporadic neoplasias, and the tumours develop at a more proximal location. Histologically, the cancers are often poorly differentiated, mucinous and are infiltrated by large numbers of lymphocytes (Conteduca et al., 2013).

### I.2.4 CRC signaling pathways

#### I.2.4.1 APC/ß-catenin/WNT Pathway

Wnt pathway, one of the most conserved signaling pathways, plays a tremendous role in cellular proliferation and embryonic development. Binding of Wnt ligands to Frizzled/low-

density lipoprotein-related protein 5/6 (LRP5/6) receptor complexes causes stabilization of β-catenin by preventing its ubiquitination and destruction by the proteasome after being phosphorelated by the complex APC ,Axin1, GSK-3β (Glycogen synthase kinase 3-β), and CK1 (casein kinase 1). Thus, the stabilized β-catenin translocates to the nucleus where it plays the role of a translation cofactor triggering the activation of many genes leading to cell proliferation, as show on in Fig.3 (Amado et al., 2014).

The mutations that affect the members of this cascade are frequently detected in colorectal cancer: mutations in the APC gene occur in up to 70% of sporadic CRC and are the cause of the FAP cancer predisposition syndrome, and gain-of-function mutations in β-catenin (CTNNB1) have been identified in as many as 50% of colon tumors with intact APC (Grady et Pritchard, 2014).

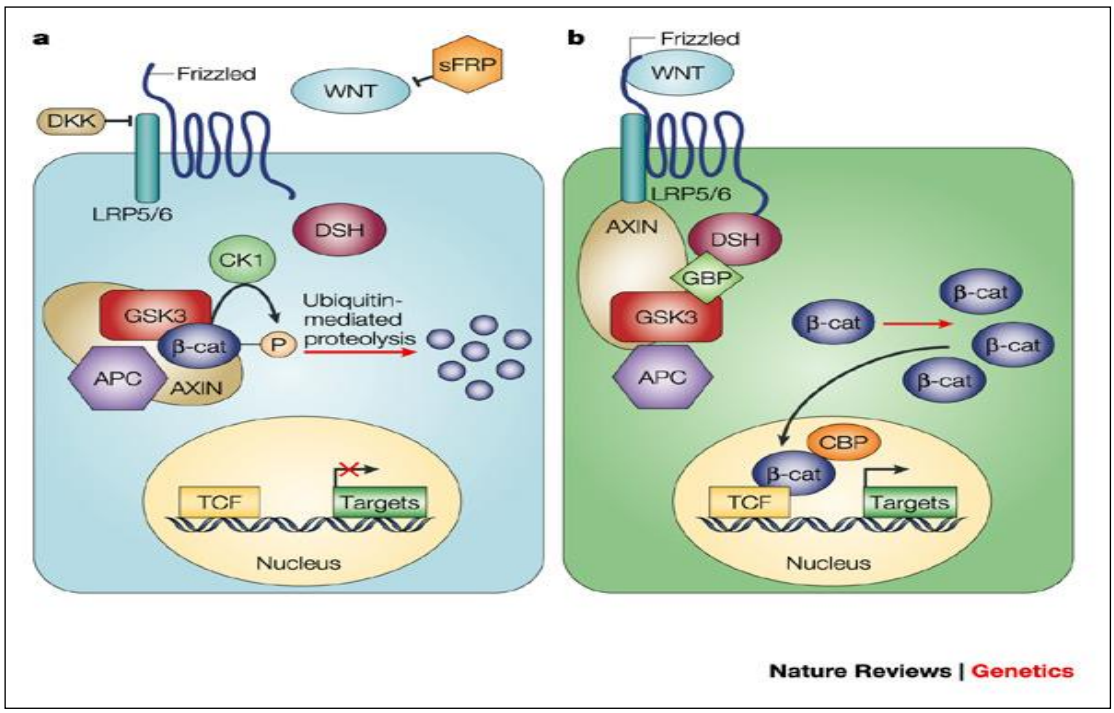


***Fig.3. Wnt/β-catenin signaling pathway.*** *In the absence of active WNT (a), β-catenin is degraded, and prospective target genes are in a repressed state. If WNT signaling (b) is active, β-catenin degradation is reduced. As β-catenin accumulates, it enters the nucleus, binds to T-cell factor (TCF)- and lymphoid enhancer-binding protein (LEF)-family transcription factors and activates transcription. APC, adenomatous polyposis coli; β-cat, β-catenin; CBP, CREB-binding protein; CK, casein kinase; DKK, Dickkopf; DSH, Disheveled; GBP, GSK3-binding protein; GSK, glycogen synthase kinase; LRP, LDL-receptor-related protein; P, phosphorylation; sFRP, secreted Frizzled-related protein; TCF, T-cell factor (Dhillon et al., 2007).*

### I.2.4.2 EGFR/RAS/RAF/MEK/MAPK signaling

The mitogen-activated protein kinase (MAPK) pathways are common contributors in many cellular features such as growth, proliferation, differentiation, migration and apoptosis. The canonical MAPK/ERK pathway is composed of three types of MAPKKK: A-RAF, B-RAF and RAF-1 or C-RAF kinases. One level below are the MAPKKs, which are composed of MEK1 and MEK2. Finally, further downstream are ERK1 and ERK2, which are the final effectors of the MAPK pathway (Fig.4) (Burotto et al., 2014). The activating mutations of this pathway can occur upstream in membrane receptor genes, such as epithelial growth factor receptor (EGFR), in signal transducers (RAS), regulatory partners (Sprouty), and in downstream kinases belonging to MAPK/ERK pathway itself (BRAF) (Fig.5).

Permanently activating of KRAS, that results from mutations disabling it from degrading GTP into GDP +Pi, can lead to a state that permits the cell to evade apoptosis and acquire a growth advantage. More than 90% of mutations in the KRAS gene happen at codon 12 and at codon 13. The mutations at codon 12 confer a more oncogenic phenotype than the mutations at codon 13, suggesting that codon 13 mutations are more involved in the adenoma-carcinoma transition, whereas codon 12 mutations predispose colorectal tumor cells to local invasion and metastasis (Colussi et al., 2013).

The majority of BRAF mutations are a single base change resulting in the substitution of glutamic acid for valine at codon 600 (V600E; sometimes referred to as “V599E”). KRAS and BRAF mutations are mutually exclusive, supporting the hypothesis that an activating mutation in either gene is sufficient to promote tumorigenesis via increased MAPK signaling. Emerging evidence supports a role for BRAF, which is mutated in ~ 10-15% of colorectal cancers, as a genetic marker for prognosis and possibly for predicting response to therapy. Alterations in EGFR ligands and the EGFR gene itself are also observed in a subset of colorectal cancers (Grady and Pritchard, 2013).

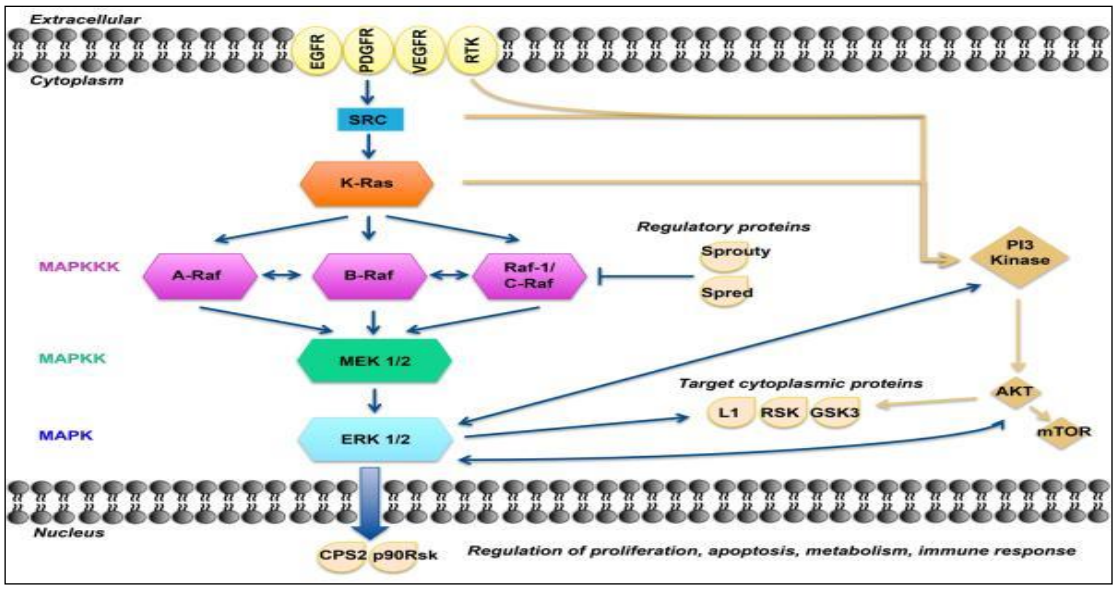


***Fig. 4. A model of the MAPK/ERK pathway***. *After membrane receptor activation, adaptor proteins recruit RAS proteins to activate steps concluding with ERK activation. Successive steps of phosphorylation amplify the signal, Raf→MEK→ERK, until ERK activates its cytoplasmic and/or nuclear targets. Regulatory phosphatases, Sprouty and Spred, modulate the intensity of the signal. The PI3K-AKT pathway interacts with the MAPK/ERK node under normal conditions and in the cancer cell. Target cytoplasmic proteins include RSK, ribosomal S6 kinases; GSK3, glycogen synthase kinase 3; L1, adhesion molecule L1. Additional proteins in nucleus include CPS2, p90Rsk (Burotto et al., 2014)*

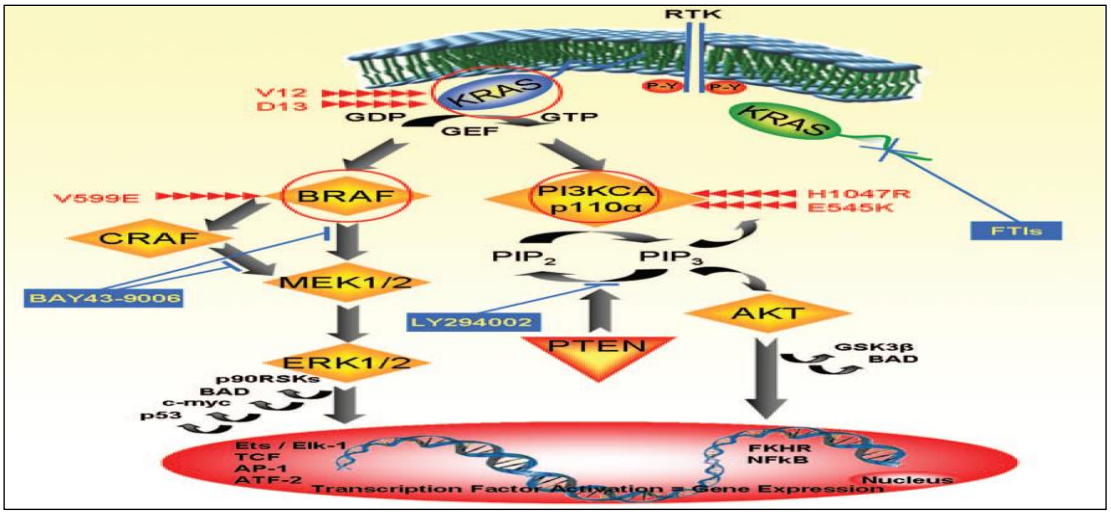


***Fig.5 Signaling upstream and downstream of RAS-BRAF and RAS-PI3KCA effector pathways mediating gene transcription.*** *Red-arrowed circles indicate the most frequent activating mutations that deregulate the pathways, while blue boxes represent therapeutic approaches in CRC (Oikonomou and Pintzas,2006)*

### I.2.4.3 PI3K/AKT Signaling Pathway

The Phosphatidylinositol-3-kinase (PI3K)/ protein kinase B (AKT) activation, which is generated by various receptor tyrosine kinases, EGFR, human EGFR 2 (HER2), insulin growth factor (IGF-1R), and platelet derived growth factor (PDGFR), promotes and regulates various cellular processes, including proliferation, survival, apoptosis, migration, and metabolism (Cathomas, 2015). Once activated, PI3K converse phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-triphosphate (PIP3) that provides a docking site for pleckstrin homology domain containing AKT, which thereby becomes activated. Activated AKT mediates the phosphorylation of a multitude of effectors that mediate its antiapoptotic/pro-survival function and induces cell growth and protein translation (Zhang et al., 2013).

Mutations affected the genes of this pathway, mainly the p110α catalytic subunit PIK3CA and the tumor suppressor gene PTEN, occurs in up to 40% of CRC and are nearly mutually exclusive of one another. The PI3K pathway is modulated by EGFR signaling in part via KRAS activation, and there is a plausible role for both PIK3CA and PTEN mutations as predictive markers of anti-EGFR therapy (Grady and Pritchard, 2013).

### I.2.4.4 Transforming Growth Factor Beta (TGF-β) Pathway

While playing a cytostatic effect on normal colorectal epithelial cells, TGF-β acts as a potent driver of cancer progression and metastasis in more advanced stages of epithelial tumors, by increasing angiogenesis and inducing epithelial-mesenchymal transition (EMT) (Stolfi et al., 2013). The TGF-β receptors (TβRI and TβRII) activation induces phosphorylation of receptor-regulated (R) SMADs (i.e., R-SMAD2 and R-SMAD3), which form heteromeric complexes with the common mediator, SMAD4, that translocate to the nucleus and binds to Smad-binding elements (SBE) to activate (p15INK4B and p21CIP1) or repress (c-MYC and CDC25A) TGF-β-responsive-gene expression (Fig. 6) (Zhang et al., 2013).

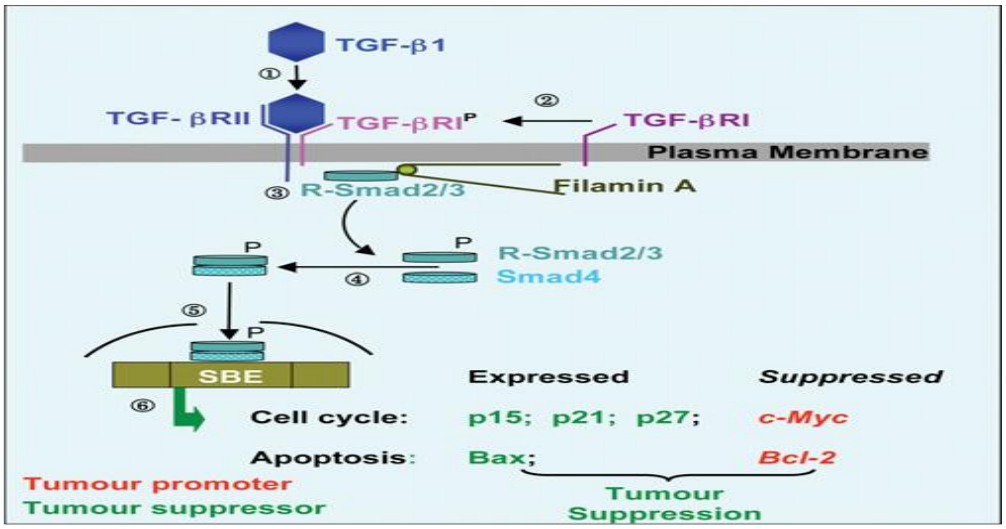


***Fig. 6.*** *The TGF-β Pathway. Step ①: on binding of TGF-β to the receptor subunit TGF-βRII, the TGF-βRI receptor is recruited (Step ②) to the complex and phosphorylated. Steps ③ and ④: receptor Smads (R-Smad2/3) are translocated to the receptor complex, phosphorylated and form a heteromeric complex with cytosolic Smads (Smad4). Step ⑤: the Smad complex translocates to the nucleus and binds to Smad-binding elements (SBE) to activate or repress TGF-β-responsive-gene expression. (Zhang et al., 2013).*

The TGF-β signaling deregulation occurs in the majority of CRC. Functionally significant mutations in TGFBR2 have been detected in as many as 30% of all CRC and are associated with the malignant transformation of late adenomas. SMAD4 is located on 18q in a region commonly deleted in CRCs, and is associated with adenoma formation and adenoma-carcinoma progression in mouse models, supporting a role for SMAD4 as a tumor suppressor gene. Furthermore, loss of SMAD4 expression as detected by immunostaining has been reported in >50% of CRC and is associated with lymph node metastases. Loss of the long arm of chromosome 18 (18q loss of heterozygosity; LOH) is the most frequent cytogenetic alteration in CRC and is observed in up to 70% of CRC, and it may influence CRC behavior by deregulating TGF-β signaling. Additional mediators of the TGF-β pathway, SMAD2 and SMAD7, are also in the 18qLOH region, suggesting that 18qLOH may promote tumorigenesis at least in part through deregulation of TGF-β signaling (Grady and Pritchard, 2013).

### I.2.4.5 p53 pathway

The p53 gene is located on the distal band of the short arm of chromosome 17p13. The tumour suppressive role of p53 is so crucial that it is referred to as “the guardian of the

genome". p53 acts as a tumour suppressor by preventing propagation of defective cells. It is up regulated by various upstream factors in response to cellular stress or damage such as DNA damage, hypoxia, telomere shortening and oncogenic stimulation or radiation. Activated p53 modifies downstream gene expression and co-factor transcription, which in conjunction with p53, lead to growth arrest (e.g., via $p21^{WAF1}$) or apoptosis (e.g., p53-upregulated modulator of apoptosis, PUMA). The most common cause of p53 inactivation is mutation, which most frequently occurs within the p53 core, and furthermore 70% occur at "hot spots"- amino acids 132-142, 151-159, 172-179, 237-249 and 272-286 (Suppiah and Greenman, 2013). The p53 loss occurs in about half of all CRC and is frequently present in the later stages of colorectal tumorigenesis (Coluussi et al., 2013) promoting the malignant transformation of adenomas. Like APC, p53 is a key tumor suppressor that has been extensively studied in colorectal cancer but currently has no predictive or prognostic role in the clinical setting (Grady and Pritchard, 2013).

### I.3 CRC risks factors

Lifestyle factors that include obesity, physical activity, and diet are emerging as potential critical elements in improving colorectal cancer survival outcomes. The association between colorectal cancer mortality and modifiable lifestyle factors is growing in evidence. Changes in individual health behaviors both before and after a diagnosis of colorectal cancer may improve outcomes of survivors. Several studies have indicated that maintaining a normal weight, participating in regular physical activity, and eating a healthy diet may be important preventative steps leading to improve survival outcomes. In addition, several epigenetic studies have demonstrated, at the cellular level, the possible mechanisms of colorectal cancer that can be positively influenced by changing lifestyle. However, extended lifestyle intervention studies, along with additional randomized trials and epigenetic studies are needed in order to provide firm evidence about the effect of lifestyle factors (including obesity, physical activity and diet) on colorectal cancer survival outcomes (Lee et al.,2015).

### I.3.1 Diet

The research about the possible associations between potentially modifiable factors, such as diet, with colorectal cancer is essential, if we are to determine an appropriate strategy for primary prevention of colorectal cancer (Vogtmann et al., 2013). A role for diet in preventing colon cancer held particular appeal in view of the direct contact of the colonic mucosa with nutrients and toxins from foods (Lee and Chan, 2011).

#### I.3.1.1 Food and nutrients

##### I.3.1.1.1 Red meat

In the last decades, several prospective studies that linked red meat consumption to CRC have been published. In his 2010 guideline, the American Cancer Society supported approximately a 15% to 20% increased risk of cancers of the colon and/or rectum per 100 grams (g) of red meat or 50 g of processed meat consumed per day (Kushi et al., 2012). In a population-based prospective cohort study in Japan, R. Takachi et al observed that higher consumption of red meat, including beef and pork, was associated with an increased risk of proximal colon cancer among women and distal colon among men (Takachi et al., 2011).

Many mechanisms may explain the association between meat and CRC. First, potentially carcinogenic N-nitroso compounds can form in the gastrointestinal tract. Second, meat cooked at high temperatures contains mutagenic heterocyclic amines (HCA). Third, epidemiologic and experimental data support the hypothesis that heme iron present in red and processed meats promotes colorectal cancer (Joshi et al., 2015).

##### I.3.1.1.2 Fruits and vegetables

Since the 1980s, the concept that a diet high in fruits and vegetables could reduce the risk of cancer has been promoted widely (Lee and Chan., 2011), but with no consistent evidence (Vogtmann et al., 2013). Some epidemiological studies have yielded a weak inverse association between fruits and vegetables consumption and colorectal incidence; meanwhile other studies have found no association. In some cases, the effect differs between different subsites and depending on other factors such as smoking and alcohol consumption.

In The European Prospective Investigation of Cancer and nutrition (EPIC) study, Duijnhoven et al. (2009) investigated how the consumption of total fruit and vegetables is related to CRC risk and the findings indicated that a higher consumption of fruit and vegetables may protect against the development of CRC, especially colon cancer. The Multiethnic Cohort Study in Hawaii and Los Angeles argued that high consumers of vegetables had a reduced risk of colorectal cancer among men but not among women (Nomura et al., 2008). A pooled Analysis of 14 Cohort Studies stated that the consumption of fruits and vegetables was not strongly associated with the risk of colon cancer overall but was inversely associated with the risk of distal colon cancer (Koushik et al., 2007).

Consumption of fruit and vegetables could confer protection through anticarcinogenic components, such as antioxidants (in particular, carotenoids and vitamin C), folic acid, flavonoids, organosulfides, isothiocyanates, and protease inhibitors that might influence DNA damage and thus reduce mutations. Furthermore, these foods provide fermentable fiber, which decreases transit time, lowers pH, and produces potentially anticarcinogenic short-chain fatty acids (Michels et al., 2000; Tayyem et al., 2014).

#### I.3.1.1.3 Grains and legumes

Whole grains are a major source of dietary fibre and contain germ, endosperm, and bran, in contrast with refined grains that contain only the endosperm. The germ and bran contain numerous nutrients, which are removed during the refining process. In addition, whole grains are a major source of several vitamins, minerals, and phytochemicals, which have anticancer properties and could plausibly influence the risk of colorectal cancer by several potential mechanisms (Slavin et al., 1999; Aune et al., 2011).

An earlier review and meta-analysis of case-control studies of whole grain intake and CRC and polyps reported a summary odds ratio of 0.79 for the highest versus the lowest intake (Jacobs and al., 1998). Over the past decade results from several cohort studies have been published on whole grain intake and risk of CRC, with varied results. Some studies suggested no association, whereas others reported an inverse association with higher whole grain intake (Aune et al., 2011).

### I.3.1.2 Trace Elements

#### I.3.1.2.1 Calcium and vitamin D

Food is an important source for calcium uptake. The common calcium-rich foods include milk, yogurt, cheese, shrimp, soybean, soy milk, broccoli, orange, kale and others. The major forms of calcium supplements are calcium carbonate and calcium citrate. Sufficient calcium intake is important for human health and calcium deficiency could lead to diseases (Pu et al., 2016).

Evidence from animal studies has suggested that high calcium intake may reduce colonic carcinogenesis. In humans, many epidemiologic studies have shown that calcium supplements reduce colonic epithelial cell proliferation and risk of recurrent colorectal adenomas. It was found that increased consumption of milk and calcium were related to a lower risk of colorectal cancer (Cho et al., 2004; Pu et al., 2016).

As protective nutrients against CRC, vitamin D and calcium are closely related to each other due to the role of vitamin D in maintaining calcium levels. In addition to preventing carcinogenesis in the colon and rectum, vitamin D and calcium are diversely linked to biological responses, including DNA synthesis and inhibition of double-strand breaks caused by endogenous or exogenous factors (Park and Kim, 2015).

There are biologically plausible mechanisms between dietary calcium intake and reduced colorectal cancer risks. Calcium plays protective role against inflammation, free fatty acids and bile acids, dietary heme iron and might directly influence cell proliferation by inducing cell differentiation (Yang et al., 2014; Pierre et al., 2013).

#### I.3.1.2.2 Folate

There is evidence from epidemiologic, animal and human studies suggesting that folate status modulates the risk of developing cancers in colorectal tissues (Du et al., 2010). Although the results from epidemiological and clinical studies are not uniformly consistent, the portfolio of evidence indicates ~20–40% reduction in the risk of CRC or adenoma in subjects with the highest dietary intake or blood levels of folate compared with those with the lowest intake or blood levels . The data from animal studies generally support a causal relationship between folate depletion and CRC risk and an inhibitory effect of modest levels of folate

supplementation on colorectal carcinogenesis. However, animal studies have also shown that folate supplementation may increase CRC risk and accelerate its progression if too much is given or if it is provided after neoplastic foci are established in the colorectum (Kim, 2004).

#### I.3.1.2.3 Fibres

The role of dietary fibre in colorectal cancer risk has been studied for many decades. However, results from intervention studies to increase fibre intake did not demonstrate any association between fibre intake and polyp recurrence. A pooled analysis of prospective cohort studies also suggested little effect of fibre on colorectal cancer risk. In the recent years, however, other large prospective cohort studies have provided evidence that fibre intake, especially from whole grains, is associated with a reduced colorectal cancer risk. While the evidence is still evolving, it is reasonable to suggest that fibre intake and consumption of whole-grain foods may decrease colorectal cancer risk Overall, diet patterns that are high in vegetables, fruits, and whole grains (and low in red and processed meats) have been associated with a decreased colorectal cancer risk (Kushi and al.,2012).

### I.3.2 Smoking and alcohol consumption

Other lifestyle factors, such as chronic cigarette smoking and alcohol consumption, contribute to CRC carcinogenesis. Smoking, in addition to the induction of inflammation and of epigenetic and genetic alterations, can affect other pathways leading to CRC (Bishehsari and al., 2014). The main carcinogens found in tobacco smoke are aromatic amines, nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. These substances undergo metabolism through cytochromes P450, leading to the formation of aberrant DNA and further gene mutation (Durko and Malecka-Panas, 2014). The smoking status can modify the protective effect of fruits and vegetables against CRC (van Duijnhoven et al., 2009), increase the risk for proximal CRC (although the point estimates were not statistically significantly different) (Limsui et al., 2010) and may also increase the risk of rectal cancer, however, the epidemiologic evidence remains insufficient to demonstrate any clear association with colon cancer (Mizoue et al., 2006).

Alcohol consumption is a causal factor in the development of CRC, with a dose-effect relationship, mainly among males (Chan and Giovannucci, 2010). Excessive chronic alcohol consumption can accelerate CRC initiation and progression through multiple cellular mechanisms, including apoptotic (e.g., PI3K/AKT), proliferative (e.g., ERK1/2) and metastatic (e.g., VEGF, and MMPs) pathways. Although one might expect epigenetic fingerprints from alcoholism, most studies could not find associations between specific molecular subtypes of CRC and alcohol intake. The effects of alcohol, however, can vary among individuals depending on genetic polymorphisms in the alcohol metabolism pathways, and this could modify CRC risk (Bishehsari et al., 2014).

### I.3.3 Physical Activity

An association between greater levels of physical activity and decreased risk of colon cancer has been one of the most consistently observed (Chan and Giovannucci, 2010). In a meta-analysis of 21 studies, there was a significant 27% reduced in risk of CRC (Teixeira et al., 2014). Another meta-analysis indicates that most physically active individuals have 24 % lower risk of CRC development than those who have a sedentary lifestyle. Even moderate levels of physical activity (eg, brisk walking for 30 min per day) are associated with substantial benefits (Gingras et Béliveau, 2011).The key mechanisms that explain the protective role of physical activity focus on increased insulin sensitivity, lower insulin levels, decreased body mass, and decreased adipose tissue volume, leading to reduction of chronic inflammation (Durko et Malecka-Panas, 2014).

### I.3.4 Obesity

Obesity, especially abdominal obesity, is associated with a higher risk of colorectal adenoma and CRC, especially in men. This association implies that obesity promotes the early stages of carcinogenesis but it may also play a role in the growth of advanced adenomas, both of which favor adenoma recurrence. The mechanistic relationship between obesity and colon cancer risk is not well established but may include the mitogenic properties of insulin, obesity‑related insulin resistance, and associated hyperinsulinemia. Insulin could also promote colorectal carcinogenesis by increasing the levels of bioactive insulin-like growth factor (IGF)-1, either directly or through a decrease of IGF binding protein levels, which leads

to increased free IGF-1. Obesity may be a pro-inflammatory state, as demonstrated by the high systemic levels of proinflammatory cytokines, chemokines, and other acute phase proteins released from adipose tissue, which consists not only of adipocytes but also of immune cells (Conteduca et al., 2013).

### I.3.5 Anti-inflammatory Drugs

Inflammation is thought to play a critical role in the development of cancer, particularly colorectal cancer. Epidemiologic evidence indicates that pro-inflammatory conditions, such as inflammatory bowel disease increase the risk of colorectal cancer **(**Ruder et al., 2011).

The first evidence of a chemopreventive role of aspirin in colorectal cancer development came from a large case-control study published in 1988 exploring potential relation between numerous medications and colorectal cancer. The authors were surprised with an inverse association between aspirin use and risk of colorectal cancer. Subsequently, substantial observational and intervention trials investigating aspirin demonstrated a risk reduction of colonic adenomas and colorectal cancer in the range of 20% to 40% (Teixeira et al., 2014). Analysis of two studies has demonstrated that administration of a high dose of aspirin (300–1500 mg/day) for 1–7 years with follow-up to 23 years was related to a significant 26% reduction in CRC incidence over the full 23-year follow-up period (RR 0.74, 95% CI 0.57 to 0.97). An even greater reduction was observed when analyzing years 10–19 only (RR 0.61, 95% CI 0.43 to 0.88) (Cooper et al., 2010).

Other nonsteroidal anti-inflammatory drugs (NSAIDs) are also associated with CRC protection in the general population, as well as in individuals with a first-degree relative with colon cancer. The strength of the association varies by drug class, but generally, a dose-response relationship is observed between increased frequency of use and cancer protection (Ruder et al., 2011). The likely mechanism of NSAIDs is that they reduce inflammatory mediators, such as high-sensitivity C-reactive protein, and interleukin-6, through the inhibition of cyclooxygenase-2, which is responsible for producing various inflammatory prostaglandins (Wang et al., 2015).

# Part II. Material and methods

## II.1 Study Design

In agreement with the aim of this study, i.e. the retrospective study of the effect of some environmental factors, mainly diet, on the incidence of CRC in the region of Jijel, we choose the model of case control study. According to this model, risk factors can be determined by comparing the exposure of colorectal cancer cases of the population of Jijel, and controls to these factors and then estimate their effect by calculating an algebraic value: the odds ratio (OR) witch estimate the strength of the association between exposure and outcome. The results of a case-control study can be presented in table 02, from this table the odds ratio is easily calculated using the formula AD/BC (Tyrrell, 1991).

**Table 02: Traditional table used in the interpretation of a case-control study.**

| | Cases | Controls | Total |
|---|---|---|---|
| Exposed | a | b | a+b |
| Unexposed | c | d | c+d |
| Total | a+c | b+d | a+b+c+d |

The odds ratio is a measure of the odds of disease in the exposed, compared to the odds of disease in the unexposed (controls) and is calculated as: (Tyrrell, 1991).

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

How odds ratio results are interpreted: an OR of 1.00 means that there is no association between the disease and the factor studied. An OR higher than 1 means that there is a positive association between the illness and the factor which is then called a risk factor. An OR of less than 1 means that there is a negative association between the event and the factor which is referred to as a protective factor. The choice of this model is comforted by some qualities of this type of studies:

- Cost effective relative to other analytical studies such as cohort studies.
- Case-control studies are retrospective, and cases are identified at the beginning of the study; therefore, there is no long follow up period (as compared to cohort studies).
- Efficient for the study of diseases with long latency periods.

- Efficient for the study of rare diseases.
- Good for examining multiple exposures.

## II.2 Population of study

All cases with colorectal cancer resident in the Jijel region were eligible to take part in the study. In each case the diagnosis, either pre-operatively or postoperatively, was confirmed histologically and with reference to the pathological report. Among the 108 colorectal cancer patients, we succeeded in interviewing 34 one. These cases were recruited in the oncology service of Mohamed Seddik Ben Yahia hospital in the Jijel region.

The control group was randomly chosen by sampling control subjects from the population to facilitate our work, 'control subjects' were unmatched.

## II.3 Data collection

### II.3.1 Pathoclinical data

Pathoclinical data of colorectal cancer cases was obtained from 34 patients records archived in the oncology service of Mohamed Seddik Benyahia hospital in Jijel region. Before reaching the data, an authorization of the hospital authority and of Doctor Sahali, main oncologist of the service, was accorded to us on the base of an application addressed by our supervisor in which she explained deeply the purpose of the study, the ethical statements and proposed a powerful cooperation. The data for each case include mainly: a) Date of diagnosis; b) Method of diagnosis; c) Colorectal site of carcinogenesis; d) Histological type of the tumor; e) Colorectal cancer stage; f) used biomarkers.

### II.3.2 Lifestyle data

A Lifestyle Questionnaire, given to each subject using face-to-face interview, was used in order to gather information about the general lifestyle of the subjects (both cases and controls) covering the period before diagnosis for the cases and last year for the controls and the questions were referred in a time period between the 3$^{rd}$ April and the 10$^{th}$ June 2016.

Baseline characteristics of the study population were assessed by means of interviews with structured questionnaire. The content of the questionnaire focused on socio-demographic variables, anthropometric measures, and comorbidity history, personal and family history of colorectal cancer, medicine intakes and lifestyle factors.

The socio-demographic data was composed of age, gender, matrimonial status, educational level, resident location, household outcome. Anthropometric measurements included height and weight. Body mass index (BMI) was further calculated from height and weight. In addition, lifestyle factors included smoking, alcohol consumption, physical activities.

Inquiry on smoking history included three status (never, former or current) and the number of cigarettes per day for the formers and currents was assessed.

Alcohol use was also divided into three categories (never, former or current) and the latter two groups were asked to choose from three types of alcoholic beverages (beer, wine, and alcohol).

Physical activities were assessed by the following questions:

- On average, how many times in a week did you exercise (a time means a minimum of 10 min) a vigorous-intensity exercise?

- On average, how many times in a week did you exercise (a time means a minimum of 10 min) a moderate -intensity exercise?

- Did you practice a sport activity (footing, football…) frequently?

- Did you make a time means a minimum of 10 min on foot/bicycle?

For each question, the frequency of the activity and the precise time were assessed.

Metabolic equivalent (MET) levels for walking, moderate and vigorous intensity activities were taken as 3.3, 4.0 and 8.0(Iswarya et al., 2016). The activities were measured separately (MET level × minutes of activity/day × days per week) and expressed as total MET min/wk. Based on the total scores, study participants were categorized in to low (< 600 MET min/wk), moderate (600-3000 MET min/wk) and high (> 3000 MET min/wk) level of physical activity.

Family and personnel history of colorectal cancer is also determined.

Finally, medicines intake was estimated by the following questions:

- Did you ever take a medicine regularly during your life?

- If yes: - did you take aspirine regularly? - did you take NSAI drugs regularly?

- did you take antibiotics regularly?

### II.3.3 Dietary data

#### II.3.3.1 Food frequency questionnaire

A frequency questionnaire consists of a list of foods with associated consumption frequency categories (number of times per day, week, month, etc.). The respondent is asked to check, for each food in the list, the frequency that is closest to his habitual consumption (Cade et al., 2002).

The food frequency questionnaires (FFQs) are widely used in epidemiological studies to assess dietary intake and to explore diet and chronic disease associations in specific populations. This instrument is advantageous because it is relatively easy and inexpensive to administer, and can measure dietary intake over a long time period (Cade et al., 2002) It is critical that a FFQ is culturally appropriate for the population being studied (Teufel, 1997)

We used a semi quantitative food frequency questionnaire to assess dietary intake. The FFQ is designed to assess usual food intake pattern during the past one year for controls and during the period before diagnosis for cases. Response options for most food items had 7 levels of 'none or little', 'once a month', '2-3 times a month', '1-3 times a week', '3-6 time a week', 'once a day', '2-4 times a day'. A set of household measurements (e.g., cup, table spoon, plate, glass, bowl) were used to assist respondents to estimate the portion size of food items.

The FFQ consisted in 100 food items divided into five groups and thirteen food subgroups. This classification is adopted from that proposed by MEKHANCHA (1998) and applied for the first version of the food composition table, TCA ALNUTS (Tableau de Composition Alaimentaire du laboratoire de recherche Alimentation, Nutrition ET Santé à l'université de Constantine), for Algeria.

Among the thirteen food subgroups, we focused our questionnaire on

-cereal products (Rice, Frick, Semolina, Wheat flour, Couscous, Tlitli ,Vermicelli ,Chakhchoukha ,Pasta ,Spaghetti pasta, Vermicelli flood, Bread, Gheraif, Kesra, Brioche, Biscuit, Puff pastry, mille feuilles

-Vegetables and Fruits (Tomato, Cucumber, Zucchini, sweet Pepper, Green salad, Cauliflower, Parsley, Carott, cabbage, Onion , Garlic, Beetroot flood, Fennel, Concentrated

tomato, Orange , Mandarine , Apple , Perry, Apricot ,Plum ,Melon ,Watermelon ,Grapes , Medlar ,Banana, Date, pitted green olives, black olive).

- Meat and Derivatives (Beef, sheepmeat, processed meat, liver, sausages)

- Poultry and eggs (Poultry, Eggs, Pisces)

- Fish (Sardine, Tuna in oil 65 g, Whiting, and shrimp)

- Dairy products (Milk, L'ben, processed cheese portion, Yogurt)

To give a quantitative assessment for the frequency of consumption, we attributed a numeric value to each frequency, and then we made the sum of these values for every participant:

**Table 3.Values attributed for each frequency**

| none or little | once a month | 2-3 times a month | 1-3 times a week | 3-6 times a week | once a day | 2-4 times a day |
|---|---|---|---|---|---|---|
| 0 | 1 | 2,5 | 8 | 20 | 30 | 90 |

### II.3.4 Data analysis

Data analysis was done using EPI INFO 3.5.4.0 version. Frequency distribution and descriptive statistics for each variable were calculated. The odds ratio (OR) which is the odds of cases exposure divided by the odds of controls exposure and t-test were used to determine the significance of the differences between cases and controls. A p-value less than 0.05 was considered statistically significant.

# Part III. Results and Discussion

## III.1Comparison of general characteristics between cases and controls

Evidence on a possible effect of life style factors on CRC incidence came from studies done on Japanese immigrants in the USA, Asian Jewish immigrants in Israel, and East European immigrants in Australia. These immigrants acquire the common CRC rates in the country of their adoption. Thus, no doubt remains that some environmental factors, probably diet, may account for these cancer rates (Tárraga et al., 2014).

In the aim of evaluating the effect of some life style factors and of food frequency consumption on the incidence of colorectal cancer in the wilaya of Jijel and even their implication in some pathological characteristics, we conduct a case control study targeting patients of Mohamed Seddik Benyahia hospital oncology service. Among 108 colorectal cancer patients, we succeeded in interviewing 34 one. Among the other cases, some were illegible to answer our questions due to health disability or bad mood. We cannot interrogate some others due to the short duration of study (two months). At the same period, we investigated life style and dietetic characteristics of 34 controls among the general population of the wilaya of Jijel who were free of colorectal cancer.

In our study, many problems have hinder our task such as case-contacting, enrolling and interviewing controls, ascertaining exposure with accuracy, and the potential problem of recall bias.

***Table 4. Comparison of general characteristics between the cases and controls groups***

| | | Cases | controls | p-value |
|---|---|---|---|---|
| | | **34** | **34** | |
| Sex | Male | 19 | 20 | |
| | Female | 15 | 14 | 0,2261 |
| Age group (years) | <40 | 6 | 7 | |
| | 40-60 | 13 | 13 | 0,1730 |
| | ≥60 | 15 | 14 | |
| Smoking status | Never | 20 | 26 | |
| | Former | 11 | 7 | 0,0174 |
| | Current | 3 | 1 | |
| Physical activity | Low | 4 | 4 | |
| | Medium | 12 | 13 | 0,8177 |
| | High | 18 | 17 | |
| Education | Illeturate | 8 | 4 | |
| | Middle classes | 11 | 4 | |
| | Secondary | 2 | 9 | 0,0075 |
| | Superior | 2 | 11 | |
| family history of colorectal cancer | yes | 19 | 6 | |
| | no | 15 | 28 | 0,0034 |
| Household income | < 18 000,00 AD | 19 | 9 | |
| | 18 000,00-50 000,00 AD | 12 | 15 | 0,0374 |
| | 50 000,00-100 000,00 AD | 2 | 8 | |
| | ≥ 100 000,00 AD | 1 | 2 | |
| Occupation | active | 12 | 14 | |
| | house keeping | 12 | 9 | 0,7298 |
| | retired | 10 | 11 | |
| Matrimonial status | Married | 30 | 29 | |
| | Single | 4 | 4 | 0,6014 |
| | Widow | 0 | 1 | |

***Table 4*** *summarizes the main characteristics of cases and controls. No significant differences have been registered between the two groups in terms of sex (p-value= 0.2261), age (p-value= 0.1730), physical activity (p-value= 0.8177), occupation (p-value= 0.7298) and matrimonial status (p-value= 0.6014).*

Familial history of colorectal cancer, with an OR= 5.2500 and a p-value = 0.0034, was found to be related to the incidence of colorectal cancer. It has been reported that up to 20% of people who develop colorectal cancer have other family members who have been affected by

this disease. The reasons for the increased risk are not clear, but it likely due to inherited genes, shared environmental factors, or some combination of them (Haggar and Boushey, 2009). Thus, the population with familial history of CRC must keep attention in screening programs.

Low educational level and low household income appeared too like risk factors in the population of study. These two variables are somewhat associated, as high educational degrees permit often to reach more lucrative occupations. Household income less than 18 000, 00 AD was significantly related to the disease with an OR of 7.8386 and p value of 0.0374, after adjustment for age, physical activity and smoking. In turn, high educational level is related to a reduction of CRC cases, with an OR of 0.0578 and a p-value of 0.0075, after adjustment for age and smoking.

Low household income families are often exposed to risk environmental factors, such as worse quality water and foods, pollution, and have less accessibility to medical care which make them more susceptible to develop chronic diseases such as cancer. As the same, high educational levels offers to the population the opportunity to learn about illnesses, their etiology, the risk factors associated to, and their symptoms and as a result contributes in incident decrease of such public health burden. Additionally well educated persons have more acceptability for diagnosis and treatment techniques, while many diseases still represent a taboo for low education level subjects.

Smoking is also a risk factor for the population of study as a protective effect was obtained when comparing never smokers to ex-smokers (OR=0.0751, p-value= 0.0174) after adjustment for educational level, household income and familial history.

It is well known that tobacco smoking is associated with a higher risk for colonic adenoma formation as well as increased of CRC incidence (Bishehsari and al., 2014). Tobacco smoke includes many pro-carcinogens substances such as aromatic amines, nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. These substances undergo metabolism through cytochromes P450, leading to the formation of aberrant DNA and further gene mutation (Durko and Malecka-Panas, 2014).

Meanwhile smoking rates decrease in developed countries because of restrictions applied on producers and smokers, the phenomenon continue to increase in our society mainly between adolescents and females, which will be traduced by a huge burden on the public health policy

within the few next decades if any prompt palpable measures are not taken. In this population of study, low educated persons with low income have to be the target of awareness programs against dangers of the cigarette.

### III.2 Association between Food groups frequency intake and CRC incidence

Dietary factors are considered to play an important role in the occurrence of colorectal cancer and differences in these factors seem to contribute to the variation of cancer incidence between countries (Chun et al., 2015).

We assessed the association between the frequency consumption of some food groups, (red meat, fruits and vegetables, cereals, dairy products, poultry, fish) and the incidence of colorectal cancer in the Jijel region.

#### III.2.1 Relation red meat frequency consumption and CRC incidence

The Figure 7 shows the frequency of intake of red meat and processed meat both in cases and controls. Although it appears that the frequency of red meat consumption is higher in cases group, we failed to find no significant association between colorectal cancer incidence and red meat consumption frequency (crude Odds Ratio: 1.0050, p-value: 0.8003), and after adjustment for covariates including age group and household income level, this non significant association remained with an OR of 1.0392 and p-value of 0.1210.

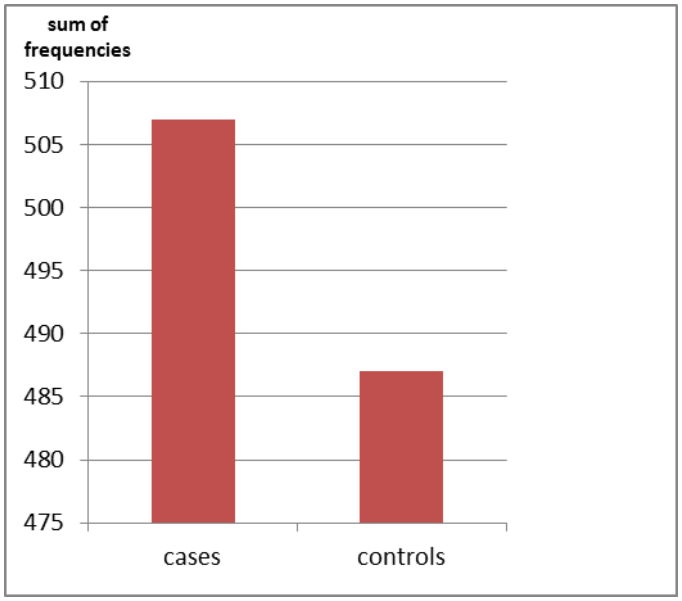


***Fig.7. Red meat frequency consumption among cases and controls***

We found that there was no significant association between red meat consumption and incidence of colorectal cancer. This result is not in accordance with many studies that have concluded that red meat intake is a risk factor for CRC. Iswarya et al. (2016) reported that red meat consumption more than 2-3 times a month was an independent risk factor in multivariate regression analysis and increased the odds of developing CRC by 5.41 (1.55-19.05) times compared to those never or hardly consume. De Stefani et al (2016), found in their study elevated risks of colorectal cancer among high consumers of total meat, red meat and processed meat. In the same way, Chun et al. (2015) showed that high red meat intake increased odds for colorectal cancer incidence. On the other hand, English et al (2004) found that consumption of fresh red meat was associated with moderately increased risks of rectal cancer but had little association with risk of colon cancer and Alexander et al (2015) in an updated and expanded meta-analysis, observed summary associations for red meat and CRC that were null or just above the null value in virtually all models.

This difference in our results could be explained by the absence of some important factors mainly the quantity of red meat consumed and the mode of cooking. Joshi et al. (2015) argued that, when ignoring cooking methods, no statistically significant associations with CRC were observed for any non processed red meats and total processed red meat. However, a positive association with CRC for pan-fried beefsteak (P trend < 0.001) and oven broiled short ribs or spare ribs were observed.

### III.2.2 Relation between fruits and vegetables frequency consumption and CRC incidence

The Figure 8 represents the frequency consumption of fruits and vegetables among cases and controls. We can observe a more frequent consumption of these diets among controls. This difference cannot be proved statistically as any significant difference was registered with a crud OR of 0.9978 and a p-value of 0.1525. This non significant result remains after adjustment for age, sex, physical activity, household income and smoking (OR: 0.9971, p-value: 0.1288).

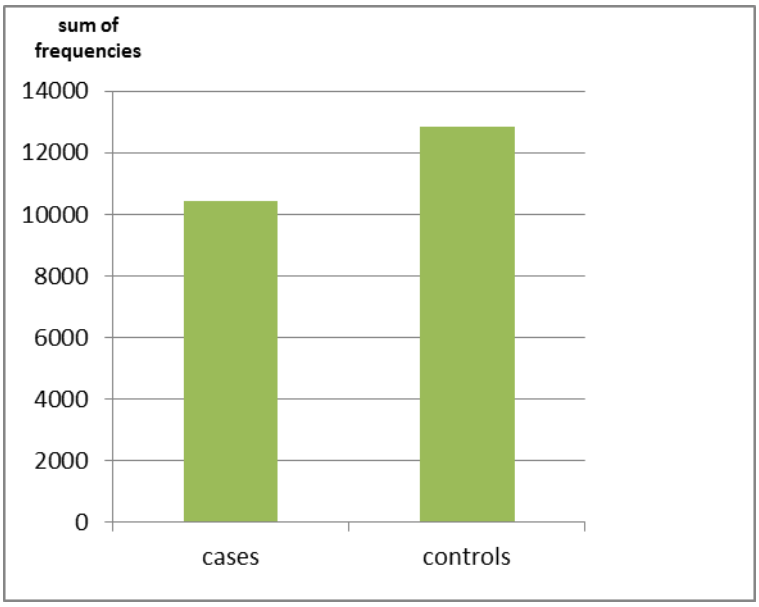


***Fig.8. fruits and vegetables frequency consumption among cases and controls***

Fruit and vegetables are rich in dietary fibre and, although there are other important sources such as unrefined cereals, it might be expected that if dietary fibre reduces the risk of colorectal cancer, then a reduction in risk would be observed in association with high intakes of fruit and vegetables (Key, 2011).

Our results demonstrate a little inverse association, but not significant statistically, between fruits and vegetables frequency consumption and CRC incidence. This finding is in agreement with that found by Flood et al; (2002) who concluded in a prospective cohort study, that there was little evidence of an association between fruit and vegetable intakes and colorectal cancer. Koushik et al., (2007), stated that fruit and vegetable intakes were not strongly associated with colon cancer risk overall but may be associated with a lower risk of distal colon cancer. The association between fruit and vegetable consumption and CRC risk is inconclusive (Tayyem et al., 2014).

Vogtmann et al., (2013), estimated that fruit consumption was inversely associated with the risk of colorectal cancer (5th vs. 1st quintile HR: 0.67; 95% CI: 0.48, 0.95; P trend = 0.03), whereas vegetable intake was not significantly associated with risk. van Duijnhoven et al., (2009), as a conclusion of their European Prospective Investigation into Cancer and Nutrition (EPIC) study, suggested that a high consumption of fruit and vegetables is associated with a reduced risk of CRC, especially of colon cancer. This effect may depend on smoking status.

Nomura et al., (2008), presented the intake of vegetables and fruit as inversely related to colorectal cancer risk among men but not among women. The association appears stronger for colon than for rectal cancer. Relative risks in the highest quintile group of 0.74 (95% CI: 0.59, 0.93; P for trend = 0.02) for vegetables and fruit combined, 0.80 (95% CI: 0.64, 0.99; P for trend = 0.09) for fruit alone, and 0.85 (95% CI: 0.69, 1.05; P for trend = 0.05) for vegetables alone.

In contrast to developed countries, fruits and vegetables frequency consumption in our society is influenced mainly by market's availability and resources income among families rather than by gustative preferences or by ideological reasons. Thus, these factors should be taken in consideration when analyzing effects of fruits and vegetables consumption on incidence of diseases such as CRC.

### III.2.3 Relation between dairies frequency consumption and CRC incidence

The figure 09 depict the frequency consumption of dairies among cases and controls. It is obviously noted that dairy frequency consumption is more important in controls, essentially among those with more than sixty years old. We found that there is no significant protective effect of dairy consumption with a crud OR value of 0.9808 and a p-value 0.0580. The protective effect became significant when we adjust dairy frequency consumption for frequency of consumption of red meat, fruits and vegetables, fish and cereal groups (OR= 0.9808, p-value= 0.0437).

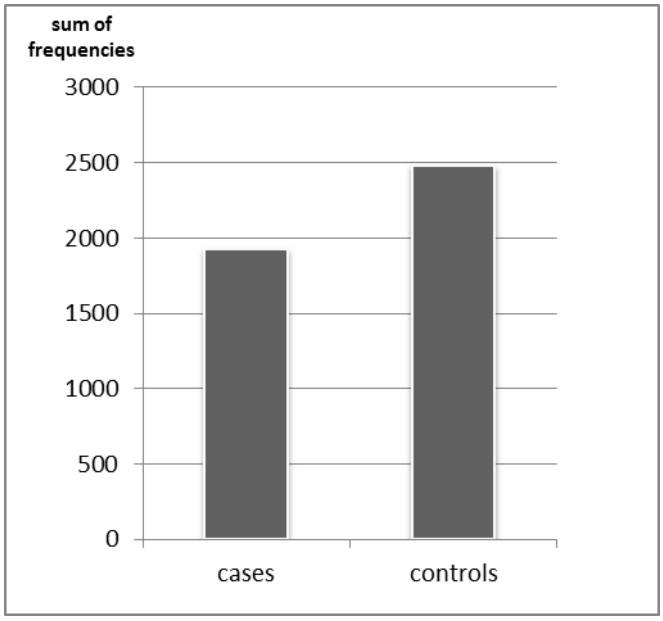


***Fig.9. dairy productions frequency consumption among cases and controls***

In 2009, Park et al. reported a decreased risk of colorectal cancer for those with a high intake of dairy food [HRs (95% CIs) for the highest compared with the lowest quintile for men and women, respectively: 0.85 (0.76, 0.94) and 0.72 (0.61, 0.84)] in the NIH-AARP study.

### III.2.4 Relation between cereals frequency consumption and CRC incidence

As showed in Figure 10, frequency consumptions of cereals are more important in controls. We found a significant protective effect of cereals consumption (OR= 0.9865, p-value= 0.0100).

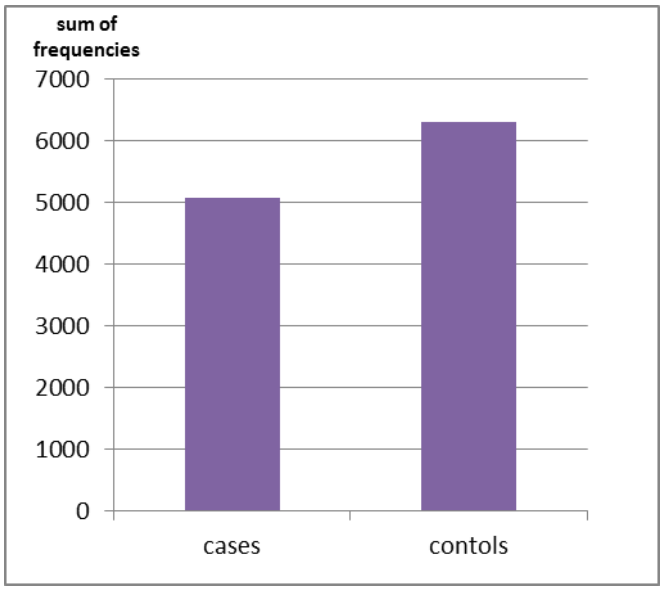


***Fig.10. cereals frequency consumption among cases and controls***

Aune et al., 2011, in their meta-analysis support an inverse association between intake of dietary fibre, cereal fibre, and whole grains and risk of colorectal cancer, and suggest that a high intake of dietary fibre, particularly from cereal and whole grains, is associated with a reduced risk of colorectal cancer. A protective effect of dietary fibre and whole grain consumption on risk of colorectal cancer is biologically plausible. Whole grain foods are important sources of dietary fibre and may decrease the risk of colorectal cancer by increasing stool bulk, diluting faecal carcinogens, and decreasing transit time, thus reducing the contact between carcinogens and the lining of the colorectum. In addition, bacterial fermentation of fibre results in the production of short chain fatty acids, which may have protective effects against colorectal cancer**.**

### III.2.5 Relation between poultry frequency consumption and CRC incidence

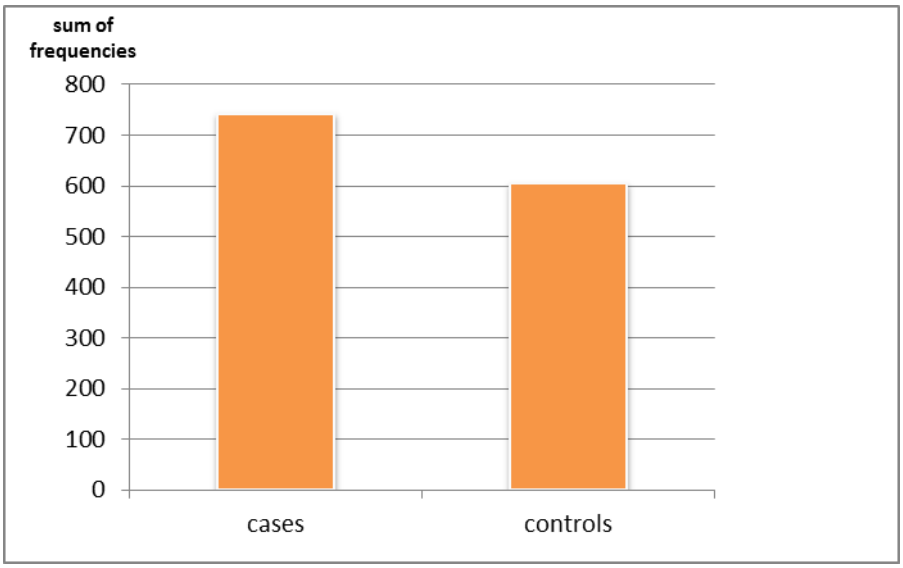


***Fig.11.*** *Poultry frequency consumption among cases and controls*

We found that poultry frequency consumption is greater in cases group specifically (figure 11). However, this result is not statistically significant (crud OR = 1.0375, p-value = 0.1255) even when we adjust the OR for age, sex, and household income (OR= 1.0402, p-value= 0.1564).

It was reported that there was no association between diets high in poultry and CRC risk (Joshi et al., 2015). Several past prospective cohort studies have reported inverse associations between poultry and colorectal cancer, although a number of others have reported positive associations (Miller et al., 2013). Like for red meat, the amount of poultry consumed and the cooking method play a role in these disparities in results.

### III.2.6 Relation between fish frequency consumption and CRC incidence

Figure 12 represents the frequency of fish consumption among cases and controls. As we can see, cases consume fish more frequently than controls, but this result failed to rich statistical significance (crud OR = 1.0426, p-value = 0.1138). After adjustment for other food group covariates, a significant association is obtained (OR= 1.0665, p-value = 0.0392).

In a large case control study, with 1189 cases and 1189 controls, association between fish intake and colorectal cancer risk among Guangdong Chinese population was examined. The

results showed that higher intake of fresh fish including freshwater fish and sea fish was associated with a lower risk of colorectal cancer (Xu et al., 2015).

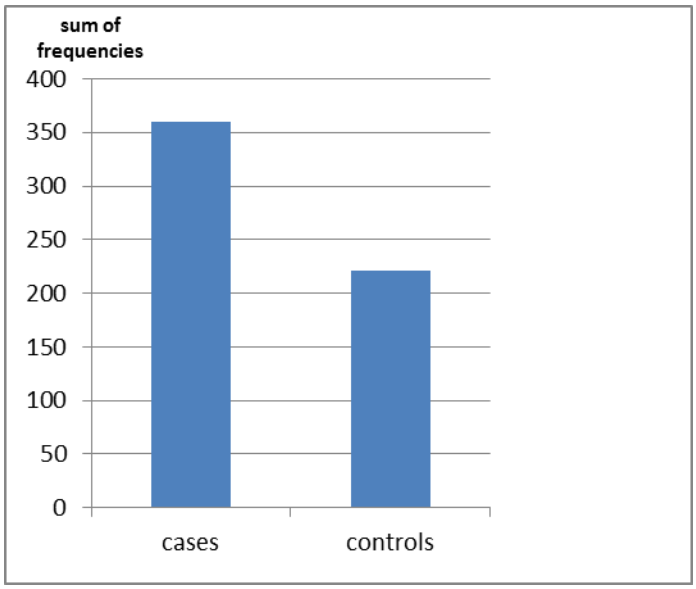


*Fig.12.fish frequency consumption among cases and controls*

**III.3Association between Food groups intake frequency and tumor subsites location:**

CRC was previously categorized as either proximal (cecum, ascending colon, and transverse colon) or distal (descending colon, sigmoid colon, rectosigmoid, and rectum) (Gonzalez et al., 2001). Since then, rectal cancer was addressed specifically as a unique type of colorectal cancer (Li and Lai, 2009).

There are many differences between the three subsites, such as embryologic differences (Proximal colon embryologically originates from the midgut, while distal colon and rectum arise from the hindgut), morphologic, and biochemical differences. In addition, tumors of the proximal and distal colon differ in their genetic nature (Li and Lai, 2009).

Comparisons have shown that proximal colon tumors tend to have different molecular characteristics, with a higher proportion of microsatellite instability, and are more likely to have CpG island methylator phenotype and K-ras mutations than distal colon and rectal tumors. However, scientists have suggested that right-sided (proximal) colon cancer is more aggressive type tumor compared to left-sided (distal) colon cancer, and patients with proximal colon cancer are more often females than males. In advanced colonic neoplasia, proximal

colonic tumors are more often flat, while distal colonic tumors are polypoid-type which is more distinguishable by colonoscopy (Hjartåker et al. 2013).

Figure 13 represents tumor subsite distribution among cases both in males and females. Distal colon tumors are more predominantly present in males than in females, whereas proximal colon and rectum tumors are just the opposite with more proportion value among females.

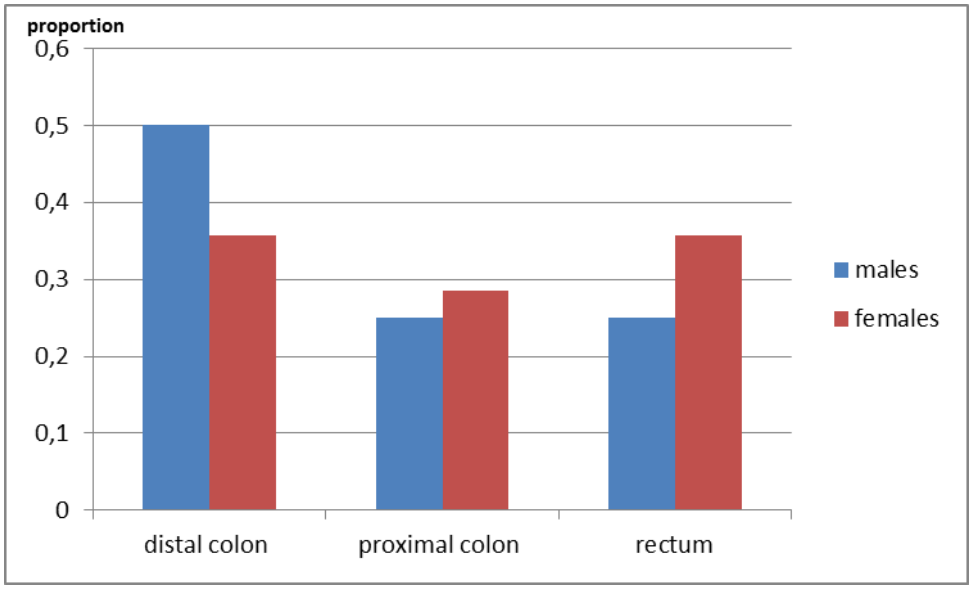


***Fig.13.*** *proportion of tumor subsite distribution among cases both in males and females*

These results are in harmony with those reported by Gonzalez et al. (2001) and Hansen and P. Jess (2012), where they suggested that women have a higher risk then men for developing proximal colon cancer, and that is associated with poor prognosis, especially among older women. Thus, detecting factors in association with such heterogeneity between different colorectal subsites is of great importance in respect with screening and therapeutic options.

Environmental factors such as diet and alcohol intake also differ in their role in the development of tumors in the three segments, proximal colon, distal colon, and rectum (LI and LAI; 2009).

We tried to assess such an effect by measuring means of frequency consumption of some food groups between cases with respect to the tumor subsite. Figures 14, 15, 16 and 17 depict the results.

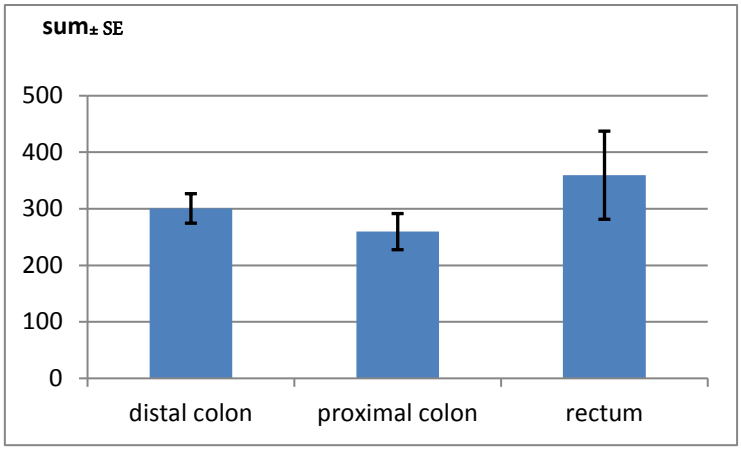


***Fig.14**.Relation between fruits and vegetables frequency consumption and tumor subsite distribution*

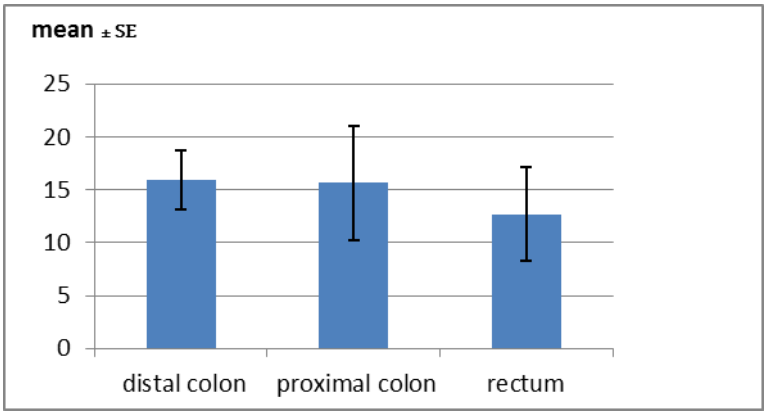


***Fig.15**.Relation between red meat frequency consumption and tumor subsite distribution*

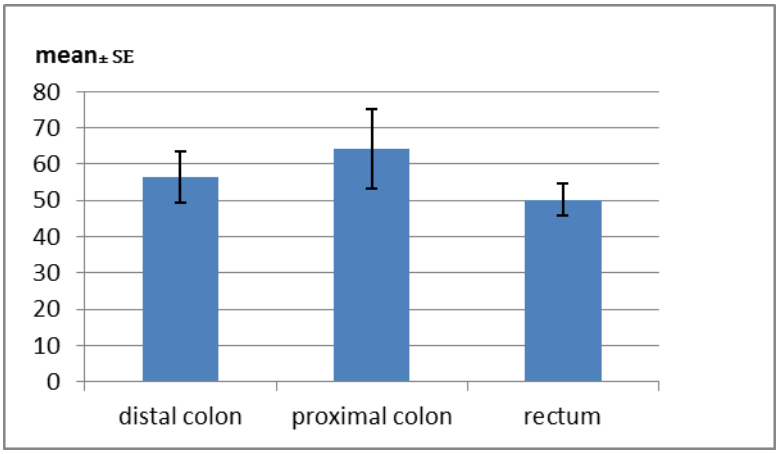


***Fig.16**.Relation between dairy product frequency consumption and tumor subsite distribution*

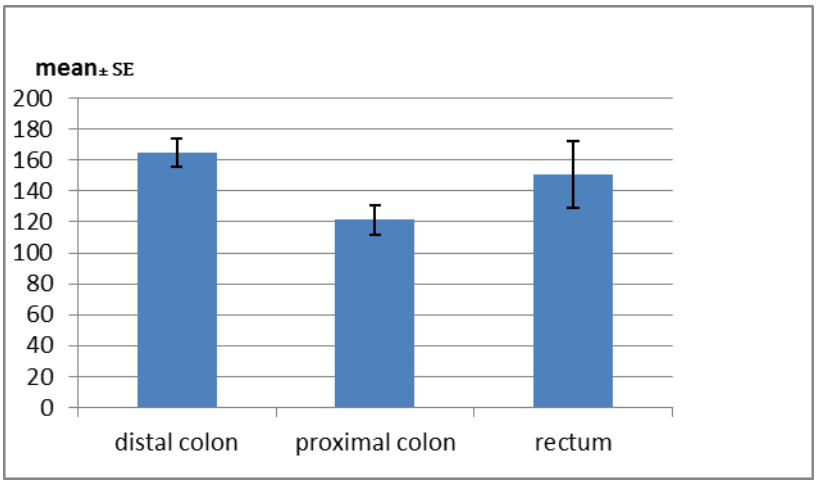


***Fig.17****.Relation between cereals product frequency consumption and tumor subsite distribution*

We found that tumors of the proximal colon are related to little consumption of fruits, vegetables and cereals but related to a high level of dairy products consumption. To the opposite, distal and rectal colon tumors seem to be related with consumption of more fruits, vegetables and cereals. Red meat consumption appeared to have no effect on subsite tumors occurrence.

Larsson and Wolk, (2006) estimated that there was a significant implication of processed red meat consumption in increased risk of distal colon cancer but not of proximal colon cancer whereas Welfare et al., (1997) stated that a more proximal shift tumors was registered by consumption of roast meat [OR=3.0 (95% CI=1.14~9.23)] at least once a week. So it is primordial to determine coking mode and the amount of consumption to achieve relevant results about the exact risk inherent to red meat consumption. Mechanistically speaking, levels of carcinogenic N-nitroso compounds, byproducts of red meat metabolism, appear to be higher in tissue from distal colon and rectum than in that of the proximal colon (Hjartåker et al., 2013).

It is presumed that total consumption of fruits and vegetables combined is inversely associated with colon and rectal cancers, (Terry et al., 2001) and this inverse association is stronger for distal colonic tumors than for proximal colonic tumors (Voorrips et al., 2000; Bingham et al., 2003).Our result can be explained by the effect of fiber fermentation, which occurs mainly in the proximal colon, leading to the formation of short-chain fatty acids and, in particular, acetic, propionic, and butyric acids. This final is particularly of interest, as it has

been shown to promot cell differentiation, cell-cycle arrest and apoptosis of transformed colonocytes; inhibiting the enzyme histone deacetylase and decreasing the transformation of primary to secondary bile acids as a result of colonic acidification. In addition, fiber may dilute the concentration of carcinogenic substances in the distal colon (Hjartåker et al.; 2013). Our results should take in count some other environmental factors such as the non rational use of pesticide in agriculture which may increase colorectal cancer risk (Lo et al., 2010).

In a study of Swedish men, a significantly reduced risk for distal colon cancer was seen for those consuming 1.5 glasses or more of milk per day compared to those consuming less than two glasses per week (RR 0.53, 95% CI 0.33–0.87) (Larsson et al., 2006). In another Swedish study restricted to high fat dairy food and conducted among women only, a significant inverse trend was observed between consumption of full-fat cultured milk and risk of distal colon cancer (*P*trend = 0.03), whereas a significant increased risk of proximal colon cancer was observed among women who consumed whole milk (1 or more servings per day compared to never/seldom consumers RR 1.58, 95% CI 1.15–2.16) (Larsson et al., 2005).

The interpretation of our results should consider different particular characteristics of our society.

Genetic polymorphism may explain the differences of the results obtained. Many studies have focused on the potential modifying effects of common genetic variants, single nucleotide polymorphisms (SNPs), on the relationship between dietary factors and risk of colorectal cancer (Figueiredo et al., 2014). In combination with dietary and genetic factors, genetic polymorphism can influence the dietary absorption level, which can affect the risk of cancer (Park and Kim, 2015), or modulate the metabolism of carcinogenic products, for example rapid acetylators might more readily activate Heterocyclic aromatics HCAs to their ultimate carcinogenic forms, increasing the risk of colorectal cancer related to these carcinogens (Budhathoki et al., 2015).

The nutritional quality of different food groups may differ considerably from that of other countries notably due to the non respects of standards inherent to picking, transformation and conservation of fruits, vegetables, cereals, milk and meat products. Use of chemical additives adds another dimension to the problem as industries use them anarchically. Pollution due to the excessive use of pesticides and to the human industrial activity could be another factor implicated in disparities in results.

# Conclusion

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. During the last decades, its incidence rate in Algeria has increased incrementally and steadily as a result of socio economic transition. Diet has been reported to play a major role in the etiology of CRC, thereby it is primordial to assess the effect of different food groups and their frequency of consumption on its incidence.

We have study the relations between some lifestyle factors, some food groups' frequency consumption and CRC in Jijel region, north east of Algeria.To do this, we conduct a case control study among CRC patients of the hospital Mohamed Seddik Ben Yahya in Jijel using a lifestyle questionnaire and a food frequency questionnaire.

In conclusion, our results don't indicate a major impact of diet on CRC incidence in the population of Jijel. This may be explained by the low number of the cases implicated in the study. Another relevant cause of such a result is the potential problem of recall bias, as the study draw on recalling of nutritional habit of the last years. Health behavior change is likely playing key roles in these results as majority of patients change their nutritional regimen after being diagnosed to a healthier one.

This work represents an introduction to the study of the effect of environmental factors, mainly diet, on the occurrence of CRC between Algerians. The results obtained should be completed by other studies taking in count other factors such as pollution and the food nutritional quality. Such studies will bring relevant approaches for primary prevention.

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**Abstract :**

To study the relations between some lifestyle factors, some food groups' frequency consumption and CRC in Jijel region, north east of Algeria, we conduct a case control study among CRC patients of the hospital Mohamed Seddik Ben Yahya in Jijel, using a lifestyle questionnaire and a food frequency questionnaire. Comparing 34 cases with 34 controls revealed that high educational level (OR= 0.0578, p-value= 0.0075), low household income (OR= 7.8386, p value= 0.0374), smoking (OR=0.0751, p-value= 0.0174) and familial history of CRC (OR= 5.2500, p-value = 0.0034) may be associated with CRC occurence in this population. A protective effect of consumption of dairy products (OR= 0.9808, p-value= 0.0437) and cereals (OR= 0.9865, p-value= 0.0100) was observed whereas fish consumption seems to be associated positively with CRC (OR= 1.0665 , p-value = 0.0392).In conclusion, besides the fact that our results don't indicate a major impact of diet on CRC incidence in the population of Jijel, this work represents an introduction to the study of the effect of environmental factors, mainly diet, on the occurrence of CRC between Algerians. Such studies will bring relevant approaches for primary prevention.

**Key words:** colorectal cancer, Diet, CRC incidence, food groups, case-control study.

**Résumé:**

Dans le but d'étudier la relation entre certains facteurs socio-économiques, la fréquence de consommation de certains groupes d'aliment et le CRC dans la wilaya de Jijel, au nord-est de l'Algérie.Nous avons mené une étude cas-témoins chez les patients atteints de CCR de l'hôpital Mohamed Seddik Ben Yahia à Jijel, utilisant un questionnaire de mode de vie et un questionnaire de fréquence alimentaire. En comparant 34 cas avec 34 témoins, les résultats ont révélé que le niveau d'instruction élevé (OR = 0,0578, p = 0,0075), le faible revenu des ménages (OR = 7,8386, valeur p = 0,0374), le tabagisme (OR = 0, 0751, p-value = 0,0174) et des antécédents familiaux de CCR (OR = 5, 2500, p-value = 0,0034) peuvent être associée au CCR dans cette population. Un effet protecteur de la consommation de produits laitiers (OR = 0,9808, p-valeur = 0,0437) et des céréales (OR = 0,9865, p-valeur = 0,0100) a été observée alors que la consommation de poisson semble être associée positivement avec CCR (OR = 1,0665, p = 0,0392). En conclusion, outre le fait que nos résultats ne montrent pas un impact majeur de l'alimentation sur l'incidence du CCR dans la population de Jijel, ce travail représente une introduction à l'étude de l'effet des facteurs environnementaux, principalement l'alimentation, sur la survenue du CCR chez les Algériens. Ces études apporteront des analyses pertinentes pour la prévention primaire.

**Mots clé :** Le cancer colorectal, Alimentation, l'incidence du CCR, groupes d'aliment, étude cas-témoins

**ملخص**

بهدف دراسة العلاقة بين بعض العوامل الاجتماعية والاقتصادية إضافة إلى وتيرة استهلاك بعض المجموعات الغذائية وسرطان القولون والمستقيم في جيجل، شمال شرق الجزائر. أجرينا دراسة الحالات والشواهد في المرضى الذين يعانون من سرطان القولون على مستوى مستشفى محمد الصديق بن يحيى بجيجل باستخدام استبيانين لنمط الحياة و وتيرة تناول الطعام .بمقارنة 34 حالة مع 34 شاهدا، كشفت النتائج أن مستوى عال من التعليم (OR =0,0578، P = 0.0075)، انخفاض الدخل الأسري (OR = 7,8386، P = 0,0374)، التدخين (OR = 0,0751، P = 0.0174) والتاريخ العائلي للإصابة بسرطان القولون والمستقيم (OR = 5,2500، P = 0.0034) عوامل يمكن ان تكون مرتبطة مع المرض في هذه الفئة من السكان . لوحظ تأثير وقائي لاستهلاك منتجات الألبان (OR = 0،9808، P = 0.0437) والحبوب (OR = 0.9865، P = 0.0100) في حين أن استهلاك الأسماك يبدو مرتبطا بشكل إيجابي مع سرطان القولون و المستقيم (OR = 1.0665، P = 0.0392).في الختام، إلى جانب كون نتائجنا لا تظهر تأثيرا كبير للنظام الغذائي على حدوث سرطان القولون والمستقيم عند سكان جيجل، فان هذا العمل هو مقدمة لدراسة تأثير العوامل البيئية، وعلى رأسها التغذية، على وقوع هذا المرض. ستوفر هذه الدراسات الاستنتاجات المتعلقة بالوقاية الاولية من المرض.

**المصطلحات :** سرطان القولون والمستقيم, تغذية, الإصابة بسرطان القولون, المجموعات الغذائية, دراسة الحالات والشواهد.