

## Research Article



## Colorectal Cancer: Epidemiological Study, Clinical, Pathological and Immunohistochemical Examination in Patients of Eastern Algeria

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### ABSTRACT

Algeria is currently experiencing the same rate of cancer progression as that registered these last years in the western countries. Colorectal cancer, constituting increasingly a major public health problem, is the most common form of cancer after breast and Neck-womb cancer at the woman and prostate cancer at the man. Our work is based on a retrospective study to determine the cases of colorectal cancer through eastern Algeria. Our goal is to carry out an epidemiological, histological and immunohistochemical study to investigate different techniques for the diagnosis of colorectal cancer and their interests and specific in detecting the disease. The study includes 110 patients (aged between 20 to 87 years) with colorectal cancer where the inclusions and exclusions criteria were established.

**Keywords:** Adenocarcinoma, Age, Colorectal cancer, Epidemiology, Histological section, Sex.

### INTRODUCTION

Colorectal cancer (CRC) is, by its frequency, the third most common cancer in men and the second in women. Its frequency increases after 45 years. The CRC is found in 73% in the colon and recto sigmoid region and 27% in the rectum. Many investigations publish that this incidence begins to increase in people reaching the age of forty. This rise becomes very important from fifty years (92% of colorectal cancers are diagnosed in persons of fifty or more years old). The elderly of eighty or more years old still at risk of colorectal cancer (12,5 % of the cases diagnosed after 85 years).<sup>1</sup> This pathology is currently experiencing the same rate of cancer progression than in recent years in Western countries where the surveys, due to the aging population. Worldwide, colorectal cancer is the third most common cancer, 850 000 people develop the disease and 500,000 people die per year.

The colorectal cancer does not affect in an identical way the various populations. The age plays an important role, but also the ethnic group and the nationality. Perhaps this can be explained by differences in lifestyle and diet that is observed between these groups.

The colon is the portion of the intestine that follows the small intestine. It begins with the caecum, location of the appendix, is extended by straight or the ascending colon, the right angle, transverse colon, left corner, descending colon, sigmoid and then continues through the rectum and ends with the anus. It is in the colon that faeces are concentrated after re-absorption of water and salt, and then transported to the rectum, which acts as a reservoir. Continence is provided by a muscle, the anal sphincter.

The colorectal cancer (CRC) develops from the cells that line the inner wall of the colon or rectum. It is Caused by mutations (or disorders) of genes. These mutations

transform progressively the normal intestinal cell into cancerous cell. In 80 % of the cases, the CCR results from a benign tumor called adenomatous, which evolved slowly and then become cancerous called Adenocarcinoma (ADK) lieberkünüen which has the particularity to grow haphazardly, to invade the colon or locally rectum and lymph nodes and later throughout the body to form metastases (liver, lung, ...).<sup>3</sup>

### Mechanisms of the colorectal carcinogenesis

CRC represents a classic model of multi-stage carcinogenesis characterized by the appearance of successive genetic alterations responsible for the transformation of a normal cell into a cancerous colon, according to in situ carcinoma sequence adenoma with dysplasia and invasive carcinoma. Three main groups of CCR are defined depending on the type of instability that is associated with them:

Chromosome instability: CRC of type Loss of Heterozygote (LOH) or chromosomal instability (CIN) represents 80 % of sporadic CRC and all hereditary CRC developed on hereditary familial adenomatous polyposis (FAP). They are characterized by a aneuploid cells, and allelic loss of chromosome (s) or chromosome fragments (the short arm of chromosome 17 and 8 on the long arm of chromosome 18, 5 and 22). The allelic losses associated with frequent mutations of tumor suppressor genes, TP53, and APC, respectively located on the short arm of chromosome 17 and on the long arm of chromosome 5 and thus contribute to the biallelic inactivation of these genes.<sup>3,4</sup>

Microsatellite instability (MSI) is characterized by the presence of microsatellite instability associated with defective mismatch repair DNA (DNA mismatch repair (MMR) MMR. This alteration of the MMR system is



caused by mutations inactivating genes hMSH2, hMLH1, hMSH6, hMSH3, and hPMS2 hMLH3. Tumors belonging to this group have called MSI + phenotype and represent 15% of CRC. Tumors belonging to this group have a phenotype called MSI and represent 15 % of CCR.<sup>4</sup>

The epigenetic alteration resulting in certain genes modifications including the hyper-methylation of hMLH1 promoter individualized gene. It explains a big part of sporadic cancers. MSI not representing mutation.<sup>4</sup>

### Different signaling pathways

**APC/β-catenin pathway:** The tumor suppressor gene APC, located in the 5q21q22 chromosomal region is the essential partner in this signaling pathway. The constitutional alteration of this gene (APC) is responsible for the PAF. It is mutated in 60-80% of CRC CIN phenotype. These mutations, which are often deletions or insertions of several bases lead to the synthesis of a truncated protein.<sup>5,6</sup> They inactivate one of the two copies of the APC gene. The other event is the loss of the other long arm of chromosome 5, or the presence of a second mutation on the other allele of the APC gene. The negative control of the APC gene on the cell cycle is through the interaction of the APC protein with β-catenin, which is the essential component of the signaling pathway Wnt mediated oncogene. After activation of the Wnt receptor, the protein β-catenin accumulates in the cytoplasm of activated cells. It forms a protein complex with the transcription factor TCF4. This complex is then translocated to the nucleus where it allows the transcription of genes that promote cell proliferation<sup>7</sup>. It has been shown that, in the APC protein deficient cells, the β-catenin-complex is stable and TCF4 constitutively active. Down regulation exerted by the APC protein β-catenin involves other partners such as Axin and glycogen synthase kinase 3β (GSK3β). This last kinase, by phosphorylating certain serine and threonine residues of β-catenin, allows its degradation by the proteasome. Another activation pathway of β-catenin TCF4-protein complex is the occurrence of activating mutations of the β-catenin, preventing its degradation by the proteasome. These mutations occur in 50% of colon cancers where no mutation of the APC gene was found.<sup>8</sup> There is thus an accumulation of β-catenin at the tumor cells. A target gene transcription induced by β-catenin-complex TCF4 is the C-MYC oncogene, is over expressed in CRC where it induces proliferation of colonic epithelial cells.<sup>9</sup>

**P53 pathway:** The tumor suppressor gene TP53 is inactivated by both allelic loss and punctual mutations in 60-80% of CCR CIN. Mutations are significantly less frequent in the CCR MSI phenotype. TP53 alterations are involved in the adenoma-cancer sequence and therefore occur relatively late in colorectal carcinogenesis.<sup>10</sup>

The role of the p53 protein is twofold. Firstly, it blocks the cell cycle in G1 / S phase, inducing transcription of the inhibitor gene in cell cycle CIP1/WAF1 DNA damage to allow the reparation of these lesions before cell division.

Moreover, it can induce apoptosis by promoting transcription of proapoptotic gene BAX if DNA damage is too large to be repaired. The p53 protein also plays the role of guardian of the genome.<sup>10</sup>

The alteration of the TP53 gene would be in the center of the malignant transformation of the cell by allowing the occurrence of multiple genetic alterations, including type of deletion or amplification, participating in CIN phenotype. However, the relative part of the APC gene alterations and TP53 gene remains to be determined. The p53-signaling pathway is not only invalid in CIN cancers, but also in cancers of MSI phenotype. Indeed, the BAX gene is a target gene mutation in MSI by a coding sequence repeated eight guanines present in 30- 50% of CRC of this category.<sup>11</sup>

**TGFβ pathway:** Members of the family of TGF beta are cellular growth and differentiation factors of and involved in several biological processes such as cell proliferation and differentiation, extracellular matrix synthesis, immune response and angiogenesis. The TGF beta 1, commonly called TGFβ, is an inhibitor of epithelial cell proliferation. Two genes, SMAD2 and SMAD4, involved in signal transduction between its serine threonine kinase membrane receptors, and TGFβRII TGFβRI activity and the cell nucleus.<sup>12</sup> The TGF activated by binding to the TGFβRII, allows the formation of a protein complex with TGFRI and the phosphorylation and this last receptor.. This activated TGF β RII / TGF β RI heterotetramer phosphorylates the intracellular protein SMAD2 which is going to form a heterodimer with SMAD4. This protein complex is then translocated to the nucleus where it contributes to transcription of genes involved in the cell cycle. Activation of the TGF beta signaling pathway is associated with inhibition of cyclin-dependent kinases and cyclins and the increased expression of cyclin inhibitors.<sup>12,13</sup> This signaling pathway is activated in 20-30% of CRC CIN phenotype by inactivating mutations of SMAD2 and SMAD4 genes (Thiagalingan and al, 1996, Eppert and al, 1996). It is also involved in the CRC MSI phenotype wherein the gene is inactivated so TGFβRII biallelic in 60-80% of cases.<sup>14</sup> This gene has, in fact, within its coding sequence a microsatellite repeated sequence of ten adenine, with replication error unrepaired by the system MMR. These mutations lead to a shift in the reading frame and to the synthesis of a truncated non-functional receptor. Another gene of this signaling pathway is inactivated in the same manner on a repeated sequence of eight guanines: it is the gene encoding the type II receptor of insulin-like growth factor (IGFIIR) located upstream of TGFβRII of the TGF signaling pathway and allows its activation. Mutations of TGFβRII and IGFIIR are mutually exclusive. Thus, this signaling pathway is inactivated in both types of CRC, almost always in the MSI phenotype of cancer and more rarely in CIN phenotypes.<sup>15</sup>

**K-ras pathway:** Nearly the half of ADK and colorectal adenomas over 1 cm in diameter have a mutation in the



ras gene which is found in only 9 % of adenomas with less than 1 cm.<sup>16</sup> The Ras proteins (HRAS, KRAS and NRAS) belong to the super family of small G proteins and are involved in the control of cell growth. When Ras is activated as the Ras -GTP, it leads to dephosphorylation/activations successive cascade of Raf1, of " mitogen-activated protein kinase " 1 and 2 ( and MAPKK1 MAPKK2 ) , then " extracellular signal-regulated kinases " 1 and 2 ( ERK1 and ERK2 ). ERK 1/2 are eventually translocate to the nucleus where they activate factors such Elk1 and c-Myc, which regulate the transcription of genes stimulating cell proliferation or with anti- apoptotic properties, such as bcl-2. Moreover, ERK 1/2 also phosphorylate c-Jun, which activates the transcription factor AP1. This last one stimulates the expression of genes that control the cell cycle, such as cyclin D1 known to promote cell division, as well as the genes of metalloproteinase's, including MMP-7, which are factors promoting angiogenesis. Furthermore, Ras may interact directly with the phosphatidylinositol 3-kinase (PI3K) and activates the anti-apoptotic AKT pathway that promotes cell survival. In tumors, Ras mutations generate an accumulation of the active form of the protein, Ras-GTP, inducing a deregulation of cell proliferation and apoptosis, which may lead to tumor transformation, promote cell invasion and metastasis.<sup>1</sup>

**Patients and methods**

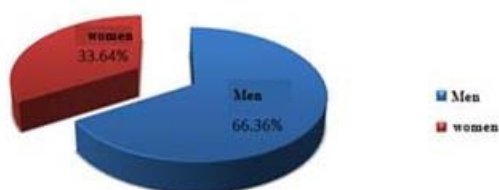
This study includes 110 patients (aged between 20-87 years) with CRC where inclusion criteria (patients with primary cancer of the colon and / or rectum, patients with colon cancer and rectal cancer, and patients with CRC ADK kind, a non-Hodgkin's lymphoma "NHL" and carcinoid tumors) and exclusion criteria (patients demonstrators secondary cancer of the colon and / or rectum, patients with anal cancer, patients with ulcerative colitis, colitis specific infectious colitis) have been established in this population.

Data records of patients with colorectal tumor tissue samples received are used to assess the progression of their disease.

Assay results in patients with CRC, blood samples received in the laboratory biochemistry and immunology are used to assess the rate of excretion of the marker: the carbohydrate antigen 19-9, is also called GICA (Gastro Intestinal Carbohydrate Antigen).

**RESULTS**

**Distribution of patients by sex (N = 110)**

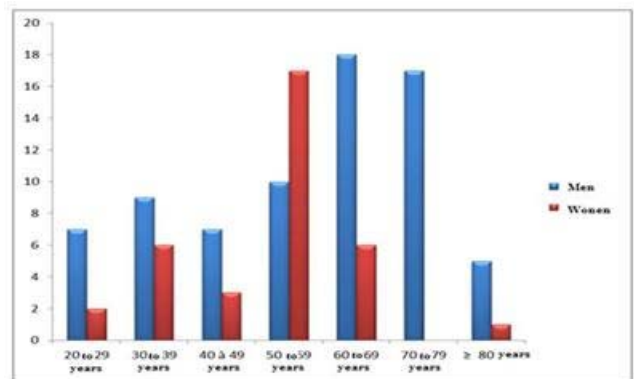


**Figure 1:** Sharing out by sex of colorectal cancers

We note a masculine predominance with a ratio men/women = 1.99.

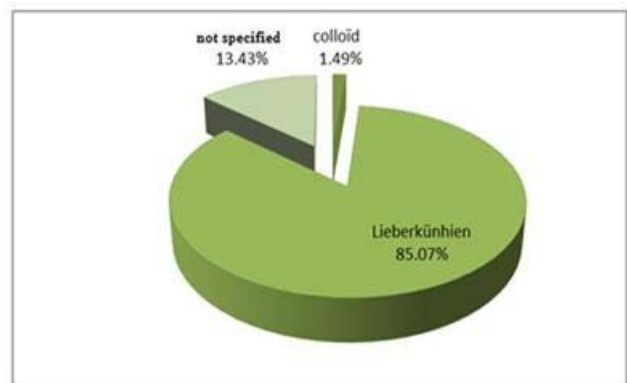
**Distribution by age and sex (N = 110)**

– Colorectal Cancers



**Figure 2:** Distribution by age and sex of colorectal cancers

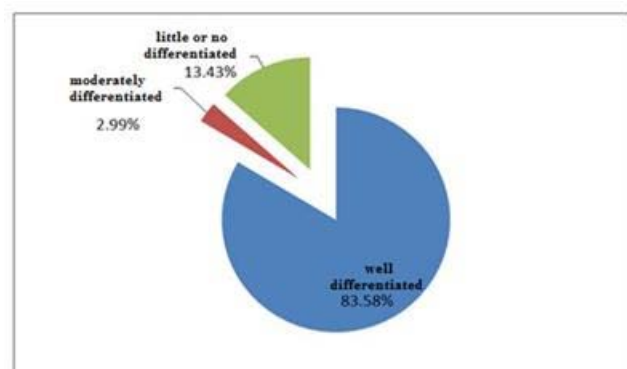
In our series they note: the peak of frequency of colorectal cancers is between 50 years and 59 years at the women while at the men it is between 60-69 years.



**Figure 3:** Histological types of Adenocarcinoma

The Cytopathologique study shows that lieberkühnien type is the most representative histological variety.

**Degree of differentiation of Adenocarcinoma**

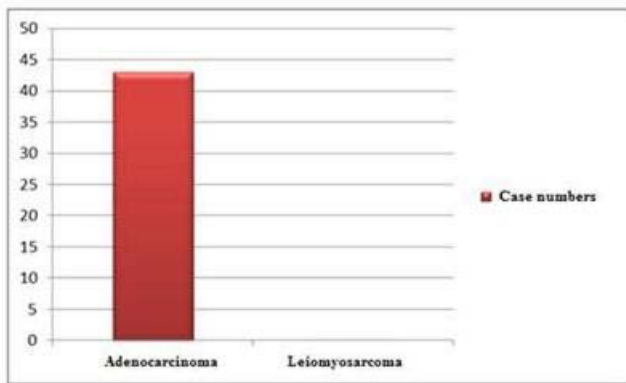


**Figure 4:** Distribution of degree of differentiation of ADK colic.

The well-differentiated ADK is majority in our series.

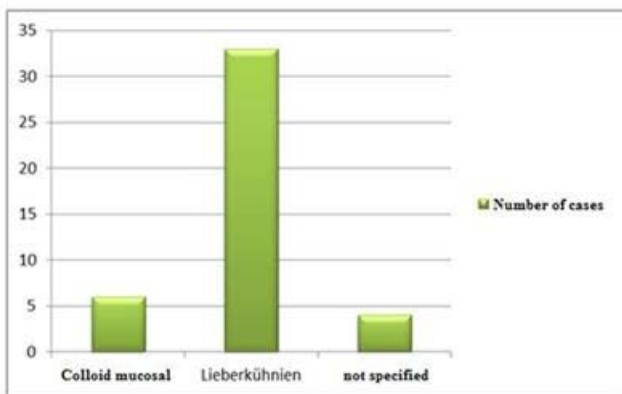
**Cancers of rectum**

**Histological types of the rectum cancers**



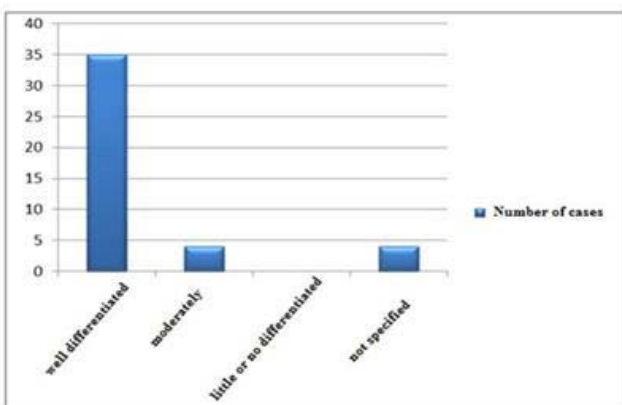
**Figure 5:** Distribution of histological types of rectal tumor. ADK represent all histological types of rectal cancer (100%) in our series.

**The histological varieties of recital ADK**



**Figure 6:** Distribution of histological types of rectal ADK. The Lieberkühnien type is the histological type most often representative.

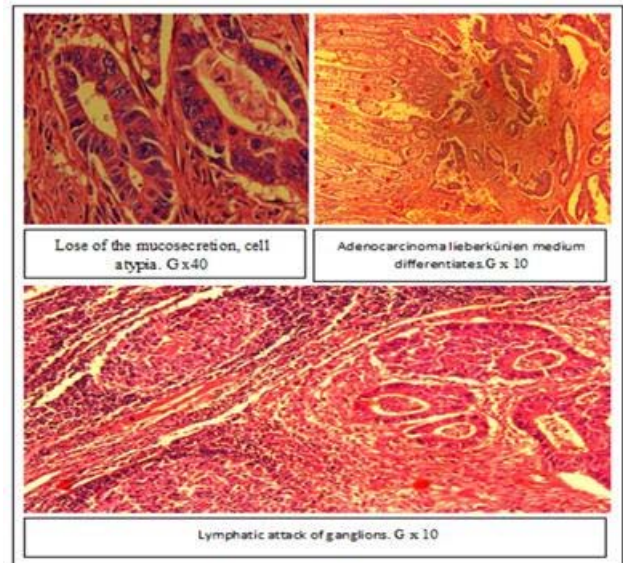
**The degree of differentiation of Adenocarcinoma**



**Figure 7:** Distribution of the degree of differentiation of rectal adenocarcinomas. The well-differentiated adenocarcinoma is the histologic type the most encountered.

**The study of blades**

- Age: 76 years
- Sex: male
- Sample: colic biopsy



**Figure 8:** Reading of blades: Coloring hematoxyline eosin (EH)

**DISCUSSION**

In our study, colorectal cancer expresses a male predominance with a rate of 66.36% against 33, 64% for female and a sex ratio of 1, 9. This result is reported by the Moroccan study (2004, 2010) which reported a male predominance with a rate of 53,33%. Our results are also comparable to those by results.<sup>18-20</sup>

In addition, we see the same phenomenon for the single colon cancer and single rectal cancer.<sup>21, 22</sup>

Taking into account the age factor, all age groups studied are affected by colon and rectum cancer. The most common age group is representative and is situated between 50 and 59 years. Our results are shared with the retrospective study by.<sup>23,24</sup>

For colon cancer as the CRC, the average age at diagnosis is 56, 33 years in both sexes.

Regarding rectal cancer, the average age of both sexes at diagnosis in our study was 56, 74 years. In a retrospective study by Tunisian<sup>25</sup> on 165 cases of rectal cancer collected and treated shows that the average age at diagnosis was 56 years. Similarly, our results are comparable to the work.<sup>26</sup> In our series, patients aged less than 40 years accounted for 22% of all patients with CRC.

Analysis of colon cancer shows that the cancer is diagnosed before age 40 years that is 13% of all patients with this cancer in our series. As for rectal cancer, patients aged less than 40 years at diagnosis, representing 10% of all patients with this pathology.

Patients aged over 70 years are 25% of all patients with colon cancer and 37% of all patients with cancer of the rectum.

In our series, we noted that colonic cancers represent a high rate compared to rectal cancers whose frequencies are respectively: 60,91% and 39,09%. This distribution is in agreement with the study<sup>27</sup> who found that the location of tumor in the colon and rectum is respectively 67,3% and 32,7%.

The topographical distribution of colon cancer (cancer of the sigmoid colon, cecum, right colon, left colon and transverse colon) and the topographic distribution of rectal cancer of the lower rectum, middle and upper rectum are not reported in our series of study.

ADKS are the histological variety that dominates the CRC in our series; they represent 95,45% of cases. This figure is comparable with the figures reported.<sup>28, 29</sup> In the study of colon cancer, Adenocarcinoma represent 94,54% in our headcount.

Carcinoid and LMNH are carcinoids tumors that represent 5,46%. Non-Hodgkin lymphomas (NHL) have not been reported on all colonic cancers. Our results are comparable to those<sup>30</sup> published 6% for carcinoid tumors in our investigation.

In our series, the ADK lieberkūnien colorectal is the most common histological form; it represents 82,72%, this proportion is similar to that reported in Algeria<sup>31</sup>, in Senegal<sup>32</sup> and in France<sup>33</sup>, which represents 80%.

In the series of colon cancer, the ADK lieberkunien is the most dominant histological type, is 85.07% of all cases. In contrast, the proportion of ADK mucinous (colloid mucous) is much lower, that is 1,49% only.

The well-differentiated ADKS, the majority in our series, represent 83,58% of cases. Similarly, for moderately and poorly differentiated Adenocarcinoma, whose proportions are respectively 2,99% and 0.00%. This result is comparable to the study.<sup>34</sup>

For histological types of rectal cancers, Adenocarcinoma represents all histological types of rectal cancer (100%) patients.

For histological varieties of rectal ADK, we find in our series, although the ADK lieberkunien represent the most common histological form, or 76,74%. While, mucosal colloid is present in 13,95% of our headcount.

As with colon cancer, well-differentiated ADK represent the majority of frequency, 81,40%. Moderately differentiated ADK representing a lower frequency of 9,31%. While, little /no differentiated ADK representing 0.05%.

## CONCLUSION

In our study, colorectal cancer, expresses a male predominance, with a sex ratio of 1, 99 and the most affected age group is between 50 and 59 years. We noted

that the colon cancer rate is higher than rectal cancer rate, whose frequencies are respectively 60,91 % and 39,09 %. In the series of colon cancer, the ADK lieberkunien is histological the most represented type, or 85,07 % of all cases.

In contrast, the proportion of ADK mucinous (colloid mucous) is only 1,49 % only. Well-differentiated ADKS, are very significant in our series, they represent 83,58 % of cases. Adenocarcinoma moderately and poorly differentiated, whose proportions are respectively 2,99 % and 0.05 %. For histological varieties of rectal ADK, we see in our workforce that ADK lieberkunien represent the most common histological form, or 76,74 %, while the mucosal colloid is 13,95 %.

Research of the mutation on the gene encoding K-ras, a major step in the targeted therapy of colorectal cancers, is underway in our study.

Colorectal cancer is the subject of much promising research concern: the evaluation of new therapies (anti-angiogenic monoclonal antibodies), the search for predictors of sensitivity to chemotherapy and new prognostic markers using techniques of molecular biology and proteomics.

## REFERENCES

1. Benson AB, Epidemiology, disease Progression, and Economic Burden of Colorectal Cancer, J Manag Care Pharm, 13(6), 2007, S5-S18.
2. De Gramont A, Housset M, Nordlinger B, Rougier P, Le cancer colorectal en questions, fondation ARCAD 2ème Ed, 2012, 1-73.
3. Laurent-Puig P, Agostini J, Maley K, Oncogenèse colorectale, Bulletin du Cancer, 11, 2010, 1311-1321.
4. Svrcek M, Cervera P, Hamelinb R. Cancer colorectal : les nouveaux rôles du pathologiste à l'ère de la biologie moléculaire et des thérapies « ciblées ». Revue francophone des laboratoires, 428, 2011, 29-41.
5. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis, Nature, 359, 1992, 235-237.
6. Laurent-Puig P, Beroud C, Soussi T, APC gene: database of germline and somatic mutations in human tumors and cell lines, Nucleic Acids Res, 26, 1998, 269-270.
7. Goss KH, Groden J, Biology of the adenomatous polyposis coli tumor suppressor, J ClinOncol, 18, 2000, 1967-1979.
8. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, et al., Identification of C-MYC as a target of the APC pathway, Science, 281, 1998, 1509-1512.
9. Sparks AB, Morin PJ, Vogelstein B, Kinzler KW, Mutational analysis of the APC/beta-catenin/TCF pathway in colorectal cancer, Cancer Res, 58, 1998, 1130-1134.
10. Lane DP, Cancer, 53, guardian of the genome, Nature, 358, 1992, 15-16.
11. Rampino N, Yamamoto H, Ionov Y, Li Y, Sawai H, Reed JC, et al., Somatic frame shift mutations in the BAX gene in colon



- ancers of the microsatellite mutator phenotype, *Science*, 275, 1997, 967-969.
12. Heldin CH, Miyazono K, ten Dijke P, TGFβ signalling from cell membrane to nucleus through SMAD proteins, *Nature*, 390, 1997, 465-471.
  13. Slingerland JM, Hengst L, Pan CH, Alexander D, Stampfer MR, Reed SI, A novel inhibitor of cyclin-CDK activity detected in transforming growth factor beta-arrested epithelial cells, *Mol Cell Biol*, 14, 1994, 3683-3694.
  14. Parsons R, Myeroff LL, Liu B, Willson JK, Markowitz SD, Kinzler KW, et al., Microsatellite instability and mutations of the transforming growth factor beta type II receptor gene in colorectal cancer, *Cancer Res*, 55, 1995, 5548-5550.
  15. Souza RF, Appel R, Yin J, Wang S, Smolinski KN, Abraham JM, et al., Microsatellite instability in the insulin-like growth factor II receptor gene in gastrointestinal tumors, *Nat Genet*, 14, 1996, 255-257.
  16. Fearon ER, Vogelstein B, A genetic model for colorectal tumorigenesis, *Cell*, 61, 1990, 759-767.
  17. Smakman N, BorelRinkes IH, Voest EE, Kranenburg O, Control of colorectal metastasis formation by K-Ras, *Biochim Biophys Acta*, 2005.
  18. Amegbor K, Napo-Koura GA, Songne-Gnamkoulamba B, Redah D, Tekou A, Aspects épidémiologiques et anatomopathologiques des tumeurs du tube digestif au Togo, *Gastroentero Clin et Biol*, 32, 2008, 430-434.
  19. Letonturier P, Colorectal cancer, from detection to treatment, *La Presse Médicale*, 37, 2008, 10, 1525-1527.
  20. Siby A, Evaluation de la prise en charge des cancers colorectaux à la polyclinique internationale sainte Anne Marie (pisam) d'Abidjan, Thèse Doctorat en médecine, faculté de médecine de pharmacie et d'odontostomatologie, Abidjan, 2010.
  21. Benamar S, Mohammadine E, Niamane R, Abbassi A, Essadel A, Résultats du traitement chirurgical du cancer du colon, *Médecine du Maghreb*, 1998, 60.
  22. Mallem D, Les cancers colorectaux dans les wilayas de Batna, Etude épidémiologique clinique et thérapeutique, Thèse doctorat en sciences médicales, Université de Batna, El Hadj Lakhdar, Faculté de médecine, Algérie, 2010.
  23. Bouzid K, Cancer des chiffres record pour l'Algérie, *Santé – MAG*, 15, 2013, 37.
  24. Sedrati Y, Cancer colorectal, A propos de 182 cas (étude descriptive) Thèse doctorat médecine, Faculté de médecine et de pharmacie, Fès. Maroc., 2013.
  25. Tebra Mrad A, Harrabi B, Belajouza A, Chaouache A, Bouaouina N, Le cancer du rectum dans le centre de la Tunisie: à propos de 165 cas. *Cancer / Radiothérapie*, 14(8), 2010, 411.
  26. Casanelli JM, Blegole C, Moussa B, N'DRI J, Aboua G, Yamossou F, Sidibe A, Keli E, N'guessan HA, Cancer du rectum, Aspects épidémiologiques, cliniques et thérapeutiques à propos de 16 cas au CHU de Treichville, Mali Médical, *Cancer du rectum, T - XX - N° 4 21*, 2005.
  27. Traore MC, Apects cliniques et thérapeutiques du cancer colorectal dans le service de chirurgie « A » du CHU du point « G, Thèse de doctorat médecine, Bamako, 2007.
  28. Sawadogo A, Ilboudo PD, Durand G, Peghini M, et al., Epidemiologie des cancers du tube digestif, Au burkina faso: Apport de 8000 endoscopies effectuées au centre hospitalier National Sanou Souro (CHNSS) de Bobo Dioulasso, *Médecine d'Afrique Noire*, 47(7), 2000, 342-345.
  29. Lelong B, Bege T, Guiramand J, Turrini O, Delpero J, Cancers du colon et laparoscopie : état de l'art en, *Bulletin du Cancer*, 4(12), 9, 2007, 1053-1058.
  30. Spread C, Berkel H, Jewell L, Jenkins H, Yakimets W, Colon carcinoid tumors, A population based study, *Dis Colon Rectum*, 37, 1994, 482-491.
  31. Ghalek M, BenAhmad F, Sahraoui T, Senhadji R, Riazi A, El-kebir Fz, Approches épidémiologiques et anatomopathologiques du cancer du colon, *Bulletin du Cancer*, XXIIIe Forum de cancérologie, 90(6), 2003, 489-565.
  32. Dem A, Kasse AA, Diop M, Gaye-Fall MC, Doui A, Diop PS, Toure P, Epidemiological and therapeutic aspects of rectal cancer in Senegal: 74 cases at the Cancer Institute of Dakar, *Dakar Med*, 45(1), 2000, 66- 69.
  33. Fabre E, Spano JP, Atlan D, Braud AC, Mitry E, Panis Y, Faivre J, Cancer of the colon: an update, *Bull, Cancer Suppl.*, 4, 2000, 5-20.
  34. O'Connell JB, Maggard MA, Ko CY, Colon Cancer Survival Rates With the New American Joint Committee on Cancer Sixth Edition Staging, *JNCI J Natl Cancer Inst*, 96(19), 2004, 1420-1425.

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