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Colorectal Cancer: Pathogenesis, Management and Prevention

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Abstract:*Colorectal cancer (CRC) is termed as a civilization disorder, with high incidence in Australia, NewZealand, Europe and US, with lower rates in Africa and Central Asia.Risk factors for CRC include genetic disorders, diet, red meat, smoking, alcohol and lack of exercise is associated with increased risk. Individuals with inflammatory bowel disease (IBD) have an increased risk of CRC.Genomic analysis have revealed that eventually cell acquires a mutation in the TP53 gene and transforms the tissue from a benign epithelial tumor into an invasive epithelial cell cancer.CRC can be categorized into hypermutated and non-hypermutated tumor type. Field defects and epigenetic changes play an important role. Common symptoms include: constipation, blood in stool, weight loss and anemia in people over 50 years. Diagnosis is by colonoscopy, sigmoidoscopy, and CT scan of chest, abdomen and pelvis. Cancer staging by TNMsystem. Treatment of CRC aimed at cure or palliation. Surgery,radiation, chemotherapy, palliative care and follow up is important. Prevention through surveillance, stool DNA screening test, fecal occult blood test,sigmoidoscopy,andcolonoscopy. CT colonoscopy cannot remove any abnormal growth.Prevention include consumption of whole grains, fruits,vegetables, calcium supplement vitamin D,and lactic acid bacteria(probiotics) have beneficial effect.*

Keywords:*Colorectalcancer,Genetics Irritable bowel syndrome, Diet, Colonoscopy,Prevention*

I. Introduction.

Colorectal cancer(CRC) or colon cancer,rectal cancer or bowel cancer, has been diagnosed in an ancient Egyptian mummy and also,was recorded in 2 Chronicles 21,Biblical king Jehoram with fatal disease of the bowel[I,2,].CRC is the development of cancer in the colon or rectum[3].Globally more than one million people get colorectal cancer every year,resulting in about 715,000 deaths as of 2010 up from 490,000 in 1990[4,5].As of 2012,it is the second most common cause of cancer in women(9.2% of diagnoses)and the third most common in men(10.0%)with it being the fourth most common cause of cancer death after lung, stomach, and liver cancer[6,7].In 2012,there were 1.4 million new cases and 694,000 deaths[8].Globally incidences vary 10-fold with highest rates in Australia, New Zealand, Europe and US and lowest in Africa and South Central Asia[9].Based on rates from 2007-2009,4.96 % of US men and women born today will be diagnosed with CRC during their lifetime[10].Risk factors for CRC include lifestyle, old age, inherited genetic disorders,diet,smoking, alcohol, lack of physical activity[11].Genetic disorders include hereditary non-polyposis colon cancer[11].Clinical symptoms may include blood in the stool, a change in bowel movements, weight loss, and feeling tired all the time[12].Diagnosis by sigmoidoscopy or colonoscopy, and medical imaging[11,3].Treatment may include combination of surgery, radiationtherapy, chemotherapy and targeted therapy[3].Five year survival rates in the United States are around 65 %,this depends on how advanced cancer is[13,3].Prevention include change in lifestyle, medication and regularCRCscreening. In-vitro evidence suggests lactic acid bacteria (e.g.,lactobacilli, streptococci or lacto cocci) may be protective against the development of CRC[14].

II. Contributory Factors

Source

Greater than 75-95 % pf colon cancer occurs in people with little or no genetic risk[15,4].Other risk factors include older age, male gender, high intake of fat, alcohol or red meat,obesity, smoking, and a lack of physical exercise[15,4].Approximately 10% of cases are linked to insufficient activity[16].The risk for alcohol appears to increase at greater than one drink per day [17].

Inflammatory bowel disease (IBS)

People with inflammatory bowel disease(ulcerative colitis and Crohn's disease)are at increased risk of colon cancer[18].The risk increases the longer the person has the disease[19],and the worse the severity of inflammation[20].In these high risk groups both prevention with aspirin and regular colonoscopies are

recommended [20]People with inflammatory bowel disease account for less than 2 % of colon cancer cases yearly [20].In those with Crohn's disease 2% get colorectal cancer after 10 years,8% after 20 years, and 18% after 30 years[20].In those with ulcerative colitis approximately 16% develop either a cancer precursor or cancer of the colon over 30 years[20].

Role of genetics

Those with a family history in two or more first-degree relatives (such as parents or sibling)have two to threefold greater risk of disease and this group accounts for about 20 % of all cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer. The most common of these is hereditary nonpolyposis colorectal cancer (HNPCCor Lynch syndrome which is present in about 3% of people with colorectal cancer [15].Lynch syndrome is one of the most common cancer predisposition syndrome affecting 1 in 200 individuals and accounting 10% of all CRC[21].HNPCC is characterized by an autosomal dominant inheritance pattern of early-onset presdisposition to CRC(average age 44 years),usually proximal to the splenic flexture(70%) and excess of synchronous and metachronousCRC.Multiple tumors occurs in 18% of all patients,metachronous CRC occur in 45% after hemicolectomy or segmental resection.Features of Lynch syndrome include the above features;whereas Lynch syndrome II is associated with carcinoma of the endometrium,ovary,smallbowel,stomach,pancreas and transitional carcinoma of ureter and renal pelvis in addition to CRC[21].

Other syndromes that are strongly associated with colorectal cancer include Gardner syndrome and familial adenomatous polyposis(FAP)[22].For people with these syndromes, cancer almost always occurs and make up 1% of the cases[23].A total proctocolectomy may be recommended for people with FAP as a preventive measure due to high risk of malignancy. Colectomy, removal of the colon, may not suffice as a preventive measure because of the high risk of rectal cancer if rectum remains [24].

Most deaths due to colon cancer are associated with metastatic disease. A gene that appears to contribute to the potential for metastasis associated in colon cancer I*(MACCI*),has been isolated[25].It is a transcriptional factor that influences the expression of hepatocytes growth factor. This gene is associated with proliferation, invasion and scattering of colon cancer cells in cell culture, and tumor growth and metastasis in mice. MACCI may be a potential target for cancer intervention, but this possibility needs to be confirmed with clinical studies [26].Epigenetic factors, such as abnormal DNA methylation of tumor suppressor promoters play a role in the development of colorectal cancer [27].

III. Pathogenesis

Colorectal cancer is a disease originating from the epithelial cells lining the colon or rectum of the gastrointestinal tract, most frequently as a result of mutations in the Wntsignaling pathway that increase signalingactivity. The mutations can be inherited or acquired, the most probably occur in the intestinal crypt stem cell[28].The most commonly mutated gene in all colorectal cancer is the APC gene,which produces the APC protein. The APC protein prevents the accumulation of β-catenin protein.Without APC β-catenin accumulates to high levels and translocate (moves) into nucleus, binds to DNA,and activates the transcription of proto-oncogenes. These genes are normally important for stem cell renewal and differentiation,but when inappropriately expressed at high levels, they can cause cancer. While APC is mutated in most colon cancers, some cancers have increased beta-catenin because of mutation in β-catenin(CTNNB1)that blocks its own breakdown, or have mutations in other genes with function similar to APC such as AXINI,AXIN2,TCF71.2 or NKDI[29].

Beyond the defects in the Wnt signaling pathways, other mutations must occur for the cell to become cancerous. The p53 protein produced by the *TP53* gene, normally monitors cell division and kill cells if they have Wnt pathway defects. Eventually, a cell acquires a mutation in the *TP53* gene and transforms the issue from a benign epithelial tumor into an invasive epithelial cell cancer. Sometimes the gene encoding p53 is not mutated, but another protective protein named BAX is mutated instead [29].

Comprehensive, genome scale analysis has revealed that colorectal carcinoma can be categorized into hypermutated and non-hypermutated tumor types[30].In addition to the oncogenic and inactivating mutations described for the genes above,non-hypermutated samples also contains mutated (CTNNB I,FAM123B,SOX9,ATM,and ARDI A.Progressing through a distinct set of genetic events,hypermutated tumors display mutated forms of ACVR2A,TGFBR2,MSH3,MSH6,SLC9A9,TCF71.2and BRAF.The common theme among these genes, across both tumor types, is their involvement in WNT and TGF-β signaling pathways, which results in increased activity of MYC, a central player in colorectal cancer[30].

Field defects

The term "field cancerization" was first used in 1953 to describe an area of "field" of epithelium that has been preconditioned by largely unknown processes, at that time, so as to predispose it towards development

of cancer[31].Since then, the terms "field cancerization", "field carcinogenesis" "field defect", and "field effect" have been used to describe pre-malignant or pre-neoplastic tissue in which new cancers are likely to arise[32].Field defects are important in progression to colon cancer[33].Rubin pointed out that vast majority of studies in cancer research has been done on well- defined tumors *in vivo*, or on discrete neoplastic foci *in vitro* [34].Vogelstein *et al*pointed out that more than half of somatic mutations identified in tumors occurred in a pre-neoplastic phase(in a field defect),during growth of apparently normal cells[35].An expanded view of field effect has been termed :etiologic field effect",which encompasses not only molecular and pathologic changes in pre-neoplastic cells but also influences of exogenous environmental factors and molecular changes in the local microenvironment on neoplastic evolution from tumor initiation to death[36].

Epigenetic

Vogelstein and colleagues described that an average cancer of the colon has only 1 to 2 oncogene mutations and 1 to 5 tumor suppressor mutations (together described "driver mutations"),with about 60 further "passenger" mutations[33].However the comparison, epigenetic alterations in colon cancers are frequent and affect hundreds of genes. For instance, there are types of RNAs .Expression of these miRNAs can be epigenetically altered.As one example, the epigenetic alteration consisting of CpG island methylation of the DNA sequence encoding miR-137 reduces its expression.[37].

Changes in the level of miR-137 expression result in changed mRNA expression of the target genes by 2 to 20 fold and corresponding, though often smaller, changes in expression of the protein products of the genes.OthermicroRNAs,with likely comparable numbers of target genes, are even more frequently epigenetically altered colonic field defects and in the colon cancers that arise from them[38].

In addition to epigenetic alteration of expression of miRNAs, other common types of epigenetic in cancers that changes gene expression levels include direct hyper methylation or hypo methylation of CpG islands of protein-encoding genes and alterations in histones and chromosomal architecture that influence gene expression[39].Recent evidence indicates that early epigenetic reductions of DNA repair enzyme expression likely lead to the genomic and epigenomic instability characteristic of cancer[33].

IV. Clinical Manifestations

The clinical manifestations of colorectal cancer depend on the location of the tumor in the bowel, and whether it has spread elsewhere in the body(metastasis).The classic warning signs include: worsening constipation, blood in the stool, decrease in the stool caliber (thickness),loss of appetite, loss of weight, and nausea or vomiting in someone over 50 years old[40].While rectal bleeding or anemia are high-risk features in those over the age of 50[41].Other commonly described symptoms including weight loss and change in bowel habit are typically only concerning if associated with bleeding[39].

V. Diagnosis

Diagnosis of colorectal cancer is via sampling of areas of the colon suspicious for possible tumor development typically done during colonoscopy or sigmoidoscopy, depending on the location of the lesion. The extent of the disease is then usually determined by a CT scan of the chest, abdomen and pelvis. There are other potential imaging test such as PET(position imaging tomography) and MRI which may be used in certain cases. Colon cancer staging is done next and based on the **TNM(T.primarytumor,N.regional lymph nodes, and M.distantmetastasis**) system which is determined by how much the initial tumor has spread, if and where lymph nodes are involved, and the extent of the metastasis disease [4].

The microscopic cellular characteristics of the tumor are usually reported from the analysis of tissue taken from a biopsy or surgery. A pathology report will usually contain a description of cell type and grade. The most common colon cancer cell is adenocarcinoma which accounts for 98% of cases. Other, rarer types include lymphoma and squamous cell carcinoma [42].

Macroscopic examination

Cancers on the right side of the large intestine (ascending colon and cecum) tend to be exophytic that is the tumor grows outwards from one location in the bowel wall.This very rarely causes obstruction of feces, and presents with symptoms as anemia.Left-sided tumors tend to be circumferential, and can obstruct the bowel lumen, much like a napkin ring,and results in thinner caliber stool [42].

Microscopic examination

Adenocarcinoma is a malignant epithelial tumor, originating from superficial glandular epithelial cells lining the colon and cecum. It invades the wall, infiltrating the muscularis mucosae layer, thesubmucosa, and then the muscularisispropria.The tumor cells describe irregular tubular structures, harboringpluristratification,multiplelumens,reduced stroma("back to back"aspect). Sometimes, tumor cells are

discohesive and secrete mucus, which invades the interstitium producing large pools of mucus.colloid(optically"empty" spaces. This occurs in mucinous (Colloid) adenocarcinoma,in which cells are poorly differentiated. If the mucus remains inside the tumor cell,it pushes the the nucleus at the periphery.this occurs in: signet-ring cell".Depending on glandular, architecture, cellular pleiomorphisim,andmucosecretion of the predominant pattern,adenocarcinoma may present three degrees of differentiation well,moderately,and poorly differentiated[43].

Immunochemistry

Most (50%) colorectal adenomas and (80-90%) colorectal cancer tumors are thought to over express cyclooxygenase-2(COX-2) enzyme. This enzyme is generally not found in healthy colon tissue, but is thought to fuel abnormal cell growth[44].Histologic studies and also reveal the type of cancer i.e.,adenocarcimona or pre-cancer stage.

Tumor staging and Tumor budding

The colon cancer staging can be made according to the TNM staging system from the WHO organization, the UICC and AJCC.TheAstler-Collerclassification (1954) or the Dukes classification (1932) are now less used [4].Tumor budding in colorectal cancer is loosely defined by the presence of individuals cells and small clusters of tumor cells at the invasive front of carcinomas. It has been postulated to represent an epithelial-mesenchymal transition (EMT).Tumor budding is a well-established independent markers of a potentially poor outcome on colorectal carcinoma that may allow for dividing people into risk categories more meaningful than those defined by TNM staging, and also potentially guide treatment decisions, especially in TI and T3 N0(stage11,Dukes' B) colorectal carcinoma. Unfortunately, its universal acceptance as a reportable factor has been held back by a lack of definitional uniformity with respect to both qualitative and quantitative aspects of tumor budding [45].

VI. Management

The treatment of colorectal cancer can be aimed at cure or palliation. The decision on which aim to adopt depends on various factors,including person's health and preferences, as well as the stage of the tumor[46].When colorectal cancer is caught early, surgery can be curative. However, when it is detected at later stages (for which metastasis are present) this is less likely and treatment is often directed at palliation, to relieve symptoms caused by the tumor and keep the person as comfortable as possible [4].

Surgical intervention

If the cancer is found at a very early stage, it may be removed during a colonoscopy [3].For people with localized cancer, the preferred treatment is complete removal with adequate margins, with the attempt of achieving a cure. This can be done by an open laparotomy or sometimes laparoscopically [4].The colon may then be reconnected or a person may have a colostomy[3].If there are only few metastasis in the liver or lungs they may be removed. Sometimes chemotherapy is used before surgery to shrink the cancer before attempting to remove it. The two most common sites of recurrence of colorectal cancer are the liver and lungs [4].

Chemotherapy

In stage 1 colon cancer, no chemotherapy isoffered, and surgery is definitive treatment. The role of chemotherapy in stage 11 colon cancer isdebatable,andusually not offered unless risk factors such as T4 tumor or inadequate lymph node sampling is identified. It is also known that the patients who carry abnormalities of the mismatched repair genes do not benefit from chemotherapy. For stage 111 and stage IV colon cancer chemotherapy is an integral part of treatment [4If the cancer has spread to the lymph nodes or distant organs, which is the case with stage 111 and stage IV colon cancer respectively, adding chemotherapy agent flurorouracil,capecitabine or oxaliplatin increases life expectancy. If the lymph nodes do not contain cancer, the benefits of chemotherapy are controversial. If the cancer is wide metastatic or unresectable,treatment is then palliative.Typically in this setting, a number of different chemotherapy medications may be used[4].Chemotherapy for this condition may include capecitabine,fluotouracil,irinotecan,oxaliplatin and UFT[47].

Radiation

While a combination of radiation and chemotherapy may be useful for rectal cancer [4],its use in colon cancer is not routine due to the sensitivity of the bowels to radiation. Just as for chemotherapy, radiotherapy can be used in the neoadjuvant and adjuvant setting for some stages of the rectal cancer [48].

Palliative care and follow- up

Involvement of palliative care may be beneficial to improve quality of life for both the person and his or her family, by improving symptoms, anxiety and preventing admissions to the hospital [49].People with incurable colorectal cancer, palliative care can consist of procedures that relieve symptoms or complications from cancer but do not attempt to cure the underlying cancer thereby improving quality of life. Surgical options may include non-curative surgical removal of some of the cancer tissue, bypassing part of the intestines, or stent placement. These procedures can be considered to improve symptoms and reduce complications such as bleeding from the tumor, abdominal pain and intestinal obstruction [50].Non-operative methods of symptoms treatment include radiation therapy to decrease tumor size as well as pain medications[51].

The aims of follow–up are to diagnose, in the earliest possible stage, any metastasis or tumors that develop later but did not originate from the original cancer (Metachronous lesions)[52].Exercise may be recommended in the future as secondary therapy to cancer survivors .A significant decrease in 8-oxo-dG was found in the urine of patients who underwent 2 weeks of moderate exercise after primary therapy[53].

Prognosis

In Europe five-year survival rate for colorectal cancer is less than 60%.In the developed world about a third of people who get the disease die from it[4].According to American Cancer Society statistics in 2006,over 20% of people with colorectal cancer come to medical attention when the disease is already advanced stage(stage IV),and up to 25% of this group will have isolated liver metastasis that is potentially resectable. In this selective group those who undergo curative resection experience a five- year outcome in a third of the cases [54,55].

VII. Prevention

Most colorectal cancers should be preventable, through increased surveillance and lifestyle changes [56].Current dietary recommendations to prevent colorectal cancer include increasing the consumption of whole grains, fruits and vegetables, and reducing the intake of red meat. Physical exercise is associated with modest reduction in colon not rectal cancer risk[57,58].Sitting regularly for prolonged periods is associated with higher mortality from colon cancer[59].Medication i.e., aspirin and celecoxib appear to decrease the risk of colorectal cancer in those at high risk. However, it is not recommended in those at average risk [60,61].There is tentative evidence for calcium supplementation but it is not sufficient to make a recommendation. Vitamin D intake and blood levels are associated with a lower risk of colon cancer [62,63].

Screening

As more than 80% of colorectal cancers arise from adenomatous polyps,screening for this cancer is effective not only for early detection but also for prevention [64].Diagnosis of cases of colorectal cancer through screening tends to occur 2-3 years before diagnosis of cases with symptoms[4].

Recommended guidelines for surveillance of first degree relatives of patients with HNPCCis[65],

a)Colonoscopy at age 25

b)Repeat every three years if negative,

c)Repeat every one year if adenoma is found,

d)Subtotal colectomy if cancer is found,

e) In females endometrial biopsy and ovarian ultrasound from age 25.

The four main screening tests are multitarget stool DNA screening test, fecal occult blood testing, flexiblesigmoidoscopy,and colonoscopy[4].Of three, only sigmoidoscopy cannot screen the right side of the colon where 42% of the malignancies are found[66].Virtual colonoscopy via a CT scan appears as good as standard colonoscopy for detecting cancers and large adenomas but is expensive, associated with radiation exposure, and cannot remove any detected abnormal growth like standard colonoscopy can[4].

In Canada, among those 50 to 75 at normal risk factor immunochemical testing or fecal occult blood testing(FOBT) is recommended every two years or sigmoidoscopy every 10 years, colonoscopy is less preferred[67].Other countries with organized screening include the United Kingdom, Australia, and Netherlands[68-70].In-vitro studies suggests lactic acid bacteria may be protective through antioxidant activity, immunomodulation and promoting programmed cell death, and proliferative effects, and epigenetic modification of cancer cells[14].

VIII. Conclusion

Colorectal cancer (CRC) is an ancient disease, with high prevalence and mortality in the west. Risk factors include diet, genetic and lack of physical activity. Early detectionbyimmunochemistry,FOBTsigmoidoscopy, colonoscopy, and removal of abnormal growth. Treatment

include surgery, chemotherapy and radiation Prevention include regular screening, change in food habits and exercise.

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