Principles and Practice of Cancer Prevention and Control

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Colorectal Cancer (CRC)

Cancer of the colon and rectum (colorectal cancer, CRC) is a major cause of cancer-associated morbidity and mortality worldwide. Colorectal cancer is the second most common cause of cancer mortality among men and women. It is the third most common malignant neoplasm worldwide. The risk of its occurrence has been shown to be increased associated with lifestyles and dietary habits, and chronic bacterial infections. Colorectal cancer, commonly known as colon cancer or bowel cancer, is due to uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix. Analysis shows that both colon and rectal tumors are essentially genetically the same. High incidence groups of CRC are those with hereditary conditions, such as familial adenomatous polyposis and hereditary non-polyposis CRC, accounting for about a quarter of all CRCs. Screening tests can detect colon cancer early. Therefore, limiting the screening or early cancer detection to only those high-risk groups would miss the majority of CRCs. Professional guidelines emphasize the importance of regular screening program including annual fecal occult blood tests, which might be found early and the chance of being cured is good.

Normal Structures of Colon and Rectum

The large intestine starts at the caecum, on the posterior medial wall of which is the appendix. The colon is made up of ascending, transverse, descending and sigmoid parts, which join the rectum at the recto sigmoid junction. The large intestine colon and rectum is about 144 cm in length and variably covered by peritoneum in its different regions. The muscle wall consists of an inner circular layer and outer longitudinal layer, the outer layer is incomplete, coming together to form the taenia coli, which produce the haustral pattern seen in the normal colon (Figure 1) [1,2].

Histology of Colon and Rectum

The layers of the intestinal wall, starting from within comprise mucosa, submucosa, muscle coat, and serosa or peritoneum. The mucosa of the colon is lined with columnar epithelial cells with crypts but no villi, so that the surface is flat. The mucosa is full of goblet cells (Figure 2). A variety of cells, mainly lymphocytes and macrophages, are found in the lamina propria. The lower crypt includes the replicative compartment. Maturing cells migrate up the crypt and reach the surface epithelium within a matter of days where they undergo apoptosis. The rectum is about 15 cm long. Its interior is divided by three crescentic circular muscles producing shelf like folds. These are the rectal valves that can be seen at sigmoid copy. The anal canal has an internal and an external sphincter [1].

Types of Colorectal Cancer

The types of tumor reflect the normal tissues that contribute to the structure of the intestinal tract. Adenomatous polyposis is an inherited colorectal cancer syndrome characterized by the early onset of large bowel tumor. Untreated cases may progress to colorectal cancer (CRC) by the age over than 35 years old. CRC can be prevented by timely implementation of rigid screening programs, life style management and certain medico-surgical interventions, and that may be depend upon the type of tumor.

Epithelial tumors

The columnar or glandular epithelium of the intestinal tract gives rise to both benign and malignant neoplasms termed adenomas and adenocarcinomas, respectively. The colon and rectum are common sites of both adenomas and adenocarcinomas. These lesions
Mucin content. The frequency of severe dysplasia increases with the size of the adenoma and is highest in villous adenomas. Flat adenomas are accompanied by increased nuclear pleomorphism, loss of nuclear polarity, atypical mitotic figures, and decreased cytoplasmic volume. Nuclear crowding and relocation create the impression of stratification. With increasing severity, the cytologic changes include considerable architectural irregularity, including crowded, back-to-back glands [4,6].

Enlarged, ovoid, or round, hyperchromatic nuclei often contain prominent nucleoli. The epithelial cells appear undifferentiated and there is a decrease in mucus secretion. In severe dysplasia, the nuclei are large, crowded, and stratified, and the cytoplasmic ratio is low. Mucus secretion is usually preserved but may be reduced. Dysplastic adenomas are classified according to the grade of evident epithelial dysplasia: mild, moderate, or severe dysplasia. In mild dysplasia, the nuclear to cytoplasmic ratio is low and the nuclei are elongated, crowded, and stratified. Mucus secretion is usually preserved, but may be reduced or absent in adenomas that include a high proportion of absorptive type cells within the epithelium. In severe dysplasia, the nuclei are enlarged, ovoid, or rounded, hyperchromatic and often contain prominent nucleoli. The epithelial cells appear undifferentiated and there is considerable architectural irregularity, including crowded, back-to-back glands [4,6].

The cellular morphological changes that distinguish an adenoma from normal include increased nuclear pleomorphism, loss of nuclear polarity, atypical mitotic figures, and decreased cytoplasmic mucin content. The frequency of severe dysplasia increases with the size of the adenoma and in highest in villous adenomas. Flat adenomas differ from the polypoid lesions by their macroscopic appearance. Polypoid lesions (type I) are defined as having a height of more than 3 mm. They are pedunculated or sessile. Non-polypoid neoplastic lesions (type II) have a height of 3 mm or less and the mucosal thickness of the lesion corresponds to twice (or less) that of the surrounding mucosa. They are probably involved in the development of so-called de novo cancers, a term introduced to describe those CRCs that apparently did not develop from a pre-existing polypoid lesion [5,6]. The head of adenoma is darker than the surrounding normal mucosa in large adenomas and may become lobulated, resembling a baby cauliflower. A rare presentation is as a large sessile mass with a soft, shaggy surface. These are called villous adenomas, although the fingerlike villi seen in two-dimensional sections are in reality leaf-like folds [3,4] (Figure 3).

Microscopic features: The microscopic growth pattern of tumour is classically described as tubular (gland-like), tubulovillous or villous (finger-like projections), depending on the presence and volume of villous tissue [4,7]. Tubules are lined by columnar epithelium and embedded with lamina propria where they proliferate by branching. Villi comprise a covering of columnar epithelium and a core of lamina propria. By forming complex, cerebriform folds of epithelium, the surface area of a villous adenoma may be considerably enlarged and lead to significant loss of fluid and electrolytes. Tubulovillous adenomas combine both architectural patterns [5].

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adenomas show cytologic and glandular abnormalities, which are similar to those, observed in polypoid lesions. In addition, it has been shown that non-polypoid adenomas gradually enlarge by the formation of new crypts producing a circular lateral growth [6].

Adenocarcinomas

Adenocarcinoma of the colon is common and often a fatal disease. It is the second most frequent diagnosed malignancy in the United States and the second most common cause of cancer deaths. The clinical presentation of colorectal carcinoma is variable and often depends on the size, site, and types of the tumor. It is a disease of the elderly, most frequently seen in patients older than 50 years of age, with a peak incidence at 60-70 years of age at the time of diagnosis. The incidence is slightly higher in men than women. Adenocarcinomas of the colon, especially those occurring on the right side, are often clinically silent for many years [8]. Virtually all carcinomas of the colon are adenocarcinomas. Almost all adenocarcinomas develop from a preexisting adenoma. Some adenocarcinomas of the colon, however, do not develop from preexisting adenomas but from a premalignant condition within flat mucosa called dysplasia. This condition may be partially responsible for the carcinoma seen in patients with the hereditary non-polyposis colon cancer syndrome [4,8].

Macroscopic features: Most cancers of the colon and rectum are ulcerating tumors with a raised and everted edge. Involvement of the bowel circumference may produce stenosis and obstruction. Sometimes this occurs when the mass of the tumor is relatively small. Sometimes, annular tumour growths called ‘string carcinoma‘ that appearances like string tied tightly around the bowel [9,10] (Figure 3).

Microscopic features: Two subtypes of adenocarcinoma (microscopic) include signet ring cell adenocarcinoma and mucinous adenocarcinoma. Signet ring cell adenocarcinoma is named for the way its cells look under a microscope. Mucinous adenocarcinoma is referred to as “mucinous” because its cells contain so much mucus [9,11] (Figure 4).

Signet ring cell adenocarcinoma

The term of signet ring cell describes the appearance of the cancer cells under a microscope, after stained and dehydrated. Signet ring cell adenocarcinomas have so much fat, once they are dehydrated, the nucleus gets pushed all the way over to one side. This makes the cell looks kind of like a ring under the microscope. Signet ring cell adenocarcinomas are considered more aggressive than regular adenocarcinomas and are harder to be treated. The signet ring cell form is very uncommon and accounts for about 0.1 percent of all adenocarcinomas [8,12].

Mucinous adenocarcinoma

Mucinous adenocarcinomas are diagnosed when more than 50% of the tumor is composed of extracellular mucin. These pools of mucin may contain calcification, allowing a histological diagnosis of mucinous adenocarcinoma to be suspected from radiographic findings. Although such cases are quite dramatic, mucinous adenocarcinomas are more commonly seen in younger patients, more likely to seed the peritoneal cavity, have an aggressive behavior, and probably associated with a worse prognosis [8,9,12]. Adenocarcinoma is
divided according to well, moderately or poorly differentiated. Well-differentiated tumor (20%) comprises well-formed glands in which nuclei are uniform in size, shape and retain a basal location. In moderately differentiated tumor (60%), the glands are less regular but remain easily recognized. The nuclei are large and lack a basal location. In poorly differentiated tumor, the glands are highly irregular and difficult to discern [9] (Figure 4).

**Epidemiology of colorectal cancer**

Colorectal cancer (CRC) is a worldwide problem with an annual incidence of approximately one million cases and an annual mortality of more than 500,000. CRC is on a rapidly rising trend in Asia. Countries such as China, Japan, South Korea, and Singapore have witnessed a two- to four-folds increase of incidence in the past decades. The incidences in many Asia countries are in fact on par with the west. The risk for this cancer varies between and within countries. The risk also varies among individuals based on diet, lifestyle, and hereditary factors. The worldwide burden of colorectal cancer estimated by the International Agency for Research on Cancer (IARC) database about 550,000 new cases annually. Colorectal cancer comprised 9.4% of global cancer burden in both sexes and is most frequent in North America, Australia, New Zealand and parts of Europe. This has led to that colorectal cancer being considered as a disease of western lifestyle [9,14].

Age standardized rates of incidence or mortality for 100,000 persons may allow to compare the risk of colorectal cancer in different regions or to assess temporal trends. Colorectal cancer is now the third most common malignant disease in both men and women in Asia. In Japan, the incidence of colorectal cancer may have exceeded that of gastric cancer [15]. The changing epidemiology is very worrying as the rising incidence in Asia has yet a plateau unlike statistics in North America and Europe. There are certain ethnic groups in Asia with substantially higher incidence of colorectal cancer. In Singapore, where Malay, Indian and Chinese live in the same environment, the incidence of colorectal cancer is significantly higher among the Chinese. Recently published studies in the Asia-Pacific Working Group for Colorectal Cancer, Japanese, Korean and Chinese were also found to have a higher incidence of advanced colonic neoplasia among the symptomatic and asymptomatic groups [15,16].

Asia accounts for 60% of the world’s population. This is more than three times of the populations in Europe and North America together with the aging population in the region and the rapidly changing epidemiology of cancer. Other studies in Asians showed the colorectal neoplasia and advanced neoplasia are asymptomatic with 18.5% and 4.5% respectively, whereas the overall prevalence of colorectal neoplasia ranged from 20.4% to 37.5% [15,17]. However, bowel cancer is the fourth most common cause of cancer death worldwide, estimated to be responsible for almost 610,000 deaths in 2008 (approximately 8% of the total). Mortality rate is the lowest in the Middle Africa and South-Central Asia and highest in Central and Eastern Europe with a six-fold variation in male and a five-fold variation in female mortality rates between the regions of the world (Figure 5) [18].

The 5-year prevalence of colorectal cancer (i.e. number of patients surviving 5 or more years following a colorectal cancer diagnosis) in 2008 was estimated at 3,260,890 worldwide (66.3 cancer survivors per 100,000 population) and 1,209,532 in Europe (165.0 cancer survivors per 100,000 population). The cumulative risk of colorectal cancer in persons aged under 75 is 1.96% worldwide (2.35% in men, 1.62% in women) and 3.29% in Europe (4.17% in men, 2.3% in women) [19].

**Etiology and prevention of colorectal cancer**

Several lines of evidence suggested that diet containing large percentages of fat predisposes to CRC, especially in the descending and sigmoid colon. Colon cancer rates are higher in populations whose total fat intake is high. Although colorectal cancer exhibits universal distribution, there is a higher incidence of the disease in developed and industrialized countries. The disease is less common in South America, Southeast Asia, Equatorial of Africa and India [21]. The etiology of CRC involves the interaction of cell molecular changes and environmental factors with a great emphasis on diet components. Considerable evidence suggests that the risk of this cancer increases by the mutagenic actions of free radicals, dietary factors, intestinal flora and lifestyle behaviors [22,23]. A healthy lifestyle with regards to the risk of colorectal cancer, and probably, the use of dietary chemo preventative agents might prevent or moderately reduce the colorectal cancer incidence (Table 1).
Lifestyle behaviors

Physical activity: Cumulative scientific evidence suggests physical activity as a mean for the primary prevention of colorectal cancer. There is a probable synergic effect among physical inactivity, high energy intake and obesity, and incidence of colorectal cancer. A growing body of evidence supports that avoidance overweight and the use of tobacco and alcohol is recommended to prevent colorectal cancer [24].

Previous study showed that disparities in the built environment, which likely contribute to differences in physical activities. Access to parks of opportunities for physical activities, such as the availability of sidewalks and those closely to stores, jobs, schools, greenways, bike paths and centers have been shown to contribute to more important of physical activities and lifestyles [25,26]. Previous studies reported the association between physical activity and colorectal cancer risk that indicated a lower risk with increasing levels of activity, the physical activity and colon adenomas or polyps also indicate a decreased risk with increasing physical activity [27].

Obesity: Colon cancer occurs more frequent among obese people than those with a healthy weight. Many researchers believe the increased rate of colon cancer is attributed to lifestyle patterns that are known to escalate colon cancer risk, particularly inactivity and a diet that is high in fat, low in fruits and vegetables. Others have suggested that high levels of insulin in obese individuals may promote tumor development. Many studies have demonstrated an increased risk of colorectal cancer with overweight and obesity. In both men and women cancer risks are highly consistent, demonstrating that abdominal fatness, indicated by a larger waist circumference or higher ratio of waist-to-hip circumference increases the risk of colorectal cancer [26].

Alcohol intake: An association between higher alcohol intake and increased risk for several cancer sites is well established. These include cancer sites that are in direct contact with ingested alcohol and cancers of the liver, where most alcohol is catabolized. However, whether alcohol consumption causally increases risk of colorectal cancer has been controversial because, most studies support the magnitude of the association to potentially confounding factors. Nonetheless, the conclusion from a report from the World Cancer Research Fund and American Institute for Cancer Research extensively summarized the evidence, that alcohol “probably” increases risk of colorectal cancer. Studies of alcohol intake and its association with colorectal cancer risk are largely supportive of an increased risk of colorectal cancer with increased alcohol intake, especially among men [24].

Smoking: Smoking is indeed a serious concern, and a major risk factor contributing to human carcinogenesis. Cigarette smoke contains at least 80 known mutagenic carcinogens, including arsenic, cadmium, ammonia, formaldehyde and benzopyrene. Also, it has other mutagens such as polycyclic aromatic hydrocarbons (PAH) and nitrosamines and other promoters as a complete carcinogen. Each will have a separate mechanism for causing cancer. Smoking is a risk factor for several types of cancers, mainly lung cancer and cancers of the upper aerodigestive tract (UADT), and to a certain extent esophagus, stomach, pancreas, liver, bladder, kidney, colorectal cancers, as well as myeloid leukemia. Heavily smoking use and excessive alcohol consumption may increase risk of colorectal cancer. Studies of alcohol intake and its association with colorectal cancer risk are largely supportive of an increased risk of colorectal cancer with increased alcohol intake, especially among men [24].

Diet and fiber intake: The role of dietary fiber in colorectal cancer risk has been studied for many decades. In recent years, however, other studies have provided evidence that fiber intake, especially from vegetables, fruits, and whole grains have been associated with a decreased colorectal cancer risk [26]. The hypothesis that dietary fiber prevents the colorectal cancer suggested an association between dietary fiber and large bowel function. High fiber content in food has traditionally been considered as a protector factor against colorectal cancer because of mechanisms by which certain dietary fibers may act to reduce the risk of colon cancer are thought to involve the dilution, absorption, and removal of carcinogens, cocarcinogens, and/or tumor promoters that are present in the gut [28].

Meat and fat intake: Estimates of risk of colorectal cancer have been either increased or null in cohort and in case control studies were examined the role of dietary meat and fat. It appears that total protein consumption in relatively unimportant. A role for red and processed meats in increasing colorectal cancer risk was subsequently evaluated the association between red meat intake and colorectal cancer risk. Several mechanisms have been proposed. For example, grilling red meat can create carcinogenic heterocyclic amines, polycyclic aromatic hydrocarbons and generate free radicals that may damage DNA [27]. Whereas red meat preparation may generate carcinogens and the saturated fat of animal origin may be associated with the risk factors [12].

Industrial chemicals

Certain industrial chemicals and pesticides persist in the environment and become concentrated in the food chain, industrial chemicals were calculated to account for less than 1% of cancer deaths [29]. Polychlorinated biphenyls (PCBs), organic compounds previously used in plasticisers, adhesives, paints, and various oils, do not readily degrade. They are more soluble in fat rather than water.
and thus accumulate in carnivorous fish such as salmon, and can be absorbed by people who eat these types of fish thus playing a role to induce colorectal cancer [30].

**Bacteria and carcinogenesis**

Annually, it is estimated that over 15% or about 1.2 million cases of malignancies worldwide can be attributed to infections [31]. Infections involving viruses, bacteria and schistosomes have been linked to highest risks of malignancy. For example, convincing evidence has linked Helicobacter pylori with both gastric cancer and mucosa associated lymphoid tissue lymphoma. Important mechanisms by which bacterial agents may induce carcinogenesis include chronic infection, immune evasion and immune suppression [32].

*Streptococcus bovis* is a normal inhabitant in the human gastrointestinal tract that can cause bacteremia, endocarditis, and urinary infection. Although, *S. bovis* was the second greatest cause of infectious endocarditis [31], it is frequently associated with gastrointestinal lesions, especially carcinoma of the colon [33]. Notably, the colonic neoplasia may arise years after the presentation of the condition of bacteremia or infectious endocarditis [31,32]. All *S. bovis* bacteremia patients had subacute bacterial endocarditis, and two had neoplastic disease, which seemed to indicate an association between *S. bovis* and colorectal carcinoma. There is a high incidence of colorectal cancer associated with *S. bovis*. Experimental, epidemiological and genetics studies suggested that the CRC develop from the complex interactions between inherited susceptibility and environmental factors, there strong hypothesis between adenomatous polyps and some pathogenic bacteria are the precursors of the vast majority of colorectal cancers [31,34]. Importantly, many reports have suggested a potential relationship between increased fecal carrier levels of *S. bovis* and human gastrointestinal disease, IBD and primarily colonic cancer in adult patients (Table 1) [34,35].

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<th>Probably Causative</th>
<th>Probably Protective</th>
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<td>• High-fat and low-fiber diet</td>
<td>• Aspirin, NSAIDs, and cyclooxygenase-2 inhibitors</td>
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<td>• Red meat consumption</td>
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<td>• Low physical activity</td>
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Screening

Diagnosis of colorectal cancer cases through screening trends may be 2–3 years before diagnosis symptoms. Screening has the potential to reduce colorectal cancer deaths by 60% [36]. There are three main screening tests of colorectal cancer firstly by using the fecal occult blood testing of the stool, which is typically recommended every two years that can be either guaiac based or immunochemical. The second is flexible sigmoidoscopy test, which medical societies recommend screening between the age of 50 and 75 years with sigmoidoscopy every 5 years and colonoscopy every 10 years. Those at high risk, the screenings usually begin at around 40. The third test is colonoscopy and CT scan appears as good as standard colonoscopy for detecting cancers and large adenomas [37].

A new screening method is the M2-PK Test. The enzyme biomarker M2-PK has been identified as a key enzyme in colorectal cancers and polyps, this test doesn’t depend on blood in the stool but it is specifically related to changes in the tumor metabolism, while it requires only a small stool sample. M2-PK features a high sensitivity for colorectal cancer and polyps and is able to detect bleeding and non-bleeding colorectal cancer and polyps [38]. The histopathology, staging and genetics are recent developments such as the pathology of neoadjuvant therapy and molecular prognostic and predictive factors in colorectal cancer.

**Conclusion**

A large number of evidence indicates that several dietary and lifestyle factors affect colorectal cancer carcinogenesis. The convincing evidences that nutrition effects on the colorectal carcinogenesis in a complex fashion. A diet with high in fat and red meat, low in fruits and vegetables, high caloric intake, low levels of physical activity, obesity, smoking and excessive alcohol intake probably increase the risk of colon cancer development. Dietary components either promote or inhibit the carcinogenic process. Numerous properties suggested carotenoids and others antioxidants present in fruit and vegetables may be valuable chemopreventive agents. Cigarette smoke is a powerful carcinogen and a source of oxidative stress. Moreover, there is increasing evidence that specific dietary patterns, foods and drinks, and dietary constituents can and do protect against cancer. A healthy lifestyle with regards to the risk of colorectal cancer includes a large consumption of vegetable and whole cereals, a limit of caloric intake with fats not exceeding 30%, avoidance of red meat and alcohol and does regularly physical exercise. Understanding the mechanisms that control cell structure and function, and so influence the cancer process, will aid not only understanding of cancer as a whole, but also the development of preventive strategies. Improved lifestyle, and probably, the use of dietary chemopreventative agents molecular prognostic and predictive factors currently employed in the treatment of colorectal cancer.

**References**
