RESEARCH COMMUNICATION

Gastro-intestinal Cancer in Indonesia

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Abstract

Back ground: Report on cancer incidence in Indonesia was presented in relative frequency. To lower the bias, the report has been presented in age standardized cancer ratio (ASCAR). The report was a department of pathology based cancer registration. The ASCAR of gastro intestinal cancer in Indonesia has some variation between pathologic centres. The incidence of rectal cancer in Jogjakarta was higher than colon cancer, and stomach cancer is very low. The risk factors of stomach cancer are H. Pylori infection and food consumption especially salt and the risk factor of colorectal cancer is food consumption.

Purpose: The article will discuss the ASCAR of stomach and colorectal cancer in Indonesia. . The histopathologic of stomach and colorectal cancer in Jogjakarta will be presented from the view point of pathology.

Method: Stomach and colorectal cancer data from 13 pathologic diagnostic centres in Indonesia were collected. The pathogenesis of stomach and colorectal cancer will be discussed in correlation with the cancer prevention.

Result: The incidence of stomach cancer in many centres in the year of 1996 are very low from 0,00% - 0,24 % for the most lowest incidence and 2.22 % - 5.60 % for the highest incidence. The higher incidence of stomach cancer was in Medan 19 males (5.6%); 10 females (2.22%); Palembang 7 males (4.75%), 1 female (0.11%); Surabaya 18 males (1.38%), 7 females (0.35%); Denpasar 12 males (2.97%), 1 female (0.24%), and Jakarta 55 males (4%), 28 females (1.39%). The incidence of colorectal cancer is almost equal in every pathologic diagnostic centres. It is interesting that the incidence of rectal cancer was higher than colon cancer. In Jogjakarta the histopathological feature of stomach cancer was predominated by poorly differentiated adenocarcinoma, while colorectal cancer was predominated by well differentiated adenocarcinoma.

Conclusion: The low incidence of gastric cancer in Indonesia in relation with H. Pylori and food consumption and the high ratio between rectal and colon cancer in correlation with the food consumption and it pathogenesis need further investigation.

Key Words: Department of pathology based cancer registry - stomach cancer - colorectal cancer - histopathological featurs

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Introduction

Report on cancer incidence in Indonesia was presented in relative frequency (Soeripto et al., 1977). To lower the bias, the report has been presented in age standardized cancer ratio (ASCAR). The report was a department of pathology based cancer registration. The ASCAR of gastro intestinal cancer in Indonesia has some variation between pathologic centres. The incidence of rectal cancer in Jogjakarta was higher than colon cancer, and stomach cancer is very low (Ahmad,1996). The risk factors of stomach cancer are H. Pylori infection and food consumption especially salt and the risk factor of colorectal cancer is food consumption (Hamilton and Aaltonen, 2001; Uemura et al., 2001; Ye et al., 1998; Chen et al., 2003). The article will discuss the ASCAR of stomach and colorectal cancer in Indonesia. The histopathologic of stomach and colorectal cancer in Jogjakarta will be presented from the view point of pathology

Methods

Stomach and colorectal cancer data from 13 pathologic diagnostic centres in Indonesia were collected. The registration was done by Indonesian Association of

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Pathologists. The pathogenesis of colorectal cancer will be discussed in correlation with the cancer prevention from the study of litterature

Result

The high incidence of stomach cancer in many centres in the year of 1996 are very low from 0,00% - 0,24 % for the most lowest incidence and 2.22 % - 5.60 % for the highest incidence. The higher incidence of stomach cancer was in Medan 19 males (5.6%); 10 females (2.22%); Palembang 7 males (4.75%), 1 female (0.11%); Surabaya 18 males (1.38%), 7 females (0.35%); Denpasar 12 males (2.97%), 1 female (0.24%), and Jakarta 55 males (4%), 28 females (1.39%). The incidence of colorectal cancer is almost equal in every pathologic diagnostic centres. It is interesting that the incidence of rectal cancer was higher than colon cancer. In Jogjakarta the histopathological feature of stomach cancer was predominated by poorly differentiated adenocarcinoma, while colorectal cancer was predominated by well differentiated adenocarcinoma.

Discussion

Cancer of the stomach is one of the most commonly diagnosed malignancies and remains an important cause of mortality worldwide. This type of cancer is not uniformly distributed among populations but shows a marked variation in both incidence and mortality (Christian et al., 1999). Athough the incidence of stomach cancer in Indonesia are very low, morbidity and mortality rates of gastric cancer in Asia remain the highest in the world. Countries with a particularly high incidence of this disease include Japan, China and Korea (Wu et al., 2000).

The incidence of adenocarcinoma of the stomach is declining worldwide. In some Western countries, rates have been reduced to less than one third within just one generation. The main reason for these good news is a change in nutrition, in particularly the avoidance of salt for meat and fish preservation, the lowering of salt intake from other sources and the avaibility in many countries of fresh fruits and vegetables throught the year (Hamilton and Aaltonen, 2001).

Previous studies indicate that environmental factors may play an important role in the carcinogenesis of gastric cancer, among which, dietary factors and Helicobacter pylori infection were most extensively investigated. Most epidemiological studies (particularly case-control studies) show that high intake of nitrates and related compounds and salted foods increase the risk (Deng, 2000). On the other hand, an adequate intake of fresh fruits and vegetable lowers the risk due to their antioxidant effect. Ascorbic acid, carotenoids, folates and tocopherols are considered active ingredients. Ascorbic acid, an anti-oxidant, is active tyransported from blood to gastric lumen by unknown mechanisms. Its putative anti-carcinogenic role is by preventing oxidatidve DNA damage (Hamilton and Aaltonen, 2001; Palli, 1994; Rood et al., 1994).

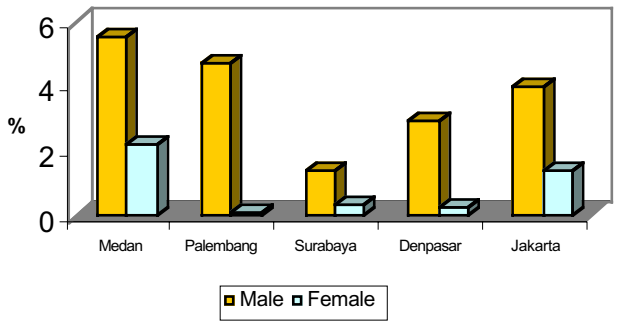

Figure 1. Stomach Cancer in High Incidence Centres 1996

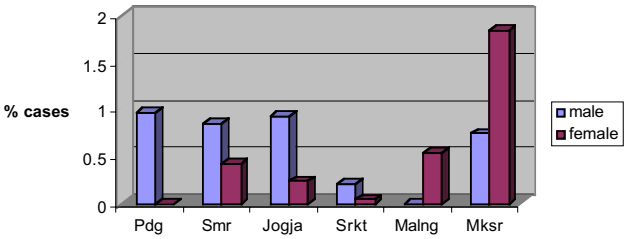

Figure 2. ASCAR of Stomach in Low Incidence Centres 1996

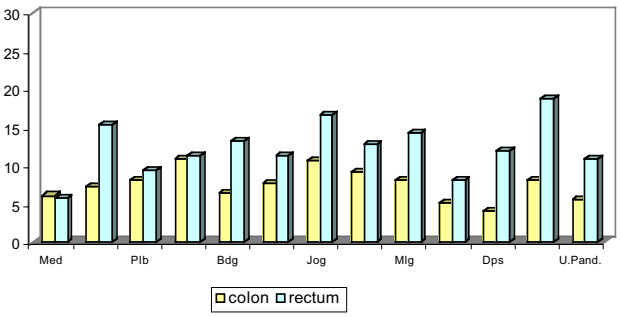

Figure 3. ASCAR of Colorectal Cancer Cases in Indonesia 1996

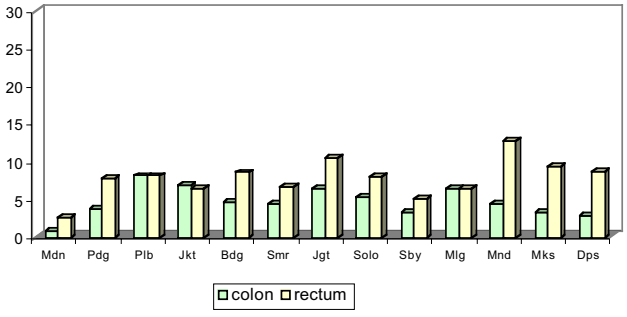

Figure 4. ASCAR of Colorectal Cancer Cases in Male 1996

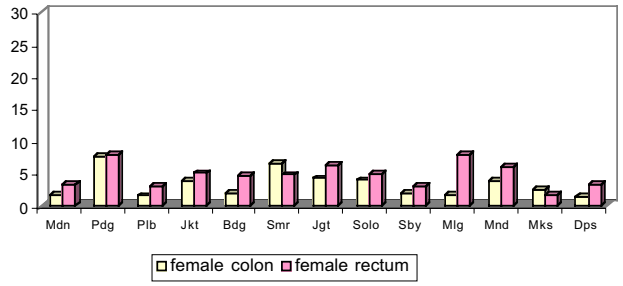

Figure 5. ASCAR of Colorectal Cancer Cases in Females, 1996

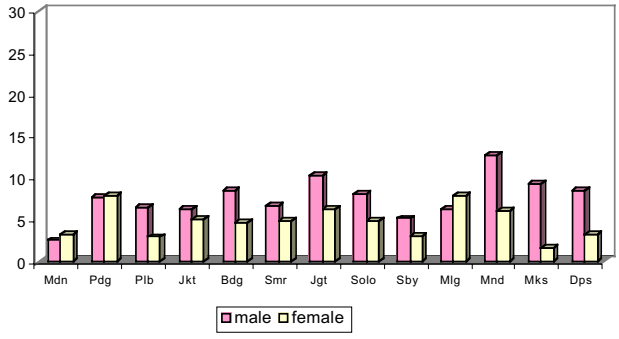

Figure 6. ASCAR of Rectal Cancer Cases, 1996

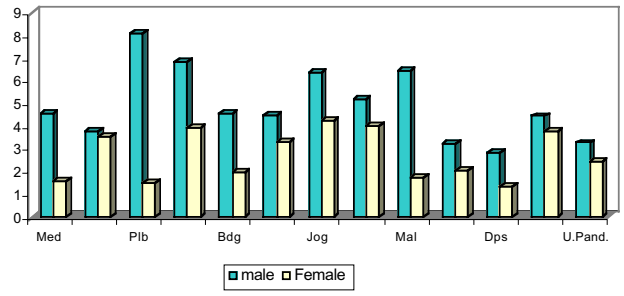

Figure 7. ASCAR of Colon Cancer Cases in Indonesia 1996

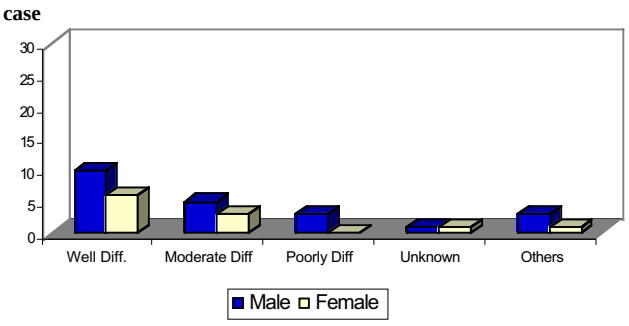

Figure 8. Colon Cancer Cases in Jogjakarta 2001

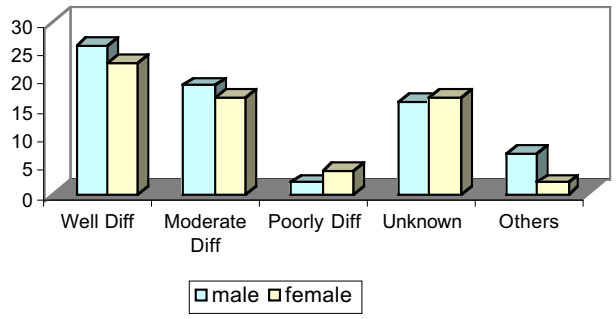

Figure 9. Rectal Cancer Cases in Jogjakarta 2001

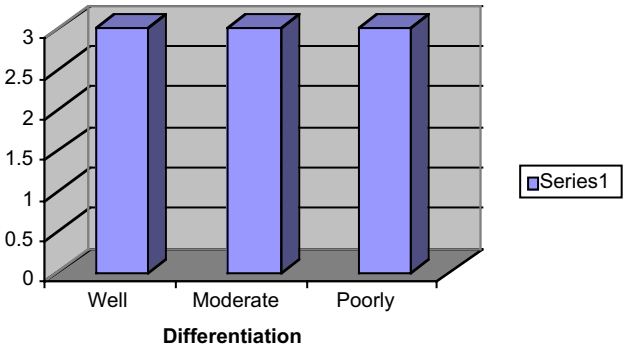

Figure 10. Stomach Cancer Case in Male in Jogjakarta 2001

A high salt diet is considered to cause temporary tissue damage, alteration of the viscosity of the protective mucous barrier and to facilitate colonization of Helicobacter pylori, resulting in gastric tumor progression (Nozaki et al., 2003). The increased colonization density of H. pylori could be potentiated through several mechanisms. A previous report indicated that gastrin appears to be a H. pylori-specific growth factor in vitro. The terminal serum gastrin concentrations were statistically increased in H. pylori-infected mice and elevated in mice fed high-salt diets. Another factor in the increase of H. pylori colonization is the induction of foveolar hyperplasia in mice fed high-salt diets. The gastric foveolae, or pits, represent the primary niche and site of attachment for H. pylori organism (Fox et al., 1999).

Chronic infection of H. pylori is an important risk factor for the development of gastric carcinoma. However, the infection leads to gastric cancer is only a small subset of infected patients. It has been suggested that enhanced cancer risk may be related either to differences in host response to bacteria, to the interaction between host and microbe or to differences in expression of strain-specific gene. The association with pre-neoplastic lesion was demonstrated in H. pylori isolates that were triple positive strains (babA2+/cagA/vacAs1) (Zambon et al., 2003; Yu et al., 2002).

There are two major types of gastric carcinoma, intestinal and diffuse ; the most frequent is the intestinal type. It was

noted that both intestinal-type and diffuse-type gastric cancer were closely associated with H. pylori infection. In the case of well- differentiated, intestinal-type gastric cancer, previous studies indicated that chronic H. pylori infection progresses over decades through stages of chronic gastritis, atrophy, intestinal metaplasia, dysplasia and cancer. The development of cancer has been attributed to alterations in DNA caused by chronic inflammation, an imbalance between epithelial-cell proliferation and apoptosis and gastric colonization by enteric bacteria with nitrate reductase activity, which facilitates the formation of carcinogenic nitrosamines in a milieu of atrophy and achlorhydria (Fox and Wang, 2001; Eguchi and Moss, 2002; Xia and Talley, 2001).

Table 1. Histological techniques for demonstrating H. pylori

Non-specific staining methods
Haematoxylin -eosin
Warthin-Starry
Modified Giemsa stain
Genta stain
Carbo-fuchsin
Specific staining techniques
Immunostain
In situ hybrididdation

The role of pathology in relation with H. pylori gastric infection and gastric cancer is very significant. H. pylori is the organism that can be confidently recognized by histology. Various histochemical technique for demonstrating H.pylori can be seen in table 1

Beside stomach, H. pylori can be found extragastric site. The most frequent extragastric site of colonization is on patches of metaplastic gastric cell in the duodenum, followed by Barret's oesophagus (Paull and Yardley, 1988; El-Guneid et al., 1991). and rectum (Dye et al., 1990). H. pylori is the major cause of non-autoimmune chronic gastritis. In order to take account of recent developments and in an attemp to remove diagnostic confusion, the Sydney system for grading and classificaton of chronic gastritis was introduced (Misiewicz et al., 1991; Dixon et al., 1996; Genta and Dixon, 1995). (see table 2)

Variables that should have to be observed in chronic gastritis are : H. pylori density, Chronic inflammation cells, Neutrophl infiltration, Gland atrophy, Intestinal metaplasia, Dysplasia, Epithelial degeneration and Lymphoid follicle. Study on H. pylori infection aspect of Dutch and Chinese population was conducted in the Nederland and China (Van der Hulst et al., 1997; Correa, 1995; Bayerdorffer et al., 1995).

Based on the discussion mention above and in the view point of pathology and prevention study of stomach cancer from distinct population with high incidence and low incidence of H. pylori gasyritis is suggested. The study will cover among others.

1. The assessment of H. pylori associated gastritis using Sydney system for classification and grading

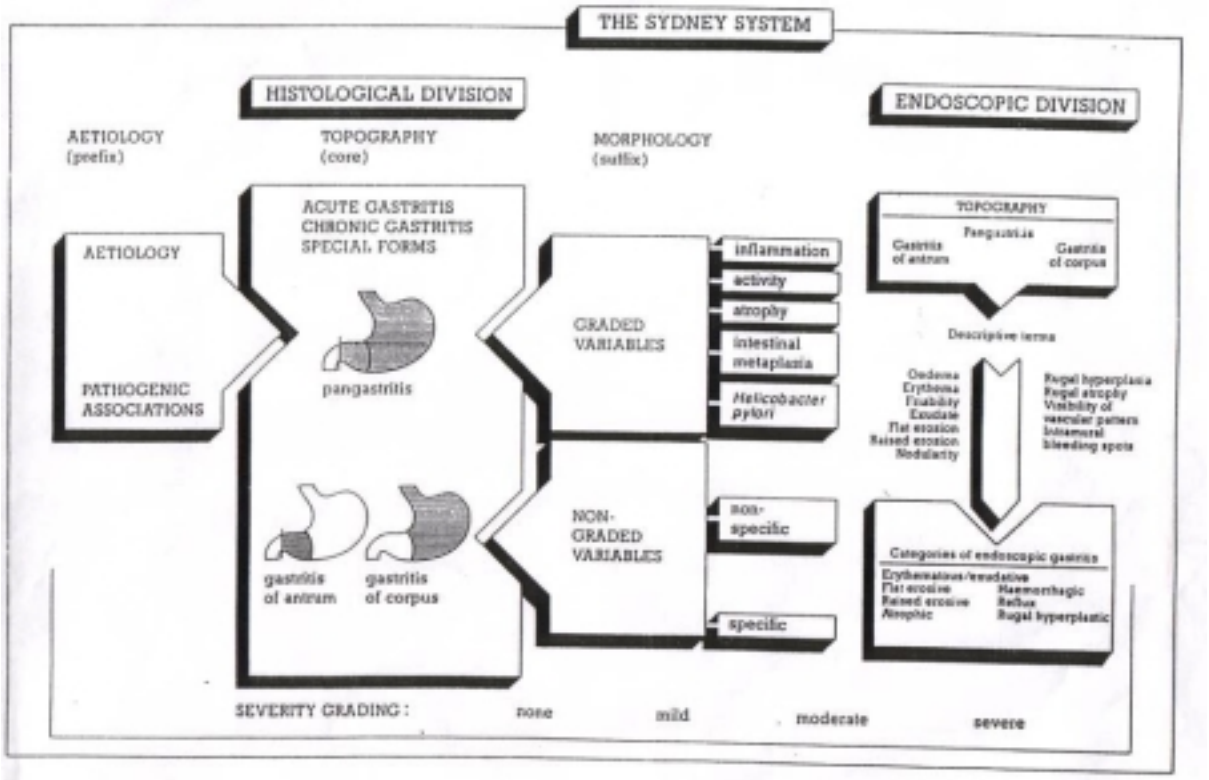

Table 2. The Sydney System

2. Prevalence of H. pylori associated gastritis, precancerous condition, atrophy, intestinal metaplasia, dysplasia, evaluation after eradication and anti oxidant intervention
3. H. pylori associated gastritis and follicles lymphoid hyperplasia. Evaluation after eradication.
4. The influence of CagA, VacA, BabA in gastric mucosal changes before and after eradication of H. pylori intervention with anti oxidant
5. COX-2 expression on H. pylori gastric infection before and after eradication and anti oxidant intervention

Despite the low incidence of gastric cancer, colorectal cancer was recently estimated to be the one of the more common cancer in Indonesia. From 13 cancer registries it was found that colorectal cancer is one of the five frequent cancer found in males and females (Sarjadi and Padmi, 2001). Worldwide, an estimated 875000 cases of colorectal cancer occurred in 1996, accounting for 8.5% of all new cases of cancer. The highest incidence rates seen in the developed world and the lowest in India. Rectal cancer is up to twice as common in men as in women, and this tumor may have a better overall survival where screening is more common (Potter, 1999). Data from cancer statistics of United States indicated that approximately 60% of colorectal cancers are found in the distal colon or rectum (Greenlee et al., 2000). In addition, according to 1980ûs report by the Research Team in China, 80% of colorectal cancers are found in the distal colon or rectum, with up to 66% in the rectum alone (Chen et al., 2003). In Jogjakarta, the incidence of colorectal cancer was higher than colon cancer, which is consistent with these previous report.Therefore, it was suggested that mass screening and following up with colonoscopy periodically might be cost-effective .

The causes of colorectal cancer are generally regarded as two aspects : hereditary and environment. The former includes family history of cancer, intestinal polyp history and so on. The later includes particularly dietary habit and physical activity (Chen et al., 2003;Chen et al., 2003). In international studies, risk is associated with an increased of dietary fat and a decreased intake of cereal grains and dietary fiber. In addition, risk is associated with a deficiency of vegetables and fruits and a sedentary lifestyle and perhaps less consistently, with increased dietary energy, meat, cooked meat, sugar and obesity (Howe et al., 1992; Howe et al., 1997).

Carcinoma of the bowel develops through a series known as the adenoma-carcinoma sequence. The mucosal changes are the result of progressive genetic alteration which occur at specific time points during carcinogenesis (Muto et al., 1975; Vogelstein et al., 1988; Fearon and Vogelstein, 1990) (see figure 11) by activation of proto oncogen, activaton of suppressor gene, and mismatch repair. The ras genes (12p) (K-ras, H-ras, N-ras) encode GTP-binding protein. A point of mutation at an appropriate site will create a Ras protein which fails to hydrolyse GTP-binding protein, resulting in a growth advantage during tumour genesis.

The p53 (17p) is a tumor suppressor gene. The wild type of p53 gene production has function as a transcription factor causing arrest of progression through cell cycle in G, and M, and repair of genotoxic damage or pushing the cell into apoptosis. About 75 % of colorectal carcinoma and 30 % of late adenoma loss of 17p.

Smad 2 and Smad 4 is suppressor genes on chromosome 18q. Inactivating mutations in the Smad genes are postulated to disrupt the growth inhibitory signal transduction pathway of the TGF_-2 receptors. Loss of 18q occurs in late adenoma (47 %), colorectal carcinoma (73%). TGF_-2 receptors is an important target gene of inactivation in mismatch repair deficient tumors. The errors are repaired by mismatch-repair genes.

The adenomatous polyposis coli (APC) tumor suppressor gene on chromosome 5q is the part of Wnt-pathway. Mutation APC and ß catenin seem to be the precondition for transformation of colon mucosa epithelium. ß catenin will bind transcription factor TCF-4, give result of ß catenin/TCF complex which will enter the nucleus and regulate the cells proliferation. Due to mutations of APC or ß catenin, the complex of APC/ß catenin is not formed and large amounts of the free ß catenin will bind TCF-4 and the ß catenin/TCF-4 complex will enter nucleus, giving result

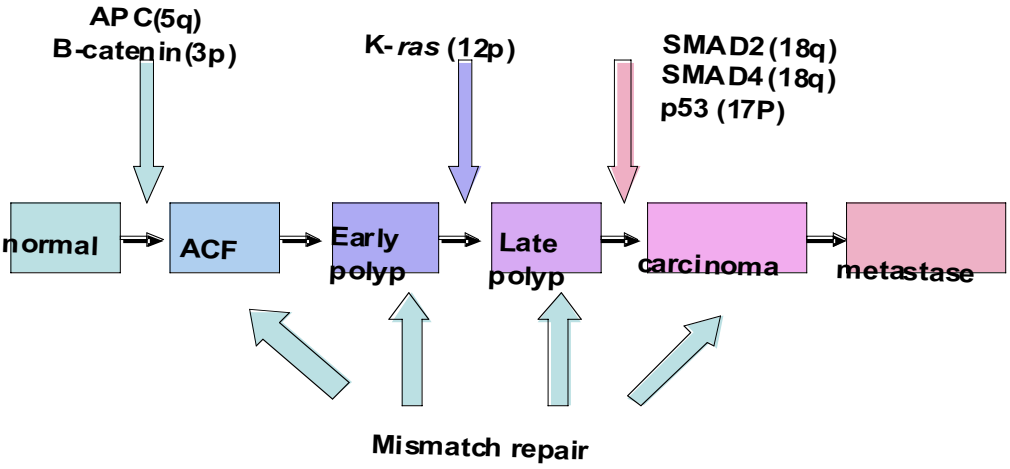

Figure 11. The Adenoma - Carcinoma Sequence (Muto et al, 1975; Volestein et al, 1988; Fearon et al, 1990)

in uncontrolled tranciption of TCF-4 target genes (Molenaar et al., 1996; Korinek et al., 1997). Transfection of mutated APC was shown to inhibit apoptosis of the transfected target cells and identified c-myc and CD44 as potential target genes (Wielenga et al.,1993; Mulder et al., 1995). Recently, CD44 variant can be used as a marker for the progression of colorectal tumor and as a prognostic marker of colorectal carcinoma (Wielenga et al.,1993; Mulder et al., 1995; Wielenga et al., 1998).

Because of genetic alterations, the epithelium of colorectal growth into a series of morphologically well described neoplastic abnormality. The early detected abnormality is dysplastic aberrant crypt focus (ACF) (Nucci et al., 1997). Failed maturation of dysplastic crypt epithelium giving result into a disturbed architecture with atypical cells throughout the crypt and up to the mucosal surface. When many crypts involved in this process, the mucosal surface will develop into early polyp followed by adenomatous polyp. If the tumor cells infiltrate the basement membrane, a carcinoma has developed. The infiltration growth continously resulting the extension of tumor spreading. In regard of the explanation mentioned and in an attemp of accurate treatment, Dukes divided the extension of colorectal cancer into four stages. Stage Dukes A if tumor confined to the bowel wall, when the carcinoma infiltrate the muscle it will be stage Dukes B, and if carcinoma metastatic in the regional lymphonode called stage Dukes C, and finally if carcinoma spread into distand organ it is called stage Dukes D.

Diet, especially fat intake, has long been regarded as the most important nutritional influence on colon cancer development. Dietary fat influences the composition of the gut microflora, which is likely to be involved in the pathogenesis of colon cancer (Reddy, 2000). Laboratory animal model assays have provided unequivocal evidence that intake of high amounts of saturated fats, such as lard, beef tallow, and polyunsaturated fats such as corn oil and safflower oil, increased the risk of chemically induced colon carcinogenesis. The varied effects of different types of fat on colon carcinogenesis suggests that fatty acid composition is one of the determining factor in colon tumor promotion. In this regard, it is noteworthy that diets high in beef tallow, lard or corn oil increase the concentration of colonic luminal (fecal) secondary bile acids, i.e., deoxycholic acid and lithocholic acid. Model assay in laboratory animals have demonstrated that these secondary bile acids induce cell proliferation and act as promoters in colon carcinogenesis (Reddy, 2000; Reddy, 1981). However, several experimental studies have failed to show that dietary saturated fat enhances faecal bile acid secretion. Moreover, in a review of several large prospective cohort studies, colon cancer risk was associated with red meat consumption and risk-increasing effect of red meat could be due to its iron or its fat content. The previous studies also indicated that dietary haem increased colonic epithelial proliferation at all fat levels (Sesink et al., 2000; Sesink et al., 1999).

In accordance with dietary fiber as the other important factor in colon carcinogenesis, several previous studies reported that a high intake of dietary fiber could reduce the risk of colorectal cancer and adenoma (Giovannucci and Willett, 1994). Dietary fiber has been postulated to prevent colorectal cancer by diluting or adsorbing fecal carcinogens, reducing colonic transit time, altering bile acid metabolism, reducing colonic pH, or increasing the production of short-chain fatty acids (Fuchs et al., 1999). However, epidemiologic studies of a possible link between dietary fiber and colorectal cancer have been inconclusive (Schatzkin et al., 2000). The limited data on other dietary factors included in most studies did not permit a clear distinction to be made between the effects of fiber and those of other constituents of plant foods. Moreover, the retrospective design of these studies may have introduced recall and selection biases (Michels et al., 2000; Goodlad, 2001; Terry et al., 2001).

Recently, there have been two other hypotheses for possible mechanisms relating diet and colon cancer risk. The first theory is the accumulating epidemiological evidence for an association between insulin resistance and colonic adenomas and cancers (Schoen et al., 1999). This evidence suggests the following mechanism: the consumption of excess dietary energy results in the development of insulin resistance with increased circulating levels of insulin, triglycerides, and non-esterified fatty acids. These circulating factors subject colonic epithelial cells to a proliferative stimulus and also expose them to reactive oxygen intermediates. These long-term exposures result in the promotion of colon cancer (Bruce et al., 2000). The second hypotheses is the continuing identification of agents that significantly inhibit experimental colon carcinogenesis. These observations suggest the following mechanism: focal loss of epithelial barrier function resulting from a failure of terminal differentiation results in the "leak" of a presently undefined toxin and a focal inflammatory response characterized by evidence of the activation of the COX-2 enzyme and an oxidative stress with the release of reactive oxygen intermediates. The resulting focal proliferation and mutagenesis give rise to aberrant crypt foci and adenomas (Corpet and Parnaud, 1999). The process is inhibited by: (a) demulcents confined to the colonic lumen that "repair" the surface; (b) anti-inflammatory agents; or (c) anti-oxidants. The two mechanisms, i.e., insulin resistance acting throughout the body and focal epithelial barrier failure acting locally, can describe most of the known relationships between diet and colon cancer risk (Bruce et al., 2000; Ritland and Gendler, 1999; Togo et al., 1999; Greenberg et al., 1994).

It seem important to have collaborative study on colorectal cancer among places and countries with various incidence of colorectal cancer in the aim of prevention and treatment. The study will cover on :

1. Diet and life style.
2. Pathogenesis of colorectal cancer.
3. Biologic marker as prognostic factor of colorectal cancer
4. Intervention study for colorectal cancer prevention

Conclusion

The low incidence of gastric cancer in Indonesia in relation with H. Pylori and food consumption and the high ratio between rectal and colon cancer in correlation with the food consumption and it pathogenesis need further investigation.

Collaborative study of H pylori infection and stomach cancer and also colorectal cancer from the view point of prevention and treatment comphrehensively between places and / or countries is strongly suggested.

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