

Colorectal Cancer: Epidemiological Trends, Screening, and Inheritability

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ABSTRACT

Colorectal cancer is one of the most common cancer worldwide. The incidence and mortality trend in different areas of the world varies. Colorectal cancer incidence and mortality are increasing in some countries. There are also epidemiological shift towards younger age (below 40). Most common non-invasive screening tests are fecal immunochemistry test (FIT) and fecal occult blood test (FOBT). Both have good sensitivity. The best invasive method for colorectal screening is still colonoscopy. Hereditary colorectal cancer is an important factor in younger age colorectal cancer. Familial adenomatous polyposis and Lynch syndrome are most common hereditary CRC. In familial or hereditary CRC, the chance of developing the cancerous form of the disease is nearly inevitable. Genetic testing may benefit the patients and their future progenies.

Keywords: *colorectal cancer, hereditary colorectal cancer, lynch syndrome, familial adenomatous polyposis*

ABSTRAK

Kanker kolorektal adalah salah satu kanker yang paling banyak ditemukan. Tren insidens dan mortalitas berbeda-beda di berbagai negara. Pada beberapa negara didapatkan peningkatan insidens kanker kolorektal. Terdapat pergeseran insidens ke usia yang lebih muda. Pemeriksaan skrining yang paling umum adalah fecal immunochemistry test (FIT) dan fecal occult blood test (FOBT) dimana keduanya memiliki sensitifitas yang baik. Metode invasif yang paling baik saat ini masih kolonoskopi. Kanker kolorektal yang bersifat herediter merupakan salah satu faktor yang penting pada kanker di usia muda. Familial adenomatous polyposis (FAP) dan Lynch syndrome merupakan sindrom yang sering dikaitkan dengan kanker kolorektal yang herediter. Pada pasien-pasien dengan FAP dan Lynch syndrome risiko terjadinya kanker kolorektal tidak dapat dihindarkan.

Kata kunci: *kanker kolorektal, kanker kolorektal herediter, lynch syndrome, familial adenomatous polyposis*

INTRODUCTION

Colorectal cancer (CRC) or bowel cancer is a malignancy condition in the colon and/or rectum.¹ Its incidence and mortality are increasing progressively in general population. However, this trend is also followed

by incidence in younger age cohorts.^{2,3} Furthermore, there is a shift of CRC incidence proportion from Western part of the world to Asian countries.

This new changes are associated with adoption of Western lifestyles and diets.⁴ There are sporadic and

hereditary CRC, albeit hereditary CRC may occur sporadically as well in small numbers.

The risk for developing neoplasia is very high in patient with hereditary CRC. Although hereditary CRC clinically can be distinguished, genetic testing may benefit for the patient and their family. This review will discuss upon these changes and early detection of the disease in the population.

Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) is one of the most common cancer worldwide, infesting as much as 9.7% of all new cancer cases.^{1,5} It ranks third in men and second in female with worldwide incidence of 746,000 cases and 614,000 cases, respectively, and fourth in cancer deaths (8%).^{1,6} In 2016, data from the United States (US) showed that there were total incidences of 134,490 cases from 70,820 men and 63,670 women with total deaths due to CRC as many as 49,190 cases; 26,020 in men and 23,170 in women.⁶ In Asia, the highest incidence is found in the Eastern part of the continent with incidence of 421,250.⁴

The incidence and mortality trend in different areas of the world varies. In countries with medium to high human development index (HDI), such as East European countries, Asian countries, and countries in South America, the incidence and death rates of CRC have increased promptly.⁵ In the contrary, countries with very high HDI (US, Australia, New Zealand, and Western European Countries) have stable or even waning incidence and mortality cases due to early detection and management through polypectomy.⁵ Based on the 2012 GLOBOCAN data of CRC incidence and mortality trends, Arnold M et al.⁵ classify countries into three groups. The first group consists of countries with inclining or stable propensity in CRC incidence and mortality (Philippines, China, Russia, Spain, Brazil, Croatia) and the second group comprises of countries with increasing incidence but decreasing mortality trend (Singapore, Canada, Denmark, Swiss, Italy, Sweden). The countries that belong to the third group underwent declining rates of incidence and mortality for the past 10 years (US, Australia, New Zealand, France, Japan, Israel). Decreasing mortality trend in the latter two groups reflects an increment of survival rates of CRC patients and is suspected to have association with good management programs. On the other hand, Brazil, which is included in the first group, has experienced emerging deaths in men and women due to CRC for the last 30 years.

Recent Predilection of Colorectal Cancer in Younger Cohorts

Nowadays, there are shifting trends of CRC incidence. Colorectal cancer is a disease renowned in developed countries such as in the US and Western European countries, occupying around 60% of all CRC cases.² However, there has been a drop of incidences from 2002 to 2008 as much as 6% in these regions for the past decades, and instead is followed by two- to four- fold increase of new cases in Asian countries.⁷ In China, for instance, the incidence rates of colon cancer between 1972 and 2005 had increased nearly three folds, whilst the increment of rectal cancer incidences was not as high.

Another changing trend is the declining incidence of CRC in patients aged 50 years and older accompanied by increasing novel cases in younger patients in Western countries.^{3,8} Data from the US from the Surveillance, Epidemiology, and End Results (SEER) database revealed that the annual incidence rate for all three types of colorectal cancers; localized (to the colon and rectum), regional (spread to neighboring structure or organ) and distant (metastases to distal area) disease; steadily decreased over the past 35 years in patients older than 50 years with the population over 75 years having the steepest decline.^{3,8} In contrast, increment of CRC cases were observed in younger cohort aged 20-34 years.^{3,8} Rectal cancer incidence in western population patients below 40 years had increase four times for the past 30 years.³

In general, there are many hypotheses to explain these shifting trends; improvements of management programs in developed countries and screening programs in developing countries, behavioral changes due to constant economical changes in developing countries, including arising incidence of obesity, physical inactivity, along with adoption of Western diets (cholesterol-rich diets from red and processed meat consumption) and lifestyles (e.g. alcohol consumption and habitual smoking) were found to link with colorectal cancer.^{3,4,6} However, other regional etiologies may remain; carcinogenic chemicals contained inside the drinking water in China and Taiwan has been associated with the increment of rectal cancer incidence and mortality.³ Others also predicted the predilection of this disease towards vulnerable ethnicities.⁷

Screening Tests for Colorectal Cancer

Some countries such as the US, Israel, and Japan have managed to reduce CRC incidence and mortality.⁵

Those countries were known to apply national screening programs for CRC since 1990.⁹ Screening programs may initially contribute to the escalating number of incidence epidemiologically.⁵ However, the number will drop in the long run if prompt management is done after the early diagnosis.⁵ Some specific screening tests include fecal immunochemistry test (FIT), fecal occult blood test (FOBT), flexible sigmoidoscopy, computed tomography (CT) colonography, and colonoscopy. The first two methods are the commonest method to be used for screening programs worldwide and are not invasive, whilst the latter three are.⁹

One time FIT procedure has sensitivity of 60-85% and 20-50% to detect colorectal cancer and advanced adenoma, respectively.^{10,11} It also has a pooled specificity of 94% according to 19 qualified studies.¹² It detects the presence of hemoglobin in the feces without requiring any dietary restrictions beforehand. In addition, when being combined with DNA marker test (FIT-fecal DNA test), the sensitivity to detect CRC and adenomas with high-grade dysplasia rise to 92% and 69%.¹⁰ Yet, its specificity drops to 87-90%.¹² Another non-invasive test is FOBT, which is less expensive than FIT to date.¹² The test, traditionally called guaiac FOBT (gFOBT), detects peroxidase activity of heme element in the blood hence could detect very mild blood loss from the gastrointestinal (GI) tract.¹² The sensitivity of this test to detect CRC and advanced adenoma is 50-75% and 20-25%, respectively.¹⁰ Moreover, annual screening in US population using gFOBT had reduced mortality rate by 33%.¹³ However, the test is not specific for human blood and susceptible to reducing agent such as vitamin C.¹⁰

Flexible sigmoidoscopy has a sensitivity above 95% for detecting CRC in the distal colon and 70% for detecting advanced adenoma.¹⁰ Whilst the utilization of flexible sigmoidoscopy can reduce incidence and mortality by approximately 20-30%, albeit this number is not significant and the tool has lower rate in detecting proximal colon adenomas.^{10,11,13} Likewise, the absence of sedation during the procedure may lead to an unhappy experience for the patients.¹¹ The CT colonography has sensitivity higher than 90% for detecting CRC and advanced adenoma more than 1 cm in size.¹⁰ Yet, lesions below 10 mm and not using laxative would reduce its sensitivity, making it less than colonoscopy, hence lesions above 6 mm in size (sensitivity of 69% and specificity of 91%) should be further confirmed with colonoscopy.¹⁰ Colonoscopy has the highest sensitivity for the detection of cancer and precancerous lesions hence becomes the gold

standard for every screening program. It allows biopsy and removal of any adenoma. It is proven to be 53-72% and 31% effective on reducing CRC incidence and mortality, respectively.¹⁰⁻¹² However, this procedure is highly operator-dependent and requires substantial amount of preparation for bowel cleansing.

Screening Programs of Colorectal Cancer

Colorectal cancer has prominent features, which allow screening to be highly beneficial; frequent incidences, chronic preclinical phase, treatable precursor, association of mortality rate with disease stages and expensive cancer treatment.⁹ Two approaches to screening include programmatic/organized screening and opportunistic screening.^{9,11} Screening offers, improved quality monitoring, and systematic follow-ups are the prominent features of the programmatic screening.^{9,11}

The International Agency for Research on Cancer (IARC) has mentioned some important characteristics for an organized screening program in the 2010 European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis.⁹ The organized screening itself requires follow-up of the positively-screened patients and the target participants for the population should be minimum 65%.⁹ Some countries had conducted organized national screening programs before, including Ireland, Denmark, France, Italy, Netherlands, Norway, Poland, Spain, Sweden, and United Kingdom (UK) in the European region; Chile, Brazil and Argentina in the South America; Hongkong, Israel, Japan, South Korea, Thailand and Singapore in Asia.⁹

Contrastly, opportunistic screening have 3 different approaches; multiple options which allows the patient to choose 2 or more options after being informed of the benefit, risk and cost of each; sequential where the patients will only be given other options if they decline the American College of Gastroenterology- and American Society Gastrointestinal Endoscopy-preferred option (colonoscopy); and risk stratified which merely allows the high risk patients to undergo colonoscopy and and the low risk ones to undergo other tests.¹¹ Most American guidelines recommend screening annually using gFOBT and/or FIT and every 10 years using colonoscopy.¹¹

Epidemiology of Hereditary Colorectal Cancer

Colorectal cancer can occur due to many factors. Approximately 15-30% of CRCs has a familial

component and around 2-5% to 1/3 of all CRCs (depends on the population) are hereditary with a highly penetrant gene mutation.¹⁴ Recently, there is rising evidence of CRC occurrences in adolescence and young adults.² As aforementioned, according to the SEER database and the World Health Organization (WHO) database from the US and European Union (EU), respectively, CRC incidence from 1992 to 2005 in younger cohorts aged 20-29 years has increased in men and women.² Interestingly, the majority of the cases have predilection on the distal colon and the rectum and mostly are poorly differentiated or have mucinous type hence they are considered aggressive. However, the rate of 5-year prognosis is either similar or slightly higher than in older patients.² Approximately 1 in 180 early onset CRC patients is considered as hereditary colorectal cancer patient, albeit it is evident that many familial cases were not always reported.² As a result, studies concluded that the frequency of familial cases ranges from 3-20% of all CRC cases.²

Familial adenomatous polyposis, except for MAP, is an autosomal dominant disorder.^{14,15,16} The classic, profuse and attenuated types of FAP are caused by mutation in the adenomatous polyposis coli (APC) gene on chromosome 5, which is a tumor suppressor gene, whilst the other types such as MUTYH-associated polyposis (MAP), Juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), Cowden syndrome, and serrated polyposis syndrome are caused by mutation in other genes.^{14,15,16} Lynch syndrome is also inherited in an autosomal dominant manner and, as aforementioned, is mostly caused by disruption of the MMR system in the DNA (76.4%) due to mutations of MMR genes, such as MLH1, MSH2, MSH6, PMS2 and EPCAM.^{17,18,19}

As a result, there will be numerous inconsistent size of microsatellite nucleotide in the gene, termed microsatellite instability (MSI). Both FAP and LS have extra-colonic malignancy. Lynch syndrome patients may come to the hospital with cancers in the endometrial, ovaries, upper urinary tract, small intestine, stomach, biliary tract, larynx and even the brain.^{17,18,19} Likewise, FAP patients may present clinical conditions such as congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, dental abnormalities, desmoid tumors, adrenal masses, hepatoblastoma, pancreatic cancer, medulloblastoma and papillary thyroid carcinoma, albeit the latter is suggestively caused by hormonal or environmental factors.^{15,16}

Familial Adenomatous Polyposis

Familial adenomatous polyposis was said to affect 1 in approximately 7,000-29,000 people and accounts for less than 1% of all CRCs.¹⁶ Without any family history, spontaneous cases could occur in 10-30% of all FAP patients, albeit there are some reports claiming that de novo APC mutation rate is 25-30%.¹⁶ One example from a study by Mork et al showed that approximately 12 out of 39 patients (30.77%) below 35 years who are diagnosed with FAP, AFAP and LS have de novo mutations.²⁰ However, studies have found that 10-15% of de novo mutations may result from somatic mosaicism.¹⁵ All FAP patients will have CRC if not treated and 95% have progressed to malignant stage by the age of 50.¹⁵ Multiple adenomas (may reach more than 100) on the colon or rectum, as its first investment, are mostly found by the age of 35 years.^{14,15} Duodenal adenomas and adenocarcinomas may also arise in 50-90% and 1-10% FAP patients, respectively, mostly in patients aged around 75 years.¹⁵ The occurrences of extraintestinal manifestations of FAP including CHRPE, epidermoid cysts, osteomas, desmoid tumours, supernumerary teeth, adrenal adenoma are 70-90%, 50%, 50-90%, 10-30%, 70-80% and 7-13% of all FAP cases, respectively.¹⁵ Pancreatic, thyroid, liver and central nervous system (usually medulloblastoma) malignancy is approximately 2%, 1-2%, 1-2% (1 hepatoblastoma cases in 235 FAP patients) and < 1%, respectively.¹⁵

Lynch Syndrome

Lynch syndrome affects 1-4% of all newly diagnosed CRCs and 2% of all endometrial cancers.¹⁸ However, the prevalence rate in patients without any family history is around 3.5-6.4% of all LS.¹⁹ Manifestation of this disease in the colon is the commonest; 63%, followed by endometrium (9%) and urinary tract (5-6%).¹⁸ Approximately, 70-90% of this disease is shown with MSI. In general population, the carrier frequency of MMR genes mutations is predicted to be 0.051% for MLH1 mutations, 0.035% for MSH2 mutations, 0.132% for MSH6 mutations and 0.140% for PMS2 mutations, albeit the latter two were factually being uncommon.¹⁹ These predictions were made by a model constructed from 5744 patients with CRC and 37,634 first-degree relatives in US, Canada and Australia who are listed in Colon Cancer Family Registry (CCFR).¹⁹ The prevalence of the disease itself is different between populations.

Due to founder mutations effect, the mutated genes in most cases likewise vary between countries. The

frequency of mutations in MLH1 and MSH2 genes in Asian, American, and European populations is 15.44%, 20.43% and 15.43%, respectively.²¹ In Iceland, Lynch syndrome has affected 0.442% of its population with highest number of patients having MSH6 and PMS2 mutations, whilst founder mutations in MSH2 and MSH6 genes are regarded to be the most common in Ashkenazi Jewish ancestry.¹⁹

Risk of Developing Neoplasia in Hereditary Colorectal Cancer Patients

Independently, family history remains tremendously devastating as a risk factor for colorectal cancer. In people with familial or hereditary CRC, the chance of developing the cancerous form of the disease is nearly inevitable. The cumulative lifetime risk of Lynch syndrome (in MMR mutation carriers), FAP, AFAP, MAP, Juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, and serrated polyposis syndrome is 50-80%, 100%, 69%, 43-100%, 38-68%, 39%, 9-16%, and 50%, respectively, albeit the latter is rarely inherited. The lifetime risks of CRC in LS patients with confirmed mutation of MLH1/MSH2, MSH6, and PMS2 are 22-74%, 10-70%, and 15-20%, respectively.

Besides the existence of the mutating gene, hereditary CRC also tends to occur in earlier age. The average age of sporadic and hereditary CRC patients is 69 and 38-66 years. In the American Clinical Guideline (ACG), it is mentioned that information regarding family history of cancer or premalignant stage in the GI should be obtained.²² Any presence of polyps in first- (parents, children, sibling) or second-degree (grandparents, nieces/nephews, aunts/uncles, grandchildren, and half siblings) relatives should likewise be explored.^{14,22} Screening for population at risk and with confirmed LS carrier condition should be done every 2 years starting from the age of 20-25 years and annually, respectively, by using colonoscopy. (14) These patients are also recommended for endometrial or ovarian cancer and gastric or duodenal cancer starting the age of 30-35 years by endometrial biopsy or transvaginal ultrasound (TVUS) and esophageal duodenoscopy (EGD) and gastric biopsy, respectively.¹⁴ In patients diagnosed or having family history of FAP/MAP/AFAP, annual colonoscopy or flexible sigmoidoscopy should be performed since puberty.¹⁴

Risk of Developing Neoplasia in First-degree Relatives

There is no current guideline to determine the amount of information needed from history taking to diagnose a hereditary colorectal cancer case. Still, focusing the data on CRC cases in first-, second-, and third- degree relatives and the age of the relatives when being first diagnosed to have CRC could be a good start. Separately collecting data from maternal and paternal lineage can be done as a next step. Self-reporting cancer cases in first-degree relatives (FDRs) and more distant relatives has the accuracy of >75% and 50-80%, respectively.¹⁴

A 6 years cross sectional study by Quintero et al in Spain showed that out of 8,500 people, patients with 2 FDRs have a significantly higher risk for developing advanced adenoma, multiple non-advanced adenomas and advanced neoplasia in comparison to the average-risk individuals who in the study are patients between the age of 50 and 69 years with no family history of CRCs.²³ Albeit patients with 1 FDR do not have any significant difference in risk of developing CRC regarding of any age when firstly diagnosed. Another study by Chau et al.²⁴ calculated the epidemiological risk of familial CRCs by using complicated calculation that inputs factors associated with closer genetic relationship such as first-, second-, and third- degree kinships into a formula termed familial aggregation index. The data was acquired from 10,066 families using the Colon Cancer Family Registry in the US, Australia, and Canada for 10 years. It suggests that a group of families with the highest familial aggregation index also have higher risk for developing CRCs (standardized index ratio of 7.11, 95% CI). Although familial aggregation index is seemed to be associated with standardized index ratio, the study did not provide any data regarding their correlation.

Genetic Testing in Hereditary Colorectal Cancer

In the clinical setting, CRC in the family from history taking and unusual appearance of the polyp may indicate hereditary CRC. However, confirmation from genetic testing may benefit the patients and their future progenies. In the clinical setting, suspicion of patients with LS should be confirmed using Amsterdam criteria, Revised Bethesda guidelines, and colorectal cancer risk assessment tool.^{22,25} These patients should be tested genetically. As aforementioned, MSI is detected in LS cases due to defective genes associated with DNA mismatch repair, such as MLH1, MSH2, MSH6, PMS2 and EPCAM genes. Mutation of

these genes is detectable through MSI testing and immunohistochemical (IHC) analysis, the latter detects the protein products of the genes.^{19,25} Both tests are cost-effective and their results are correlated one another.^{19,22,25} The sensitivity of MSI testing for MLH1 and MSH2 along with MSH6 and PMS2 mutations are 80-91% and 55-77%, respectively, and the specificity of this test is 90%.

The sensitivity and specificity of IHC testing is 83% and 89%, respectively.²² Patients with loss of expression in MLH1 should be further assessed for BRAF V600E mutation or analysed for methylation in the MLH1 promoter to rule out sporadic cases.^{22,25} Suspicion towards FAP rises from specific clinical findings such as >10 colorectal adenomas, family history, and extra colonic manifestations. Syngal et al recommend doing genetic sequencing for APC and MUTYH gene mutations in patients suspected adenomatous polyposis syndromes.²² It predicts the patient's phenotype but may miss large insertion or deletion.¹⁵ Other methods include protein truncation testing (PTT), which detects abnormal shortened APC proteins, and multiplex ligation probe amplification that can detect large deletions and insertions. Mutations are detectable in nearly 85% of FAP patients, but only 20-30% in AFAP patients.¹⁵

There is a slight dilemma, however, to do genetic testing by some of hereditary CRC relatives. Psychological studies have found that even though genetic counseling enhance the accuracy of risk perception in hereditary cancer patients and their relatives, findings also suggest that genetic testing may cause little psychological distress.²⁶ A study by Keogh et al towards 33 relatives of confirmed LS patients who declined offers of genetic testing showed that many patients believed that the test would not change their habits, including their regular checkups and their lifestyles.²⁶ Others are not comfortable knowing the truth would impede them from getting health insurance policy.

CONCLUSION

As the incidence of the sporadic and hereditary colorectal cancer rises along with its mortality rate, people should be more aware on reducing their risk of having the disease by improving their way of life. Countries worldwide should support national screening programs for colorectal cancers, as well as genetic testing for possible carriers. Essentially, a challenging task for clinician is to educate hereditary CRC patients and their relatives to do early detection and prompt

treatment of the cancer as patients with lynch syndrome and familial adenomatous Polyposis are susceptible not only to CRC but also cancer in other organs as well and screening tools have been proven to reduce mortality rate of CRC patients. Still, genetic counseling and psychological support from medical personnel are likewise much needed as a way to help improving their quality of life.

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