Review Article

Screening Colonoscopy: Focusing on Age and Gender

Rerknimitr R, M.D.

INTRODUCTION

In Asian Pacific countries including Thailand, colorectal cancer (CRC) screening has become a target for health care improvement. Colonoscopy is one of the most effective tools to achieve early cancer detection and clearance. However, there are a lot of limitations to adopt this technique as a standard tool for average risk persons. Many factors are to be considered; cost effectiveness, manpower, and different subgroup individual risks. Many reports confirmed that age and gender have major impact on the development of CRC[1,2]. Therefore, stratify patient according to these factors may help us utilizing and prioritizing patients for colonoscopy. This review will highlight the important of age and gender for CRC risk and also will provide concept regarding when to start and stop CRC screening with colonoscopy when the resources are limited.

Why women are at lower risk for CRC?

Many reports have shown a lower risk of CRC development in female than male[1,2]. A multivariate analysis reported by Imperiale TF, et al. shows that male sex, adjusted for age and distal findings, increased the risk of advanced proximal neoplasia by 3.3 (95% confidence interval, 1.5 to 7.1). Gender-related biologic differences may result in different risks for CRC presentations in female. For instances, female progestin has been well known for decreasing in bile acid production, this in turn can lead to less colonic epithelial irritation and hence may decrease the risk of colonic epithelial dysplasia development[3,4]. In addition, immunological influences of ABO-incompatible fetal antigens may play and important role in degradation of cancerous colonic tissues[5]. Tamakoshi, *et al*. did a prospective analysis in Japanese women and indicated that colon cancer risk was likely to be lower in parous than nulliparous women[6]. In addition, they also observed that the RR of colon cancer among postmenopausal women significantly decreased with increasing age at menarche (trend P = 0.01). Many inflammatory cytokines including tumor necrosis factor and IL-6[7], and inflammatory cells including macrophages[8], take significant roles in the development and spread of some experimental tumors. In one experiment in mice, only male mice were found to contain IL-6[9]. In addition, male mice and men are three to five times as likely to develop liver cancer as females because estrogens are key inhibitors of IL-6 production[10].

Men and their risky behaviors

Comparing to women, men are at higher risk for CRC due to their sex related background and their behaviors. Smoking and alcohol consumption are predominant in men and have been demonstrated as major risks for many cancers including CRC[11-13]. A study from New York area showed that patients who smoked had a higher prevalence of villous adenoma when compared to non smokers[14]. In addition, years of smoking increased prevalence of multiple adenomatous polyps, whereas cigarettes/day and years of smoking were associated with a higher prevalence of large adenomas (≥1 cm) as compared with small lesions (≤0.5 cm). Moreover, longer than 35 years of smoking habit was significantly associated with an increased risk of adenoma recurrence.

The p53 tumor suppressor gene is one of commonly mutated genes in colorectal cancer. Terry MB, *et al*. collected cases of early CRC and they used a

Address for Correspondence: *Rungsun Rerknimitr, M.D., Division of Gastroenterology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

Division of Gastroenterology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

study from collecting paraffin-embedded tissue blocks to study for anti p53 monoclonal antibody[15]. From their intensive analysis of behavioral factors of subjects that specimens belonged to, they found that heavy beer consumption (>8 bottles per week) was associated with over-expression of p53 (OR = 4.0, 95% CI = 1.3-12.0)[11].

Implications of age and neoplasm location at screening in men and women

The standard guidelines recommend to start screening for CRC at age of 50 for both men and women[16-18]. However, applying this protocol for Asian countries may not be applicable for all due to financial constrain. Therefore, modification can be done for practical use especially in limited resources area. One technique is to delay the age to start screening and another is to use flexible sigmoidoscopy for individual with lower risk to develop proximal cancers. By using the data during years 2000-2003 from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Programme, Brenner, *et al*. discovered that men had cumulative incidence of CRC in the subsequent 10 years increased from 0.8% at age 50 to 1.2% at age 55 and 1.9% at age 60. Among women, the comparable levels of 10-year cumulative incidence were reached at ages 54, 60, and 66 only (Figure 1)[19].

In addition, the 10-year cumulative mortality from CRC from both sexes in the next 10 years also increased with age, and it was more at any age between 50 and 75 years among men than among women. Cumulative mortality within the next 10 years was 0.23, 0.39 and 0.63% at age 50, 55 and 60, respectively, among men. Of note, comparable levels were approached by women at age 54, 60, and 66 only, for example 4, 5, and 6 years later than men, respectively (Figure 2)[19].

These results can translate into the recommendation for CRC screening average risk women at 4-8 years later than men; perhaps screening at age 55 seems to be logical. Given the fact that life expectancy in women is generally longer than men[19], there are further reasons to define gender-specific age ranges for CRC screening. However, this protocol can make the CRC guideline becoming more complicated.

Can we use flexible sigmoidoscopy as a screening tool for CRC in Asia? To answer this question as çyesé, the incidence of proximal cancer in target population has to be low enough for the ignorance of full colonoscopy. Our recent publication in Thai patients with colorectal neoplasm who came for colonoscopy and surveillance found that left sided lesions were found commonly (60% VS 40%) regardless to patients' age (Table 1)[20]. Soon et al. reported a higher incidence of distal colon neoplasm in Taiwanese cohorts than

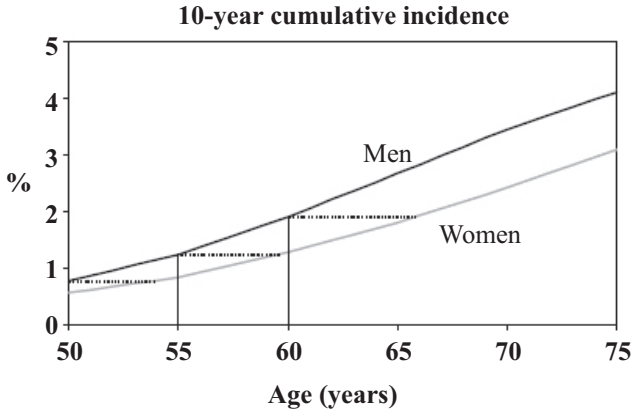

Figure 1 10-year cumulative incidence of colorectal cancer in subsequent 10 years among men and women at various ages. The dot lines indicate the age differences at comparable levels of cumulative incidence between women and men. (copied from Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007; 12: 96:828-31).

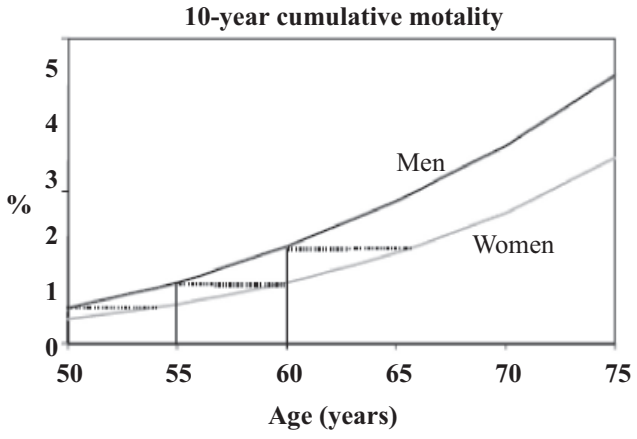

Figure 2 10 year cumulative mortality from CRC in subsequent 10 years among men and women at various ages. The dotted lines indicate the age differences at comparable levels of cumulative mortality between women and men. (copied from Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007; 12: 96:828-31).

Table 1 Colorectal neoplasm distritbution in Thai population Copied from Rerknimitr R, *et al*. Differences in characteristics of colorectal neoplasm between young and elderly Thais. World J Gastroenterol 2006; 21: 12:7684-9.

Cancer site	Younger age group (<60 yr) (%)	Older age group (≥60 yr) (%)	Total	
			n	%
Right-side	37.5	39.3	115	38.6
adenoma	20.3	29.1	75	24.7
cancer	17.2	10.2	40	13.7
Left-side	62.5	69.7	180	61.4
adeoma	38.7	37.1	110	37.9
cancer	23.8	22.9	70	23.5
Total (%)	100	100	-	100
N	120	175	295	-

Seattle cohorts in asymptomatic patients who presented for CRC screening (66.4% VS 52.6%; p = 0.0004)[21]. Roughly, we can state that CRC lesions in Asians are located predominantly within the reach of sigmoidoscope. Another important study from Indiana group[1] has shown that after adjustment for sex and distal findings, older patient was significantly associated with the risk of advanced proximal neoplasia, with a relative risk of 1.3. Similarly, being male increased the risk of advanced proximal neoplasia by 3.3 (95%CI 1.5 to 7.1). Given all these facts, flexible sigmoidoscopy may be applicable for CRC screening only in young Asian female who is at average risk. The risk of missing proximal lesion from flexible sigmoidoscopy may be too high to be accepted for CRC screening in male and elderly.

When to stop CRC screening?

The concept of cancer screening is to prevent the development of cancer that can drag the patients' life before they die from natural course. Life expectancy is the main determining factor before considering screening since shorter life expectancy will not get benefit from any screening. We have to expect the duration of the protective benefit for screening before applying the protocol in patients with short life expectancy. Many other factors are also needed to keep in mind including the result of past screening and patient' s preference. Generally, life expectancy is determined by age and co-morbid diseases of the patient. Five years lag is practically accepted as a standard for the protective duration of cancer screening. Kahi, *et al*. reported a study in >75 years cohorts who presented for colonoscopy screening[22]. They found that the median survival of patients aged 75-79 years was >5 years if the Charlson score (co-morbidity index) was ≤4. Among patients aged ≥80 years, the median survival was <5 years regardless of Charlson score (Figure 3). The translation from this study is "CRC screening in person who is older than 80 years or elderly with a lot of co-morbid illness may have very limited benefit".

Should we modify the CRC screening guideline?

Here is my modified guideline for screening CRC:

1) CRC screening in female can be delayed until the age of 55

2) Use flexible sigmoidoscope as a screening tool in young female patients

3) Use full colonoscope for male CRC screening regardless of the age

4) Stop screening at the age of 80 or 75, this is depended on co-morbid illness

The advantages of modifying the guideline are 1) Optimization of the appropriate test, 2) To safe the cost of screening and 3) It is practical application in limited resource country.

However, the cons site of customization of the protocol are 1) It is more complicated and difficult to remember protocol for health care practitioners, 2) There is not enough data to defy how long to delay the CRC screening in female, and 3) Universal protocol may not be applicable to every country since different Asian countries have their own risk that related to ethnicity.

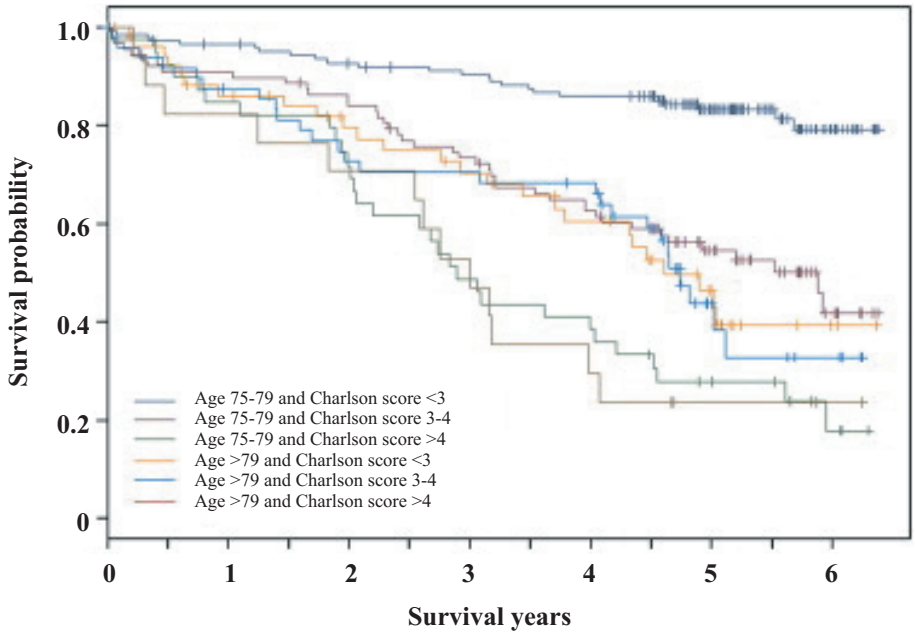

Figure 3 Survival probability in elderly patients who come for CRC screening (Copied from Kahi CJ, Azzouz F, Juliar BE, *et al*. Survival of elderly persons undergoing colonoscopy: implications for colorectal cancer screening and surveillance. Gastrointest Endosc 2007;66:544-50)

CONCLUSION

Age and gender are important issues before considering for CRC screening in average risk persons. Female seems to have significant protective components for CRC development. General guideline usually accepts the CRC screening to be started at age of 50. In country with very limited resource, the modified protocol can be used. The modifications are to delay screening in female and using flexible sigmoidoscope in young female. However, this proposal has not been used widely and the outcomes can be made only by assumption. Therefore, the future research needs to prospect and focus on the pros and cons of this modified protocol.

REFERENCES

1. Imperiale TF, Wagener DR, Lin CY, *et al*. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003; 139: 959-65.
2. Cancer facts & figures, 1996. Atlanta: American Cancer Society, Publication No. 5008-96.
3. van Berge Henegouwen GP, van der Werf SD. Serum bile acids and the bile acid tolerance test under oral contraception. Hepatogastroenterology 1992; 39: 177-80.
4. Flynn C, Montrose DC, Swank DL, *et al*. Deoxycholic acid promotes the growth of colonic aberrant crypt foci. Mol Carcinog 2007; 46: 60-70.
5. Yuan M, Itzkowitz SH, Palekar A, *et al*. Distribution of blood group antigens A, B, H, Lewis a, and Lewis b in human normal, fetal, and malignant colonic tissue. Cancer Res 1985; 45: 4499-511.
6. Tamakoshi K, Wakai K, Kojima M, *et al*. A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study. Cancer Sci 2004; 95: 602-7.
7. Moore RJ, Owens DM, Stamp G, *et al*. Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. Nat Med 1999; 5: 828-31.
8. Lin EY, Nguyen AV, Russell RG, *et al*. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. J Exp Med 2001; 19; 193: 727-40.
9. Naugler WE, Sakurai T, Kim S, *et al*. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. Science 2007: 6; 317: 121-4.
10. Giovannucci E, Rimm EB, Stampfer MJ, *et al*. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 1994: 2; 86: 183-91.
11. Lee WC, Neugut AI, Garbowski GC, *et al*. Cigarettes, alcohol, coffee, and caffeine as risk factors for colorectal adenomatous polyps. Ann Epidemiol 1993; 3: 239-44.
12. Erhardt JG, Kreichgauer HP, Meisner C, *et al*. Alcohol, cigarette smoking, dietary factors and the risk of colorectal adenomas and hyperplastic polyps-a case control study. Eur J Nutr 2002; 41: 35-43.

13. Reid ME, Marshall JR, Roe D, *et al*. Smoking exposure as a risk factor for prevalent and recurrent colorectal adenomas. Cancer Epidemiol Biomarkers Prev 2003; 12: 1006-11.
14. Terry MB, Neugut AI, Mansukhani M, et al. Tobacco, alcohol, and p53 over expression in early colorectal neoplasia. BMC Cancer 2003: 6; 3: 29.
15. Leddin D, Hunt R, Champion M, *et al*. Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening. Can J Gastroenterol 2004; 18: 93-9.
16. Winawer SJ, Fletcher RH, Miller L, *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594-642.
17. Winawer S, Fletcher R, Rex D, *et al*. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003; 124: 544-60.
18. Brenner H, Hoffmeister M, Arndt V, *et al*. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007; 12; 96: 828-31.
19. United Nations. Department of International Economic and Social Affairs. Population Division Sex differentials in life expectancy and mortality in developed countries: an analysis by age groups and causes of death from recent and historical data. Popul Bull UN 1988; 25: 65-107.
20. Rerknimitr R, Ratanapanich W, Kongkam P, *et al*. Differences in characteristics of colorectal neoplasm between young and elderly Thais. World J Gastroenterol 2006: 21; 12: 7684-9.
21. Soon MS, Kozarek RA, Ayub K, *et al*. Screening colonoscopy in Chinese and Western patients: a comparative study. Am J Gastroenterol 2005; 100: 2749-55.
22. Kahi CJ, Azzouz F, Juliar BE, *et al*. Survival of elderly persons undergoing colonoscopy: implications for colorectal cancer screening and surveillance. Gastrointest Endosc 2007; 66: 544-50.