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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review of the Recent Literature

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Colorectal cancer (CRC) remains a major clinical and public health challenge, with 148,810 new cases and 49,960 deaths expected in the United States in 2008.[1] The field of CRC research is dynamic and expanding in several directions, encompassing areas of clinical and outcomes research, epidemiology, public health, and molecular sciences. In this review, we summarize important developments in CRC screening and surveillance over the past several years and discuss the present state of the art of this field.

Risk Factors for Colorectal Neoplasia

Metabolic Syndrome

According to the National Cholesterol Education Program's Adult Treatment panel III, metabolic syndrome is the presence of 3 or more of the following factors: hypertension (blood pressure of 130/85 mm Hg or greater), central adiposity (waist circumference greater than 102 cm in men or greater than 88 cm in women or a body mass index [BMI] greater than 27 [kg/m^2]), low high-density lipoprotein (HDL) cholesterol (HDL <40 mg/dL in men or <50 mg/dL in women), hypertriglyceridemia (150 mg/dL or greater), and impaired glucose tolerance (fasting serum glucose of 110 mg/dL or greater).[2] Colorectal neoplasia has been associated with markers of glucose and insulin control; insulin resistance, which is the cornerstone of the metabolic syndrome, may be the mechanism by which several risk factors (obesity, diabetes mellitus, [lack of] fitness) affect colorectal carcinogenesis.[3,4]

Four of the most recent studies of metabolic syndrome and CRC are summarized in Table 1.[5–8] These studies comprise different study populations and different study designs but use the same or comparable definitions of metabolic syndrome, similar methods of analysis, and either adenoma or cancer as outcomes. The study findings are quite consistent: either the metabolic syndrome or its components increase the risk for colorectal neoplasia pears to be greater in men than in women. The relationship between metabolic syndrome and large bowel location of neoplasia reported by Chiu et al[6] is interesting and requires validation in analyses of other populations.

Cigarette Smoking

The epidemiologic evidence that cigarette smoking increases the risk of CRC was elegantly reviewed by Giovannucci in 2001.[9] An association between colorectal neoplasia and cigarette smoking is supported by several studies, with the association more consistently established for smoking and adenomas, including large adenomas, than for cancer.[9–24] Recently, the bulk of the evidence supports an association with CRC as well. With men having begun smoking several decades earlier than women, the temporal pattern of the studies supports an induction period of 3–4 decades between exposure and the diagnosis of CRC.[9] Despite the volume of studies, several questions remain unanswered: What is the relationship between dose and duration and risk of neoplasia? Which persons are most susceptible to the effects of cigarette smoking? Is smoking associated to specific subgroups of cancer, perhaps having one or more prevalent mutations? By how much and how quickly does risk drop after quitting smoking?

Table 2 summarizes recent selected endoscopic and population-based studies on smoking and risk for colorectal neoplasia.[25–29] The 5 studies use different study designs: cohort, case-control, and cross-sectional, with sample sizes ranging from 1154 to 146,877 individuals. All 5 use multivariable analysis, which provides the inde-

Abbreviations used in this paper: CAD, coronary artery disease; CCSA, colon cancer-specific antigen; CTC, computed tomographic colonography; FDR, first-degree relative; gFOBT, guaiac-based fecal occult blood testing; HNPCC, hereditary nonpolyposis CRC; iFOBTs, immunochemical fecal occult blood tests; MMR, mismatch repair; MSI, microsatellite instability.

Table 1. Summary of Selected Studies on Metabolic Syndrome and Risk of Colorectal Neoplasia

First author, year (ref)	Study population	Study design	Criteria for metabolic syndrome	Outcomes	Type of risk model	Main findings
Ahmed, 2006 (5)	14,109 subjects from the Atherosclerosis Risk in Communities (ARIC) multicenter study)	Cohort	ATP III	Colorectal cancer	Multiple logistic model, adjusted for age, gender, family history of CRC, physical activity, NSAID use, aspirin use, smoking, alcohol use, hormone replacement use	MS associated with increased risk of CRC (age and gender adjusted RR, 1.49; 95% CI: 1.0–2.4), which attenuated after multivariate adjustment (RR, 1.39; 95% CI: 0.9–2.2). Adjusted risk was increased in men (RR, 1.78; 95% CI: 1.02–3.6) but not in women (RR, 1.16; 95% CI: 0.6–2.2)
Sturmer, 2006 (8)	22,071 healthy male physicians initially ages 40–84 years	Cohort	BMI of ≥27 kg/m², total cholesterol of ≥240 mg/dL or use of lipid-lowering drugs, blood pressure of ≥130/85 mm Hg or use of antihypertensives, and a diagnosis of diabetes mellitus	Colorectal cancer	Multiple logistic model, adjusted for age, smoking, exercise, alcohol use, multivitamin use, and consumption of fruits and vegetables	BMI >27 kg/m² (RR, 1.4; 95% CI: 1.1–1.7) and diabetes (RR, 1.5; 95% CI: 1.1–2.0) were associated with CRC; hypertension and hypercholesterolemia were not.
Kim, 2007 (7)	3584 consecutive subjects undergoing screening colonoscopy	Cross-sectional	Modified ATP III criteria	Colorectal adenoma	Multiple logistic model, adjusted for age, gender, smoking, alcohol use	17% of subjects with adenomas and 11% of those without adenomas had MS. MS associated with increased risk of adenoma: OR, 1.51; 95% CI: 1.19–1.93. Waist circumference was an independent risk factor for adenoma: OR, 1.39; 95% CI: 1.15–1.68
Chiu, 2007 (6)	4277 consecutive ethnic Chinese who had screening or surveillance colonoscopy as part of a medical health checkup	Cross-sectional	Modified ATP III criteria, modified Asian criteria (HDL cholesterol of <40 mg/dL, waist circumference ≥90 cm for men, ≥80 cm for women)	Colorectal neoplasia, anatomic location	Multiple logistic model, adjusted for age, gender, BMI, smoking, alcohol use, previous adenoma, family history of CRC	MS associated with increased risk of any neoplasia (OR, 1.35; 95% CI: 1.05–1.73), proximal neoplasia (OR, 1.62; 95% CI: 1.14–2.30), synchronous lesions (OR, 2.15; 95% CI: 1.40–3.31), and synchronous lesions both proximal and distal (OR, 2.30; 95% CI: 1.42–3.72).

MS, metabolic syndrome.

pendent effect of smoking after adjustment for covariates such as age, sex, BMI, and others.

The study by Lieberman et al, a colonoscopy-based study, examined the effect of several candidate risk factors on the risk of advanced neoplasia in a cohort of 3121 asymptomatic patients aged 50–75 years from 13 Veterans Affairs medical centers.[27] Using a multivariate model that included family history of CRC, BMI, physical activity, smoking, alcohol use, and several dietary components, the investigators found that the effect of smoking on advanced neoplasia (odds ration [OR], 1.85; 95% confidence interval [CI]: 1.33–2.58) was comparable with having a first-degree relative (FDR) with CRC (OR, 1.66; 95% CI: 1.16–2.35). In a retrospective, cross-sectional analysis of 1988 persons undergoing screening colonoscopy, Anderson et al found that cigarette smoking increased the risk for any colorectal neoplasia (OR, 1.89; 95% CI: 1.42–2.51) and for significant neoplasia (OR, 2.26; 95% CI: 1.56–3.27) that was predominantly left-sided.[26]

Results of recent population-based studies have shown somewhat inconsistent results. The findings of the case-control study by Verla-Tebit et al are consistent with those of several earlier epidemiologic studies that support that risk reduction requires at least 20 years and increases with increasing duration of smoking cessation. In addition to the findings described in Table 2, the study by Akhter et al, which studied only men, found that longer smoking duration, age of 18 or younger at onset of smoking, and consumption of 20 or more cigarettes per day significantly increased the risk of CRC, with risk ratios ranging from 1.46 to 1.86.[25]

In the study from the Women's Health Initiative,[28] which is a pooled analysis of participants in the observational study and 3 clinical trials, the risk of rectal cancer was increased with longer smoking duration and its confounder, older age at smoking cessation; however, the risk of colon cancer was not increased. This study has limitations, including self-reported smoking exposure that did not allow for changes in smoking behavior after initial reporting and a rate of cigarette smoking that was lower than US women of similar ages.

In summary, the majority of evidence indicates that CRC is a tobacco-associated malignancy. In the United States, it has been estimated that as many as 1 in 5 CRCs is attributable to cigarette smoking.[11,13,14,20] The magnitude of the increase in risk for CRC and large

Table 2. Summary of Selected Studies on Cigarette Smoking and Risk of Colorectal Neoplasia

First author, year (ref)	Study population	Study design	Outcomes	Type of risk model	Main findings
Lieberman, 2003 (27)	3121 asymptomatic patients aged 50-75 years from 13 Veterans Affairs medical centers	Cross-sectional	Advanced neoplasia (CRC or advanced polyps)	Multiple logistic regression that adjusted for age, family history, BMI, physical activity, alcohol use, NSAID use, certain dietary features	Current smoking was a risk factor for advanced neoplasia (OR, 1.85; 95% CI: 1.33-2.85) and was of comparable magnitude to having an FDR with CRC (OR, 1.66; 95% CI: 1.16–2.35).
Anderson, 2003 (26)	1988 persons aged 40 and older undergoing screening colonoscopy	Cross-sectional	Significant neoplasia (CRC, advanced polyps, or >2 adenomas of any size)	Multiple logistic regression that adjusted for age, alcohol consumption, exercise, BMI, ethnicity, education, and consumption of fruits and vegetables	Current smokers were more likely to have any neoplasia (OR, 1.89; 95% CI, 1.42–2.51) and significant neoplasia (OR, 2.26; 95% CI: 1.56–3.27). Risk of significant neoplasia was greater for smokers than for those with a family history of CRC.
Verla-Tebit, 2006 (29)	540 patients with incident CRC and 614 population-based, matched to cases by 5-year age group, sex, county of residence	Case-control	CRC	Multiple logistic model that adjusted for age, sex, history of CRC in first-degree relatives, BMI, alcohol use, physical activity, fruit and vegetable intake, red meat consumption, NSAID use, previous endoscopy of the large bowel, education level, and use of hormone replacement therapy	Compared with nonsmokers, smokers for ≥40 years had increased risk (OR, 1.92; 95% CI: 1.13–3.28). Among smokers ≥30 years, risk was greater among women (OR, 3.5; 95% CI: 1.29–9.52) than men (OR, 1.15; 95% CI: 0.69–1.91). Risk reduction observed after ≥20 years of quitting smoking and was significant for ≥40 years (OR, 0.46; 95% CI: 0.21–0.98).
Akhter, 2007 (25)	25,279 Japanese men recruited when aged 40-64 years	Cohort (7 years of follow-up)	CRC	Proportional hazards model that adjusted for age, family history of CRC, education, BMI, alcohol use, time spent walking per day, and consumption frequency of fruits, green-yellow vegetables, and red meat	Compared with never smokers, the risk of CRC was increased for past smokers (RR, 1.73; 95% CI: 1.04–2.87) and current smokers (RR, 1.47; 95% CI: 0.93–2.34). Among current smokers, a greater number of cigarettes smoked per day and an earlier age of smoking onset were associated with a significant linear increase in CRC risk.
Paskett, 2007 (28)	146,877 women's Health Initiative participants	Cohort (mean of 7.8 years of follow-up)	CRC	Proportional hazards model that adjusted for age, ethnicity, study type (observational or clinical trial) study arm, family history of CRC, total physical activity metabolic equivalents, alcohol use, NSAID use, hormone therapy use, colonoscopy, diabetes, waist circumference, certain dietary features	Current smokers had increased risk for rectal cancer (HR, 1.95; 95% CI: 1.10–3.47) but not colon cancer (HR, 1.03; 95% CI: 0.77–1.38).

the incremental effect of smoking on risk of advanced neoplasia that considers sex; age of smoking onset; degree and duration of cigarette consumption; and, for former smokers, time since smoking cessation. Greater consideration should be given to cigarette smoking when considering whether, when, and how best to screen patients.

Coronary Artery Disease

In a study from Hong Kong, Chan et al compared the prevalence of colorectal neoplasia in 206 subjects with angiographically proven coronary artery disease (CAD), 208 subjects whose angiogram did not show CAD, and an age- and sex-matched control group of 207 subjects who were asymptomatic (other than having functional dyspepsia with a normal upper endoscopy) but who did not have angiography.[30] Colonoscopy was scheduled within 8 weeks after eligibility was determined or after revascularization. Endoscopists were blinded to CAD status.

The prevalence of advanced neoplasia in the CAD-positive, CAD-negative, and control groups was 18.4%, = .02). After adjustment for age and sex, CAD remained associated with advanced neoplasia (OR, 2.51; 95% CI: 1.43–4.35). Of interest, both metabolic syndrome and cigarette smoking were strong independent predictive factors for the positive association between CAD and advanced neoplasia, meaning that persons who were smokers and/or had the metabolic syndrome were much more likely to develop both conditions.

Although it is not clear that the CAD-positive group was free of symptoms of signs of early CRC, this study links CAD with advanced neoplasia and is consistent with previously published studies.[31,32] It is unclear whether and to what extent the association would remain after further adjustment for other confounding factors. Nevertheless, most likely because of a common set of risk factors that includes cigarette smoking, waist circumference, diabetes, and others, CAD appears to be a marker for colorectal neoplasia. Although the prevalence of advanced neoplasia in persons with CAD suggests the need for earlier or more aggressive CRC screening, the extent to which CAD as a comorbid

Diabetes Mellitus

Previous studies have shown that the risk of CRC is higher among persons with diabetes, although this finding is not consistent among studies nor is the contribution of confounding factors to the increased risk well established. In a population-based cohort study, Limburg et al identified incident cases of CRC among 1975 type 2 diabetic individuals and compared them with what was expected from the general population.[33] Overall risk of CRC was increased among diabetic individuals (standardized incidence ratio= 1.39; 95% CI: 1.03–1.82). However, the increased risk was present among men only, both overall (SIR, 1.67; 95% CI: 1.16–2.33) and proximally (SIR, 1.96; 95% CI: 1.16–3.10). Furthermore, current and former cigarette smokers were at higher risk for CRC than diabetic individuals who never smoked.

In addition to increasing baseline risk for colorectal neoplasia, insulin resistance also increases the risk for recurrent neoplasia. In an analysis from the Polyp Prevention Trial, Flood et al compared fasting insulin and glucose levels in 375 subjects with and 375 subjects without recurrent adenoma.[34] After adjustment for age, sex, BMI, and intervention group, risk for recurrent adenoma was higher for subjects in the highest quartile compared with the lowest quartile: OR, 1.56; 95% CI: 1.00–2.43 for insulin; OR, 1.49; 95% CI: 0.95–2.31 for glucose. The highest quartile of glucose was associated with advanced adenoma as well: OR, 2.43; 95% CI: 1.23–4.79. The strength of the associations between high fasting glucose and risk of recurrent adenoma increased when the analysis was restricted to subjects with no family history of CRC.

These studies support other research in which diabetes has been associated with increased risk for CRC and are consistent with a larger body of literature that links insulin resistance, metabolic syndrome, and coronary artery disease with colorectal neoplasia. Understanding both the mechanisms leading to neoplasia and the independent contribution of each of these factors to advanced adenoma and CRC risks requires further study.

Although the literature is replete with data on risk factors for CRC and adenoma, most established risk factors are not incorporated into current screening guidelines. Current guidelines stratify risk with age and family history alone. Age is used only as a threshold factor, although CRC incidence increases with age in an approximately linear fashion. The risk of CRC in average-risk persons doubles by 10 years—approximately the same increase in risk as having an FDR with CRC.[35] We need a way to integrate all risk factors (age, sex, family history, cigarette smoking, metabolic syndrome, and others) quantitatively to estimate absolute risk for CRC and advanced adenoma. One study has integrated age, sex, sex, and most advanced distal finding to estimate the risk of advanced proximal neoplasia.[37] Both systems require validation and further development before they can be applied to clinical practice. Furthermore, the effect of more extensive risk stratification on screening remains to be determined. On the one hand, providing risk-specific information to patients and providers has the potential to improve screening rates and screening efficiency. On the other hand, if risk stratification is perceived as making CRC screening too complicated, there is the potential to adversely affect further uptake of screening. Whether incorporating several factors with modest relative risks would add significantly to using age, sex, and family history alone is also important to determine.

Screening Colonoscopy

Several recent studies have described the findings of screening colonoscopy in an asymptomatic average-risk population.[38–43] Table 3 summarizes the study characteristics of this body of literature. Although the study objectives, settings, and designs vary, the variation does not necessarily preclude comparing the findings.

Descriptively, the studies are from Japan, Poland, Israel, Korea, and the United States. The number of persons analyzed varies from 994 to 43,042. The mean age ranges from 48.2 years in a study in which 57% of subjects were younger than 50 years old, to 62.2 years. The proportion of men ranges from 0% in a screening study of military women to 72% in a Japanese study of asymptomatic adults who participated in a comprehensive health examination.

The endoscopic findings, expressed as the proportion of persons according to the most advanced histology, are shown in Table 4. Despite differences in the study populations, the fraction of persons with no colorectal neoplasia is consistent, ranging from 75% to 83%. Ranges of persons with nonadvanced adenoma, advanced adenoma, and cancer are 8.9%–16.5%, 3%–6.3%, and 0%–1.3%, respectively, with the variation largely because of age and sex.

The prevalence of findings in these recent studies is comparable with previously published screening studies,[26,37,44–47] with the possible exception of VA Cooperative Study No. 380, in which rates of neoplasia were numerically greater, reflecting the high-risk features of the study population, particularly the high predominance of men.[46]

These studies are a reminder that the majority of screening colonoscopies will show no adenomas. They highlight the need to identify a way to estimate absolute risk for individual persons so that screening colonoscopy may be more efficiently targeted to those with advanced neoplasia. Considering these more recent studies in the aggregate, the number of persons required to undergo

Table 3. Description of Screening Colonoscopy Studies

First author (ref)	Year	Study objective	Study population	Study design	Study setting	Recruitment period	Study findings
Schoenfeld (40)	2005	To determine prevalence and location of advanced neoplasia	Consecutive, average risk, asymptomatic women referred for screening[a]	Prospective, cross-sectional	4 Military medical centers	7/1999–12/2002	Advanced neoplasia was distal in 1.7% (n = 25) and proximal in 3.2% (n = 47). Sigmoidoscopy would have detected only 35.2% of advanced neoplasia.
Morikawa (43)	2005	To determine the test characteristics of an immunochemical FOBT	Asymptomatic adults who participated in a comprehensive health examination	Retrospective, cross-sectional	A general hospital and its affiliated clinic	4/1983–3/2002	Sensitivity and specificity of 1-time iFOBT were 65.8% and 94.6%, respectively, for cancer and 27.1% and 95.1%, respectively, for advanced neoplasia.
Lin (38)	2006	To compare estimated life-years saved with screening colonoscopy in very elderly vs younger persons	Consecutive asymptomatic adults undergoing screening colonoscopy in age categories 50–54 years (n = 1034), 75–79 years (n = 147), and >80 years (n = 63)	Prospective, cross-sectional	Tertiary referral single medical center	1/2002–1/2005	Despite higher prevalence of neoplasia in elderly patients, mean extension in life expectancy was much lower in persons aged 80 years or older than in the 50–54-year-old groups (0.13 vs 0.85 years, respectively).
Regula (39)	2006	To derive and validate a model for detection of advanced neoplasia. To quantify the number of persons needed to screen to detect 1 advanced neoplasm	Consecutive, asymptomatic adults age 50-66 years in good general health; and those age 40-49 years with a family history of cancer of any type	Retrospective, cross-sectional	Database from a national colonoscopy-based screening program	10/2000–2004	Advanced neoplasia and to quantify was more prevalent in men in all age groups, with lower numbers needed to screen in men (range, 10–23) than in women (range, 18–36).
Strul (41)	2006	To evaluate the prevalence and anatomic location of adenoma and carcinoma	Consecutive average risk adults who were asymptomatic regarding cancer-related symptoms or alarm signs	Retrospective, cross-sectional	Databases of procedures from 1 of 6 outpatient gastroenterology clinics of a health maintenance organization in Tel-Aviv, Israel	1/1996–2/2001	Prevalence of neoplasia increased with older age. Among persons with neoplasia, 21%–43% had isolated proximal neoplasia (beyond the sigmoidoscope).
Kim (42)	2007	To evaluate the usefulness of colonoscopy to detect polyps	Consecutive adults who voluntarily underwent colonoscopy as part of a health examination program	Retrospective, cross-sectional	Database of a company-based screening colonoscopy program	1/2003–9/2005	Adenomatous polyps were present in 17.9%, advanced adenomas in 3.4%. Adenomas were more prevalent in men (23.6%) than in women (11.5%) and increased with age in both groups.

[a]Includes only persons aged 50 years and older.

23 to detect an advanced adenoma, 20 for advanced neoplasia, and 143 for cancer. One goal of outcomes research in this area should be to identify a cluster of factors that define a subgroup at such low risk for advanced neoplasia that screening may be either deferred or performed confidently with noninvasive testing. Another goal is to identify a high-risk subgroup among "average-risk" persons for which colonoscopy is preferred over other screening tests.

Emerging Screening Modalities

Fecal DNA

The rationale for detecting mutated genes in feces of patients with CRC arose from studies published during the 1990s that established the following: continuously, and (3) polymerase chain reaction technology could identify altered DNA in feces. Between 2000 and 2004, several teams of investigators examined a variety of fecal-based genetic markers for colorectal neoplasia.[48–52] Most of these studies were case-control studies that involved an advanced spectrum of CRC. A subgroup of these studies used a 21-component DNA panel where sensitivity for cancer ranged from 62% to 91% and from 27% to 82% for adenomas with a specificity ranging from 93% to 96%.[48,53–55] These studies begged the question of how this panel would perform in the screening setting.

A multicenter study published in 2004 compared the 21-component DNA panel with Hemoccult II among 4404 asymptomatic average-risk subjects.[44] A subgroup

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