Chapter 2
Risk Factors and Screening for Colorectal Cancer

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Keywords Risk factors • Tobacco use • Body mass index

Screening for colorectal cancer (CRC) involves consideration of only a patient's age and their family history of CRC [1, 2], but there are other risk factors which can potentially affect screening. This section will examine known risk factors and how some of these can affect one's risk and subsequent screening for CRC. Other factors such as personal and family history of colorectal neoplasia as well as aspirin and other chemo-preventative agents will be discussed elsewhere. This section will serve as an overview of the various factors and the respective studies that examine their association with CRC as well as advanced adenomas. Age has been shown to be one of the strongest predictors of CRC [3] and will not be discussed as there is little debate as to the importance of this factor. In addition, this chapter will examine the modifiable risk factors since this is where clinicians can help patients to reduce their risk of CRC. A study by Platz et al. demonstrated that over two thirds of CRC may be preventable in men [4].

Prospective Studies

We will also review the four large prospective studies that examined risk factors and CRC. Table 2.1 shows the salient results of these large trials, and the details will be discussed in the subsequent sections. These include the Cancer Prevention Study II (CPS-II), which is a prospective cohort study funded and conducted by the American Cancer Society (ACS). The goal of the study is to examine the impact of environmental and lifestyle factors on cancer etiology in a large group of American men and

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Table 2.1 Results of selected prospective longitudinal studies

	Smoking	Red meat	Alcohol	Obesity	Physical activity	Fiber	Diabetes mellitus
Cancer prevention Study II	↑ CRC mortality	↑ Distal cancer	–	↑ Risk for ↑ WHR and ↑ BMI	↓ Colon but not rectal cancer	↑ CRC Intake fruit/veg ↑ CRC	↑ Men and ↔ women
Nurse's Health Study	↑ CRC after 35 years	↑ Colon but ↔ rectal cancer	↑ Colon but not rectal	↑ CRC 1.5 X women w/ BMI<21	↓ >21 MET's/week	↔	↑ But ↔ for HbA1c
HPFS	↑ CRC after 35 years	↑ For 5 servings/ week	↑ CRC > 15g/day	↑ BMI> 22.5, 29.5% of CRC attributed to this increase	↓ > 27 METS/week	↔	–
EPIC	↑ In proximal CRC in ever smokers	↑ Red meat but ↓ fish	↑ Highest risk in rectum	↑ With ↑ WHR	↓ for right sided cancer	↓ Especially distal CRC	↑ Risk for ↑ HbA1c

↑ Arrows refer to risk for CRC except where indicated

women [5]. Study participants (known as the CPS-II Baseline Cohort) completed an initial study questionnaire in 1982 that obtained information on a range of lifestyle factors such as diet, use of alcohol and tobacco, occupation, medical history, and family cancer history. Cause of death has been documented for 99% of all deaths that have occurred. The CPS-II Nutrition Cohort is a subgroup of 184,194 men and women who were mailed additional questionnaires in 1997, 1999, 2001, 2003, 2005, and 2007, to update exposure information and to obtain self-reported cancer diagnoses. The European Prospective Investigation into Cancer (EPIC) was set up to examine the association between diet, nutritional status, lifestyle and environmental factors, and the incidence of cancer. EPIC has recruited over half a million people in ten European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom [6]. The Health Professionals Follow-Up Study (HPFS) was started in 1986 by Walter Willett and Meir Stampfer [7] and has enrolled 51,529 men. The HPFS is sponsored by the Harvard School of Public Health and is funded by the National Heart, Lung, and Blood Institute and National Cancer Institute. The Nurses' Health Study (NHS) is designed to complement the HPFS and consists of a similar number of women [8].

Risk Factors

Red Meat

Red meat, in the form of beef or lamb, has been examined as a risk factor in many case control and longitudinal population studies. In most of these studies, consumption of red meat is associated with an increased risk for CRC. A recent longitudinal study from Europe, the EPIC, demonstrated an increased risk for people who consumed more than 160 g of red or processed meat per day [9]. In another prospective study from the United States, the HPFS, there was an increased risk of approximately threefold for those who consumed more than five servings per week of red meat. The comparison group ate less than one serving per month. In a study that combined the NHS and the HPFS, red meat was a risk for colon but not rectal cancer [3]. In the CPS II Nutrition Cohort, Chao et al. observed an increased risk of red meat for distal and rectal CRC [10].

There are many hypotheses regarding the increased risk from red meat, which include an increased fat consumption, increased heme absorption, and stimulation of insulin secretion. Furthermore, there are data to indicate that increased cooking time may be associated with an increased risk [11, 12] due to the increased production of heterocyclic amines [13]. In addition, how these meats are processed in the patients may also be important. A recent study NHS demonstrated that those women with a faster acetylation of the carcinogens from red meat had an increased risk of CRC [14]. With regard to the risk from fat in red meat, many studies have disputed this risk [15–17]. Regardless of the mechanism, it appears that regular consumption of meat, especially if it is cooked well, increases the risk for CRC.

Fiber Intake

Fiber, especially in the form of fruits and vegetables, has been considered beneficial in helping to lower one's risk for CRC [18–20]. Proposed mechanisms regarding the benefit from fiber include increased folic acid consumption, increased binding of carcinogens, lower colonic pH, decreased colonic transit time, an increased production of short chain fatty acids as well as micronutrients found in vegetables including anti-oxidants [21, 22]. However, results of randomized controlled studies using fiber in the form of fruits and vegetables [23] or cereal did not lower the risk of colorectal adenomas [24]. These studies contradict previous data demonstrating a decreased risk of colorectal neoplasia associated with fiber consumption. The majority of case control studies have demonstrated a benefit with a meta-analysis of 16 case control trials showing an approximately 50% reduction in CRC from fiber consumption [25]. With regard to prospective studies, the results have been mixed. While the EPIC trial demonstrated a reduction of 40% in CRC incidence in patients who consumed the most fiber [26], the NHS showed no difference in colorectal neoplasia risk in those who consumed fiber [27]. One study combining the NHS and HPFS showed no effect of fruit and vegetable consumption on CRC [28]. A more recent analysis of the EPIC trial showed similar results, but there was a positive association between fruit and vegetable intake and current smokers [29]. However in the CPS-II, risk of fatal colon cancer decreased with more frequent consumption of vegetables and high-fiber grains [30]. A more recent analysis of the CPS-II showed that men and women with low intake of fruit and vegetable increased the risk for CRC, but a higher intake did not offer protection [31]. In summary, the benefit from fruits and vegetables with respect to lowering the risk for CRC is still in question.

Physical Exertion

It has been hypothesized that increased physical activity may decrease the risk for CRC by reducing body mass, decreasing colonic transit time, better glucose tolerance, and lower insulin levels [32, 33]. One case control study from Kaiser Permanente in Northern California, Utah, and Minnesota observed that those patients with a high Body Mass Index and low physical activity had the highest risk for CRC [34]. Results from the CPS-II, a prospective mortality study of over 700,000 patients, showed an association between physical activity and lower risk for death from CRC [30]. Data from the HPFS showed a significant reduction in risk for CRC in men who had the most physical activity vs. those who had the least [35]. This dose-related effect was evident in the results of a meta-analysis of 52 patients, which demonstrated an inverse relationship between level of physical activity and risk for CRC in men and women [36]. A more recent analysis of the HPFS showed that men who engaged in more than 27 MET hours per week of physical activity had a lower adjusted hazard ratio for CRC-related death than men

who had 3 MET hours or less (HR = 0.47, 95% confidence interval, 0.24–0.92) [37]. An analysis from the NHS showed a similar protective effect of exercise and CRC reduction in women [38]. Data from the EPIC study reduced the risk for right-sided cancers in lean participants but had no effect on rectal cancer [39]. Chao et al. observed in the CPS-II Nutrition Cohort that recreational physical activity reduced the risk for colon cancer as well as rectal cancer in older men and women [40]. Thus, there appears good evidence to suggest that physical exercise can lower the risk for CRC as well as the mortality associated with the disease.

Gender

Although most studies have observed an increased risk for men with regard to advanced colorectal neoplasia as well as CRC, the overall lifetime risk for CRC for men and women is numerically similar [41, 42]. In addition, women have a 5-year lag with respect to incidence of CRC. For example, a woman at 55 has a similar risk to a man at 50 years of age [43]. With regard to the risk for CRC, Nguyen et al. in a meta-analysis observed a twofold increase risk for CRC and advanced adenomas in men as compared to women [44]. Furthermore, in the CONCeRN trial, Schoenfeld et al. observed a lower risk for advanced adenomas in women compared to men [45]. A study by Bressler et al. showed that women were more likely than men to have subsequent CRC after having a colonoscopy [46]. Thus it appears that changes with respect to how we screen women as compared to men may be reasonable. More data, however, is needed to explain the paradox of different advanced adenoma rates but similar CRC rates for the genders.

Alcohol

Ethanol-based beverages have been thought to increase the risk of rectal and colon cancer through a variety of mechanisms including abnormal DNA methylation and repair, induce cytochrome p450 enzymes to increase carcinogen production and alter bile acid composition [47, 48]. An analysis from the HPFS showed that there was a positive correlation between risk of CRC and alcohol in men [49]. This risk increased after 15 g per day which is about one drink per day. In a study that combined the NHS and HPFS, alcohol increased the risk of colon but not rectal cancer [3]. Data from the EPIC trial demonstrated that after controlling for smoking and other known risk factors, alcohol increased the risk of CRC [50]. However in a sub population of the EPIC study, Park et al. observed no risk association between alcohol and CRC [51]. They did find a decrease in risk associated with wine. A study, which combined eight studies for a total of a half a million patients, observed an increased risk for patients who had more than two alcohol beverages per day [52]. In that study, all forms of alcohol increased risk including wine. However, overall it appears that regular alcohol consumption may be associated with an increased risk for CRC and that moderation of alcohol beverage intake may be the best strategy.

Tobacco

Tobacco exposure, most commonly in the form of cigarette smoking, has only been recognized recently as an important risk for CRC in both men and women. The lag in association may be due to two factors [53]. The first is that it may take up to 35 years of exposure to tobacco to increase the risk of CRC [54, 55]. Second, the increase in smoking among men and women may coincide with the two world wars respectively. Since the earliest reports which included analyses of adenoma risk [56], there have been numerous case control [57, 58] and population studies [59–62] that demonstrate the increased risk associated with smoking. Smoking is now considered to be a risk, which is responsible for 20% of all CRC in the United States [63]. Several studies report a 30% increase risk for colon and rectal cancer for male and female smokers [54, 55, 57, 62, 64] as well as an increase of up to 50% in deaths from CRC [60, 65].

An important observation that underscores the importance for screening smokers earlier is the younger age at which smokers are diagnosed with CRC. Although there may be other factors that explain this observation, an age difference of at least 5 years between smokers and nonsmokers has been noted in four separate populations over 2 decades [42, 66, 67]. Smokers may also be more likely to present with an advanced stage of CRC than nonsmokers [68]. Furthermore, smokers have perceptions which may decrease their likelihood to be screened [69, 70]. Thus focusing on smokers as a high risk group may aid in increasing screening in a population that is at risk but may be reluctant to receive appropriate testing.

Obesity

Several studies have demonstrated that obesity increases the risk of CRC in men [35, 71–75] and women [71–73, 75], although this association appears to be stronger in males. In a study examining the HPFS, the men with the highest BMI had a twofold increase risk for CRC as compared to the thinnest men [35]. For women in NHS, the risk for obese women was 1.5 times that of their thinner counterparts [38]. In the CPS-II Nutrition Cohort, there was a correlation between increased waist circumference and CRC [76]. In the EPIC trial, waist to hip ratio and waist circumference, indicators of abdominal obesity, were positively correlated with the risk for CRC [77]. Obesity is a strong risk factor for type 2 diabetes mellitus; a probable independent risk factor for CRC [78]. This association also appears to be stronger for men [79]. Hyperglycemia [80–82], hyperinsulinemia [83], and elevated levels of free insulin-like growth factor (IGF-1) [84] have tumor-promoting properties [85–87]. Carcinogenesis may result from insulin resistance leading to increased cellular proliferation and reduced apoptosis [85, 88, 89].

The identification of BMI as a risk factor for CRC is important for many reasons, especially in light of the increasing prevalence of obesity in the United States [90]. While there are many reasons for health care providers to promote good health, the

possibility of reducing the risk of colorectal neoplasia with weight loss [91] and the implication of an increased risk of cancer represent one further reason to counsel patients regarding weight reduction. Current guidelines recommend colonoscopic screening every 10 years beginning at age 50 for healthy, low risk individuals. However obese women have been shown to be less likely to have colon cancer screening [92]. Obesity may represent a risk that justifies beginning screening at an earlier age in order to reduce the progression of colorectal polyps to cancer [2].

Diabetes Mellitus

The risk of CRC associated with type II diabetes mellitus is important given the anticipated prevalence of type II diabetes by 2030, which will be over one third of a billion [93, 94]. In the Breast Cancer Detection Demonstration Project (BCDDP), women with diabetes had an over 1.5-fold increase risk for CRC than non-diabetics [95]. The risk for CRC associated with diabetes has been shown in large case control studies [96, 97] as well as a prospective study of women [98]. There are many hypotheses regarding the pathogenesis of CRC in diabetics, which include endogenous insulin, exogenous insulin [99], insulin growth factors, and glucagon-like peptide-1 [100]. The hyperinsulinemia theory is based on the premise that elevated levels of insulin and free IGF-1 promote growth of the number of colon cells and lead to a survival benefit of transformed cells, ultimately resulting in CRC [101]. An analysis of the CPS-II Nutrition Cohort showed an association between CRC and diabetes in men but not women [102]. Data from the NHS showed a direct correlation between CRC and a diagnosis of diabetes mellitus [103]. Data from the EPIC study demonstrated that increasing glycated hemoglobin was a risk for women but not men [104]. However, in the Norfolk sample of the EPIC study, patients with Diabetes Mellitus had a threefold increased risk of CRC [105]. In this study, there was direct correlation between risk and glycated hemoglobin. In an analysis of the NHS, there was no association between glycated hemoglobin and CRC [106].

Race

CRC rates are the highest for African Americans for both incidence [107] as well as overall mortality [108] when compared to white patients of both genders. The authors of a recent study hypothesized that the reasons for these differences may be related to etiologic factors such as smoking or diabetes mellitus or the decreased use of screening and diagnostic examinations among African Americans [107]. Alexander et al. conducted an exhaustive review of studies from SEER and population-based cancer registries, Veterans Affairs (VA) databases, healthcare coverage databases, and university and other medical center data sources [109]. In this review,

they observed an increase in stage-specific risks of CRC mortality as well as a shorter survival for African Americans compared with Caucasians. The biggest disparities were observed in university and non-VA hospital-based medical center studies, while a smaller discrepancy was evident in VA-based studies. They concluded that an advanced stage is responsible for the increased mortality. Laiyemo et al. concluded that the difference in mortality may be related more in access to screening rather than biology. In their analysis of data from the PLCO trial, they observed that when compared with whites, blacks were less likely to have a diagnostic test (adjusted risk ratio = 0.88, 95% confidence interval = 0.83–0.93). There was no statistically significant difference between blacks and whites with regard to the prevalence of adenomas, advanced adenomas, or CRC [110]. Agrawal et al. presented a rationale for screening African Americans at the age of 45 years [111]. They cited the increased incidence and mortality, a younger age of CRC diagnosis, a more proximal colonic distribution of cancers and adenomas in, and a decreased utilization of diagnostic testing and screening for CRC in African Americans compared to whites.

Asymptomatic Screening Populations

Cross-sectional studies of asymptomatic screening populations can yield important data regarding the relative strengths of various CRC risk factors [112–114]. Large studies, which often involve symptomatic patients, cannot provide data on prevalence. Unlike studies relying on second hand data or self-report, cross-sectional studies performed in gastrointestinal suites offer the added advantage of accurate and complete endoscopic evaluation of all patients. This ensures that controls have no polyps. An example of this may be found in the risk of smoking and colorectal neoplasia. The risk of tobacco exposure in two screening population was twofold with respect to the risk for advanced neoplasia [112, 114, 115]. The magnitude of this increased risk for adenomas was confirmed in a meta-analysis published recently, which observed an Odds Ratio of 1.82 for people who had ever smoked and 2.14 for current smokers [116]. However, the risk associated with CRC was significantly less in a meta-analysis of 106 observational studies (OR = 1.25) [117]. The authors hypothesized that the difference may be due to the fact that many of the studies examining CRC are based on large population studies, which may have a limitation with respect to the evaluation of controls. Specifically, since the controls may not be endoscoped, there is no way of ensuring that they are neoplasia free with regard to adenocarcinoma or advanced neoplasia. This limitation may blunt the observed risk associated with smoking. In addition, in large population studies, there is often no distinction between those who were diagnosed and those who were screened for CRC. When the authors examined the trials in which controls were endoscoped, the risk for CRC was higher for smokers.

Another advantage of cross-sectional studies is that they can examine risk factors that may be associated with a recent trend. A good example of this is smoking, which

was identified as a risk for colorectal neoplasia in patients with adenomas prior to those with adenocarcinoma [53]. Another example may be obesity, which has been increasing in prevalence. Although a gender difference has been observed in advanced adenomas, there has been consensus in the positive association between obesity and CRC in men and women. With regard to advanced neoplasia, there has been an increased risk for women and no association in men [114, 118, 119].

In addition, since the cross-sectional studies in asymptomatic populations allow for a complete endoscopic evaluation of the enrolled patients. This allows for examination of anatomic location of polyps as well as the morphology. These aspects allowed for the identification, for example, of smoking as a risk for patients with isolated advanced neoplasia [120] as well as patients with flat neoplasia [121]. Finally, since the goal of screening for CRC with colonoscopy is prevention through identification and removal of advanced adenomas [2], identifying risk factors for these lesions may be as important as identifying risks for CRC.

Translation into Screening

Models

One of the concepts behind the strategy for individualizing CRC screening is to utilize the resources for patients that will benefit the most from these tests. Furthermore, guidelines for CRC screening recommend that patients without a family history of CRC be screened at the age of 50 with a colonoscopy. There has been a concern regarding the possibility of insufficient resources to screen all eligible patients with colonoscopy [122]. One author has suggested that perhaps there may be alternative strategies such as a sigmoidoscopy as a first step and a colonoscopy at a later age [123]. Another author has suggested that perhaps CRC screening commence for different risk groups at different ages [43]. He identified gender as a potential variable since women may lag men by 5 years with respect to their risk for colorectal neoplasia. Thus the development of models may be useful in triaging patients.

Most models have used CRC risk factors in developing the risk assessments. Betes et al. used age, gender, and BMI in their model for advanced neoplasia [124]. Kim et al. validated a model based on data from the NHS and HPFS [125, 126]. In that model, they used BMI, vegetable intake, red meat consumption, physical activity, and alcohol intake in addition to other known risk factors such as multivitamin and aspirin use. Driver et al. developed a model predicting the risk for CRC in men based on the 21,581 United States male physicians in the Physician's Health Study [127]. In that model, points were assigned based on strength of risk for each variable. The model included 2 points for every decade over 50, 1 point for history of smoking, 1 point for BMI 25–29.9, 2 points for BMI ≥30, and 1 point for drinking alcohol once or more per week.

Freedman et al. developed a model which examined the risk for CRC by anatomical subsite, proximal vs. distal, for white men and women [128]. For men, personal history of colorectal neoplasia, family history of CRC, not using aspirin, smoking, consuming <5 servings of vegetables per day, and higher BMI were associated with an increased risk for proximal CRC. For distal CRC in men, the same variables except smoking and lower vegetables were associated with an increased risk. For women proximally having personal history of colorectal neoplasia, family history of CRC, not using aspirin, no regular physical activity, consuming <5 servings of vegetables per day, and negative estrogen status were associated with an increased risk. For distal CRC in women, a personal history of colorectal neoplasia, family history of CRC, not using aspirin, higher BMI, older age, and estrogen negative status increase the risk.

On the National Cancer Institute web site (http://cisnet.cancer.gov/projections/colorectal/), there is an interactive model with risk factors based on Health People 2010. Included in the model are smoking status (yes/no), obesity (based on body mass index (BMI)), physical activity (met-hours per week), fruit and vegetable intake (servings per day), multivitamin use (yes/no), red meat intake (servings per day as a main dish), and aspirin and HRT use. The model uses data from the Nurses Health Study (NHS) and the HPFS to estimate the effect of risk factors on CRC [129].

Screening Guidelines

The American College of Gastroenterology recently published guidelines on which they recommend that African Americans begin screening at the age of 45 years [2]. In addition, they identified people who smoke and those who are obese as populations who require special attention from practitioners. They tempered their recommendation that these patients be screened earlier by adding that these patients may have comorbidities that may reduce the benefit from screening. These are the first guidelines regarding CRC screening to consider factors other than age and family history of CRC when forming a screening paradigm.

New Problems in Screening

One of the biggest problems facing endoscopists is the proximal colon and the lack of effectiveness of colonoscopy in reducing the risk for advanced colorectal neoplasia [130, 131]. There have been many hypotheses regarding an explanation for this observation. One plausible answer may lie in the serrated pathway that is associated with BRAF and methylation abnormalities, which may account for a large percentage of interval cancers [132, 133], or those lesions that are diagnosed between scheduled colonoscopy surveillance. Serrated polyps are often proximal and associated with synchronous advanced colorectal lesions [134]. Since smokers often have cancers that

are located in the rectum and proximal colon where serrated lesions are often found, one expert has suggested that smoking may be associated with serrated histology. Recently, a trial examining aberrant crypt foci observed an association between serrated histology and smoking [135]. In addition, there was a study demonstrating a higher rate of flat adenomas in smokers [121]. In addition, Anderson et al. identified smoking as a risk for sessile serrated adenomas [136]. Thus, smokers may be at higher risk for lesions that may be difficult to detect and may require special techniques for screening. This is a good example of incorporating risk factors into a screening algorithm.

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