Colorectal Cancer: A Women’s Health Issue

by Grace Shih and Radhika Srinivasan

In Memory of Radhika Srinivasan, M.D.
September 3, 1962–April 11, 2005

Articulate, intelligent, and compassionate, Dr. Radhika Srinivasan of the Division of Gastroenterology at the University of Pennsylvania was the type of person you would want on your side. In the field of gastroenterology, she was an effective advocate for women and minority groups. She served as the Chair of the Women in Gastroenterology Committee of the American College of Gastroenterology (ACG). Her research involved the risk of colorectal cancer and polyps in women who have been diagnosed with breast or gynecological cancers. Radhika was also a member of the Committee of Minority Affairs and Cultural Diversity, which helped recognize the need for earlier colorectal screening in African Americans.

Fortunately, her energy and enthusiasm were not limited to her research interests. Radhika had a generosity that extended to everyone who met her. At the University of Pennsylvania, she was awarded the 2004 Sidney Cohen Teaching Award in Gastroenterology as well as the Department of Medicine Teaching Award. She was always willing to listen and lend an unbiased ear to any problems—whether it be work related or not.

Radhika was never one to proclaim her achievements, but one does not have to read her Curriculum Vitae to know that she was an outstanding physician, researcher, and person. She is greatly missed. In honor of her memory, the ACG has created the Radhika Srinivasan Gender-based Research Award. This award will be given annually to the best abstract related to identifying gender-based differences in gastrointestinal disease. In addition, the Department of Medicine at the University of Pennsylvania has also created an award for professionalism and humanism in her honor and memory.

Grace Shih, M.D.
Co-author and friend
Colorectal cancer is the third leading cause of cancer death behind lung and breast cancer for women. Unique risk factors such as gynecological cancers and possible delayed diagnosis in pregnancy make colorectal cancer screening an important part of women’s health along with PAP smears and mammograms. In the United States, less than one half of women have ever undergone a sigmoidoscopy or colonoscopy. Because of this, there has been increasing interest in advancing adherence to and acceptance of colorectal cancer screening and surveillance in women. With the continued emphasis on the importance of preventing and treating colorectal cancer, we as health care providers can improve mortality and morbidity associated with colorectal cancer in women.

**INTRODUCTION**

The American Cancer Society estimated that 73,320 women would be diagnosed with colorectal cancer (CRC) in 2004, and 28,410 women would die from it (1). The lifetime risk of developing CRC is 1 in 17 (2). Overall, incidence rates of CRC have stabilized since 1995, and death rates have declined more steeply since the mid 1980s (3). Although the importance of colon cancer screening is undeniable, only about half of the white women in the United States have ever undergone a sigmoidoscopy or colonoscopy. The percentage is lower for African-American women.

**EPIDEMIOLOGY AND RISK FACTORS**

CRC is the fourth most common carcinoma in the U.S but is third behind lung and breast cancer as a cause of cancer deaths in women. The incidence rate of CRC in women for 2000 was 47.0 per 100,000 (4).

Over the past decade, there has been interest in subsite specific incidence rates and stage of CRC by race, gender, and age group. Subsites are usually divided into distal colon (descending, sigmoid, and rectosigmoid—areas within reach of flexible sigmoidoscopy), and proximal colon (splenic flexure, transverse colon, ascending colon and cecum). Starting at age 50, there seems to be significant shift toward more proximal lesions with increasing age (5). Based on their study of 77,163 cases of invasive colon adenocarcinoma from the California Cancer Registry from 1988–1993, Saltzstein and Behling reported that among white women, the age at which the proportion of CRC within reach of a sigmoidoscopy fell below 50% was 70–74 years, while the age among black women was 40–44 years (5). In a more recent study, Cucino and colleagues found a 6%–7% increase in the proportion of proximal lesions in both black and white women (6).

Men and women share similar risk factors for developing CRC: age, family history of colorectal carcinoma or polyps, personal history of colorectal carcinoma or polyps, and inflammatory bowel disease. Prior pelvic radiation may also pose a risk for CRC. In 1983, Sandler and Sandler estimated that women who are irradiated for gynecological cancers have an increased risk of developing CRC (RR = 2.0–3.6) (7). The authors recommended CRC surveillance ten years after irradiation.

Genetic factors strongly increase risk of CRC for both women and men. An individual with two affected family members is 2.57–5.7 times more likely to develop CRC (8). In addition, there are hereditary syndromes such as familial adenomatous polyposis (FAP) which can confer almost a 100% risk of developing CRC. FAP is inherited in an autosomal dominant fashion with inactivation of the APC (adenomatous polyposis coli) gene. Normal APC gene promotes apoptosis in colonic cells. Thus, an inactivation would lead to uncontrolled stimulated cell growth. This leads to the development of hundreds to thousands of polyps which often appear by 15–20 years of age.

Another syndrome, hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), is characterized by the early onset of CRC and possible array of other malignancies (ovary, pancreas, bile duct, genitourinary, and stomach). When compared to people with sporadic cancers, people with HNPCC have more proximal CRC. Two approaches have been developed to help direct when genetic testing should be done to find HNPCC: Amsterdam II Criteria and Bethesda Guidelines. The easiest approach to remember is the Amsterdam II criteria which were developed because of the concern that the original Amsterdam criteria (continued on page 22)
were too exclusionary. These criteria state that there must be three relatives with an HNPCC associated cancer (CRC and/or cancer of endometrium, small bowel, ureter or renal pelvis) plus all of the following: one affected patient is a first degree relative of the other two, two or more successive generations affected, one or more affected relative received CRC diagnosis at age <50 years, FAP excluded, and tumors verified by a pathologist. The mutation in HNPCC is thought to be a defect in the mismatch repair genes which causes regions of DNA called microsatellites to get longer or shorter. This lengthening and shortening phenomenon is MSI. Testing for MSI helps determine whether a person is likely to have HNPCC.

GENDER SPECIFIC RISK FACTORS

Male Genitourinary Cancer
Research on gender specific risk factors for CRC is sparse. A cohort study of 1406 men who had a secondary cancer after testicular cancer reported a significant observed -to-expected ratio of 1.27 for colon cancer and 1.41 for rectal cancer (9). Although prostate cancers have occasionally been found in families with HNPCC, a man’s risk of CRC with a history of prostate cancer is unknown.

Breast Cancer
The risk of CRC in women with a prior history of breast cancer is ambiguous. Two reviews published in 1994 estimated relative risks of 1.1 and 1.15 respectively (10,11). On the other hand, Newschaffer and colleagues looked at the Surveillance Epidemiology and End Results (SEER) database and determined that overall women with a history of breast cancer were 5% less likely to be subsequently diagnosed with colon cancer (12). Comparing standardized incidence rates, the authors found that women diagnosed after 65 years of age, white women, women with local breast cancer, and women during the first 6 months of follow-up had this reduced risk. In addition, rectal cancers were 13% less likely in the women with breast cancer. This reduction was limited to the same profile of women as colon cancer except that decreased incidence was seen five years after diagnosis. No clear protective or harmful factors have been identified linking the two, although women who develop breast cancer may share certain risk factors such as diet, fiber consumption, and hormone exposure. Women with a history of breast cancer without any other increased risk factors for CRC should follow guidelines for average risk persons.

Ovarian Cancer
Women with a history of ovarian cancer seem to have a higher risk of CRC. One study suggests that these women were equal to average risk women four to eight years older, with a relative risk of 1.6 (11). Evidence from SEER database also corroborates this, suggesting that white women, women under 65 years of age, and women with local and regional disease were at increased risk (14). Diagnosis was made often during the initial 6 months after diagnosis of ovarian cancer; this may reflect intensified surveillance following ovarian cancer diagnosis.

Endometrial Cancer
For non HNPCC women who have a history of endometrial cancer the age adjusted relative risk of CRC is 1.4 (11) In this study, the increased risk in rectal cancer may be in part due to receiving radiation therapy; however, the risk of colon cancer was independent of radiation therapy. Analysis of the SEER database showed that increased risk for CRC was seen in black women with a prior history of endometrial cancer and women diagnosed before age 50 years (14).

Cervical Cancer
Evidence from SEER database does not suggest any increased risk of CRC development with a history of cervical cancer (14). Thus, women with cervical cancer should follow average risk screening guidelines for CRC.

Pregnancy
Colon cancer is generally a disease of the elderly and less common in younger patients. The risk of develop-
ing CRC before the age of 40 is 1 in 2000 (2). The incidence of colon cancer during pregnancy is about 1 in 10,000, translating to about 400 cases annually. In general, because pregnant patients are usually younger patients, there is a higher incidence of hereditary syndromes and inflammatory bowel diseases. In a review of nineteen pregnant patients with CRC, four had strong risk factors for CRC (15).

Many of the symptoms of CRC can be similar to or masked by symptoms of pregnancy. For example, nausea, vomiting, rectal bleeding, and altered bowel habits can occur in pregnancy as well. Rectal bleeding is often attributed to hemorrhoids, and altered bowel habits may occur because of external compression on intestinal structures by the gravid uterus. Weight loss seen in CRC can be masked by weight gain during pregnancy. Furthermore, laboratory abnormalities seen in CRC can also be attributable to pregnancy: iron deficiency anemia, hypoalbuminemia, and elevated alkaline phosphatase.

**SCREENING AND SURVEILLANCE**

Screening and surveillance of CRC are feasible in part because of the biology of the disease. First, malignant CRC is thought to arise from adenomatous polyps that undergo several genetic transformations, a process that occurs over years. This period of time allows opportunity to intervene. Second, survival of cancer is dependent on its stage at detection. Thus, the earlier a polyp is found the more likely that the intervention will be curable. In addition to biology, screening for CRC has been found to be cost effective and relatively low risk with acceptable positive and negative predictive values that are acceptable to the larger population (16).

CRC screening is recommended in asymptomatic average risk women or men 50 years or older. Risk factors other than age have been identified (Table 1). In 2003, the American Gastroenterological Association updated its guidelines for CRC screening (17). Several screening modalities are endorsed; only one screening strategy need be adopted for each patient (Table 2) (18). A recent study supports continuing screening regardless of advancing age because the risk of malignant neoplasia increases with age (19). Although there is no age limit in the AGA guidelines to CRC screening, the risks and benefits of screening must be weighed with the patient’s individualized risk of cancer death, life expectancy, as well as values and preferences.

**Increased Risk**

Women or men with a first degree relative (parent, sibling, or child) with CRC or adenomatous polyps diagnosed at age <60 years or 2 first degree relatives diagnosed with CRC at any age should have screening starting at age 40 or 10 years younger than the earliest diagnosed CRC age in the family, whichever comes first.

In addition, women individuals whose families have a diagnosis of familial adenomatous polyposis (FAP) or who are at risk of having FAP should have

(continued from page 22)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk Factors for Developing Colorectal Cancer (CRC).</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥50 years</td>
<td></td>
</tr>
<tr>
<td>• History of CRC or adenomatous polyp in a first degree relative</td>
<td></td>
</tr>
<tr>
<td>• Personal history of adenomatous polyps or CRC</td>
<td></td>
</tr>
<tr>
<td>• Previous diagnosis of endometrial or ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>• History of pelvic irradiation</td>
<td></td>
</tr>
<tr>
<td>• Longstanding Crohn’s colitis or ulcerative colitis</td>
<td></td>
</tr>
</tbody>
</table>

(continued on page 30)
sigmoidoscopy done starting at 10–12 years of age. Those who have this risk should consider genetic testing to determine if they carry the same genetic defect as the index patient. Before any genetic testing is performed, counseling should be obtained to help make an informed decision as well as to help understand the results of the test. Ultimately, if polyposis is found on screening, a decision regarding the timing of colectomy should be discussed since there is nearly a 100% chance of developing CRC if colectomy is not undertaken.

Women or men with a family history of CRC and cancers in other sites in multiple close relatives may have hereditary nonpolyposis colorectal cancer (HNPCC). People who are part of HNPCC kindred should have a colonoscopy every 1–2 years beginning at age 20–25 years or 10 years younger than the youngest family member with a diagnosis of CRC. Genetic testing is available to first degree relatives of probands with a known inherited mismatch repair gene mutation and to patients when the family mutation is not known but who meet criteria for HNPCC. In a Norwegian group of 12 families with an identified founder mismatch repair defect, data on carrier status, development of CRC and mortality suggested that men had higher risks for CRC and death from cancer than females. In addition, females who inherited the mutation from their fathers were at a higher risk of CRC than females who inherited the mutation from their mothers (20).

Individuals who have had sporadic adenomatous polyps removed at the time of colonoscopy should have follow-up colonoscopy depending on the findings. Those who have 1–2 small (<1 cm) tubular adenomas should follow-up in 5 years. Women and men with multiple adenomas (3,4) or at least one adenoma greater than one cm should have follow-up in 3 years. Those with greater than 4 adenomas should have surveillance endoscopy in one year. Those with high grade dysplasia, villous histology, or family history of CRC should be followed up in three years as well. Any incomplete endoscopic resections should be followed up in three to six months to ensure complete removal. If unable to remove the polyp in its entirety after two to three colonoscopic attempts, surgery should be considered.

A recent study surveying gastroenterologists and general surgeons performing screening colonoscopy has found that follow-up screening is being performed in excess, especially in regards to hyperplastic polyps and small adenomas (21). Although there are limitations to this survey, it suggests that scarce resources are being spent on frequent surveillance colonoscopic examinations that are not required and that we should redirect this resource to ensure that more of the eligible subjects get their initial screening colonoscopy.

Gender Issues in Screening

Although the screening guidelines are applicable equally to both men and women, there exists a gender bias in patients undergoing CRC screening; studies have shown that fewer women than men undergo CRC screening (Table 3). According to the Behavioral Risk Factor Surveillance System in 1999, 33.9% of men and 32.6% of women had ever had a sigmoidoscopy or colonoscopy. Both of these numbers have improved since then with 47.6% of men and 47.9% of women having ever had a sigmoidoscopy or colonoscopy (22). Although the difference seems to becoming smaller, the impact of gender on CRC screening participation is still of interest.

Part of the differences in screening may lie in the physician recommendations. In a retrospective review looking at internal medicine residents’ screening methods for breast, cervical, and colorectal cancer for women 50 years or older, residents preformed rectal exams in 37.3% of patients, FOBT in 39.1%, and flex-

(continued from page 24)
Sex-Based Differences in GI Disease, Series #3

Colorectal Cancer: A Women’s Health Issue

Table 3
Gender Differences in Screening Sigmoidoscopy/Colonoscopy

WOMEN are LESS likely than men to
• undergo a sigmoidoscopy or colonoscopy
• adhere to follow-up endoscopy
• have a complete colonoscopy

WOMEN are MORE likely than men to
• be embarrassed about the procedure
• want a same sex endoscopist
• find scheduling a screening sigmoidoscopy an inconvenience
• have a technically more difficult colonoscopy
• find the procedure painful and uncomfortable

ible sigmoidoscopy in 11.8% (23). Female residents were more likely than male residents to perform the rectal exam (48.8% vs 28.6%, p = 0.05) and FOBT (44.4% vs 21.4%, p = 0.02). However, there was no data detailing screening practices on men in this study.

The barriers to screening of CRC in women are not just limited to physician practice. Gerlach and colleagues looked at four top women’s magazine in the years 1987–1995 and counted how many articles were on cancers (24). Of 492 articles, articles on breast cancer was the highest (33.7%), followed by general (articles talking about more than one cancer, 22.2%), and then skin cancer (11.4%) (24). CRC ranked the lowest at 3.3%. There were no lead articles about CRC. Since these studies, there has been a growing emphasis on CRC screening in the area of women’s health, helping to make women more aware of its importance.

Attitudes toward CRC screening may also play a role. In a study looking at asymptomatic patients 50 years or older, Farraye, et al found that women were significantly more embarrassed and frightened about having a flexible sigmoidoscopy (FS) than men and preferred to have the same sex endoscopist (p < 0.0001 for each) (25). Interestingly, women also found FS to be more inconvenient in their daily schedule and less important to undergo FS for screening/surveillance than men (p = 0.006 for each). Of the 334 patients surveyed who were eligible for screening, only 53 people completed screening within one year—28 of them were women accounting for 57% of eligible women. The authors found that women who had a longer doctor-patient relationship with their primary care doctors and who believed strongly about screening in asymptomatic individuals were more likely to complete screening. Similar findings on screening sigmoidoscopy were also reported in a group of women who had undergone mammography (25). In this study, factors associated with having screening endoscopy were compliance with FOBT, family history of CRC, and indifference toward gender of endoscopist. These studies stress the importance of educating physicians about offering screening to asymptomatic individuals, and offering the choice of female endoscopists whenever possible.

Adherence to repeat screening flexible sigmoidoscopy is also lower in women than in men (Weissfeld, et al, 2002). Risk factors for failure to adhere include technically inadequate baseline sigmoidoscopy, and pain during the examination (27,28). In fact, medical literature also suggests that performing endoscopy is more difficult in women than in men (28,29). Women were more likely than men to have examinations of less than 50 cm of colonic length; however, the female population in this study was also more likely to have had previous pelvic or abdominal surgery than men (28). In addition, some have proposed that this may be in part because of a longer transverse colon in women despite shorter stature (30).

Given the pain and likelihood of suboptimal examinations, women may be less inclined to have follow-up endoscopy or even their initial screening for fear of discomfort. Recently, Farraye, et al published a study looking at the use of the upper endoscope for screening flexible sigmoidoscopy (31). They found that women overall reported less pain and discomfort with the upper endoscope than the standard sigmoidoscope (p = 0.006). There was no difference in pain and discomfort in women with hysterectomies; however those who had not undergone hysterectomies found the upper endoscope less painful than the sigmoidoscope (p = 0.005). Endoscopists did not report a greater technical difficulty with use of the upper endoscope.

To improve rates of CRC screening in women, physicians should stress the importance of CRC screening to women in addition to other preventive (continued on page 35)
TREATMENT

CRC death rates have been decreasing 1.8% per year on average since 1984 for both men and women (32). Classification of CRC most commonly employed is the modification of the Dukes system by Aster and Coller. This classification uses the following designations, with five year survival rate in parentheses:

- **A** tumor involving the mucosa, submucosa (80%);
- **B1** tumor going into but not through, the muscularis propria and without nodal involvement (65%);
- **B2** tumor penetrating through the bowel wall but without regional lymph nodal involvement (43%);
- **C1-B1** tumor characteristics with regional nodes involved (53%);
- **C2-B2** tumor characteristics with regional nodes involved (15%);
- **D** distant metastases (5%).

Treatment of CRC depends on the stage of disease at presentation. Without evidence of metastasis, surgery is believed to be the mainstay of treatment. Furthermore, because of a reported 24% chance of concurrent ovarian metastases in women less than 40 years old, some clinicians have recommended oophorectomies as well, especially in patients with low lying rectal cancers.

If there is lymph node involvement at the time of resection, postoperative chemotherapy is recommended. Levamisole and 5-fluorouracil are used as adjuvants, decreasing recurrence by 41% and mortality by 33%. Patients with extension of the tumor through the muscularis propria may also benefit from adjuvant chemotherapy. For metastatic CRC disease, a new class of chemotherapy is available. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (a protein which promotes growth of blood vessels), was studied in a large randomized clinical trial. Hurwitz and colleagues randomized 813 patients who had received no previous chemotherapy for metastatic CRC to receive either irinotecan, fluorouracil, and leucovorin with either placebo or bevacizumab (33). The study demonstrated that bevacizumab increases the survival benefit of the other chemotherapeutics: median overall survival (20.3 months vs. 15.6 months, p < 0.001) and median progression free survival (10.6 months vs. 6.2 months, p < 0.001). As for rectal cancer, radiotherapy plus 5-fluorouracil preoperatively have been shown to decrease recurrence rate in patients with evidence of metastasis to regional lymph nodes or invasion of carcinoma through the bowel wall (34).

Gender Differences in Response to Treatment

Based on the clinical and experimental findings that show gender differences regarding post-traumatic immune functions, with significant advantages for women, Wichmann, et al prospectively looked at a database of 894 patients who underwent curative CRC resection between 1990–1995 (35). No gender differences were noted regarding type of surgical procedure performed and tumor stage. Women lived significantly longer after resection than men (57.8 vs 52 months, P < 0.05) with longer disease free survival as well (51.6 vs 46 months, p < 0.05). A study at the NIH showed no gender differences in five year survival after adjustment for age and extent of disease (36).

Gender differences may exist in tumor response to adjuvant chemotherapy. In a prospective study looking at 656 consecutive patients with Dukes C CRC who received chemotherapy, patients with right sided tumors showed significant survival benefit (over 5 years) with chemotherapy (48% vs 27%, p < 0.0001) whereas patients with left sided tumors showed a non-significant benefit (37). The authors found that women were more likely to have right sided tumors than men (57% vs 42%) and those who had received chemotherapy had a survival benefit compared to those who did not (53% vs 33%, p < 0.0001). Men had no such survival benefit. Multivariate analysis of adjuvant chemotherapy showed that gender was an independent predictor of survival but not of histological grade, tumor site, and age. The explanation for this gender differences is unknown. However, a Japanese study did show that females had lower expression of the enzyme dihydropyrimidine dehydrogenase (DPD) in
tumor tissue than in men’s tumor tissue and non-tumor tissue. DPD is the rate limiting enzyme in the catabolism of 5 fluorouracil. Thus, a high DPD expression results in a low sensitivity to 5-fluorouracil (38).

**Post Colon Cancer Surgery Surveillance Colonoscopy**

In patients with rectal cancer who did not have radiation therapy, repeat flexible sigmoidoscopy should be performed within one year for recurrence at the anastomotic site (39).

For patients with CRC who have undergone resection for curative intent and whose preoperative colonoscopy was otherwise normal, they should receive subsequent surveillance in three years and then every five years if the findings are negative after two follow-up colonoscopies. In a cohort study of 3,278 patients with stage II and stage III CRC, Green, et al found that the cumulative incidence rate of second primary CRC was high 1.5% (CI 1.1%–2.0%) at 5 years (40). They compared this cohort group to two reference groups: SEER and the National Polyp Study; the standardized incidence ratios were 1.6 (CI, 1.2–2.2) and 6.8 (CI, 2.7–22.0), respectively. Given these findings, the need for continued surveillance is apparent. Further studies are needed to address whether increased surveillance would decrease the incidence of second primary CRC.

**Pregnancy**

Pregnant patients with CRC exhibit a difference in pathology than the general population. There is a higher relative rate of rectal cancer during pregnancy compared to the general population. In a literature review by Bernstein and colleagues, 86% of all CRCs during pregnancy were in the rectum (41). In their own reported series for 1993, 64% were in the rectum. Perhaps because of the difficulty in appreciating symptoms of CRC during pregnancy, pregnant patients also have more advanced pathological stage: Dukes A, 0%; Dukes B, 41%; Dukes B, 41%, Dukes, C 44%; Dukes D, 14%. There has been no report of fetal metastases, although placental metastases have been reported.

The evaluation of the pregnant patient for CRC is challenging. Serum carcinoembryonic antigen (CEA) levels are generally unaffected by pregnancy. This lab test is not useful as a screening tool but may be followed pre and post operatively for cancer recurrence. Abdominal CT scans are contraindicated during pregnancy because of teratogenicity by radiation. MRI appears to be safe during pregnancy although there is a theoretical problem with magnetic power in that it may elevate body temperature in the gravid uterus. However, measurements of intrauterine temperature have been studied during MRI procedures with no evidence of temperature elevations (42). Despite negative studies, MRI should be performed only after the first trimester for added safety precautions. Transrectal ultrasound to evaluate rectal cancer can be used although fetal safety has not been directly studied. Colonoscopy and sigmoidoscopy can be done, but are usually reserved for therapeutic measures when gastrointestinal bleeding is a concern. The theoretical risks from these procedures include placental abruption from mechanical pressure on the gravid uterus, teratogenicity from medications given, and fetal toxicity from hypoxia or hypotension during the procedure. The available data looking at safety is inadequate, comprising of small case series whose outcomes vary from healthy baby to still births and spontaneous abortions (2).

Treatment of pregnant patients with CRC is medically, ethically, and emotionally difficult. The well being of both mother and fetus must be considered, and what is beneficial for the mother is not necessarily so for the fetus. All treatment decisions should be done in a multidisciplinary fashion. Nutritional support is paramount in these patients, especially in anticipation of possible surgery. The timing and type of operation is dependent on the following: colon cancer versus rectal cancer, first versus second half of pregnancy, elective versus emergent (perforation, obstruction), and resectability of CRC. Because delay in intervention may lead to progression of the cancer, there is a general consensus that if malignancy is diagnosed within the first 20 weeks of pregnancy, surgery should be done. After that, surgery will have to be postponed until after delivery. Fetal viability is thought to occur at 32 weeks of gestation age. Surgery is performed a few weeks later to allow the involution of the uterus and resolution of the vascular engorgement of pregnancy.

The use of adjuvant chemotherapy like 5-FU may be considered in the second and third trimester after (continued on page 39)
informed and written consent. Teratogenicity has been shown in animal models in the first trimester, there is less of an effect in later trimesters. Leucovorin, another chemoagent used for CRC is listed as FDA category C which indicates there are no controlled trials in women and should only be given if potential benefits justify the potential risk to the fetus. Adjuvant chemotherapy is generally recommended in Dukes C cancer.

Adjuvant radiation provides a dose of 4500 cGY applied to the pelvis to treat rectal cancer. This is absolutely contraindicated in the pregnant patient. Because of the proximity of the rectum to fetus, the uterus cannot be shielded. Postpartum women should be counseled about the possibility of radiotherapy induced sterility.

Advanced pathologic stage at diagnosis likely explains the poor prognosis of pregnant patients with CRC. The five-year disease free survival rate is estimated to be 42% in a study of 26 patients with rectal cancer while in colon cancer survival rate is worse (41). The maternal mortality rate is at least 50% (43). Fetal prognosis is dependent on pathologic stage of the maternal cancer and month of gestation at diagnosis. Overall fetal prognosis is favorable since most cancers are diagnosed close to term (43).

PREVENTION OF COLORECTAL CANCER

Diet

Diets rich in saturated fats, low in vegetables and fiber have been implicated in increasing risk of CRC (44). The American Cancer Society and the National Cancer Institute recommend more than five servings of fruit and vegetables and 20–30 grams of dietary fiber per day (45). In a prospective Swedish study looking at dietary habits assessed by food frequency questionnaires, women consuming less than 1.5 gm of fruit and vegetables per day had a relative risk of developing CRC of 1.65 (95% CI 1.23–2.20; p = 0.001) when compared to women consuming >2.5 servings daily (46). The American Gastroenterological Association published a position paper regarding the evidence for dietary fiber (45). Combined analyses and meta-analyses of case control studies suggested a 50% reduction in risk of CRC between individuals taking highest and lowest quartile of fiber intake.

However, findings from large prospective cohort studies are contradictory. The Nurses Health Study, which followed 88,757 women, found no protective effect of dietary fiber in 787 cases of CRC identified (47). On the other hand, the European Prospective Investigation into Cancer and Nutrition (EPIC) study which looked at 519,978 individuals (69% women) found that dietary fiber was protective when comparing highest versus lowest quartile of intake: adjusted relative risk 0.75 (95% CI, 0.59–0.95) (48). The protective effect was significant for colonic cancer but not for rectal cancer.

Lifestyle

Aspects of lifestyle have also been suggested to impact on risk of CRC. Studies have shown a positive correlation between alcohol intake and CRC for both men and women (49). In addition, cigarette smoking has been identified specifically in women as a risk factor (50). The length of time smoking is directly related to the risk of developing CRC. Former smokers still had a higher incidence of CRC than nonsmokers.

Chemoprevention

Interest in chemoprevention of CRC has increased in the past decade. Studies have reported 30%-50% reductions in rates of CRC with regular intake of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) (51). The chemopreventive mechanisms are not completely understood. Nonselective NSAIDs inhibit both of the cyclooxygenase enzymes (COX). COX catalyzes the conversion of arachadonic acid into prostaglandins and lipoxygenases. Overexpression of COX-2 is a common feature of CRC (52). Thus by inhibiting the COX enzymes, NSAIDs may reduce proliferation, induce apoptosis, promote immunological surveillance, or reduce neoangiogenesis. Various case control studies and prospective cohort studies indicate that aspirin reduces the risk of recurrent adenomas in patients with previous colorectal adenomas and cancers (51). However, it is still controversial if aspirin should be used as secondary prevention in such patients. It is estimated that as a secondary prevention one would need to treat ten individuals to prevent one polypectomy, yet clinicians must also consider the potential side effects of aspirin use (53). In
Colorectal Cancer: A Women’s Health Issue

the same article, it is also estimated that 1,250 individuals with no previous history of colorectal neoplasia would have to be treated with aspirin 10–20 years or longer to prevent one death from colorectal cancer.

The literature on non-aspirin NSAID use has been more limited than aspirin (51). In a retrospective cohort study, nonaspirin NSAID use in 104,217 subjects (76% women) in the Tennessee Medicaid Program 1985–1992 was studied (54). Users of nonaspirin NSAIDs for at least 48 months of the previous five years had a relative risk of 0.49 for colon cancer (95% CI, 0.24–1.00). Those with shorter duration of use had higher relative risks (0.57 to 0.95). No specific NSAID showed a protective benefit over another. Thus, it would seem that duration of NSAID use was important but the effect may attenuate after cessation. Interestingly, the most protection was seen for right sided lesions. The selective COX-2 inhibitor, celecoxib, at 400 mg twice daily was shown to reduce the mean number of polyps by 28% in patients with familial adenomatous polyposis (55). Celecoxib has been approved as an adjunctive therapy to colectomy. However, trials are still needed to evaluate the effect of COX-2 inhibitors on sporadic colorectal cancer and polyps. Recent concerns about cardiovascular side effects from COX-2 inhibitors will likely dampen enthusiasm for using COX-2 agents for CRC risk reduction.

Calcium and vitamin D intake, especially in postmenopausal women, has gained widespread attention. Randomized controlled trials have shown calcium and vitamin D supplements help to prevent bone loss in postmenopausal and elderly women (56). It is also hypothesized that calcium may also help prevent colorectal cancer by binding bile acids in the colon. Bile acids are thought to increase cell proliferation in the colonic mucosa and have been found to be carcinogenic in animal models (51). Baron and colleagues tested this hypothesis by randomly assigning 930 patients with history of colorectal adenomas to receive daily either supplements of 3 gm calcium carbonate or placebo (57). Endoscopic evaluations one and four years after the start of the study showed a reduction in development of further adenomas in the calcium group; the protective effect was seen as early as one year out. The Nurses’ Health Study and the Health Professionals’ Follow-up Study also found that higher calcium intake was associated with significantly lower risk of distal CRC (58). A recent meta-analysis of ten cohort studies from five different countries assessing calcium intake and CRC risk also found similar results (59).

The literature also contains studies showing reduction in the risk of colorectal adenomas and cancer with folic acid intake (60,61). In the Nurses’ Health Study, women who took multivitamins containing folic acid regularly for 15 years showed the greatest reduction in risk of developing colonic cancer (RR = 0.25, 95% CI 0.13–0.51, p = 0.0003). However, there was no influence on the risk of rectal cancer (62). If the woman had a family history of colon cancer, the relative risk reduction of colon cancer for those consuming >400 µg/day was 0.48 (95% CI 0.28–0.83; p = 0.02) versus no family history (RR + 0.81, 95% CI 0.62–1.07) (63). Thus, the authors predicted that the use of multivitamin supplements with folic acid could reduce the risk of colon cancer by almost 50% for those women who had a family history of the disease.

The Women’s Health Initiative (WHI) was a randomized controlled trial that compared estrogen plus progestin with placebo in postmenopausal women, and showed a significant decrease in incidence of CRC (64). Possible biologic explanations include favorable changes induced by estrogen in bile synthesis and excretion as well as estrogen receptors in colonic epithelial cells that may serve to inhibit proliferation (65). Chlebowski and colleagues then further analyzed the results and showed that 43 invasive CRC were found in the hormone group while 72 were found in the placebo group (hazard ratio, 0.56; 95% CI 0.38–0.81; p = 0.003) (65). However, the hormone group had more positive lymph nodes. Overall analysis of global index indicated that the use of estrogen plus progestin provided no evidence of benefit for women at increased risk for CRC (hazard ratio 1.12; CI 1.01–1.23) or for those with prior polyps (hazard ratio 1.04; CI 0.72–1.50). Further studies are needed to support the use of hormone replacement as chemoprevention; however, these findings do support the need for CRC screening in postmenopausal women who are taking hormonal replacements.

Obesity and Physical Activity

Being overweight increases both the incidence and lethality of colon cancer (67,68). The First National Health and
Nutrition Examination Survey showed that obese individuals had a 3-4 time higher hazard ratio for colon cancer than those with normal body mass index (BMI) (69). BMI is the weight of an individual in kilograms divided by the height squared in meters. Men showed increased risk across the range of BMI (highest at BMI of 32.5 or greater). Women, on the other hand, had a similar but somewhat weaker relationship. Whether the gender differences may be driven by the protective effects of estrogen is unknown, just as why adiposity increases the risk of colon cancer is unclear. It is has been proposed that perhaps hyperleptinemia may contribute to carcinogenesis. Leptin, an adipocyte hormone, may stimulate colonic proliferation via leptin receptors that have been identified on colonic epithelial cells (70).

Physical activity seems to exert a protective effect on the risk of colon cancer. The US Nurses Health Study reported that nurses engaging in activities of moderate intensity (walking at normal or brisk pace) for 1h/d was associated with a 46% reduction of risk (71). This finding was consistent with a cohort of Norwegian women where the equivalent of walking or biking for at least 4h/week was associated with a 38% reduction when compared to a sedentary group (72). In addition, protection seems higher for colon than rectum (72,73).

The similarity of risk factors for type 2 diabetes mellitus and CRC such as high BMI and obesity has led to the hypothesis that diabetes itself might be a risk factor for CRC. In a prospective study looking at women enrolled in the Nurses’ Health Study, Hu and colleagues found that diabetic women had a 43% increased risk of CRC than women without diabetes, after controlling for age, BMI, and other potential confounders (74). However, other studies showed no consistent association between diabetes and CRC (75,76). In fact, Nilsen and Vatten found an association between diabetes and CRC in women but not in men (76). Hyperinsulinemia has been proposed to be the underlying link since insulin is an important growth factor of tumor cell growth (77).

CONCLUSION

Colorectal cancer is a preventable disease, yet less than 50 percent of the men and women in the US have received screening measures. Health practitioners should continue to educate and stress the importance of CRC screening along with other preventive care. Some gender differences exist with respect to participation in CRC screening. Unique risks to women such as prior history of endometrial or ovarian cancers should reinforce the need for CRC screening. Screening strategies are the same for women and men, as are treatment recommendations. Women tend to have more right sided cancers than men and may respond better to adjuvant chemotherapy. CRC can be difficult to diagnose in a pregnant patient, but should be considered when pregnant women display signs or symptoms consistent with CRC, in particular rectal cancer.

Chemoprevention is an exciting field, and several agents have been identified that may lower CRC risk. Choosing a chemopreventive strategy should be individualized, taking into account the risks and benefits for each patient.

References

(continued on page 45)
(continued from page 41)


Colorectal Cancer: A Women’s Health Issue

SEX-BASED DIFFERENCES IN GI DISEASE, SERIES #3

Crohn’s & Colitis Foundation of America
REQUEST FOR APPLICATIONS
BIOMARKERS OF COLON CANCER IN IBD

Letter of Intent Deadline: January 14, 2006
Application Submission Deadline: January 14, 2006
Total Award: $143,00 per year for 2 years
Direct Costs: up to $130,000
Indirect Costs: Up to 10% ($13,000) of direct costs

RFA: CCFA continues to seek applications to identify biomarkers for colon cancer in patients with IBD. The proposed studies can focus on the exploration of possible candidate biomarkers to be identified through blood tests, stool tests, or tests on simple biopsies of the rectum (no colonoscopies). Potential groups of biomarkers include antibodies against proteins found in precancerous lesions or early cancers, proteins or DNA from cancerous or pre-cancerous lesions that are shed into the stool, and/or identification of genetic mutations that predispose IBD patients to develop colon cancer. This RFA is limited to human investigation and excludes basic in vitro research or preclinical studies in animal models. Specifically, proposed studies could involve:

- Clinical validation of candidate biomarkers
- Studies to identify candidate biomarkers
- Retrospective longitudinal study to evaluate potential biomarker
- Optimize potential biomarker assay (throughput, reproducibility, etc.)
- Development of innovative imaging tests for pre-cancerous lesions

For all applicants:

- You must be an MD, PhD or equivalent degree
- The proposed research projects must be relevant to the inflammatory bowel diseases
- You must be employed by a public non-profit, private non-profit, or government institution engaged in health care and/or health-related research
- Eligibility is not restricted by citizenship or geography

Further information, guidelines and applications can be found at www.ccfa.org