Scanning the Literature

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Are We Ready for Laparoscopic Colon Cancer Resection?

Weeks JC, Nelson H, Gelber S, et al. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 2002; 287:321-328.

Context: Laparoscopic-assisted colectomy (LAC) has emerged as the preferred minimally invasive surgical strategy for diseases of the colon. The safety and efficacy of LAC for colon cancer are unknown, and the nature and magnitude of any quality-of-life (QOL) benefit resulting from LAC for colon cancer is also unknown. **Objective**: To compare short-term QOL outcomes after LAC vs open colectomy for colon cancer. **Design, Setting, and Participants**: Multicenter, randomized controlled trial (Clinical Outcomes of Surgical Therapy [COST]). Between September 1994 and February 1999, 37 of 48 centers provided data for the QOL component of the trial for 449 consecutive patients with clinically resectable colon cancer. **Main Outcome Measures**: Scores on the Symptoms Distress Scale (SDS), Quality of Life Index, and a single-item global rating scale at 2 days, 2 weeks, and 2 months postoperative; duration of postoperative in-hospital analgesic use; and length of stay. **Results**: Of 449 patients, 428 provided QOL data. In an intention-to-treat analysis comparing SDS pain intensity, SDS summary, QOL Index summary, and global rating scale scores at each time point, the only statistically significant difference observed between groups was the global rating scale score for 2 weeks postsurgery. The mean (median) global rating scale scores for 2 weeks postsurgery were 76.9 (80) for LAC vs 74.4 (75) for open colectomy (P =.009). While in the hospital, patients assigned to LAC required fewer days of both parenteral analgesics compared with patients assigned to open colectomy (mean [median], 3.2 [3] vs 4.0 [4] days; P<.001) and oral analgesics (mean [median], 1.9 [1] vs 2.2 [2] days; P =.03). **Conclusion**: Only minimal short-term QOL benefits were found with LAC for colon cancer compared with standard open colectomy. Until ongoing trials establish that LAC is as effective as open colectomy in preventing recurrence and death from colon cancer, this procedure should not be offered to patients with colon cancer.

Comments: Over the last several years, many surgical procedures have evolved to where they can be done laparoscopically in certain cases. Patients see this as an "easier to tolerate" surgery and frequently inquire preoperatively if their surgery can be done this way. Recently, through better technology and increased surgeon skill, there has been interest in extending this technique to include curative resection of colon cancer. In this situation, it would be necessary to establish whether the same rate of cure and prevention of recurrence occurs with this method compared with the open method. Not unlike prior laparoscopic surgery studies, this study demonstrated less required analgesia and a shorter hospital stay. There was, however, a failure to demonstrate a significant difference in quality of life scores. One possible reason for this may be that this was investigated as a strategy for managing unselected patients with colon cancer, and, therefore, those converted to open surgery were evaluated in the laparoscopic group. Possibly, "surgeon selected" laparoscopic candidates as a group would have scored statistically differently from a purely open group. At this time, until ongoing trials establish the clinical effectiveness of this technique, laparoscopic-assisted colectomy does not seem to be advantageous compared with the open method.

Does Prior Cancer Diagnosis Elevate the Risk of Colorectal Cancer?

Newschaffer CJ, Topham A, Herzberg T, et al. Risk of Colorectal Cancer After Breast Cancer.
Lancet 2001; 357: 837-840.

Background: History of breast cancer has been reported as a risk factor for colorectal cancer in women. In view of the ambiguous nature of existing evidence and the growing interest in targeted colorectal cancer prevention, we sought to quantify this risk. **Methods**: We used the Surveillance Epidemiology and End Results (SEER) database to estimate risk of colorectal cancer after breast-cancer diagnosis in women with first incident breast cancer between 1974 and 1995. Observed colon and rectal cancer risk was compared with that expected in the general population. We stratified comparisons by age at breast-cancer diagnosis, stage of cancer, ethnic origin of patient, and follow-up time. **Findings**: Overall, women with previous breast cancer were 5% less likely (95% CI 1-9) to develop colon and 13% less likely (6-19) to develop rectal cancer than women in the general population. Stratified analyses suggested that the risk reductions observed for colon and rectal cancer were most pronounced for women with breast cancer diagnosed after age 65 years, in white women, women with local stage breast cancer, and women diagnosed in the later study years (1990-94). **Interpretations**: Breast cancer does not increase subsequent colorectal cancer risk, and reduced risk was seen for certain subgroups of women. Because no biologically plausible endogenous protective factor has been identified, we suggest that reduced risk could stem from an accumulation of exposures that increase breast-cancer frequency but protect against colorectal cancer.

Comments: As a primary care physician, it is often difficult to convince some patients to have colorectal cancer screening tests; they refuse or decline for various reasons. It is usually not difficult, however, to convince a patient who has already had another form of cancer. Breast cancer, for instance, has been cited as a risk factor for colorectal cancer, and this study attempted to quantify that risk. Over 227,000 women were included in the study and the results were interesting. Women with breast cancer did not have excess risk of subsequent colorectal cancer--and certain groups had a lower risk than the general population. Theories explaining these findings are merely speculative. One possibility is that prior hormone use offers protection. Genetic factors related to breast cancer genes are also being investigated. Another important factor may be that increased vigilance in routine screening in the breast cancer group may lead to increased removal of polyps that could have eventually become cancerous. Although these findings suggest that breast cancer may not be associated with an increased risk of colorectal cancer, it is important that these patients, along with all patients, continue to be encouraged to get routine colorectal cancer screenings.

Colorectal Cancer Screening: The Debate Continues

Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon.
N Engl J Med 2001; 345: 555-560.

Background: Fecal occult-blood testing and sigmoidoscopy have been recommended for screening for colorectal cancer, but the sensitivity of such combined testing for detecting neoplasia is uncertain. At 13 Veterans Affairs medical centers, we performed colonoscopy to determine the prevalence of neoplasia and the sensitivity of one-time screening with a fecal occult-blood test plus sigmoidoscopy. **Methods**: Asymptomatic subjects (age range, 50 to 75 years) provided stool specimens on cards from three consecutive days for fecal occult-blood testing, which were rehydrated for interpretation. They then underwent colonoscopy. Sigmoidoscopy was defined in this study as examination of the rectum and sigmoid colon during colonoscopy, and sensitivity was estimated by determining how many patients with advanced neoplasia had an adenoma in the rectum or sigmoid colon. Advanced colonic neoplasia was defined as an adenoma 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer. Classification of subjects according to the findings was based on the most advanced lesion. **Results**: A total of 2885 subjects returned the three specimen cards for fecal occult-blood testing and underwent a complete colonoscopic examination. A total of 23.9 percent of subjects with advanced neoplasia had a positive test for fecal occult blood. As compared with subjects who had a negative test for fecal occult blood, the relative risk of advanced neoplasia in subjects who had a positive test was 3.47 (95 percent confidence interval, 2.76 to 4.35). Sigmoidoscopy identified 70.3 percent of all subjects with advanced neoplasia. Combined one-time screening with a fecal occult-blood test and sigmoidoscopy identified 75.8 percent of subjects with advanced neoplasia. **Conclusions**: One-time screening with both a fecal occult-blood test with rehydration and sigmoidoscopy fails to detect advanced colonic neoplasia in 24 percent of subjects with the condition.

Comments: Colon cancer screening remains an important aspect of primary medical care. There is debate, however, as to which type of test should be recommended and, certainly, there is still variance between insurance companies as to which screening tests are covered. This study evaluated the sensitivity of fecal occult blood testing and sigmoidoscopy both alone and in combination. The results were very interesting. Nearly 25% of the cases of advanced neoplasia may have been missed with one-time screening with fecal occult blood and sigmoidoscopy. This may be improved with appropriate repeat interval screening; however, periodic colonoscopy would seem to be more effective in cancer prevention and detection than the occult blood/sigmoidoscopy combination. This information will need to be thoroughly considered when future screening guideline policies are evaluated.

Colonoscopy? Yes…But How Often?

Sonnenberg A, Delco F. Cost-effectiveness of a single colonoscopy in screening for colorectal cancer. Arch Intern Med 2002; 162:163-168.

Background: A single colonoscopy at the age of 65 years has been recommended as a potential option to screen for colorectal cancer. This study compares the cost-effectiveness of 2 screening programs based on a single or repeated colonoscopy. **Methods**: The cost-effectiveness of screening is analyzed with a computer model of a Markov process. A hypothetical population of 100 000 subjects aged 50 years undergoes a single colonoscopy at the age of 65 years or repeated colonoscopy every 10 years starting at the age of 50. Transition rates are estimated from US vital statistics and cancer statistics and published data on polyp incidence, patient compliance, and efficacy of colonoscopy plus polypectomy in cancer prevention. Costs of screening and cancer care are estimated from the 1998 Medicare reimbursement data using the perspective of a third-party payer. **Results**: Compared with no screening, the incremental cost-effectiveness ratio of a single or repeated colonoscopy amounts to $2981 or to $10 983 per life year saved, respectively. A single colonoscopy saves most life years if done at the age of 60, but becomes most cost-effective after the age of 70. Depending on the level of compliance, repeated colonoscopies save 2 to 3 times more lives than a screening program based on a single colonoscopy. **Conclusions**: A repeated colonoscopy every 10 years offers better prevention against colorectal cancer and represents a medically more desirable screening option. If high costs or low patient compliance renders this option not feasible, a single colonoscopy at the age of 65 would represent a highly cost-effective alternative.

Comments: This article looked at the cost-effectiveness of a single colonoscopy for colorectal cancer screening and the best timing of this test to save both lives and money. Colonoscopy prevents more cancers than sigmoidoscopy and fecal occult blood testing; however, screening every adult over age 50 every 10 years would be quite a large health care expenditure. This study used a computer model to compare the periodic screening strategy with the one-time only model. The results were not surprising. Colonoscopy repeated every 10 years offers the better prevention of colorectal cancer but would be quite expensive to the health care industry. Unfortunately, because of patient noncompliance with screening (in the "real world" of medicine) this would be a difficult goal to achieve anyway. On the other hand, a single colonoscopy was more cost-effective than the periodic screening strategy: costs of $2981 compared with $10,983 per life-year saved. In the study model, 1352 cancers were prevented in the single screening group compared with 4428 in the multiple screening group. When the single screening strategy was evaluated further, the best age to perform the test was found to be 65. The single screening is better than no screening, and multiple periodic screening (if insurance or the patient will pay for it) is better than single screening. Now all that is left is the tough task of convincing our patients to have the test done.

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Do NSAIDS Decrease Polyps In FAP?

Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac.
N Engl J Med 2002; 346:1054-1059.

Background: Familial adenomatous polyposis is caused by a germ-line mutation in the adenomatous polyposis coli gene and is characterized by the development of hundreds of colorectal adenomas and, eventually, colorectal cancer. Nonsteroidal antiinflammatory drugs can cause regression of adenomas, but whether they can prevent adenomas is unknown. **Methods**: We conducted a randomized, double-blind, placebo-controlled study of 41 young subjects (age range, 8 to 25 years) who were genotypically affected with familial adenomatous polyposis but phenotypically unaffected. The subjects received either 75 or 150 mg of sulindac orally twice a day or identical-appearing placebo tablets for 48 months. The number and size of new adenomas and side effects of therapy were evaluated every four months for four years, and the levels of five major prostaglandins were serially measured in biopsy specimens of normal-appearing colorectal mucosa. **Results**: After four years of treatment, the average rate of compliance exceeded 76 percent in the sulindac group, and mucosal prostaglandin levels were lower in this group than in the placebo group. During the course of the study, adenomas developed in 9 of 21 subjects (43 percent) in the sulindac group and 11 of 20 subjects in the placebo group (55 percent) (P=0.54). There were no significant differences in the mean number (P=0.69) or size (P=0.17) of polyps between the groups. Sulindac did not slow the development of adenomas, according to an evaluation involving linear longitudinal methods. **Conclusions**: Standard doses of sulindac did not prevent the development of adenomas in subjects with familial adenomatous polyposis.

Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis.
N Engl J Med 2000; 342:1946-1952.

Background: Patients with familial adenomatous polyposis have a nearly 100 percent risk of colorectal cancer. In this disease, the chemopreventive effects of nonsteroidal antiinflammatory drugs may be related to their inhibition of cyclooxygenase-2. **Methods**: We studied the effect of celecoxib, a selective cyclooxygenase-2 inhibitor, on colorectal polyps in patients with familial adenomatous polyposis. In a double-blind, placebo-controlled study, we randomly assigned 77 patients to treatment with celecoxib (100 or 400 mg twice daily) or placebo for six months. Patients underwent endoscopy at the beginning and end of the study. We determined the number and size of polyps from photographs and videotapes; the response to treatment was expressed as the mean percent change from base line. **Results**: At base line, the mean (+/-SD) number of polyps in focal areas where polyps were counted was 15.5+/-13.4 in the 15 patients assigned to placebo, 11.5+/-8.5 in the 32 patients assigned to 100 mg of celecoxib twice a day, and 12.3+/-8.2 in the 30 patients assigned to 400 mg of celecoxib twice a day (P=0.66 for the comparison among groups). After six months, the patients receiving 400 mg of celecoxib twice a day had a 28.0 percent reduction in the mean number of colorectal polyps (P=0.003 for the comparison with placebo) and a 30.7 percent reduction in the polyp burden (the sum of polyp diameters) (P=0.001), as compared with reductions of 4.5 and 4.9 percent, respectively, in the placebo group. The improvement in the extent of colorectal polyposis in the group receiving 400 mg twice a day was confirmed by a panel of endoscopists who reviewed the videotapes. The reductions in the group receiving 100 mg of celecoxib twice a day were 11.9 percent (P=0.33 for the comparison with placebo) and 14.6 percent (P=0.09), respectively. The incidence of adverse events was similar among the groups. **Conclusions**: In patients with familial adenomatous polyposis, six months of twice-daily treatment with 400 mg of celecoxib, a cyclooxygenase-2 inhibitor, leads to a significant reduction in the number of colorectal polyps.

Comments: Familial adenomatous polyposis (FAP) is an autosomal-dominant inherited disease characterized by the development of hundreds of colorectal adenomas throughout adolescence. Typical treatment is total colectomy since colorectal cancer will develop in nearly all affected persons by the sixth decade of life without the procedure. These articles show that medical research can be confusing to patients and lead individuals to believe that various medications can cure colon cancer or even reduce an individual's likelihood to have the disease. Colectomy is still the treatment of choice since sulindac cannot be used as primary prevention. Studies have shown a place for sulindac in preventing the recurrence of further adenomas and in reducing polyp numbers in selected individuals who already have had the total colectomy. But Giardiello and colleagues showed no significant difference in preventing adenomas in individuals with the APC gene responsible for FAP.

While sulindac works by inhibiting both cyclooygenase-1 and –2, celecoxib inhibits cyclooxygenase-2 selectively and offers some hope for medical treatment for FAP. Unlike in the sulindac study, individuals had not undergone colectomy and were evaluated by baseline endoscopy followed by repeat endoscopy at 6 months. There was a quantitative decrease in the number of polyps visualized in the high-dose celecoxib group. This, however, does not address clinical changes in the progression of the disease. Three patients eventually had total colectomy after completing the study, but the study medications were stopped since efficacy was unknown at the time.

Can Calcium Prevent Colon Cancer?

Wu K, Willett WC, Fuchs CS, et al. Calcium intake and risk of colon cancer in women and men.
J Natl Cancer Inst 2002; 94:437-446.

Background: Calcium has been hypothesized to reduce the risk of colon cancer, and in a recent randomized trial, calcium supplementation was associated with reduction in the risk of recurrent colorectal adenomas. We examined the association between calcium intake and colon cancer risk in two prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). **Methods**: Our study population included 87 998 women in NHS and 47 344 men in HPFS who, at baseline (1980 for NHS and 1986 for HPFS), completed a food frequency questionnaire and provided information on medical history and lifestyle factors. Dietary information was updated at least every 4 years. During the follow-up period (1980 to May 31, 1996 for the NHS cohort; 1986 to January 31, 1996 for the HPFS cohort), 626 and 399 colon cancer cases were identified in women and men, respectively. Pooled logistic regression was used to estimate relative risks (RRs), and all statistical tests were two-sided. **Results**: In women and men considered together, we found an inverse association between higher total calcium intake (>1250 mg/day versus < or =500 mg/day) and distal colon cancer (women: multivariate RR = 0.73, 95% confidence interval [CI] = 0.41 to 1.27; men: RR = 0.58, 95% CI = 0.32 to 1.05; pooled RR = 0.65, 95% CI = 0.43 to 0.98). No such association was found for proximal colon cancer (women: RR = 1.28, 95% CI = 0.75 to 2.16; men: RR = 0.92, 95% CI = 0.45 to 1.87; pooled RR = 1.14, 95% CI = 0.72 to 1.81). The incremental benefit of additional calcium intake beyond approximately 700 mg/day appeared to be minimal. **Conclusions:** Higher calcium intake is associated with a reduced risk of distal colon cancer. The observed risk pattern was consistent with a threshold effect, suggesting that calcium intake beyond moderate levels may not be associated with a further risk reduction. Future investigations on this association should concentrate on specific cancer subsites and on the dose-response relationship.

Comments: Earlier studies found a weak and nonsignificant inverse association between increased calcium intake and risk of colorectal or colon cancer. The Calcium Polyp Prevention Study noted that daily supplementation with 1200 mg of calcium resulted in a 20% reduction in risk of recurrent colorectal adeomas. This study, using the data from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) examined about 135,000 individuals. The data were obtained using a food frequency questionnaire and subsequently computing calcium intake from dairy and non-dairy sources. While data are available on the validity and reproducibility of these data, some of the findings are still questionable. The only significant findings are in the pooled data of the NHS and HPFS. Nevertheless, Wu et al. found a threshold effect of calcium intake (at approximately 700 mg) on distal, but not proximal, colon cancer in both men and women. This association was restricted to non-aspirin users and appeared to be stronger in male smokers. While there may be some questions in regard to the strength of the data and its validity, the possible benefits of calcium supplementation are worth examining.

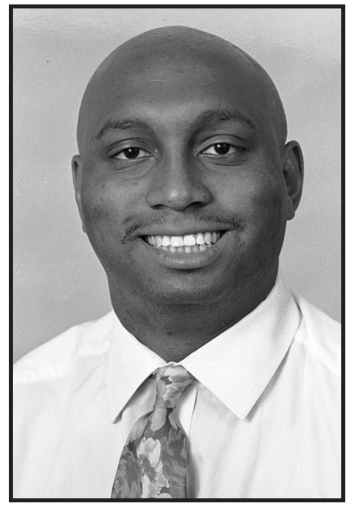
Patient Education and Office Reminder Systems Increase Screening

Pignone M,Harris R, Kinsinger L. Videotape-based decision aid for colon cancer screening. A randomized, controlled trial.
Ann Intern Med 2000; 133:761-769.

Background: Rates of colon cancer screening in the United States are low, in part because of poor communication between patients and providers about the availability of effective screening options. **Objective**: To test whether a decision aid consisting of an educational video, targeted brochure, and chart marker increased performance of colon cancer screening in primary care practices. **Design**: Randomized, controlled trial. **Setting:** Three community primary care practices in central North Carolina. **Patients:** 1657 consecutive adult patients 50 to 75 years of age were contacted. Of these, 651 (39%) agreed to participate; 249 of the 651 participants (38%) were eligible. Eligible patients had no personal or family history of colon

cancer and had not had fecal occult blood testing in the past year or flexible sigmoidoscopy, colonoscopy, or barium enema in the past 5 years. **Intervention**: The 249 participants were randomly assigned to view an 11-minute video about colon cancer screening (intervention group) or a video about automobile safety (control group). After viewing the video, intervention group participants chose a color-coded educational brochure (based on stages of change) to indicate their degree of interest in screening. A chart marker of the same color was attached to their charts. Controls received a generic brochure on automobile safety, and no chart marker was attached. **Measurements**: Frequency of screening test ordering as reported by participants and frequency of completion of screening tests as verified by chart review. **Results**: Fecal occult blood testing or flexible sigmoidoscopy was ordered for 47.2% of intervention participants and 26.4% of controls (difference, 20.8 percentage points [95% CI, 8.6 to 32.9 percentage points]). Screening tests were completed by 36.8% of the intervention group and 22.6% of the control group (difference, 14.2 percentage points [CI, 3.0 to 25.4 percentage points]). **Conclusion**: A decision aid consisting of an educational video, brochure, and chart marker increased ordering and performance of colon cancer screening tests.

Comments: Colon cancer is the second leading cause of cancer-related death in the United States. Screening has been shown to decrease colorectal cancer incidence and mortality rates; however, numerous studies have demonstrated that the use of screening tests (e.g. fecal occult blood testing, flexible sigmoidoscopy) in clinical settings is low. This article reinforces the fact that patient education in regard to screening tests increases compliance. This suggests that multiple modes of providing information in addition to physician reminders are helpful in increasing patients' colon cancer screens.



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