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INSIDE

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It's Time to Have the Talk

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Terminally ill cancer patients who had end-of life discussions with their physician had better quality of life during their last week and their caregivers had an easier bereavement.*

Source: Wright AA, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665-1673.

ALTHOUGH THERE ARE MULTIPLE BENEFITS TO ADMISSION TO HOSpice for a terminally ill patient and the patient's family, frequently referral never happens or occurs too late. There are many real and perceived roadblocks to admission, including a paucity of hospice services, patients' overly optimistic self-prognoses, physicians' inadequate skills at prognostication and end-of-life (EOL) communications, and a concern that the necessary conversations leading to hospice referral might precipitate a major depressive episode.

This prospective, longitudinal, cohort study, conducted at seven outpatient cancer centers in five cities (four in New England and one in Texas) was designed to examine what really happens when physicians have EOL discussions with end-stage cancer patients. Subjects were recruited from September 2002 until February of this year. To be eligible patients had to have distant metastases or cancer refractory to first-line chemotherapy, be at least 20 years old, and have an informal caregiver (i.e., family or friend). Six hundred thirty-eight (638) patient-caregiver dyads were enrolled. Only the 332 patients who died were included in this study. Patients were on average 58 years old at the time of enrollment. Most were married (60%), white (64%), male (55%), and had health insurance (57%). Breast,

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colorectal, pancreatic, and lung cancers comprised 58% of the diagnoses. Caregivers were on average 51 years old and predominantly female (77%). Most were spouses (51%) or adult children (24%).

Psychosocial factors and functional status were determined. The use of aggressive treatment (e.g., admission to an intensive care unit [ICU], ventilation, resuscitation, chemotherapy, feeding tubes) was documented by chart review. Patients and caregivers were interviewed. Patients were asked, "Have you and your doctor discussed any particular wishes you have about the care you want to receive if you are dying?" Shortly after death, caregivers were asked, "In your opinion, how would you rate the overall quality of the patient's death/last week of life?" A median of 6.5 months after death, the caregivers were interviewed about their psychological adjustment.

Patients died a median of 4.4 months after enrollment. Most (63%) could not remember having an EOL discussion with their physician. There was a wide disparity between sites of care in this regard, ranging from 62% to 16%. There were no associations between EOL discussions and patients' demographic characteristics, whether they had insurance, what kind of cancer they had, how close they felt to their physician, whether they were religious, or whether they had social support. Positive associations were found for lower performance status, higher symptom burden, and shorter survival times. There was no association of EOL discussions with a patient feeling depressed or developing any DMS4 diagnosis. Patients who had an EOL discussion with their physician were more likely to accept that their illness was terminal, prefer palliative over curative care, and have completed "Do Not Resuscitate" declarations. They received less aggressive treatment and were more likely to have been in hospice for more than a week. Caregivers rated the quality of life (QOL) of their loved ones' last week of life as significantly worse if they received aggressive care. They reported feeling less prepared for the patient's death and were more likely to develop a major depressive disorder, to feel regret over their loved one's death, and have worse QOL and self-reported health following their loved one's death.

■ COMMENTARY

This was not a randomized study, so no causal relationships can be inferred. On the other hand, the size of the study lends weight to its conclusions. Although the patients were recruited from cancer centers, there is no reason to believe that they differ from your patients who have advanced cancer. How similar are you to their doctors? Intuitively, oncologists should be more skilled at EOL discussions simply by dint of practice, but primary care physicians may have an edge by virtue of long association. We can only hope that these patients suffered a dementia or were overly medicated to explain the dismal rate of EOL conversations.

Physicians are programmed to "do something" when presented with a patient in need. What can we do to help our terminally ill patients? We can employ a wider range of palliative options. Kutner showed that for advanced cancer patients, massage therapy can have an immediate beneficial effect on pain and mood.[1] We can be better stewards of limited resources. In the current study, admission to an ICU was one of the factors associated with no EOL discussion. Rady looked at this in 2004 from the perspective of informed consent.[2] In his study, none of the patients transferred to the ICU, all of whom died there, had an EOL or palliative care discussion. Not only was this a violation of patient autonomy, it was outrageously expensive ($33,252 for those who were transferred vs. $8,549 for those who weren't). We can learn to be better communicators. Even when presented with opportunities to connect with terminally ill patients, we don't take advantage of them.[3] We can help the caregivers. Caregivers who report greater religiousness have lower rates of depression at follow-up,[4] suggesting collaboration with religious support groups. We can begin our discussions about hospice much earlier, even as we attempt treatment. On average, patients in the current

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study died after 4 months. Admission to hospice when the patient is near death (i.e., death within 3 days) is associated with major depressive disorders in caregivers.[5] We can do more; our patients deserve it. ■

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Venous Thromboembolism and Cancer

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Previously undiagnosed cancer is frequent in patients with an unprovoked VTE and is more often detected with an extensive cancer screening strategy than with a limited screening strategy.*

Source: Carrier M, et al. Systematic review: The Trousseau syndrome revisited: Should we screen extensively for cancer in patients with venous thromboembolism? *Ann Intern Med* 2008;149:323-333.

In 1865, Armand Trousseau described the association between venous thrombophlebitis (VTE) and cancer by noting, "The diagnosis in a patient with gastric pain and leg or arm phlegmasia alba dolens is the presence of cancer."[1] Two years later, after suffering weeks of abdominal pain, he died of gastric cancer shortly after he declared to one of his students, "I'm lost. A thrombosis developed overnight, which doesn't leave me any doubt of the nature of my disease."[1]

Over the ensuing years, multiple studies have revealed that VTE manifested as deep venous thrombosis and/or pulmonary embolism can be the first manifestation of cancer.[2-5] Of course, identifying a previously undiagnosed cancer in patients with VTE is important because the cancer may be curable if detected early or, if detected when no longer curable, early treatment may still prevent cancer-associated morbidity such as pathologic fractures and compression syndromes. Retrospective studies in patients with VTE suggest that a careful medical history, a thorough physical examination, and basic blood work will detect most cases of undiagnosed cancer[6,7]; however, more recent prospective studies have revealed that a more extensive screening strategy involving limited screening plus imaging studies and/or tumor marker measurements can increase the rate of cancer detection.[7,8] Because screening and surveillance for occult cancer in patients with unprovoked VTE is poorly understood, many physicians have criticized the concept of "extensive screening" because it may provoke anxiety, may be associated with test complications, may result in unnecessary further testing for false-positive results, and, finally, may be invasive and expensive.

Carrier and his colleagues performed an intensive and systematic review of the literature to evaluate the available data on the risks and benefits of cancer screening in patients with VTE.[9] They evaluated 36 studies between 1950 and 2007 to estimate the absolute risk of previously undiagnosed cancer being present in patients and patient subgroups with either provoked or unprovoked VTE, to estimate the additional cases of cancer detected by extensive screening strategies when compared with more limited screening strategies, and to estimate the potential additional morbidity or mortality risks and/or benefits of an extensive screening strategy. The primary outcome measure was detection of previously undiagnosed cancer. The combined prevalence of occult cancer was 6.1% at baseline and 10.0% at 12 months after VTE diagnosis. Limited screening detected 47.6% of all occult cancers in patients with VTE and the detection rate increased to 66.1% in the patients who were subjected to extensive screening, which included abdominal and pelvic CT examinations.

■ COMMENTARY

Although Trousseau first described the association between VTE and cancer,[1] Illtyd and his colleagues in 1935 more widely promulgated the idea that clinically

inapparent cancer could trigger VTE.[10] In fact, only small numbers of cancer cells with a procoagulant phenotype are all that is needed to initiate coagulation reactions that are amplified by host coagulation proteins to produce massive clots[11-13]; this reaction has often been described by the common phrase that "a nickel's worth of cancer can give a dollar's worth of clot."[14] The question arises as to how extensive a workup should be performed in patients with VTE given the psychological and physical harm often produced by false-positive results and the frequency of complications secondary to investigative procedures instigated by true- and by false-positive test results. Also, it is of course important to know how frequently a cancer is detected when patients with VTE are subjected to a thorough investigation.

Carrier and his colleagues reported that the period with the highest prevalence of previously unrecognized and newly discovered cases of cancer was within the first month of an idiopathic VTE episode (6.1%) and the rate then dropped to 2% for months 1-6 and 1.4% for months 6-12.[9] Limited cancer screening detected only about one-half of the total cases compared to extensive screening and it was also noted that CT scanning of the abdomen and pelvis had the most impact on improving the case findings in the extensive screening group. Even though extensive screening detected more cancer cases at baseline than usual care, at least one-third of the cases were not detected even by extensive screening. Unprovoked VTE was more commonly associated with cancer than provoked VTE. Finally, adequate data were not available to demonstrate any survival benefit associated even with extensive cancer screening in the relatively short 12-month screening period in the studies that were reviewed.

In conclusion, it must be recognized that previously undiagnosed cancer is common in patients with unprovoked VTE and that an extensive screening strategy (including CT examinations of the abdomen and pelvis) is more likely to detect the occult lesions. However, recognizing that early diagnosis may not affect the natural history of cancer,[8] should the practicing clinician even screen for occult cancer in patients with VTE? This question will best be answered by the results of a large, randomized trial; however, even if the clinician does not know whether improved survival can be achieved in VTE patients with early cancer diagnosis and even though an intensive search for occult cancer may cost thousands of dollars, an intensive evaluation of the patient with unprovoked VTE will be successful in detecting occult cancer in at least 10% of patients with previously undiagnosed cancer.

Is it worth it? The outcome value of early detection will only be known after the results of an appropriate well-designed clinical trial becomes available and these results appear to be many years off. I personally would recommend continued extensive clinical evaluation of all patients with VTE, especially if it is of the unprovoked variety and, of course, vigorous treatment of all detected cancers should then be performed following the widely published guidelines. ■

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Can Lubiprostone Improve PEG-based Colonoscopy Prep?

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG, AGAF

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Dr. Robinson reports no financial relationship to this field of study.

Synopsis: *Lubiprostone, the new drug for idiopathic constipation, improved PEG-based colonoscopy preparation.*

Source: Stengel JZ, Jones DP. Single-dose lubiprostone along with split-dose PEG solution without dietary restrictions for bowel cleansing prior to colonoscopy: A randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2008;103:2224-2230.

ALTHOUGH COLONOSCOPY IS WIDELY RECOMMENDED as a screening tool for the detection of polyps and early colon cancer, as well as for the diagnosis of many other important disorders, colon preparation prior to colonoscopy has been a major obstacle to patient acceptance. Poor preparations make colonoscopy difficult, potentially more dangerous, and impair diagnostic accuracy. Polyethylene glycol electrolyte solutions (PEG) are commonly used for colon cleansing, and they are considered to be generally safe and potentially effective. However, the high volumes that have to be consumed by patients are often poorly tolerated. For this reason, some clinicians have adopted a split-dose regimen that involves drinking half the solution the evening before the procedure and the other half early the next morning. To purge remaining liquid within the colonic lumen along with residual fecal material, bisacodyl tablets are often added to the PEG regimen. However, a significant number of patients experience bisacodyl-related abdominal cramping and/or nausea. Lubiprostone (Amitiza™) is a recently approved medication for the treatment of idiopathic constipation that stimulates the secretion of a chloride-rich fluid into the colonic lumen without affecting colonic fluid and electrolyte absorption. Lubiprostone is effective for the treatment of chronic constipation and constipation-predominant IBS. It is generally quite well tolerated. The present study enrolled 200 patients who were referred for colon cancer screening. All received split-dose PEG, and half took lubiprostone as a 24 μg oral gel cap at noon the day before the procedure and half received a matching placebo. All patients consumed a regular diet until 4:00 p.m. the day prior to colonoscopy and clear liquids thereafter until the time of the procedure. Endoscopists were blind to treatment allocation. The validated 5-point Ottawa bowel preparation scale was used to rate each section of the colon for cleanliness (right, mid, rectosigmoid). A 14-point scale for the amount of residual fluid was also utilized. Participants rated their degree of satisfaction with the colon preparation regimen using a 5-point scale. Ultimately, 94 patients completed each arm of the study. Mean age for participants was about 55 years. Gender and other clinical characteristics were evenly divided. Bowel preparation quality was superior in all colon segments in the patients who received lubiprostone ($P < 0.001$). There was no significant difference between active drug and placebo in the amount of residual colon fluid. The time required to complete the colonoscopy was lower in lubiprostone recipients ($P = 0.021$) Lubiprostone was preferred by patients in terms of the overall preparation experience ($P = 0.003$), and no difference in any adverse events was identified between active drug and placebo. The authors point out that these outpatients are likely to have had better colonoscopy preparation results than might have occurred in inpatients with their immobility and comorbidities. The study was funded by Takeda Pharmaceuticals.

■ COMMENTARY

There is no doubt that colonoscopy preparation remains unsatisfactory for many patients, and poor colon preparation continues to occur frequently. Anything that might improve colonoscopy preparation would be most welcome. It appears that the anti-constipation drug lubiprostone offers a promising adjunct to PEG-based colon cleansing prior to colonoscopy. There is little doubt that the active drug provided significant benefits when compared to placebo. However, as the authors themselves point out, the conventional adjunct to PEG is bisacodyl. It seems to me that the ideal lubiprostone study would have compared lubiprostone plus PEG to a PEG preparation that utilized bisacodyl. Perhaps such a study is already planned, and I sincerely hope that this is the case. Meanwhile, we really don't know whether lubiprostone is a good alternative to bisacodyl. It certainly will be more expensive. A comparative study using bisacodyl in one arm and lubiprostone in the other arm would have uncertain results, and pharmaceutical companies often avoid performing studies where the outcome cannot be reasonably well predicted. ■

Pharmacology Update

Romiplostim Injection (Nplate™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliot is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

A NEW AGENT HAS BEEN APPROVED BY THE FDA FOR THE treatment of thrombocytopenia associated with chronic immune thrombocytopenia purpura (ITP). Romiplostim is a thombopoietin receptor agonist. It is marketed by Amgen, Inc., as Nplate™ and is only available through the Nplate™ NEXUS Program.

Indications

Romiplostim is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura who have insufficient response to corticosteroids, immunoglobulin, or splenectomy. It should be used in patients with increased risk of bleeding and not for normalizing platelet counts.[1]

Dosage

The initial recommended dose is 1 μg/kg administered subcutaneously once weekly. The dose may be titrated by 1 μg/kg increments to achieve and maintain a platelet count of 50×10^9/L or greater as necessary to reduce the risk of bleeding. The dose should not exceed 10 μg/kg. Romplostim should not be used or continued if the platelet counts exceed 400×10^9/L or if platelet counts do not increase after 4 weeks at the maximum dose.[1]

Romiplostim is supplied as 250 μg and 500 μg single-use vials.

Potential Advantages

A majority of splenectomized (79%) and non-splenectomized (88%) patients showed an overall response to romiplostim.[1,2]

Potential Disadvantages

Romiplostim increases the risk for development or progression of reticulin fiber deposits within the bone marrow that may lead to marrow fibrosis and cytopenia. The risk of hematologic malignancies may be increased. Excessive production of platelets may lead to thrombotic or thromboembolic complications and discontinuation of romiplostin may result in worsening of thrombocytopenia.1 In clinical trials, common adverse events that occurred more frequently than placebo include dizziness (17% vs 0%), insomnia (16% vs 7%), myalgia (14% vs 2%), abdominal pain (11% vs 0%), and pain in extremities (13% vs 5%). The incidence of development of neutralizing antibodies to romiplostin is 5%.[1]

Comments

Romiplostin is a recombinant Fc-peptide fusion protein (peptibody). The peptide portion of this molecule binds to the thrombopoietin receptor resulting in stimulation, generally in a dose-related manner, of platelet production.[1,3,4] The efficacy in ITP was shown in two similarly designed 24-week studies; one with splenectomized patients (n = 63) and the other in non-splenectomized patients (n = 63).[1,2] The median baseline platelet counts were 19×10^9/L and 15×10^9/L, respectively. Prior treatment included corticosteroids, IVIG, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients were allowed to continue these therapies if they were on a constant dosing schedule. Rescue therapies for bleeding, wet purpura, and immediate risk for hemorrhage included corticosteroids, IVIG, platelet infusion, and anti-D-immunoglobulin. Patients were randomized (2:1) to romiplostim starting at a weekly injection of 1 μg/kg or placebo and titrated to a target platelet count of 50×10^9/L to 200×10^9/L. The primary endpoint was durable response. This was defined as a weekly platelet count of 50×10^9/L or higher for 6 or more weeks of the last 8 weeks of therapy. Durable response was achieved in 38% of spenectomized patients and 61% of non-splenectomized patients. Lower body weight (< 70 kg) and no splenectomy were associated with increased rates of durable response. Transient response was any weekly platelet count 50×10^9/L or greater for any 4 weeks without a durable response. A majority of patients had an overall response (durable plus transient), 79% and 88%, respectively, vs 0% and 14% for placebo. Fifty percent of patients achieved the target by week 2-3, but overall the mean time to target is about 14 weeks. Platelet counts generally returned to levels less than 50×10^9/L after discontinuation of the drug with only 7 of 83 patients (8.4%) maintaining that level 12 weeks after discontinuation.[2] About one-half of patients (52%) on romiplostim discontinued their ITP medication compared to 19% for the placebo group. More patients in the placebo group required rescue

treatment (59.5% vs 21.7%) and had significant bleeding events (12% vs 7%). The drug was generally well tolerated. One patient assigned to romiplostim had increased baseline bone marrow reticulin and thrombosis occurred in 3 patients assigned to romiplostim.

Clinical Implications

Idiopathic thrombocytopenia purpura is an acquired autoimmune disorder characterized by antibody-mediated destruction of platelets but platelet production may also be affected.[3,4] The most serious consequence of the disease is risk of bleeding, particularly intracranial hemorrhage. Treatment has generally been targeted at the antibody-mediated platelet destruction with splenectomy, corticosteroids, IVIG, rituximab, and cytotoxic agents. The potential of romiplostim to be used as a splenectomy-sparing agent is being investigated in a long-term study.[5] Romiplostim provides a new mechanism of action by stimulating platelet production. It is only available through the Nplate™ NEXUS Program. Only prescribers and patients registered with the program can prescribe, administer, and receive product. ■

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CME Questions

46. In terminally ill patients, end-of-life discussions are associated with:
a. less frequent admission to intensive care units.
b. more frequent "Do Not Resuscitate" declarations.
c. less depression in caregivers following loved one's death.
d. hospice stays greater than one week.
e. All of the above

47. Previously undiagnosed cancer in patients with unprovoked VTE is:
a. found in more than 80% of these patients with intensive screening studies.
b. rarely found in these patients even with intensive screening studies.
c. found in 10% of patients from baseline to 12 months.
d. found with the same degree of frequency with limited screening when compared to extensive screening testing.

48. Lubiprostone accomplished which of the following?
a. Improved colon cleansing vs placebo
b. Achieved greater patient acceptance than the PEG preparation with placebo
c. Led to less fluid in colon segments vs. placebo
d. 1 and 2
e. 1 and 2 and 3

Answers: 46. (e), 47. (c), 48. (d).

CME Objectives

The objectives of *Internal Medicine Alert* are:
- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Early intensive anti-diabetic treatment may improve β-cell function

Source: Chen HS, et al. Beneficial effects of insulin on glycemic control and b-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 2008; 31:1927-1932.

Approximately 50% of β-cell function has been lost at the time of initial diagnosis of type 2 diabetes. The UKPDS suggested that neither insulin, metformin, nor oral agents demonstrated any particular advantage as far as progressive subsequent decline in β-cell function is concerned. Whether intensive initial glucose control with insulin followed by routine diabetic control with either insulin or oral agents improves control and/or beta cell function was the subject of this publication by Chen et al.

Newly diagnosed type 2 diabetics with severe hyperglycemia (n = 74) were hospitalized and received intensive basal-prandial insulin therapy to maintain near-normal fasting, preprandial, and bedtime glucose; once good glycemic control had been attained and maintained for 10-14 days, subjects were discharged and randomized to either continued maintenance of tight control with basal-prandial insulin or oral agents (metformin and/or sulfonylurea titrated to maintain FBS 90-130 mg/dL).

The insulin-maintenance group had significantly greater improvements in A1c at 6 months, although FBS levels were similar to the oral agent group. A comparison of β-cell function at 6 months indicated that patients receiving basal-prandial insulin treatment had better outcomes than those on oral agents.

Evolution of management techniques for type 2 diabetes continues to suggest an earlier and more prominent role for insulin therapy. These data suggest that how one gets to goal may be important, and that early introduction of insulin may have advantages over oral agents. ■

The Swedish Diabetes CVD Risk Score

Source: Cederholm J, et al. Risk prediction of cardiovascular disease in type 2 diabetes: A risk equation for the Swedish National Diabetes Register. *Diabetes Care* 2008;31:2038-2043.

Cardiovascular disease (CVD) risk prediction helps to identify persons at high risk, stratify treatment groups, and motivate healthful behaviors and modification of risk factors. Diabetic patients are at particularly high risk of CVD, yet currently available risk scoring systems have not performed particularly well.

The Swedish National Diabetes Register provided the patient population from which a new CVD risk predictor has been developed.

During a mean follow-up of 5.6 years (n = 11,646 adult diabetics), 1482 first cardiovascular events occurred. Risk factors with strong association to CVD events were confirmed to be A1c, age at onset of diabetes, duration of diabetes, gender, BMI, smoking, SBP, use of antihypertensive medication, and use of lipid-lowering medication. When these risk factors were used in randomly selected subgroups from the population, accuracy of CVD risk prediction was excellent.

Because this risk prediction tool utilizes information that is generally readily clinically available, and is structured to inform us about predicted 5-year risk (rather than 10-year risk in several other popularly used risk scores), the Swedish Diabetes CVD Risk Score may find popular utility. ■

Ethnic disparity in colon polyps detected during routine screening

Source: Lieberman DA, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA* 2008; 300:1417-1422.

Both the incidence and rate of mortality of colon cancer (CCa) is higher in black men and women than whites; CCa also occurs at a younger age in blacks than in whites. Health care access issues, lesser adherence to screening recommendations, or less frequent screening recommendations by health care providers to some minority groups might explain some—but not all—of this disparity. Sociopolitical and economic issues aside, there may simply be a greater incidence of CCa and precancer (i.e., polyps) in black men and women.

Lieberman et al evaluated data from sites (n = 67) routinely performing screening colonoscopy in asymptomatic individuals. During the 2004-2005 interval, 80,061 white and 5464 black persons underwent screening colonoscopy. The primary endpoint of the data analysis was the prevalence of large polyps (> 9.0 mm).

Overall, black women were 62% more likely than white women to have a large polyp discovered on screening colonoscopy; black men were 16% more likely to have a large polyp found. This information should encourage clinicians to be particularly vigilant that black men and women participate in timely screening colonoscopy. ■