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Helicobacter pylori and Pancreatic Cancer

ABSTRACT & COMMENTARY

Synopsis: *The association of whole-cell H pylori or cytotoxin-associated gene-A-positive (CagA+) strains of H pylori carriage with exocrine pancreatic cancer was investigated in a nested, case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of 29,133 male Finnish smokers. The seroprevalence of H pylori was 82% among cases and 73% among control subjects. Two-sided statistical tests demonstrated an elevated risk of pancreatic cancer in subjects seropositive for H pylori or CagA+ strains compared to seronegative controls (odds ratio [OR] = 1.87; 95% confidence interval [CI] = 1.05-3.34); OR = 2.01, 95% CI = 1.09-3.70, respectively). A possible role is suggested for H pylori carriage as a risk factor for pancreatic cancer.*

Source: Stolzenberg-Solomon, et al. *J Nat Cancer Inst.* 2001;93(12):937-941.

Helicobacter pylori carriage is a known risk factor for peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma.[1-3] The CagA+ strains of *H pylori* have especially been reported to have an association with inflammation, ulceration, and cancer.[1] Since the mechanism of *H pylori*-associated gastric cancer is potentially related to persistent inflammation in the stomach[1] and chronic pancreatitis has been associated with pancreatic cancer,[4] it was postulated that carriage of *H pylori* may have an association with inflammation in the pancreas and pancreatic cancer. This possible association of *H pylori* carriage and pancreatic cancer was also suggested by an earlier case-control study.[5] Thus, the potential association of *H pylori* and pancreatic cancer was evaluated in the current study.

This study by Stolzenberg-Solomon and colleagues was a nested, case-control study of male smokers who previously participated in a double-blind, placebo-controlled, primary prevention trial (ATBC Study) that tested whether alpha-tocopherol or beta-carotene could reduce the incidence of cancer in male smokers.[6,7] A total of 29,133 men participated in the original ATBC study from 1985 through 1988, and all cases of pancreatic cancer diagnosed from January 1985

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through December 1995 were identified by the Finnish Cancer Registry and death certificates. A total of 130 pancreatic cancer subjects and 260 matched control subjects were identified. Control subjects were selected from ATBC study participants based on being alive at the same time as the pancreatic cancer subjects and were matched by age, month of baseline blood draw, completion of dietary history, study center, and study assignment from the original ATBC study. The final sample size was composed of the 121 case subjects with baseline serum measurements of *H pylori* whole-cell (WC) and CagA strains and matched control subjects (n = 226). Nonsignificant trends were seen for *H pylori* seropositivity and a history of ulcer disease. Seropositivity for *H pylori* WC (82% vs 73%; P = 0.07) and CagA+ strains (60% vs 51%; P = 0.05) was greater in cases than controls. Following adjustment for years of smoking, patients with *H pylori* carriage with CagA+ strains had a 2-fold increase in likelihood of having pancreatic cancer as those who did not (OR = 2.01; 95% CI = 1.09-3.70). Stolzenberg-Solomon et al conclude that this prospective study demonstrates a significant relationship between *H pylori* carriage and pancreatic cancer.

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COMMENT BY MARK R. ALBERTINI, MD

The association of infection with *H pylori* and duodenal ulcer has been established.[8] This association offers treatment strategies aimed at eradication of the *H pylori* infection. The role of *H pylori* as a carcinogenic factor for gastric cancer has also been reported and is thought to result from changes progressing from superficial gastritis to precancerous gastritis to dysplasia.[1] An ability to intervene in this process appears possible and requires investigation. The potential mechanisms for *H pylori* infection and pancreatic cancer remain speculative, and it is unknown whether actual pancreatic colonization with *H pylori* even occurs. Other factors associated with *H pylori* infection, including formation of other carcinogenic compounds or associations with other infectious agents, remain possible.

The current study is a relatively large study with prospective blood collection from similar cohorts of individuals. The association of *H pylori* infection with inflammation provides a possible biological mechanism for *H pylori* carriage and pancreatic cancer. However, it should be noted that the entire study was based on male smokers. In addition, the association between *H pylori* carriage and pancreatic cancer in the current study became more significant once the analysis was additionally adjusted for years of cigarettes smoked. While these observations are intriguing, confirmation of the relationship of *H pylori* infection and pancreatic cancer needs to be evaluated in additional studies. It is hoped that identification of risk factors for pancreatic cancer may help identify pathogenesis of this disease as well as offer insight into treatment and/or prevention strategies. ❖

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Paclitaxel and High-Dose Oral Estramustine in Patients with Hormone-Refractory Prostate Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Weekly paclitaxel chemotherapy combined with 3 days of high-dose oral estramustine was evaluated in a Phase I trial for patients with hormone refractory prostate cancer. PSA declines of 50% occurred in 8 of 12 patients treated at the 2 highest dose levels. This regimen was generally well tolerated with less hematologic, neurologic and gastrointestinal toxicity than had been seen with other regimens combining these 2 agents. However, thromboembolic events were still problematic. The PSA response rate was similar for other paclitaxel/estramustine regimens and may prove more acceptable for this patient population.*

Source: Ferrari AC, et al. *Cancer*. 2001;91:2039-2045.

Over the last decade, chemotherapy has been used with increasing frequency for patients with hormone refractory prostate cancer. Mitoxantrone combined with prednisone has been approved by the FDA for this indication but the need for more effective and well-tolerated regimens is clearly recognized. The combination of estramustine and paclitaxel, 2 agents with minimal single agent activity in prostate cancer, has been promising. PSA and measurable disease response rates of 53% and 44%, respectively, were observed when paclitaxel was given as a 96-hour infusion with daily estramustine.[1] One-fifth of the patients developed grade 3 or 4 granulocytopenia and neuropathy and 10% had serious gastrointestinal toxicity and thrombotic complications.

In an attempt to decrease the toxicity and increase the acceptability of the regimen, Ferrari and associates conducted a Phase I trial of weekly intravenous paclitaxel over 1 hour combined with 3 days of estramustine starting 2 days before chemotherapy. The MTDs for paclitaxel and estramustine were 90 mg/m^2 and 600 mg/m^2, respectively. Eighteen patients were studied in cohorts of 3, 3, 6, and 6 patients. Three patients experienced grade 3 or 4 toxicity: one patient had grade 3 nausea and diarrhea (cohort 3), one patient grade 3 neutropenia (cohort 4), and one patient developed edema followed by a thromboembolic event (cohort 4). Grade 1 or 2 toxicities included neuropathy (3 patients) and gastrointestinal side effects (8 patients). Eight of the 12 patients entered into the 2 highest cohorts had reductions of their PSAs by at least 50% and 7 of these had reductions of at least 75%. Only 3 patients had measurable disease, one of whom had a 50% decrease in tumor size. The median duration of response was 16.7 weeks (range 3+ to 48.6 weeks).

COMMENT BY MICHAEL J. HAWKINS, MD

Low dose, well-tolerated regimens have had some limited activity in prostate cancer. Increased dose intensity has often been associated with an unacceptable toxicity profile. Paclitaxel and estramustine is a potentially attractive combination for the treatment of hormone refractory prostate cancer but had previously been associated with a high incidence of grade 3 and 4 toxicities. Neurotoxicity and gastrointestinal side effects appear to be substantially less using this regimen of low-dose weekly paclitaxel and intermittent high-dose estramustine. A high incidence of side effects and poor patient tolerance has limited greater use of chemotherapy in this disease. This regimen requires more extensive testing but appears to reduce to an acceptable level some of the side effects associated with these drugs when given on other regimens. ❖

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Prostate Cancer: No Bones About It

ABSTRACT & COMMENTARY

Synopsis: *Do hormone-naive men with prostate cancer have low bone mineral density? Greater underlying bone loss was suggested by quantitative CT than by dual-energy X-ray absorptiometry. Suggestions for management are given.*

Source: Smith M, et al. *Cancer*. 2001;91:2238-2245.

What happens to the bones of osteoporotic prostate cancer patients when treated with bone-depleting androgen-deprivation therapy? Therapy-related loss of bone mineral density (BMD) is not an issue normally addressed in the therapy of prostate cancer, yet all oncologists are familiar with the ravaging effects of bone metastases on patients with prostate cancer. Therefore, Smith and colleagues enrolled 41 men with locally advanced, lymph-node-positive, or recurrent

prostate cancer to determine their baseline BMD. Patients with positive bone scans were specifically excluded to avoid interference with BMD calculations. In addition, patients with any medical risk factors for osteoporosis were also excluded.

BMD was evaluated by 2 methods: quantitative computed tomography (QCT) of the lumbar spine, and dual-energy x-ray absorptiometry (DXA) of the hip, lateral-lumbar spine and posterior-anterior (PA) lumbar spine. According to the QCT results, 95% of the patients had diminished BMD. Two-thirds of these patients had a T score < -2.5 consistent with osteoporosis, and one-third had a T score > -2.5 but < -1.0 consistent with osteopenia. The DXA results, on the other hand, revealed that only 14 of the men had a T score < -1.0 at 1 or more of the 3 skeletal sites, with only 2 of these patient's scores < -2.5.

COMMENT BY KENNETH W. KOTZ, MD

T scores, expressed in "standard deviation units," are determined by taking the difference between the calculated BMD and the BMD of a 30 year old (same gender and race) and dividing by the standard deviation of the mean. A patient with a BMD that is normal (ie, the same as the mean) would have a score of 0, with positive and negative scores representing above and below normal results, respectively. Z scores are formulated the same way as T scores but the calculated BMD is compared with an age-specific standard rather than the peak young adult standard. The average Z score in this study (as determined by QCT) was -0.7, suggesting at most a minimal decrease compared with age-matched controls. As a general rule, T scores of -1 to -2 and below -2 are associated with a doubling and quadrupling, respectively, of the risk of a fracture.

The title of this study is "Low Bone Mineral Density in Hormone-Naive Men with Prostate Carcinoma." This would appear to be the case when looking at the QCT results as presented in this study when compared with young adult males (mean T score -2.8 ± 1.1). However, when compared with age-matched controls, the mean Z score for QCT was only -0.7 ± 0.9 suggesting that these patients are not much different than age-matched controls. The results as determined by DXA were discordant with the QCT results. In fact, the DXA results of the T and Z scores of the PA lumbar spine were greater than 0.

It is not surprising that the DXA and QCT results were discordant as each modality is limited by the standard database it uses for comparisons as well as inherent differences in technique. QCT provides 3-dimensional BMD based on a direct measurement of mass per volume, compared with DXA results that are calculated from the mass per area scanned. QCT can differentiate between cortical and trabecular bone and can also occasionally visualize unsuspected lesions. However, DXA has superior precision and excellent accuracy. The DXA scan is also associated with significantly less radiation exposure for the patient (10-100 times less than even a CXR), is less expensive, and scans can be performed in several minutes. DXA of the lateral spine (not the PA spine), as performed in this study, is generally not used anymore as it is not really clinically useful and cannot be calculated in overweight individuals, as occurred in 15 of the 41 patients on this study. Therefore, the oncologist looking for underlying osteopenia would most likely order the readily available DXA of the PA spine and/or hip.

Others have also evaluated the BMD of prostate cancer patients. Daniell and associates found that prostate cancer patients had lower femoral neck BMD compared with controls, and that this density decreased by 2.4% and 7.6%, respectively, during years 1 and 2 of medical or surgical castration, followed by additional loss of about 2% per year up to 8 years later.[1] Wei and colleagues also found that pre-existing osteopenia and osteoporosis were common in prostate cancer patients.[2] Their cross-sectional study also noted significant loss of bone in patients who were on androgen deprivation therapy for more than a year compared with patients on the same therapy for less than a year. Interestingly, they used a regression analysis to estimate that it takes 48 months of androgen deprivation therapy to cause osteopenia in a patient with normal baseline measurements.[2]

Whereas hypogonadism due to medical or surgical castration clearly leads to loss of BMD, the effects of antiandrogens are less defined. Antiandrogens may suppress osteoblastic production of IL-6, a hormone that promotes bone resorption.[3] On the other hand, antiandrogens also inhibit the contribution that adrenal androgens make to the maintenance of bone mass through their effect on the androgen receptor.[3]

A real concern is whether the complications of bone metastases are worse when progressive bone loss from androgen depletion is not addressed. Unfortunately, it is not known whether treating a low BMD in patients ready to start androgen ablation will lead to any clinical benefit. For example, there are no data demonstrating fewer metastatic lesions or diminished complications (pain, fractures, etc) in prostate cancer patients. Nevertheless, one approach would be to obtain a baseline DXA scan and start patients at greater risk (such as a T score less than -2) on calcium 500 mg/d (assuming diet also contains at least 500 mg), vitamin D 400 IU/d (often found in a multivitamin), and a bisphosphonate (either alendronate or risendronate). Those at lower risk

could receive calcium and vitamin D with a follow-up DXA scan. Relevantly, the study by Smith et al revealed that 17% of the patients had hypovitaminosis D and 59% of the patients had dietary calcium intakes below the recommended daily allowance. ❖

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Detecting Colorectal Cancer in Stool With the Use of Multiple Genetic Targets

ABSTRACT & COMMENTARY

Synopsis: *A reproducible method was developed for reliably detecting 3 tumor-associated genetic alterations in the stool of 51 colorectal cancer patients with all stages of malignancy. The results support the concept of early tumor identification by detection of molecular markers in ex vivo bodily fluids or products. This technology could potentially mitigate the need for unnecessary invasive screening tests in patients without disease or improve the chance for earlier diagnoses and cure for those with disease.*

Source: Dong SM, et al. *J Natl Cancer Inst*. 2001;93: 858-865.

Colorectal cancer remains one of the most prevalent tumors in the Western world and certainly one of the most widely studied in Western medicine. Our understanding of this cancer has been enhanced by the discovery of sequential genetic mutations driving the process of neoplastic transformation.[1,2] In the more common adenoma-to-carcinoma pathway, the initial mutation occurs in the adenomatous polyposis coli (APC) gene, associated with aberrant crypt foci and eventually polyp formation, growth, and dysplasia. Next, an oncogene such as K-RAS is activated, incurring further clonal expansion of the dysplastic lesion. Subsequently, mutation or deletion of a tumor-suppressor gene such as TP53 and/or deleted in colon cancer (DCC) occurs, leading to the requisite disruption of at least 2 growth control pathways. Malignant transformation has also been associated with germline or somatic mutations of mismatch repair genes, most notably among hereditary nonpolyposis colorectal cancer (HNPCC) patients.[3] These mutations manifest as instability in microsatellite sequence loci, eg, BAT26.

Screening for any of these markers individually may be a painstaking process with sensitivities and specificities no better than the well-entrenched, fecal-occult blood screen. However, a relatively simple, highly sensitive and specific screening method for some optimal combination of these markers could be very useful indeed. In this study, Dong and colleagues devised a protocol for reproducibly isolating DNA from stool in sufficient quantity to allow detection of mutations in K-RAS, TP53, and BAT26 genes. They validated the presence of alterations by testing tumor specimens resected from the same patients.

Fifty-one patients with colonoscopy-diagnosed tumors and no history of familial adenomatous polyposis (FAP) or HNPCC were recruited for this study. One patient had Dukes' A disease; the others had Dukes' B (n = 17), Dukes' C (n = 21), and Dukes' D (n = 12). Thirteen patients had right-sided lesions and 37 had left-sided lesions. One patient had a transverse colon lesion. Stool samples and primary tumor samples were obtained from each patient and subjected to molecular analysis separately.

TP53 mutations in stool-derived DNA were detected using mismatch-ligation assays (MLAs) and confirmed with repeated testing of separate preparations. TP53 mutations in processed tumor specimens were identified after polymerase chain reaction (PCR) amplification using ligation-detection reaction (LDR) and confirmed with MLA. BAT26 deletions were assessed by minisequencing after PCR in both stool-derived and tumor-derived specimens. K-RAS gene mutation status was examined using digital PCR for stool-derived DNA. Status of the K-RAS gene in tumor-derived DNA was determined by both MLA and PCR/LDR, and confirmed with digital PCR in some specimens.

Overall, Dong et al developed methods to isolate a sufficient quantity of DNA from all 51 stool samples for evaluation of TP53 and BAT26 mutations, and 48 samples for digital PCR analysis of K-RAS. Tumor TP53 mutations were observed in 30 of 51 specimens (59%) and identical TP53 mutations were observed in each of the matched stool-derived specimens, including 1 patient with stage A disease in the right colon. No mutations were detected in stool specimens from patients who did not have mutations in the tumor specimens.

BAT26 deletions were identified in 5 of 51 stool specimens, although an exact match occurred in only 3 of the 51 corresponding tumor specimens (6%). No BAT26 deletions were seen in stool from the 46 patients without BAT26 mutations in their tumor specimens. All tumors with BAT26 deletions were located in the right

colon (a frequent site of microsatellite unstable tumors).

K-RAS gene alterations, the best studied in stool due to a low number of codon sites, were assessed in 50 tumor specimens and 48 stool specimens due to technical limitations. K-RAS mutations were present in 17 of the 47 tumor specimens that had a corresponding stool specimen. K-RAS alterations were revealed in 8 of the 17 stool specimens corresponding to these K-RAS-positive tumors for an overall sensitivity of 17% (8/48). All 8 primary tumors with K-RAS alterations were located in the left colon. None of the stool specimens from patients with K-RAS mutation-negative tumors had evidence of K-RAS mutations.

Taken together, evaluation of stool-derived DNA for presence of any of these 3 genetic alterations revealed 71% sensitivity (36/51) and 100% specificity. Sensitivity increased to 92% (36/39) when only cases with mutation-positive tumors were considered. Dong et al note that this represents progress in the search for reliable, noninvasive tests for colorectal cancer, although specificity needs to be further examined in early-stage and asymptomatic patients.

COMMENT BY ARDEN MORRIS, MD

Genetic alterations leading to identifiable tumor markers have provided powerful new tools for detection and characterization of tumors. Identification of these tumor markers from sloughed cells in cancer patients may be an excellent source for detecting abnormalities. Despite technically challenging contaminants, stool is a particularly useful medium for development of such tests, given its reflection of mucosal cells from the entire organ and the well-documented sequence of genetic changes in colorectal cancer. Furthermore, the prevalence of this malignancy both assures availability of tissue for study and compels ongoing investigation into early diagnosis as the best hope for cure.

In this study, Dong et al have undertaken 2 tasks. First, they sought to generate an efficient and reliable method for extracting DNA from the stool of colorectal cancer patients. Their ability to examine nearly all specimens (51/51 for TP53 and BAT26; 48/51 for K-RAS) attests to their success in this endeavor. Second, they developed and validated assays to detect a limited number of common cancer-associated genetic alterations. This latter goal was slightly compromised by a lower sensitivity in detecting K-RAS (17% overall, 47% in those cases with positive tumors), which decreased overall sensitivity for the combined genetic markers. The presence of K-RAS on only 3 codons has made it the most frequently studied single genetic marker in stool.[2,4,5] However, targeting K-RAS is limited by its presence in only about 50% of colorectal cancers, ultimately halving the sensitivity of even the most precise assay. Moreover, K-RAS is also found in normal mucosa and nonmalignant lesions, potentially leading to false-positive results.[6] Additionally, although the test for BAT26 deletion had better accuracy (60%), the low prevalence of BAT26 deletions decreased sensitivity for this marker. The development of a simple and reliable assay for detection of APC, one of the most commonly mutated genes in colorectal cancer, could substantially improve the effectiveness of this multitargeted panel.

In summary, Dong et al have presented a protocol that may provide a template for future reliable analysis of stool for colorectal cancer-associated genetic mutations. The reliability of this multitargeted test was noteworthy in tumors of all stages and in both right- and left-colon lesions. With modification for better overall sensitivity and trials incorporating asymptomatic patients, we may anticipate the availability of a noninvasive tool for identifying early stage patients in the clinical setting. ❖

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Effect of Hormone Replacement Therapy in Breast Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *Hormone replacement therapy (HRT) has been found to increase the risk of developing breast cancer and, for that and other reasons, it is often avoided in women previously diagnosed with breast cancer. Scientists from the University of Washington published the results of a sophisticated case-control study and concluded that HRT after breast cancer has no adverse effect on recurrence or mortality.*

Source: O'Meara ES, et al. *J Natl Cancer Inst*. 2001;93:754-762.

The medical records of 400,000 group health Cooperative of Puget Sound HMO patients were searched for women with primary invasive breast cancer

from 1977 to 1994, and 2755 were identified. Only those women without distant metastatic disease were selected. HMO pharmacy data were used to determine which subjects in the study group used HRT. Other factors, including parity, gravidity, age at first full-term pregnancy, age at menarche, age at and reason for cessation of menses, menopausal symptoms, hysterectomy, oophorectomy, smoking history, family history, height, weight, details of breast cancer treatment, and tumor characteristics were also extracted from the patients' records. An HRT user was defined as any woman who filled 2 or more HRT prescriptions within any 6-month period after breast cancer diagnosis and prior to diagnosis of a recurrence.

There were 175 women who were classified as HRT users and were evaluable. Forty-three percent used vaginal preparations exclusively, 41% used only oral agents, and 16% used both. Adherence to the prescribed HRT regimen was assumed. Dose-equivalents of conjugated estrogen were calculated for esterified estrogen and ethinyl estradiol. Tubes of vaginal HRT were counted. Four non-HRT users from a pool of 698 women were then matched to each user based on age, year of diagnosis, and stage at diagnosis. Nonusers were still included even if they subsequently began HRT at some date later than that date chosen to match a user's interval from the time of their breast cancer diagnosis to the entry point in the study. HRT was used before diagnosis by 68% of HRT users after diagnosis and by 48% of nonusers. Patients were followed for a median of 3.7 years for recurrence and 4.6 years for mortality.

Recurrences were diagnosed in 16 HRT users (9%) and 101 nonusers (15%). The unadjusted relative risk (RR) was 0.58, and the RR after adjusting for potential confounding features such as those mentioned above, was 0.50. Analysis by type of hormone replacement did not change the RR results. Five HRT users (3%) and 59 nonusers (8%) died during the follow-up period. The unadjusted RR was 0.31, and the adjusted RR was 0.34.

O'Meara and colleagues concluded from their results that women who used HRT after a diagnosis of breast cancer had lower risks of recurrence and death than nonusers. They stated that their results should be interpreted with caution given the limitations of the study.

COMMENT BY EDWARD J. KAPLAN, MD

Menopausal symptoms can result in significant discomfort and impaired quality of life for sufferers. Symptoms can be severe and prolonged. No agents offer efficacy equivalent to HRT with regard to amelioration of these symptoms. Given that estrogen has been associated with an increased risk of breast cancer, and tamoxifen, with its antiestrogen properties, has been shown to decrease breast cancer recurrences, there is great concern over whether HRT in breast cancer survivors is wise. For the most part, HRT is discouraged in the latter group. However, data are very limited. O'Meara et al used a detailed, meticulous approach in their case-control study and determined that HRT does not put breast cancer survivors at increased risk of new events. On the contrary, HRT appeared to offer a protective effect.

In an accompanying editorial, Cuzick suggests that, even if HRT is found to be neutral with respect to an effect on breast cancer prognosis, it would represent an important advance in patient management.[1] Potentially, it would enable physicians to treat patients' menopausal symptoms without fear of provoking breast cancer into recurring.

Col and associates from Brigham and Women's Hospital in Boston performed a MEDLINE search for studies published from 1966 to 1999 and calculated RR values for 11 papers reporting on HRT following a diagnosis of breast cancer. Their objective was to combine all the existing data to establish the effect of HRT in this patient cohort. Their results coincided with the findings of O'Meara et al in that no significant increase in the risk of breast cancer recurrence was identified. O'Meara et al suggested that, although not conclusive, their results indicated that any risk associated with HRT must be of a limited magnitude.

Despite the data showing the absence of a deleterious effect of HRT on outcomes in breast cancer survivors, clinicians must continue to proceed with caution when counseling patients regarding the use of estrogens or estrogen derivatives. We are awaiting the results of 2 randomized trials that may offer further insights into this vexing issue.[3,4] ❖

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CME Questions

5. What percentage of patients with hormone refractory carcinoma of the prostate who are treated with paclitaxel and estramustine can be expected to have declines of their PSA by at least 50%?

a. < 1%
b. 5-10%
c. 20-30%
d. 40% or more

6. **Which of the following is true?**
   a. Supplementation of calcium and vitamin D reduces new bone metastases in prostate cancer patients.
   b. DXA exposes patients to higher levels of radiation than QCT.
   c. Osteoporosis in prostate cancer seems to be a paraneoplastic process.
   d. Z scores, unlike T scores, are based on age-matched controls.

7. **A typical sequence of genetic alterations in development of colorectal cancer would be:**
   a. APC, K-RAS, TP53.
   b. DCC, K-RAS, APC.
   c. TP53, BAT26, APC.
   d. TP53, DCC, K-RAS.

8. **In the O'Meara study, hormone replacement therapy:**
   a. was definitively shown to exert an adverse effect on survival in breast cancer.
   b. had a positive influence on outcomes following breast cancer.
   c. included oral but not vaginal forms.
   d. was defined as any HRT use prior to the diagnosis of breast cancer.

9. **O'Meara et al used which type of statistical approach in their study?**
   a. A randomized, controlled study
   b. A prospective, nonrandomized trial
   c. A placebo-controlled, nonblinded trial
   d. A case-control study

10. **Which of the following statements is true about the association of *H pylori* and pancreatic cancer?**
    a. It is known to be caused by *H pylori* infection of the pancreas.
    b. The association is stronger after controlling for years of smoking.
    c. The association is weaker after controlling for years of smoking.
    d. It is known to be related to another GI colonizing or infecting organism.

Attention Readers

A special supplement to *Clinical Oncology Alert* is included with this issue, as a bonus to our subscribers. This includes special, in-depth articles on stress-induced genetic instability and carcinogenesis, the role of ganglioside GD3 in angiogenesis, selective laser-photothermal interaction and immunoadjuvant metastatic tumor treatment, and a special look at funding news within the industry. The editorial team at *Clinical Oncology Alert* will continue to provide cutting-edge analyses and updates on developments in clinical oncology research.

This edition also includes the first of a series of coding inserts to help assist oncologists with any questions or concerns that might arise in daily practice. ❖

In Future Issues:

Novel Cellular Modification of Chemotherapy

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ONCOLOGY CODING AL

The practical monthly advisor for ethically optimizing coding reimbursement and efficiency in oncology offices and clinics

AAPC Approved

Expert Answers to Your Most Vexing Oncology Coding Questions

Supervising Physician

Question: *We are a freestanding clinic next to a hospital. Our medical oncologist is a contracted hospital physician. Can he bill Medicare for services provided in our office by our nurse if an emergency-room physician (who is not on the premises) acts as the supervising physician?*

New York Subscriber

Answer: You must first determine whether your practice is hospital-based or a physician office. Some oncologists have offices in hospital buildings and either have their employees administer chemotherapy or use facility personnel and supplies.

If the physician uses hospital employees or facilities for chemotherapy services, he cannot bill. To consider chemotherapy as office-based, the oncologist must administer it:

1. In an office that is leased to the physician and not in a hospital outpatient department area
2. Using nurses employed by the physician
3. With the physician's supplies and equipment.

Some non-Medicare payers and certain Medicare carriers might impose additional requirements. If the above are met, Medicare requires supervision of services, including administration of drugs and fluids provided by a nurse or other nonphysician. This is covered by Medicare as services "incident to" a physician's, meaning a physician must be present in the office and immediately available to assist when services are furnished.

The supervising physician does not have to be the patient's personal physician but can be another member of the group practice. In this case, the emergency-room physician, who is in a separate building, does not meet this requirement.

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Supplies and Office Visits

Question: *We have patients who come into our office to pick up a few weeks' worth of supplies at a time. These include empty syringes, needles, dressings and Heparin. I was told supplies are considered part of the office visit, but because there is no visit, what is the best way to bill?*

Arizona Subscriber

Answer: Medicare does not reimburse for the supplies listed because it includes them in patient care. Medicare will pay for supplies such as syringes and needles (A4206-A4209) when they are related to certain procedures like bone marrow biopsies (85102). However, this does not apply in the case you describe. Heparin (J1642) is a drug that Medicare carriers still pay for, but because the patient is taking it home, it is not reimbursable. If the patient's insurance is a non-Medicare insurance plan, it is possible to bill for some of these supplies. You should check with your commercial payers to determine what will be covered.

If the quantity represents a lot of money, you should call the carrier to preauthorize the supplies. You should be prepared to explain why you want to send these home with the patient — for example, convenience or lack of pharmacy benefit that would require the patient to pay out of pocket. And, there is no office visit to code because one did not occur.

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Dosimetry

Question: *What is the "real" date of service for basic dosimetry calculations, 77300? Is it the day the patient is being simulated for radiation treatment, or is it the day the dosimetrist is calculating?*

Indiana Subscriber

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Answer: The dosimetrist does not require the presence of the patient to complete his professional services. Therefore, the date of service should be when the calculations are done. For example, if the patient was seen on Monday, and the calculation was performed the following day, 77300 (*basic radiation dosimetry calculation, central axis depth dose, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, as required during course of treatment, only when prescribed by the treating physician*) should be billed on Tuesday.

Calculation can be done on the date of simulation, but does not need to be. For example, the patient is simulated on Monday but the dosimetrist does not complete the calculations until Wednesday. Wednesday's date should be used as the date for billing 77300, while the simulation, 77280-77295, would be billed on Monday.

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Billing an Incomplete Test

Question: *A patient comes in for a bone marrow test, but the doctor cannot reach the bone because the patient is obese. He reviews the laboratory test with the patient and proceeds with the test, but it is not completed. How should this be coded for Medicare?*

Colorado Subscriber

Answer: If a bone marrow aspiration (85095) or biopsy (85102) was begun but not completed, i.e., the skin was incised or a needle was inserted, appending modifier -53 (*discontinued procedure*) might be appropriate. The CPT definition for modifier -53 states that "Under certain circumstances, the physician may elect to terminate a surgical or diagnostic procedure. Due to extenuating circumstances or those that threaten the well-being of the patient, it may be necessary to indicate that a surgical or diagnostic procedure was started but discontinued. This may be reported by adding modifier -53 to the discontinued procedure code."

But appending modifier -53 might not be the deciding factor for reimbursement. *The Medicare Carriers' Manual* in the Fee Schedule for Physicians' Services, section 15900, addresses modifier -53 by stating, "... codes billed with this are subject to carrier medical review and priced by individual consideration."

In this instance, the proper coding for a bone marrow aspiration is 85095 with modifier -53. To withstand review of this claim, the patient record should include notes describing the procedure and when it was ended. A description of the patient's obesity and the physician's problem should also be included.

*— Questions answered by **Risë Marie Cleland,** co-founder of Oplinc Oncology Services, a coding consulting firm in Lawton, Okla.; **Laurie Lamar, RHIA, CCS, CTR, CCS-P,** assistant director of reimbursement, public policy and practice department of the American Society of Clinical Oncology in Alexandria, Va. Her position does not reflect the opinion of ASCO; **Elaine Towle, CMPE,** practice administrator for New Hampshire Oncology and Hematology in Hooksett, N.H.; and **Margaret Hickey, MS, MSN, RN, OCN, CORLN,** an independent coding consultant and former director of the Tulane Cancer Center in New Orleans.* ❑

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