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Cancer Survivorship… The Marriage Effect?

SPECIAL FEATURE

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study.

Synopsis: *Compared to cancer patients who were never married, divorced, widowed, or separated, married patients are significantly more likely to present at an earlier stage, undergo therapy with definitive or curative intent, and live longer among each of the 10 most common cancers killers in the United States. The data suggest the effect is rooted in better social support mechanisms among this cohort and highlight a modifiable "at-risk" population.*

Source: Aizer AA, et al. Marital status and survival in patients with cancer. *J Clin Oncol* 2013; Sep 23. 10.1200/JCO.2013.51.5080 [Epub ahead of print].

THE POSITIVE EFFECT OF MARRIAGE ON CANCER SURVIVORSHIP PREVIOUSLY has been reported but is not universal among various investigations.[1,2] The authors set out to examine the impact of marital status on stage at diagnosis, use of definitive therapy, and cancer-specific mortality between each of the 10 leading causes of cancer-related death in the United States. To interrogate a sample large enough to adjust for the various covariates, they identified more than 1.2 million cancer patients registered in the Surveillance, Epidemiology and End Results (SEER) program diagnosed between 2004 and 2008. Ten primary tumor sites (lung, colorectal, breast, pancreatic, prostate, liver/intrahepatic bile duct, non-Hodgkin lymphoma, head/neck, ovarian, or esophageal cancer) were addressed, as they represented the most common diagnoses associated with cancer-specific morality. After eliminating cases with inadequate clinical and follow-up information, 734,889 patients were available for analysis. The authors found that married patients were less likely to present with metastatic disease

(adjusted odds ratio [OR], 0.83; 95% confidence interval [CI], 0.82-0.84; $P < 0.001$), more likely to receive definitive therapy (adjusted OR, 1.53; 95% CI, 1.51-1.56; $P < 0.001$), and less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79-0.81; $P < 0.001$) than unmarried patients. These associations remained significant when each individual cancer was analyzed ($P < 0.05$ for all endpoints for each malignancy) and regardless of unmarried status ($P < 0.001$ for each unmarried category). The benefit associated with marriage was greater in males than females for all outcome measures analyzed ($P < 0.001$ in all cases). For prostate, breast, colorectal, esophageal, and head/neck cancers, the survival benefit associated with marriage was larger than the published survival benefit of chemotherapy. The authors concluded that unmarried patients are at significantly higher risk of presentation with metastatic cancer, undertreatment, and death resulting from their cancer, even after adjusting for known confounders. This study highlights the potentially significant impact that social support can have on cancer detection, treatment, and survival.

■ COMMENTARY

"My wife says I never listen to her…at least I think that's what she says…."

The impact of marriage on survivorship in cancer patients has been extensively examined in previous reports, but with inconclusive independent results. Most have shown a benefit but have been confounded by small samples size for individual malignancies, regionality, lack of information regarding follow-up, and survival not linked to cancer-specific events. However, the current study's design and analysis, while not optimal (e.g., a randomized trial), does provide some confidence the association is credible. This comes from several considerations. First, the sample was based on cancer-specific survivorship, that is, those cases in which death was recorded as a cancer event. This type of analysis censors patients who die before progression or from causes not related to cancer. In treatment trials, this endpoint is often considered to be biased because elderly patients are more likely to die of intercurrent disease leading to extensive censoring. However, for the current analysis, it provides cleaner data to assess the effect of the variable (marriage at diagnosis) on cause-specific outcomes across a variety of tumors. The second aspect affording credibility to this study's hypothesis-generating suppositions is the multi-regional patient inclusion. The SEER database captures more than 95% of the incident cancers from registries representing more than a quarter of the U.S. population. There are well-documented deficiencies in this database (e.g., no pathology review, lack of information regarding chemotherapy, oversimplified, and lack of confirmation of staging), but the demographics, diagnoses, stage category, some treatment, and outcomes recorded have been continually validated and updated for years. Third, the sample is large enough to consider important covariates such as, age, race, gender, residence, income, education, tumor and nodal stage, and treatment. In the context of marriage, these are important variables since married cancer patients tend to be younger, have higher incomes and education level, may have broader and better access to health care, and live in rural homesteads with larger family support mechanisms.[3] Considering these factors, marriage was still significantly protective and remained so against the 10 tumor types examined and relative to each unmarried category. Further, the effect in many tumor types (prostate, breast, colorectal, esophageal, and head/neck) was stronger than the impact of chemotherapy.

The primary takeaway message from this article, and others on the topic, is that marriage provides a critical internal social support system that is less often present among patients who are unmarried — these patients represent a risk group that deserves attention. While the quality of marriage among those married and the contribution of live-in unmarried cohabiters could not be directly assessed, it appears the marriage at the time of diagnosis is associated with important primary treatment variables that would be expected to result in better outcomes. For instance, most primary outcome measures, such as overall survival, progression-free survival, and objective response, are directly associated with tumor stage at presentation; earlier stage = better outcomes. Thus, tumors in which symptomatology

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may be reflective of an early-stage diagnosis (e.g., epistaxis in head and neck cancer) are more likely to be associated with better outcomes if a partner encourages ("nagging") a doctor's appointment at first occurrence.[4] Earlier stage at presentation would also increase the likelihood of definitive treatment options and increase the odds of finishing a prescribed treatment plan. Each of these factors has been broadly associated with more favorable survival in a variety of cancers. In ovarian cancer, symptomatology is not associated with earlier stage at presentation, but may be associated with lower metastatic tumor burden, affording a higher likelihood to undergo primary surgical debulking, to have a better cytoreduction outcome, and complete definitive adjuvant therapy. Finally, chronic stress has been implicated as negatively impacting cancer survivorship, particularly in regard to immune function and the tumor microenvironment, where stress is associated with accelerated angiogenesis and immune escape.[5,6] The hypothesis that married patients are less likely to suffer chronic stress and depression than their unmarried counterparts has been previously raised and may contribute to the study's findings.

So how can this information be leveraged? The knowledge that unmarried cancer patients represent an at-risk group provides an opportunity to develop and evaluate social support mechanisms that can act as surrogates for a live-in partner. Most cancer centers have regular patient supportive-expressive group therapy sessions. However, their impact on survival has been mixed in the few randomized controlled studies that have been conducted.[7,8] Nevertheless, comprehensive programs that provide not only social-expressive opportunities but also assessment/management of depression and anxiety and assistance with decision making represent the best opportunity to close the "survival gap" observed in unmarried individuals. Increased awareness and assessment of depression/anxiety should be afforded to all cancer patients. However, knowing the risks that may further impact and complicate a patient's treatment program, clinicians are encouraged to thoroughly evaluate the social support structure of unmarried patients at presentation and during their follow-up. ■

References

1. Nelles JL, et al. The impact of marriage on bladder cancer mortality. *Urol Oncol* 2009;27:263-267.
2. Goodwin JS, et al. The effect of marital status on stage, treatment, and survival of cancer patients. *JAMA* 1987;258:3125-3130.
3. Ayanian JZ, et al. The relation between health insurance coverage and clinical outcomes among women with breast cancer. *N Engl J Med* 1993;329:326-331.
4. Aizer AA, et al. Multidisciplinary care and pursuit of active surveillance in low-risk prostate cancer. *J Clin Oncol* 2012;30:3071-3076.
5. Sephton SE, et al. Diurnal cortisol rhythm as a predictor of lung cancer survival. *Brain Behav Immun* 2013;30(Suppl):S163-S170.
6. Sephton SE, et al. Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst* 2000;92:994-1000.
7. Spiegel D, et al. Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: A randomized prospective trial. *Cancer* 2007;110:1130-1138.
8. Temel JS, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-742.

Heavy Menstrual Bleeding and Underlying Bleeding Disorders: Should All Women Be Tested?

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports no financial relationships relevant to this field of study.

Synopsis: *In this sample of 102 consecutive Dutch patients with heavy menstrual bleeding, the overall prevalence of an underlying bleeding disorder was 29%, with the most common being disorders of platelet function. There was no difference in the prevalence of a bleeding disorder among women with and without a gynecologic explanation for their bleeding (fibroids or polyps).*

Source: Knol HM, et al. The prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding with and without gynecologic abnormalities. *Am J Obstet Gynecol* 2013;209:202.e1-7.

This prospective study enrolled 102 consecutive patients presenting to the gynecology clinic at the University Medical Centre of Groningen in the Netherlands between March 2007 and December 2010 who had a history of heavy menstrual bleeding. The investigators used the Pictorial Bleeding Assessment Chart (PBAC) to assess the amount of bleeding and patients with a score of < 100 were excluded as well as any women with known bleeding disorders, IUD use in the past 2 months, and treatment

with anticoagulants, antifibrinolytics, NSAIDs, combined oral contraceptives, or progestins. Women then underwent a workup including a transvaginal ultrasound and sonohysterogram if indicated. Women with documented fibroids > 2 cm, uterine polyps, endometrial hyperplasia, or endometritis were classified as heavy menstrual bleeding explained by gynecologic abnormalities; all others were classified as unexplained. Women were then tested for bleeding disorders, including von Willebrand disease, coagulation factor deficiencies, and platelet defects, in the early follicular phase of their cycle. No sample size calculation was reported.

The median age of the sample was 42.5 years (range, 17-55 years) and 95% were white. Seventy-four percent of the women had unexplained and 26% had explained heavy menstrual bleeding (9% uterine polyps and 17% submucosal fibroids). Overall, 31% of the patients in the unexplained group had a bleeding disorder compared to 27% in the group with gynecologic abnormalities (P = 0.48). The distribution of bleeding disorder types was no different between the two groups. Among those with a bleeding disorder, the most common diagnosis (76%) was a platelet defect followed by von Willebrand disease (20%), low factor XI (13%), combination disorder (13%), and factor VII deficiency (3%). The investigators also compared the study sample to a group of 28 healthy volunteers who did not have subjective heavy menstrual bleeding. Their rationale was to compare the levels of coagulation factors in the subjects to controls, in addition to standard normal lab ranges. However, the inclusion criteria were different for these women, so they don't appear to be an appropriate control group. Nevertheless, the remainder of the study yields interesting information.

■ COMMENTARY

This is yet another study reminding us that bleeding disorders are not uncommon among women with heavy menstrual bleeding. According to the authors, the novel finding in this study was the presence of bleeding disorders among women who may have a gynecological explanation for their heavy menstrual bleeding as well. However, in this study, the authors did not prove or disprove which abnormality was the actual cause of the heavy menstrual bleeding. In addition, endometrial polyps are not a common cause of regular heavy menstrual bleeding. Despite this, the study tells us that if treatment of the gynecologic cause of bleeding is unsuccessful, then perhaps an assessment for bleeding disorders is indicated. The overall diagnosis of von Willebrand disease among women with heavy menstrual bleeding was on the lower end in this study (6%) than previously reported in other studies (5-20%). The authors speculated that this was due to the study population being ethnically homogeneous.

Abnormal uterine bleeding (AUB) is now classified according to the PALM-COEIN system. PALM stands for the structural causes: Polyp, Adenomyosis, Leiomyoma, and Malignancy and hyperplasia. COEIN refers to the non-structural causes: Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified. AUB is paired with descriptive terms such as heavy menstrual bleeding and intermenstrual bleeding. It is then further classified by one (or more) letter qualifiers that indicate the etiology or etiologies. The American College of Obstetricians and Gynecologists recommends that all women with heavy menstrual bleeding be screened for the possibility of bleeding disorders.[1] For a positive screen, women must report heavy menstrual bleeding since menarche or one of the following: postpartum hemorrhage, surgery-related bleeding, bleeding associated with dental work, or two or more of the following symptoms: bruising one to two times per month, epistaxis one to two times per month, frequent gum bleeding, or family history of bleeding symptoms. For those who screen positive, initial tests include a complete blood count, prothrombin time, and partial thromboplastin time. The diagnosis of von Willebrand disease can be complex and referral to a hematologist is advisable if a bleeding disorder is suspected.[2] Although we commonly think of diagnosing bleeding disorders in adolescence, many women are not diagnosed until adulthood, as this study shows.

The first-line treatment for menorrhagia in women with bleeding disorders, including von Willebrand disease, is typically oral contraceptive pills.[3] Combined oral contraception increases coagulation factors as well as induces endometrial atrophy. Another appealing option includes the levonorgestrel intrauterine system (LNG-IUS), especially in women with contraindications to estrogen. One study evaluated LNG-IUS use in 16 women with inherited bleeding disorders and menorrhagia.[4] Nine women became amenorrheic; in the remaining 7 women, PBAC scores decreased significantly from a median of 213 to 47. Quality of life was improved and long-term effectiveness has been documented up to a median duration of 53 months. Other options for women who desire pregnancy or have failed hormonal options include DDAVP, antifibrinolytics such as transexemic acid, and von Willebrand factor concentrates.[2] It seems that it would behoove obstetrician-gynecologists to develop a relationship with a hematologist in their area to assist in comanaging these women. ■

References

1. ACOG Practice Bulletin No. 128. Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women. July 2012.
2. James AH, et al. Von Willebrand disease: Key points from the 2008 National Heart, Lung, and Blood Institute guidelines. *Obstet Gynecol* 2009;114:674-678.

3. ACOG Committee Opinion No. 451. Von Willebrand Disease in Women. *Obstet Gynecol* 2009;114:1439-1443.
4. Kadir RA, Chi C. Levonorgestrel intrauterine system: Bleeding disorders and anticoagulant therapy. *Contraception* 2007;75(6 Suppl):S123-S129.

Folic Acid and Neural Tube Defects

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

Synopsis: *In a recent case-control study involving more than 1000 patients whose fetus's had neural tube defects, analysis of their dietary intake showed a protective effect of folic acid in diabetics and in the overall population, but not in obese patients.*

Source: Parker SE, et al. The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. *Am J Obstet Gynecol* 2013;209:239.e1-8.

The incidence of neural tube defects (NTD) at birth has diminished somewhat over the last 20 years to < 1 in 1000 because of an improvement in screening and diagnosing this condition and, probably, an increased emphasis on adequate intake of folic acid in pregnancy.

Diabetes represents a well-known risk factor for NTD and obesity also has been implicated. Authors from a large consortium of centers in the United States and Canada (the Epidemiology Center Birth Defects Study) have recently published a case-control study to identify whether adequate dietary/supplemental intake of folic acid was associated with a decrease in the incidence of spina bifida (SB) in pregestational diabetics and obese patients.[1]

Data on 1154 cases of SB were accumulated between 1976 and 2011, as well as another 9439 control patients registered during that time. Information was also filed on dietary and/or vitamin intake on all patients in the study over the month before and 1 month post-conception. In addition, any history of diabetes was documented and maternal body mass indices (BMIs) were recorded.

NTD mothers were more likely to have pre-existing diabetes (0.7% vs 0.4%) or be obese (19% vs 10.8%) than controls. Folic acid intake of < 400 ug per day had an adverse effect in both diabetics and non-diabetics. For example, in those diabetics in the low folic acid group, the risk of SB was four times higher than controls (odds ratio [OR], 3.95; 95% confidence interval [CI], 1.56-10.0). In non-diabetics, there still was a difference in the rate of SB with low intake of folic acid (OR, 1.99; 95% CI, 1.69-2.34) compared with those with adequate intake. However, while obese patients did have an increased risk of SB (OR, 1.87; 95% CI, 1.46-2.65), folic acid did not seem to lower the rate of SB in these women.

■ COMMENTARY

This study sends the message that folic acid does decrease the rate of SB in all patients and in pre-existing diabetics in particular — who again are shown to have a higher incidence of SB than in the overall population. It is unclear why obese patients are seemingly resistant to the protective effect of folic acid.

Years ago, Reece at al[2] showed in an in vitro rat embryo model that the higher the concentration of glucose to which the embryo was exposed, the greater the chance of an NTD. The neural tube closes in human pregnancy between days 20 through 28 post-conception. Therefore, it is very important for diabetics to be in good glucose control and to have folic acid on board during this early window of time.

Folic acid also helps to protect against a recurrence of NTD. In some areas of Great Britain (for example, Liverpool) the rate of NTD had been unusually high, but Smithells et al[3] showed that with folic acid supplementation the recurrence rate of SB decreased from 4% to about 1.4%.

Although diabetics and those with a previous history of NTDs are among the most vulnerable to this complication, together they still contribute only a modest percentage of cases to the overall pool of NTDs, which in part could be that many lower-risk patients are not as apt to plan for early pregnancy coverage with folic acid. For this reason, in 1982 the Public Health Service recommended intake of folic acid to be at least 400 ug per day for everyone of childbearing age. It should not be difficult to attain that goal with diet alone, but for various reasons such as malabsorption problems, a lack of dietary knowledge, or, commonly, a well entrenched fast-food mentality, it has been more effective to simply prescribe prenatal vitamins. The most commonly used prenatals generally contain 800 ug of folate, which provides a cushion by doubling the above recommendation. However, some high-risk patients may need more, such as obese mothers, patients with methylene tetrahydrofolate reductase deficiencies, those having had bariatric procedures, those being maintained on certain antiepileptic medications, and those who have already had a NTD pregnancy.

Since 1991, the Centers for Disease Control and Pre-

vention has recommended that patients at high risk for NTD have 10 times the usual requirement of folic acid per day (4000 ug) — an intake that might only be attained through a vitamin supplement. Interestingly, in 1998 the FDA decreed that cereal grains be fortified with folic acid by adding 140 ug of it to every 100 g of grain. Frankly, the concept would be more effective if the Big Mac were targeted for fortification. The company claims to help feed 60 million people around the world, and this item (576 calories), combined with a coke and fries, tally out at 1386 calories. This combination, while providing more than half our daily requirement of calories, contains only about one-tenth of the daily requirement of folic acid.

This study alerts us to the increased risk of NTD in diabetics and how folic acid can decrease the risk in everyone — except, seemingly, obese patients who probably should be put in an increased requirement category. ■

References

1. Parker SE, et al. The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. *Am J Obstet Gynecol* 2013;209:239.e1-8.
2. Reece EA, et al. Ultrastructural analysis of malformations in the embryonic neural axis induced by in vitro hyperglycemic conditions. *Teratology* 1985;32:363-373.
3. Smithells RW, et al. Further experience in vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983;1:1027-1031.

Fluoride in Postmenopausal Osteopenia

ABSTRACT & COMMENTARY

By Michael A. Thomas, MD

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Dr. Thomas reports no financial relationships relevant to this field of study.

Synopsis: *In this randomized, controlled trial, three low doses of fluoride demonstrated no significant positive effect on bone mineral density or markers of bone turnover over placebo.*

Source: Grey A, et al. Low-dose fluoride in postmenopausal women: A randomized controlled trial. *J Clin Endocrinol Metab* 2013;98:2301-2307.

Over 12 months, these authors performed a randomized, controlled, double-blind trial where 180 postmenopausal women with osteopenia were randomized to receive either oral placebo or one of three oral fluoride (FL) tablets (2.5 mg, 5 mg, or 10 mg). To be enrolled in the study, subjects had to be postmenopausal for > 5 years **and** have a bone mineral density (BMD) T-score between -1 and -2.5 at either the lumbar spine, total hip, or femoral neck **or** they could have a BMD T-score < -2.5 at any site. Women who were actively treating their osteopenia or osteoporosis were not included. The primary endpoint was a change in lumbar spine BMD at baseline, 6 months, and 12 months. Secondary endpoints included changes in BMD in the total hip or total body as well as changes in the bone turnover markers serum procollagen type I N-terminal propeptide (P1NP) and beta-C-terminal telopeptide of type I collagen (beta-CTX). The bone turnover markers were collected at baseline, then 1, 3, and 12 months.

Of the 394 women who received study material, 180 were evenly randomized into four groups (45 subjects in each group to receive either placebo, 2.5 mg FL, 5 mg FL, or 10 mg FL). A total of 173 women completed the 12 months of study, but all 180 were included in the analysis of BMD and bone turnover. At the study's conclusion, all four groups demonstrated no differences in change in total body weight or compliance with study drug. There was no statistical difference in the change in BMD in the lumbar spine between placebo and any of the FL doses (-0.4% with placebo, -0.7% with 2.5 mg FL, 0.0% with 5 mg FL, and 0.2% with 10 mg FL). No differences were noted in BMD at the total hip or total body with any of the FL doses compared to placebo. The bone turnover markers showed mixed results. Beta-CTX showed no differences between the four groups, but the P1NP was significantly greater in groups taking the 5 mg and 10 mg doses when compared to placebo. However, despite the P1NP findings, the authors concluded that fluoride at 2.5, 5, and 10 mg was unlikely to be an effective treatment option for women with osteopenia or osteoporosis.

■ COMMENTARY

The primary purpose of this study was to investigate if FL could potentially serve as a less-expensive option for the prevention and treatment of osteopenia and osteoporosis. Drugs used for these conditions act either by decreasing bone resorption, which slows bone loss, or by increasing the formation of bone. Pharmacologic agents that decrease the rate of bone resorption include calcium, vitamin D and calcitrol, estrogen, selective estrogen receptor modulators, calcitonin, bisphosphonates, and RANK-ligand inhibitors (denosumab).[1] However, medications that decrease bone resorption may eventually decrease the rate of bone formation. Therefore, BMD values in bone resorptive drugs may actually plateau after a

year or two of therapy, but their reduction in fracture risk may still be the same as a woman who shows a continued increase in BMD. Bisphosphonates are commonly used bone resorption agents and have been known, depending on the skeletal site, to reduce fracture risk by 50-60%. Though gastrointestinal issues are common with these medications, recent reports of bisphosphate-related osteonecrosis of the jaw has caused some patients and physicians to seek alternatives for treatment of osteopenia and osteoporosis.[2]

Bone-forming or anabolic agents include FL, androgens, parathyroid hormone (PTH), and strontium ranelate. PTH is an anabolic daily injection that has proven efficacy in this patient population.[3] Studies have demonstrated that PTH, when given for approximately 21 months, can reduce the incidence of vertebral fractures by 60% and nonvertebral fractures by 50%. However, some have argued that PTH may be unacceptable because of its high cost. Additionally, it is has to be given subcutaneously on a daily basis for almost 2 years to see these positive effects. Therefore, FL offers a more cost-effective option and is also an anabolic alternative.

Elemental FL is plentiful and has previously been shown to stimulate osteoblast growth, increase bone formation, and increase BMD in trabecular bone.[4] Other investigators have found FL to show no improvement in cortical BMD and actually increase risk of fracture in a daily dose of 34 mg. Lower doses of FL ranging from 13-27 mg showed mixed results with either protective or no effect on bone.[5-7] But these lower-dose FL studies were not designed appropriately or not powered to give clear results.

The current study by Grey and colleagues offered a randomized, placebo-controlled design and was powered appropriately. And if FL was found to work at 2.5, 5, or 10 mg, it would offer a nonhormonal option without the high costs and side effects that limit use of PTH or bisphosphonates.

However, low-dose FL was not shown to have a consistent beneficial effect for the treatment of osteopenia or osteoporosis. This study clearly points out that doses of 10 mg or below should not be administered. Higher doses of FL (≥ 10 mg) are even suspect and may cause bone demineralization in some subjects. In my opinion, low-dose FL should not be given for the prevention or treatment of osteoporosis because the data do not support its use for this condition. Also, studies using higher doses have been inconsistent and may actually cause harm. It is my hope that the door is now closed on FL as an alternative treatment for osteopenia and osteoporosis. ■

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References

1. Chen JS, Sambrook PN. Antiresorptive therapies for

osteoporosis: A clinical overview. *Nat Rev Endocrinol* 2011;8:81-91.
2. Khosla S, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Min Res* 2007;22:1479-1491.
3. Pleiner-Duxneuner J, et al. Treatment of osteoporosis with parathyroid hormone and teriparatide. *Calcif Tiss Int* 2009;84:159-170.
4. Farley JR, et al. Fluoride directly stimulates proliferation and alkaline phosphatase activity of bone-forming cells. *Science* 1983;222:330-332.
5. Pak CY, et al. Slow-release sodium fluoride in the management of postmenopausal osteoporosis. A randomized controlled trial. *Ann Intern Med* 1994;120:625-632.
6. Reginster JY, et al. The effect of sodium monfluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized, controlled trial. *Ann Intern Med* 1998;129:1-8.
7. Reid IR, et al. Addition of monofluorophosphate to estrogen therapy in postmenopausal osteoporosis: A randomized controlled trial. *J Clin Endocrinol Metab* 2007;92:2446-2452.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Instructions

To earn credit for this activity, follow these instructions:

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2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. Marriage was associated with a stronger effect on overall survival than chemotherapy in which of the following cancers?
a. Ovarian
b. Liver
c. Pancreatic
d. Lung
e. Colorectal

2. In the study by Knol et al, there was a higher prevalence of underlying bleeding disorders in women with unexplained compared to explained heavy menstrual bleeding.
a. True
b. False

3. Which of the following is appropriate regarding the data on folic acid and neural tube defects (NTDs)?
a. Folic acid was not protective for NTD in diabetes.
b. Those patients in the overall study who had low folic acid intake had a lower rate of NTDs.
c. Folic acid did not seem to protect obese patients from fetal NTDs.
d. Folic acid did not protect against a recurrence of NTD.

4. The Public Health Service's recommendation of > 400 ug of folic acid per day is exceeded by the amount commonly contained in prenatal vitamins.
a. True
b. False

5. Which medication for the prevention and treatment of osteoporosis is considered an anabolic agent that increases bone formation?
a. Estrogen
b. Fluoride
c. Bisphosphate
d. Calcitonin
e. Vitamin D

In Future Issues: **A Final Word on Safety of Vaginal Ring Contraception**

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 18, NUMBER 11 PAGES 21-22 NOVEMBER 2013

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

Clinical Briefs in Primary Care is going digital!

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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