

Clinical Briefs in Primary Care™

The essential monthly primary care update

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HPV Infection as a Risk Factor for Squamous-Cell Carcinoma of the Head and Neck

Source: Mork J, et al. *N Engl J Med.* 2001;344:1125-1131.

Human papillomavirus (hpv) is a well recognized oncogenic substrate for cervical cancer, as well as other anogenital cancers. HPV DNA has been found in some head and neck cancers. In persons with head and neck cancer who do not harbor HPV DNA, it is conceivable that they have suffered previous transient HPV infection that has passed. HPV capsid antigen antibody indicates past HPV infection in the absence of HPV DNA.

Data were obtained from almost 1 million Scandinavians who donated serum samples to serum banks, all of whom were negative for head and neck cancer at the time of their donation. In this population, 292 head and neck carcinomas were ultimately identified.

Because cigarette smoking is a potent risk factor for head and neck cancer, level of smoking was ascertained by measurement of serum cotinine. Smokers were stratified by cotinine levels, which separates those exposed to passive smoke, light-to-moderate smokers, and heavy smokers. Statistical relationships between head and neck cancer and HPV were adjusted for smoking status.

In persons with head and neck cancer, the odds ratio for HPV antibody presence was more than doubled. As has been demonstrated for genital cancer, not all HPV subtypes produce risk; in this trial,

HPV-16 was the only subtype associated with increased risk.

Though this study does not prove causation, the relationship is plausible and merits further focus on the role of HPV-16 as a head and neck cancer oncogenic trigger. ■

Cognitive Behavior Therapy for Chronic Fatigue Syndrome

Source: Prins JB, et al. *Lancet.* 2001; 357:841-847.

Chronic fatigue syndrome (cfs) has been characterized as a symptom complex of persistent fatigue, without demonstrable organic cause, of at least 6 months duration. Pharmacologic treatment results have been generally disappointing. Prins and colleagues performed a randomized trial of cognitive behavior therapy (CBT) compared to support groups and placebo in a large population of CFS patients (n = 278). The purpose of the support group comparator was to address criticisms of previous studies that simply providing a supportive attention to the patient might account for the benefit observed with a counseling therapy. Hence, a support group (including a therapist, but without performance of CBT) should provide a plausible clarification of this issue.

CBT and support group sessions were provided as 11-16 brief (1-1.5 hour) encounters over 8 months time; the placebo control group was given no intervention.

At the 8 months conclusion of the trial, CBT produced a statistically significant improvement (over placebo and support

group subjects) in Karnofsky performance status, psychological well-being, and quality of life. Persons assigned to the support group fared no better than the placebo group, despite uniformly positive evaluation of the support group experience. One of the most encouraging aspects of this study was that therapists enrolled had not had prior experience in CBT; hence, we may be hopeful that counselors with varying levels of experience may anticipate favorable outcomes when CBT is provided for CFS. ■

Use of Statins and Risk of Fractures

Source: van Staa TP, et al. *JAMA.* 2001;285:1850-1855.

Geranylgeranyl pyrophosphate (GGPP) is a protein that exerts control over osteoclast-mediated bone resorption. Statins (ie, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) block production of mevalonic acid, a precursor of GGPP. It has been suggested that currently used osteoporosis treatments like bisphosphonates may have an effect upon bone resorption through GGPP suppression in this same pathway. Recent epidemiologic data have suggested that statins may reduce fracture risk.

van Staa and colleagues studied a large population (n = 81,880) of cases from general practices in the United Kingdom of persons who had sustained a fracture (vertebra, clavicle, humerus, radius, ulna, carpal bone, hip, ankle, or foot), and compared this information with an equal body of age and sex-matched controls. Odds ratios were

determined for use of statins vs. non-use of statins and likelihood of fracture.

Regardless of statin dose studied, no difference in odds ratio of fracture between current statin users and non users was discerned. This lack of effect was unaltered by duration of use of statin dose. van Staa et al suggest that the previously reported observational reports of statin-associated reduced fracture rates may have been due to the confounding effects of obesity in these patients. ■

Parathyroid Hormone (1-34) in Postmenopausal Women with Osteoporosis

Source: Neer RM, et al. *N Engl J Med.* 2001;344:1434-1441.

Though numerous agents for prevention and treatment of osteoporosis (OSPS) are available, none is ideal for all women, and each has a distinct limitation. The dominant function of most

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agents is to inhibit bone resorption, thereby reducing bone loss, but doing little to increase, or stimulate, new bone formation. Hence, the idea of using a therapy that stimulates bone formation is appealing.

Neer and associates point out that parathyroid hormone (PTH) has various effects upon bone, depending upon administration method. To test the hypothesis generated by successful animal studies, Neer et al studied PTH (vs. placebo) in postmenopausal women (n = 1637) with prior vertebral fractures. PTH was self-administered by injection daily for 24 months. All subjects also received vitamin D and calcium supplementation.

There were statistically fewer new nonvertebral fractures in the PTH treatment group than placebo (RR = 0.47); similarly, bone mineral density increased 9-13% more than placebo recipients. The medication was well tolerated, with no serious side effects. PTH has been shown to be effective in preventing fractures and stimulating bone formation. ■

Biochemical Markers of Liver Fibrosis in Patients with Hepatitis C Virus Infection

Source: Imbert-Bismut F, et al. *Lancet.* 2001;357:1069-1075.

It is common practice to perform liver biopsy for definition and prognostication of hepatitis C (HEPC). This process is not without consequence: although mortality is rare (0.03%), other serious complications are significantly more common (0.3%), not to mention the pain at the time of biopsy, and in 30%, postbiopsy pain. Imbert-Bismut and colleagues sought to evaluate the predictive value of basic serum biochemical markers for the diagnosis of liver fibrosis, (early as well as advanced). If indeed such markers had valuable predictive capacity, some liver biopsies might be avoided.

Imbert-Bismut et al studied 11 different serum markers, including traditional transaminases, alpha-2 macroglobulin, haptoglobin, gammaglobulin, apolipoprotein A-1, gam-

maglutamyltranspeptidase, and total bilirubin. The study group included 205 HEPC patients who had undergone liver biopsy. Serum markers were assayed in years 1 and 2.

Twelve percent of patients had sufficiently low scores using multiple serum markers that liver biopsy could have been avoided with 100% certainty that no significant fibrosis was present. Imbert-Bismut et al suggest that use of serum markers may substantially reduce unnecessary liver biopsy in patients with HEPC. ■

Management of Chronic Tension Type Headache

Source: Holroyd KA, et al. *JAMA.* 2001;285:2208-2215.

Chronic tension type headache (CTH) is defined by the International Headache Society criteria as occurring 15 or more days/month for at least 6 months. Since this disorder is not infrequent (1.5% of men, 3% of women) and results in decrements in quality of life, as well as decreased work performance, choosing the most efficacious management is of great clinical relevance.

The current study was a randomized placebo-controlled trial (n = 203) comparing tricyclics (TCA) with stress management, or the combination. TCA therapy used amitriptyline or nortriptyline, titrated from a low starting dose, to maximize tolerability, up to 100 mg/d of amitriptyline or 75 mg/d nortriptyline.

Stress management techniques (SMT) included deep muscle relaxation, instruction in cognitive coping skills, and guidance in stress management. Treatments (or placebo) were administered for 6 months.

Each active treatment arm was significantly more effective than placebo. TCA therapy had the greatest number of individuals with improved headache score (38%), followed by stress management (35%). The combination of treatments was most effective, producing a favorable response in 64% of subjects. Holroyd and colleagues conclude that a combined approach to CTH results in the most favorable outcome. ■