



# Harvard Women's Health Watch

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## Bioidentical hormones: Help or hype?

*Do these heavily promoted hormones justify the claims made for them?*

Ever since *Harvard Women's Health Watch* began publication in 1993, our readers have been concerned about the risks and benefits of postmenopausal hormones. In the past few years, there's been growing interest in "bioidentical" hormones, which are promoted as safer and more effective than FDA-approved hormones. The interest is driven in no small part by claims made in entertainer Suzanne Somers' 2006 book, *Ageless: The Naked Truth About Bioidentical Hormones* (and her January 2009 appearance on the "Oprah Winfrey Show").

Somers endorses the use of bioidentical hormones not just for the relief of menopausal symptoms but as a veritable fountain of youth. She says that it "gives you back your lean body, shining hair, and thick skin, provided you are eating correctly and exercising in moderation. This new medicine allows your brain to work perfectly and offers the greatest defense against cancer, heart attack, and Alzheimer's disease." According to Somers, bioidenticals work by tricking the body into thinking it's still "reproductive." Ironically, similar claims were made for hormone replacement therapy (HRT), now called hormone therapy (HT), nearly 50 years ago by the British gynecologist Robert Wilson in his book *Feminine Forever*. Wilson wrote that HRT reversed a postmenopausal woman's status as a "castrate" and ensured that she wouldn't "become dull and unattractive." Like Wilson, Somers appears to view menopause as a deficiency disease and hormone replacement as a lifelong necessity.

It's understandable that women would be interested in a new approach after hopes

that conventional HT would prevent cardiovascular disease were dashed by the Women's Health Initiative (WHI). In 2002, study researchers stopped giving HT to women with an intact uterus when it became clear that the risks of taking combined hormones (estrogen plus a progestin)—higher rates of stroke, breast cancer, heart attack, and blood clots in the lungs and legs—outweighed the benefits, namely, reductions

in osteoporotic fractures and colorectal cancer. In 2004, WHI researchers also stopped giving HT to women who had undergone hysterectomy, because those taking estrogen alone had a higher rate of stroke than those taking the placebo. Finally, in the WHI Memory Study, women over age 65 who took hormones were twice as likely to develop dementia as those taking a placebo.

All the women in the WHI took conjugated equine estrogens synthesized from the urine of pregnant mares, either alone (as Premarin) or with the progestin medroxyprogesterone acetate (as Prempro). Similar data are not available for other estrogens or progestogens (natural progesterone or synthetic progestin).

As a result of the WHI findings, the FDA required manufacturers to add a "black box" warning (the strongest warning in prescription labeling) not just to Premarin and Prempro, but to all approved estrogens and progestogens. And most clinicians now counsel midlife women differently than they once did. Instead of urging women to weigh the risks and benefits of long-term HT for health, most now suggest HT only for short-term symptom relief. But many women ▶▶

*"Please advise me about the safety and effectiveness of using bioidentical instead of synthetic hormones."*

—HWHW READER QUESTION

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## Bioidentical hormones *continued*

want more from HT, and some are now looking to bioidenticals.

### What are bioidentical hormones?

The term “bioidentical” doesn’t have a precise medical definition. The Endocrine Society defines bioidentical hormones as “compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body.” Clinicians usually use the word to describe preparations containing either progesterone or one or more of three estrogens—estradiol (the predominant estrogen in premenopausal women), estrone, and estriol (the main estrogen produced during pregnancy). Somers and other advocates of bioidentical hormones generally mean something more. They are usually talking about the following regimen, called bioidentical hormone replacement therapy (BHRT):

- A woman’s hormones are measured via a saliva test, and “deficiencies” are identified.
- Her clinician prescribes a mix of hormones to correct any deficiencies and bring the hormones into balance.
- The prescription is filled at a compounding pharmacy using hormones derived from “natural” sources, usually soy or Mexican yams.
- Besides estrogen and progesterone, the prescription may include other hormones, such as testosterone, dehydroepiandrosterone (DHEA), and adrenal hormones extracted from animal glands.
- The woman’s hormone levels are retested periodically and her prescription revised as the clinician deems necessary.

### Evaluating the claims for bioidenticals

Here are some of the main claims Somers makes for BHRT, along with the medical evidence.

- ▶ **Claim:** BHRT hormones are not drugs because they are molecular copies of the hormones made by women’s bodies.
- ▶ **Evidence:** The FDA defines drugs as “articles (other than food) that are intended to affect the structure or any function of the body.” Somers’ claims for custom-

compounded bioidentical hormones haven’t been scientifically validated, but if they accomplish any of the things she says they do—such as relieve hot flashes or improve the skin—their effects on the body’s structure or function are undeniable. They’re drugs—just unapproved ones.

▶ **Claim:** Drug companies don’t invest in bioidentical hormones because they can’t make money from them; you can’t patent natural substances.

▶ **Evidence:** This is at best a half-truth. A drug company can’t patent a naturally occurring hormone, but it can patent a process needed to render it absorbable as a drug. Several large drug companies have done just that (or have licensed process patents) and are now selling FDA-approved bioidenticals. For example, natural progesterone (Prometrium) is manufactured by Abbott Laboratories, which uses a patented technique called micronization. Micronization permits the oral ingestion of progesterone by pulverizing it into particles small enough to pass through the walls of the intestine and into the bloodstream. Other drug companies market a micronized form of estradiol—a bioidentical estrogen—in pill form (Estrace) and in transdermal (applied to the skin) patches (Alora, Climara, Estraderm, Menostar, Vivelle), sprays (Evamist), gels (Divigel, Elestrin, Estrogel), lotions (Estrasorb), and vaginal rings (Estring).

To bring a drug to market, drug companies invest millions of dollars in research and development, including the randomized clinical trials testing its safety and effectiveness that are required for FDA approval. A drug company must also keep tabs on a drug after it’s in use, reporting side effects and monitoring quality.

▶ **Claim:** Bioidenticals are safer than synthetic hormones.

▶ **Evidence:** The WHI results understandably sent some women looking for a safer alternative for symptom relief. Premarin is synthesized from the urine of pregnant mares and contains a mix of estrogens (some unique to horses), steroids, and various other substances. Might some unidentified molecule be responsible for the

health risks? To many, the claim that bioidentical hormones are safer because they have the same chemical structure as those produced by our own bodies would seem plausible.

Yet there's no good evidence to support this claim. Although bioidentical progesterone and the bioidentical estrogen estradiol have been approved, they haven't been studied in large, long-term trials like the WHI. They're FDA-approved because they've been shown in trials to relieve menopausal symptoms and reduce the risk of osteoporosis. These claims are allowed on their packaging. And because the FDA has applied the results of the WHI to all approved estrogens and progestogens, these bioidenticals also carry black box warnings. Hormones from compounding pharmacies, which aren't FDA-approved, don't come with package inserts bearing the black box warning, giving the illusion of being safer than commercially marketed drugs. But the lack of a warning doesn't mean they're safer, only that compounding pharmacies aren't required to detail potential risks. To date, hormones from compounding pharmacies haven't been tested in clinical trials. Until then, the risks associated with them cannot be fully known. Finally, while compounding pharmacies are regulated by state pharmacy boards, they're not required—as manufacturers of approved drugs are—to report on side effects or other adverse outcomes from their products.

There actually may not be much difference between an FDA-approved bioidentical and the custom-compounded version. Both are made from the same hormones and manufactured according to the requirements of the United States Pharmacopeia (a nongovernmental authority that sets standards for prescription and over-the-counter drugs). At a compounding pharmacy, hormones are placed in a capsule, gel, cream, suppository, or other vehicle. A pharmaceutical company follows the same procedure, but it must use a standard dose in a specific vehicle because the two have been tested and approved as a unit. In this respect, an FDA-approved bioidentical may be more reliable. In 2001, the FDA randomly tested 37 products from 12 compounding pharmacies and found that nine (24%) were less potent than indicated. In contrast, only 2% of FDA-approved products failed the potency test when randomly sampled.

► **Claim:** Estriol, a weak estrogen used in compounded BHRT, offers women protection from breast cancer.

► **Evidence:** In laboratory studies, estriol has been shown to prevent and even reverse breast tumors in rats—but there's no evidence that it does so in women.

► **Claim:** Saliva and blood tests are reliable indicators of a woman's hormone levels.

► **Evidence:** FDA-approved blood and saliva tests indicate a woman's hormone levels at a moment in time. That can sometimes help in determining whether a woman has entered the menopausal transition—but they are not useful

## If you're considering bioidenticals

If you want to use FDA-approved bioidentical hormones for menopausal symptom relief, you can be confident that they are safe and effective, and contain what their labels say they do. (For a list of FDA-approved bioidenticals, go to [www.health.harvard.edu/womenextra](http://www.health.harvard.edu/womenextra).) If you want custom-compounded bioidentical hormones, get them through your clinician and not from the Internet. If you plan to rely on saliva or blood testing to establish the dose, bear in mind that you're venturing into scientifically uncharted territory. And any prescription that adds testosterone or DHEA to your hormonal mix is taking you even farther from the tested path. In effect, you're experimenting with your body and your health.

for setting hormone doses. In a menstruating or perimenopausal woman, hormone levels change from hour to hour, and in menopausal women, there's no stable "normal" value at all for salivary or blood levels of these hormones or levels that correlate with symptoms.

### Bioidenticals in mainstream practice

Is there a valid role for bioidenticals? We took the question to two gynecologists who have followed the field for decades and treated thousands of midlife women—*HWHW* advisory board member Dr. Martha K. Richardson, and Dr. JoAnn Pinkerton, who will be leading a workshop on bioidentical hormones at the North American Menopause Society's annual meeting in September 2011. Both usually prescribe FDA-approved bioidentical hormones, but only for symptom relief and only for the shortest time that works (often three to five years but sometimes longer). Richardson prefers to prescribe transdermal rather than oral estrogen because it doesn't pass through the digestive system and liver and therefore is less likely to cause gallbladder disease or have a negative effect on blood lipids, in particular, triglycerides or clotting factors.

Pinkerton cautions that transdermal progesterone may not prevent endometrial overgrowth in women who have a uterus: "It's questionable whether the particles are small enough to be absorbed through the skin." (Interestingly, Somers says that despite daily applications of progesterone cream, she required a hysterectomy because of endometrial hyperplasia.)

Both Richardson and Pinkerton occasionally prescribe compounded hormones—chiefly for women who are allergic to vehicles used in FDA-approved hormones, or whose symptoms can be managed with a lower dose of estrogen or progesterone than is commercially available. But both physicians are more comfortable with FDA-approved bioidentical hormones, not only because research has shown them to be safe and effective, but also because their purity and potency are held to rigorous standards with periodic testing. ♥

# Tinnitus: Ringing in the ears and what to do about it

*Constant noise in the head rarely indicates a serious health problem, but it sure can be annoying. Here's how to minimize it.*

**T**innitus (pronounced tih-NITE-us or TIN-ih-tus) is sound in the head with no external source. For many, it's a ringing sound, while for others, it's whistling, buzzing, chirping, hissing, humming, roaring, or even shrieking. (To get an idea of what people with tinnitus hear, go to [www.ata.org/sounds-of-tinnitus](http://www.ata.org/sounds-of-tinnitus).) The sound may seem to come from one ear or both, from inside the head, or from a distance. It may be constant or intermittent, steady or pulsating.

Almost everyone has had tinnitus for a short time after being exposed to extremely loud noise. For example, attending a loud concert can trigger short-lived tinnitus. Some medications (especially aspirin and other nonsteroidal anti-inflammatory drugs taken in high doses) can cause tinnitus that goes away when the drug is discontinued. A more serious problem is chronic tinnitus—symptoms lasting more than six months. As many as 50 to 60 million people in the United States suffer from this condition; it's especially common in people over age 55 and strongly associated with

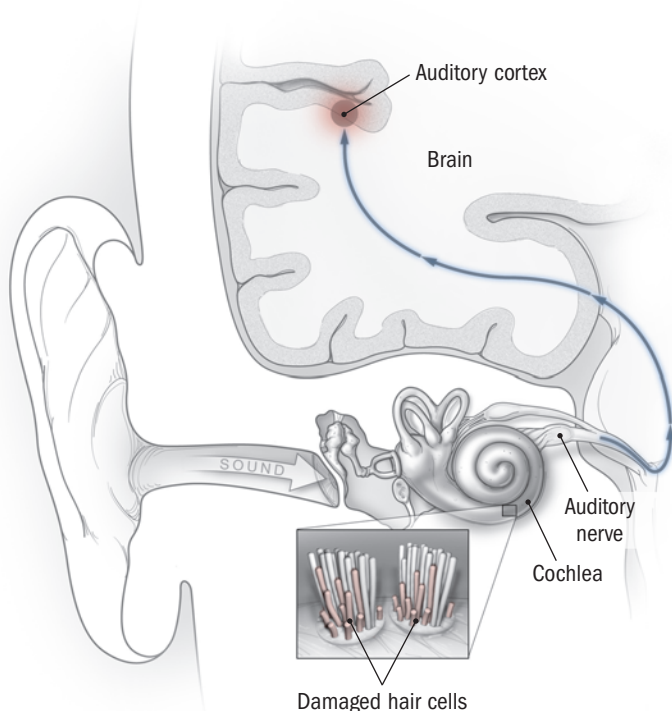
hearing loss. Many people worry that tinnitus is a sign that they are going deaf or have another serious medical problem, but it rarely is.

Most tinnitus is subjective, meaning that only you can hear the noise. But sometimes it's objective, meaning that someone else can hear it, too. For example, if you have a heart murmur, you may hear a whooshing sound with every heartbeat; your clinician can also hear that sound through a stethoscope. Many people can hear their heartbeat—a phenomenon called pulsatile tinnitus—especially as they grow older, because blood flow tends to be more turbulent in arteries whose walls have stiffened with age. Pulsatile tinnitus may be more noticeable at night, when you're lying in bed, because more blood is reaching your head, and there are fewer external sounds to mask the tinnitus. If you notice any new pulsatile tinnitus, you should consult a clinician, because in rare cases it is a sign of a tumor or blood vessel damage.

The course of chronic tinnitus is unpredictable. Sometimes the symptoms remain the same, and sometimes they get worse. In about 10% of cases, the condition interferes with everyday life so much that medical help and psychotherapy are needed.

While there's no cure for chronic tinnitus, it often becomes less noticeable and more manageable over time. You can help ease the symptoms by educating yourself about the condition—for example, understanding that it's not dangerous. There are also several ways to help tune out the noise and minimize its impact.

## Auditory pathways and tinnitus



Sound waves travel through the ear canal to the middle and inner ear, where hair cells in part of the cochlea help transform sound waves into electrical signals that then travel to the brain's auditory cortex via the auditory nerve. When hair cells are damaged—by loud noise or ototoxic drugs, for example—the circuits in the brain don't receive the signals they're expecting. This stimulates abnormal activity in the neurons, which results in the illusion of sound, or tinnitus.

## What's going on?

Most people who seek medical help for tinnitus experience it as subjective, constant sound, and most have some degree of hearing loss. Things that cause hearing loss (and tinnitus) include loud noise, medications that damage the nerves in the ear (ototoxic drugs), impacted earwax, middle ear problems (such as infections and vascular tumors), and aging. Tinnitus can also be a symptom of Ménière's disease, a disorder of the balance mechanism in the inner ear.

Tinnitus can arise anywhere along the auditory pathway, from the outer ear through the middle and inner ear to the brain's auditory cortex, where it's thought to be encoded (in a sense, imprinted). One of the most common causes of tinnitus is damage to the hair cells in the cochlea (see "Auditory pathways and tinnitus"). These cells help transform sound waves into nerve signals. If the auditory pathways or circuits in the brain don't receive the signals they're expecting from the cochlea, the brain in effect "turns up the gain" on those pathways in an effort to detect the signal—in

much the same way that you turn up the volume on a car radio when you're trying to find a station's signal. The resulting electrical noise takes the form of tinnitus—a sound that is high-pitched if hearing loss is in the high-frequency range and low-pitched if it's in the low-frequency range. This kind of tinnitus resembles phantom limb pain in an amputee—the brain is producing abnormal nerve signals to compensate for missing input.

Most tinnitus is “sensorineural,” meaning that it's due to hearing loss at the cochlea or cochlear nerve level. But tinnitus may originate in other places. Our bodies normally produce sounds (called somatic sounds) that we usually don't notice because we are listening to external sounds. Anything that blocks normal hearing can bring somatic sounds to our attention. For example, you may get head noise when earwax blocks the outer ear.

### Evaluate and treat underlying problems

If you develop tinnitus, it's important to see your clinician. She or he will take a medical history, give you a physical examination, and do a series of tests to try to find the source of the problem. She or he will also ask you to describe the noise you're hearing (including its pitch and sound quality, and whether it's constant or periodic, steady or pulsatile) and the times and places in which you hear it. Your clinician will review your medical history, your current and past exposure to noise, and any medications or supplements you're taking. Tinnitus can be a side effect of many medications, especially when taken at higher doses (see “Some drugs that can cause or worsen tinnitus”).

Musculoskeletal factors—jaw clenching, tooth grinding, prior injury, or muscle tension in the neck—sometimes make tinnitus more noticeable, so your clinician may ask you to tighten muscles or move the jaw or neck in certain ways to see if the sound changes. If tight muscles are part of the problem, massage therapy may help relieve it.

Tinnitus that's continuous, steady, and high-pitched (the most common type) generally indicates a problem in the auditory system and requires hearing tests conducted by an audiologist. Pulsatile tinnitus calls for a thorough evaluation by an otolaryngologist (commonly called an ear, nose, and throat specialist, or ENT) or neurotologist, especially if the noise is frequent or constant. MRI or CT imaging may be needed to check for a tumor or blood vessel abnormality.

Your general health can affect the severity and impact of tinnitus, so this is also a good time to take stock of your diet, physical activity, sleep, and stress level—and take steps to improve them. You may also be able to reduce the impact of tinnitus by treating depression, anxiety, insomnia, and pain with medications or psychotherapy.

If you're often exposed to loud noises at work or at home, it's important to reduce the risk of hearing loss (or further hearing loss) by using protectors such as earplugs or earmuff-like or custom-fitted devices.

### Some drugs that can cause or worsen tinnitus

**Aspirin and other nonsteroidal anti-inflammatory drugs**, including ibuprofen (Motrin) and naproxen (Aleve, Naprosyn)

**Certain antibiotics**, including ciprofloxacin (Cipro), doxycycline (Vibramycin, others), gentamicin (Garamycin), erythromycin (Ery-Tab, others), tetracycline (Sumycin), tobramycin (Nebcin), and vancomycin (Vancocin)

**Antimalarial drugs** such as chloroquine and quinine

**Benzodiazepines** such as alprazolam (Niravam, Xanax), diazepam (Valium), lorazepam (Ativan), and clonazepam (Klonopin)

**Certain anticonvulsants**, including carbamazepine (Tegretol, others) and valproic acid (Depakote, others)

**Certain cancer drugs**, including cisplatin (Platinol) and vincristine (Oncovin, Vincasar)

**Loop diuretics**, especially when given intravenously, including bumetanide (Bumex), furosemide (Lasix), and torsemide (Demadex)

**Tricyclic antidepressants** such as amitriptyline (Elavil, others), clomipramine (Anafranil), and imipramine (Tofranil)

### Managing tinnitus

In addition to treating associated problems (such as depression or insomnia), there are several strategies that can help make tinnitus less bothersome. No single approach works for everyone, and you may need to try various combinations of techniques before you find what works for you. If you have age-related hearing loss, a hearing aid can often make tinnitus less noticeable by amplifying outside sounds.

There is no FDA-approved drug treatment for tinnitus, and controlled trials have not found any drug, supplement, or herb to be any more effective than a placebo. That includes ginkgo biloba, which is sometimes promoted for this purpose. Some patients believe that acupuncture helps, but it too has been found to be no better than a placebo.

The most effective approaches are behavioral strategies and sound-generating devices, often used in combination. They include the following:

**Cognitive behavioral therapy (CBT).** CBT uses techniques such as cognitive restructuring and relaxation to change the way patients think about and respond to tinnitus. Patients usually keep a diary and perform “homework” to help build their coping skills. Therapy is generally short-term—for example, weekly sessions for two to six months. A 2010 review of six studies by the Cochrane Collaboration (an international group of health authorities who evaluate randomized trials) found that after CBT, the sound was no less loud, but it was significantly less bothersome, and patients' quality of life improved. ▶▶

**Tinnitus retraining therapy (TRT).** This technique is based on the assumption that tinnitus results from abnormal neuronal activity (see “What’s going on?,” page 4). The aim is to habituate the auditory system to the tinnitus signals, making them less noticeable or less bothersome. The main components of TRT are individual counseling (to explain the auditory system, how tinnitus develops, and how TRT can help) and sound therapy. A device is inserted in the ear to generate low-level noise and environmental sounds that match the pitch, volume, and quality of the patient’s tinnitus. Depending on the severity of the symptoms, treatment may last one to two years. The cost (including the sound generator) can be as much as \$5,000.

When TRT was developed more than 20 years ago by neuroscientist Dr. Pawel Jastreboff (now at Emory University in Atlanta), it was designed to be administered according to a strict protocol. Today, the term TRT is being used to describe modified versions of this therapy, and the variations make accurate assessment of its effectiveness difficult.

Individual studies have reported improvements in as many as 80% of patients with high-pitched tinnitus. In a recent Cochrane review of the one randomized trial that followed Jastreboff’s protocol and met the organization’s standards, TRT was much more effective in reducing tinnitus severity and disability than a technique called masking (see below).

**Masking.** Masking devices, worn like hearing aids, generate low-level white noise (a high-pitched hiss, for example) that can reduce the perception of tinnitus and sometimes also produce residual inhibition—less noticeable tinnitus for a short time after the masker is turned off. A specialized device isn’t always necessary for masking; often, playing music or having a radio, fan, or white-noise machine on

in the background is enough. Although there’s not enough evidence from randomized trials to draw any conclusions about the effectiveness of masking, hearing experts often recommend a trial of simple masking strategies (such as setting a radio at low volume between stations) before they turn to more expensive options.

**Biofeedback and stress management.** Tinnitus is stressful, and stress can worsen tinnitus. Biofeedback is a relaxation technique that helps control stress by changing bodily responses. Electrodes attached to the skin feed information about physiological processes such as pulse, skin temperature, and muscle tension into a computer, which displays the output on a monitor. Patients learn how to alter these processes and reduce the body’s stress response by changing their thoughts and feelings. Mindfulness-based stress reduction techniques may also help.

**Other therapies.** Other treatments that have been studied for tinnitus include transcutaneous electrical stimulation of parts of the inner ear by way of electrodes placed on the skin or acupuncture needles, and stimulation of the brain using a powerful magnetic field (a technique called repetitive transcranial magnetic stimulation, or rTMS). Transcutaneous electrical stimulation has been shown to be no more effective than a placebo. In two small trials, rTMS compared with a sham procedure helped improve the perception of tinnitus in a few patients.

Not all insurance companies cover tinnitus treatments in the same way, so be sure to check your coverage. If you’re willing to enroll in a research study, you may be able to receive a cutting-edge treatment free. (For more information, go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and enter the search term “tinnitus.”) ♥



### Selected resources

American Academy of Audiology  
800-222-2336 (toll-free)  
[www.audiology.org](http://www.audiology.org)

American Tinnitus Association  
800-634-8978 (toll-free)  
[www.ata.org](http://www.ata.org)

National Institute on Deafness and  
Other Communication Disorders  
800-241-1044 (toll-free)  
[www.nidcd.nih.gov/health/hearing/tinnitus.htm](http://www.nidcd.nih.gov/health/hearing/tinnitus.htm)



## IN THE JOURNALS

### Napping boosts sleep and cognitive function in healthy older adults

**W**ith age come changes in the structure and quality of our sleep. After about age 60, we have less deep (slow-wave) sleep and more rapid sleep cycles, we awaken more often, and we sleep an average of two hours less at night than we did as young adults. It was once thought that older people didn’t need as much sleep as younger ones, but experts now agree that’s not the case. Regardless of age, we typically need seven-and-a-half to eight hours of sleep to function at our best. So if you’re not getting enough sleep at night, what about daytime naps? Or does napping disrupt the sleep cycle, ultimately yielding less sleep and more daytime drowsiness?

These questions were addressed in a recent study by re-

searchers at the Weill Cornell Medical College in White Plains, N.Y., and published in the *Journal of the American Geriatrics Society* (February 2011). The authors concluded that napping not only increases older individuals’ total sleep time—without producing daytime drowsiness—but also provides measurable cognitive benefits.

**The study.** This small but well-designed study involved 22 healthy women and men ages 50 to 83 who agreed to be evaluated in a sleep laboratory. During a one- to two-week preliminary period, participants kept sleep logs at home and wore monitors to track their nighttime movements. They were then brought into the sleep laboratory for three nights and two days and given a thorough sleep evaluation

(using polysomnography and other techniques) and a battery of cognitive tests. After this initial laboratory session, participants started a month-long daily napping routine at home: half took short (45-minute) naps, and half took longer (two-hour) naps. After the second and fourth weeks, all returned to the lab for repeat assessments.

**The results.** By study's end, total sleep time had increased by an average of 65 minutes in the participants assigned to two-hour naps, and by an average of 20 minutes in those assigned to 45-minute naps. Participants found it harder to adhere to the two-hour nap schedule, but neither long naps nor short naps disrupted nighttime sleep or led to daytime sleepiness. Napping increased the time spent in slow-wave and rapid-eye-movement (REM) sleep, which are thought to play important roles in restoring the body and brain. Whether they took long naps or short naps, participants

showed significant improvement on three of the four tests in the study's cognitive-assessment battery.

**Limitations and implications.** Only people in good physical and mental health were included in the study, so it's unclear whether a 45-minute or two-hour napping regimen would be as helpful to older adults with sleep disorders or medical conditions. The study tells us nothing about the effects of shorter naps (for example, so-called power naps) on waking function. Moreover, the study was brief: napping-related cognitive function was measured after only two weeks and four weeks. Whether the improvements observed during the study would continue during subsequent weeks of napping is not known. Nevertheless, the findings provide further evidence that for older people, a daily nap can add to total sleep (as well as time in restorative sleep) and improve daytime function. ♥

## Large trial finds annual screening doesn't reduce deaths from ovarian cancer

**A**nnual screening for ovarian cancer with the CA-125 blood test and transvaginal ultrasound (TVUS) does not reduce a woman's risk of dying from the disease, according to the results of a large clinical trial sponsored by the National Cancer Institute. Ovarian cancer is 90% curable when treated early, but most cases are diagnosed late, when the five-year survival rate is less than 30%. Nearly 14,000 women die from the disease every year.

As part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, researchers at the University of Utah evaluated whether yearly screening could lead to earlier detection and reduce mortality. Results were presented at the American Society of Clinical Oncology meeting in Chicago and published online in *The Journal of the American Medical Association* on June 4, 2011.

**The study.** Investigators at 10 centers across the United States enrolled 78,216 women ages 55 to 74 who were at average risk for ovarian cancer and followed them for up to 13 years. Participants were assigned at random to either annual screening or usual medical care without screening. Women in the screening group were offered an annual CA-125 blood test (a nonspecific test for ovarian cancer) for up to six years, and TVUS annually for up to four years. The women and their physicians were informed of any suspicious abnormalities found during screening; the physicians were responsible for managing any further diagnosis and therapy.

**The results.** In the screening group, there were 212 cases of ovarian cancer and 118 deaths from the disease. In the usual care group, there were 176 cases of ovarian cancer and 100 related deaths. When the researchers took into account the total number of participants and factored in

the total surveillance time—that is, when they calculated mortality per “10,000 person-years”—they found that the death rate was slightly higher in the screening group, but the difference wasn't statistically significant, meaning that it might have been due to chance. Screening not only failed to improve the survival rate but also led to unnecessary invasive procedures. In the screening group, there were false-positive results in 3,285 women, of whom 1,080 underwent surgery as part of their diagnostic workup. Of those who underwent surgery, 15% had at least one major complication as a result.

**Limitations and implications.** Although this large-scale trial found that screening women at average risk for ovarian cancer with CA-125 and TVUS did not decrease their risk of death from the disease, the results don't necessarily mean that these tests are useless. The researchers suggest that the thresholds for abnormal results that were used in this study may not have been low enough to catch cancers at their earliest stages. Also, studies suggest that ovarian cancer often advances quickly in the early stages, so yearly screening may be insufficient. Monitoring changes in CA-125 levels more frequently might lead to more accurate diagnoses.

Another clinical trial currently under way is expected to provide additional insight into the potential of screening with CA-125 and TVUS. The U.K. Collaborative Trial of Ovarian Cancer Screening is following more than 200,000 women randomly assigned to usual care, annual TVUS, or annual CA-125 testing followed by TVUS if indicated by the blood test results. Preliminary data from this study suggest that both screening methods are more effective at detecting early ovarian cancer than usual care. However, final results won't be known until 2015. ♥



## Does creatine improve strength in postmenopausal women?

**Q** Could you discuss the benefits of creatine supplements for older, postmenopausal women? Are there any drawbacks?

**A** Creatine is a substance made in our bodies from the amino acids arginine, glycine, and methionine. Amino acids are the chemical building blocks of protein; we get them from dietary protein. The body makes 1 to 2 grams of creatine a day, and we also get creatine from certain foods, such as fish and meat. Most (95%) of the body's creatine is located in muscle, though some is found in other tissues, including the brain and retina.

Creatine increases energy by producing adenosine triphosphate, a high-energy compound released in muscle during intense, anaerobic exercise. Creatine supplements promote protein manufacture and provide a quick source of energy for muscle contraction.

Some studies suggest that supplemental creatine can help young athletes increase muscle mass and strength and improve their athletic performance during brief, high-intensity activity that requires short bursts of energy—one reason why it's incorporated in various nutritional supplements used by bodybuilders and by adolescent and professional athletes. But most of these studies have found that creatine doesn't enhance performance in older men and women, and doesn't improve endurance at any age.

There are a few exceptions to that conclusion. In a 2003 Canadian study of men and women ages 65 and over participating in a six-month strength-training program, those who took creatine had a twofold increase in lean muscle mass compared with a placebo group. In a small European study published in 2008, creatine seemed to confer a short-term benefit on postmenopausal women. At the start of the study, the women were evaluated for muscle performance (bench press, hand grip, tandem walking, and leg press). After one week, women who took creatine, compared with those taking a placebo, showed significant increases in bench-press and leg-press strength (measures of upper- and lower-body strength) and improvement in tests of coordination and balance.

### Grams of protein in certain foods

Food	Grams of protein
Meat and poultry, 3 ounces	21-30
Fish, 3 ounces	20-25
Dried beans, cooked, 1 cup	16
Yogurt, 8 ounces	10
Milk, 1 cup	8
Cheese, 1 ounce	8
Egg, 1 large	6

Source: USDA National Nutrient Database for Standard Reference, Release 23, available at [www.ars.usda.gov/ba/bhnrc/ndl](http://www.ars.usda.gov/ba/bhnrc/ndl).

These studies and others, while informative, have involved only a small number of participants. Moreover, there are no studies of the long-term effects of creatine supplementation. Its most common known side effects include weight gain, stomach upset, diarrhea, muscle cramps, headache, anxiety, nervousness, sleepiness, and dizziness. Less common but potentially serious side effects include liver problems, kidney damage, and interaction with insulin. Women with diabetes or kidney or liver disease should not take creatine supplements.

My conclusion is that there's not yet enough evidence that creatine can help women your age build muscle or increase strength. And even if creatine isn't harmful, other substances used in making the supplements could be. The FDA doesn't regulate supplements and their ingredients. So your best way to build and maintain your muscle strength is to exercise and get the recommended amount of dietary protein. Healthy women ages 19 to 70 need 46 grams of protein per day (see the chart "Grams of protein in certain foods"), and they should perform regular strength training and aerobic exercise.

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### Send us a question for Ask the Doctor

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(Please write "Ask the doctor" in the subject line.)

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