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# UPDATES in cancer screening

The number of cancer-screening guidelines can be overwhelming. Fortunately, the major medical organizations have never been more consonant. Here are their suggestions and recommended practices and current technologies for early detection of colon, cervical, breast and prostate cancer.

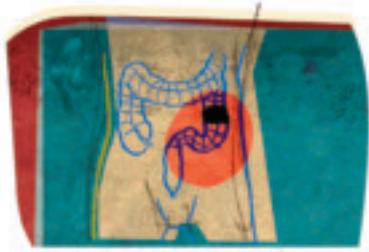
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Although minor differences among organizations still exist, major guidelines for colon, cervical, and breast cancer screening as well as testing for early prostate cancer are quite similar. Even so, a large subset of the general population either continues to go unscreened or is screened inconsistently. For example, few men and women (< 30%) reported the recent use of any colorectal screening test in 2000.<sup>1</sup>

The reasons for this are multifaceted, and many (e.g., insurance coverage, access, and patient discomfort) are beyond the physician's control.<sup>2,3</sup> However, the evidence shows that doctors can make a huge difference in two key areas: recommending testing and raising patient awareness about the importance of regular testing. This article presents up-to-date guideline-recommended practices for colon, cervical, breast, and prostate cancer screening to enable you to better inform patients about their options and help them decide which tests are most advantageous to their long-term health (see Table 1).

Guideline: American Cancer Society recommendations for early cancer detection			Table 1
	Patient population	Screening test	Interval
	<b>Breast</b> Average-risk women ≥ 20 y	BSE, optional CBE	Annually Every 3 y
	<b>Colon</b> Average-risk men and women ≥ 50	Any one of these tests: 3-panel FOBT or FIT FSIG FOBT or FIT plus FSIG Barium enema Colonoscopy	Every 2 y Every 5 y Annual (FOBT) and every 5 y (FSIG) Every 5 y Every 10 y
	<b>Prostate</b> High-risk men ≥ 40/45 y* Average-risk men ≥ 50 y	PSA test plus DRE Offer PSA test plus DRE, discussing risks and benefits	Annually Annually
	<b>Cervix</b> Women, ~3 y after first sexual intercourse or by age 21	Either one of these tests: Traditional Pap test Liquid-based cytology	Annually Every 2 y
	Women ≥ 30 y, who have had 3 normal findings on consecutive Pap tests <sup>†</sup> Liquid-based cytology	Either one of these tests: Traditional Pap test or Pap test with HPV test	Every 2-3 y Every 3 y
	Women ≥ 30 y who have had an abnormal Pap test finding within the past 3 consecutive tests	Either one of these tests: Traditional Pap test Liquid-based cytology	Every 1-2 y Every 1-2 y

**key:** BSE, breast self-examination; CBE, clinical breast examination; DRE, digital rectal examination; FIT, fecal immunochemical test; FOBT, fecal occult blood test; FSIG, flexible sigmoidoscopy; HPV, human papilloma virus; PSA, prostate-specific antigen. \* African-American men and men with a first-degree family member with prostate cancer < 65 y are considered to be at high risk. † Women who have had a total hysterectomy for benign reasons do not require Pap tests.



## Colon

Screening for colorectal cancer is strongly recommended by all major Canadian and U.S. medical organizations for

average-risk men and women aged 50 or older, although actual screening rates have not been studied formally. With respect to the modalities, referral for colonoscopy is becoming more common, in-office flexible sigmoidoscopy use is declining, and physicians may not have a high degree of confidence that patients will complete a 3-panel fecal occult blood test (FOBT). Other hindrances include fear of embarrassing the patient with the discussion and reservations about the patient's following through with the screening procedure. However, one of the most common patient-reported reasons for poor screening compliance is absence of physician advice. Recommending colon screening with conviction is important, as well as discussing the benefits and potential detriments of testing, so the patient can make an informed choice. Failing to do so can result in undetected cancers, with greater risk of morbidity and premature mortality for patients, and unwanted lawsuits for clinicians.

### Colon cancer screening options

Both the Canadian Association of Gastroenterology (CAG) and the Canadian Digestive Health Foundation (CDHF) outline the same four screening options and intervals from which patients, starting at age 50, may choose in consultation with their physician:

- FOBT every two years
- flexible sigmoidoscopy (with or without FOBT) every five years
- double-contrast barium enema (DCBE) every five years
- colonoscopy every 10 years.

Although controlled studies of efficacy are lacking, most gastroenterologists would agree that colonoscopy is the gold-standard test for average-risk patients over the age of 50. For those with increased risk (a family history of cancer or adenomatous polyps in first-degree relatives, or inflammatory bowel disease of significant duration) or very high risk (individuals at inherited risk due to hereditary nonpolyposis colorectal cancer [HNPCC] or familial adenomatous polyposis [FAP]), initiating screening at an earlier age (possibly as young as age 20) is recommended, generally with colonoscopy. Patients with a family history of colon cancer have a 3-fold increased risk; this increases to 5-fold if the relative was younger than 50 at the time of diagnosis. It is recommended that patients with a first-degree relative with colon cancer or a first-degree relative

## Article at-a-glance

### Colon

- Average-risk men and women should receive some form of colon screening starting at age 50, whether it be colonoscopy, flexible sigmoidoscopy, double-contrast barium enema (DCBE) or fecal occult blood testing (FOBT).
- Digital rectal examination (DRE) and in-office single-FOBT for colon cancer are not recommended. Newer technologies such as stool DNA testing and CT colonography show promise, but further study is needed before they can be implemented into routine screening practice.
- Newer fecal immunochemical tests (FITs) are reported to have improved performance compared to guaiac tests, and they do not require dietary restrictions.

### Cervix

- Significant changes have been made to the cervical cancer screening guidelines within the past few years to incorporate medical advances such as liquid-based cytology and HPV testing.
- New evidence has led to the recommendation that initial screening be conducted later than was previously recommended, and screening intervals be increased to 2-3 years in women older than 30 who remain low-risk.

### Breast

- All major guidelines state that average-risk women should begin regular mammography screening in their 40s, and that women should be counseled about the importance of recognizing new symptoms and reporting them to a health care provider.
- MRI and ultrasound should be reserved for women at very high risk for breast cancer.

### Prostate

- Informed decision-making and patient preference are strong determinants in making the decision to screen for prostate cancer.
- A combination of prostate-specific antigen (PSA) testing and DRE remains the most sensitive method available for early prostate cancer detection.
- Age is an important factor in determining when to stop testing.

## Whether one test is more effective than another is unclear, but it is clear that these options are only relatively comparable over the long-term if the recommended regimens are followed.

with FAP begin screening at age 40 or 10 years younger than the earliest diagnosis in the family, whichever comes first. Patients with a family history of two second-degree relatives with colorectal cancer should also start screening at age 40.

Whether one test is more effective than another is unclear, but it is clear that these options are only relatively comparable over the long-term if the recommended regimens are followed. A single colonoscopic examination is considered the most accurate test, but repeated colonoscopies do not necessarily detect more cancers than the other testing strategies when conducted every 10 years for several decades. Because DCBE has demonstrated lower sensitivity compared with colonoscopy, the interval for its use in screening was changed from every five or 10 years to every five years when the U.S. Multisociety Task Force on Colorectal Cancer updated its guidelines for colorectal cancer screening in 2003.<sup>7</sup>

Colonoscopy now dominates all strategies for high-risk screening and surveillance; aside from accuracy, a strong benefit is the ability to sample or remove lesions during screening. However, because no randomized controlled clinical trials have been done to evaluate the effectiveness of colonoscopy for colon cancer screening, the CAG-CDHF notes a lack of direct evidence that colonoscopy is effective in reducing colorectal cancer mortality.<sup>6</sup>

A recent study showed that women in particular may benefit from screening with colonoscopy rather than flexible sigmoidoscopy.<sup>8</sup> Investigators compared the diagnostic yield of screening colonoscopy in 1,463 average-risk women to that of average-risk male counterparts in a previous Veterans Affairs study.<sup>9</sup> They found that the diagnostic yield of flexible sigmoidoscopy for advanced neoplasia is much lower among women than among men (35.2% vs 66.3%,  $P < 0.001$ ) and concluded that flexible sigmoidoscopy is an inadequate method of predicting advanced neoplasia in the proximal colon of women. This study suggests that gender may someday be a factor in test suitability, although it should be noted that the presence of advanced neoplasia overall in this sample of women was relatively low.

Test choice may also be influenced by physician and patient comfort, availability, access, benefit-to-risk ratio, cost, sensitivity, specificity, and insurance coverage. For example, patients who fear or refuse colonoscopy may be more inclined to accept biennial FOBT; others may choose flexible sigmoidoscopy every five years if colonoscopy is not accepted by their insurance plan. All these tests are included in the major guide-

lines.<sup>4,7</sup> They are also all underutilized, as evidenced by a high rate of avoidable advanced cancers.

A positive FOBT or DCBE screening result should be followed by colonoscopy because of the possibility that a significant lesion will be visualized and a biopsy will need to be performed. The recommendation for follow-up of abnormalities detected by flexible sigmoidoscopy is less clear.

Debate continues as to whether it is necessary to perform colonoscopy on every patient in whom a distal colonic adenoma has been detected. The CAG-CDHF position is that colonoscopy should be offered to all such patients, but further studies are awaited.

### Screening tests no longer recommended

Digital rectal exams (DRE), toilet bowl FOBT, and in-office single-panel FOBT for colon cancer screening are not recommended due to the high number of false-negative findings that they yield. DRE is not proven for colorectal screening and is not associated with reduction in mortality from distal rectal cancer. If the patient and physician determine that FOBT is the preferred colon screening test, only the at-home procedure following manufacturer's recommendations should be used, and annual testing must be done. Negative results from digital in-office FOBT do not decrease the odds of advanced neoplasia.<sup>11</sup>

### Emerging technologies

New modalities show promise in colon cancer screening, since they are considered less invasive, more accurate, and more palatable to patients. With further study, CT colonography and stool DNA testing may soon join other tests as part of the guideline-based approach to detecting early cancer in average-risk patients.

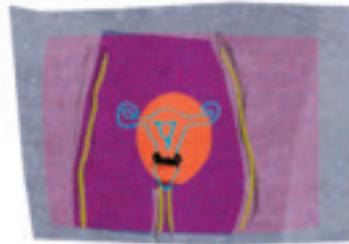
**Fecal immunochemical test (FIT)** Older guaiac-based FOBTs have a poor test sensitivity for premalignant and early-stage lesions, and irregular testing limits the potential to detect colorectal cancer early. Newer FITs are reported to have improved performance characteristics compared to guaiac tests, and they do not require dietary restrictions. If hemoglobin is present in the stool, the monoclonal and/or polyclonal antibodies employed by such tests will attach to its antigens, showing a positive result.<sup>12</sup> FITs do not react with nonhuman hemoglobin or uncooked fruits and vegetables with peroxidase activity known to cause false-positive results on guaiac-based tests.

In a study of InSure, an immunochemical FOBT approved in 2001, in a normal patient population 40 and older, specificity was 97.9%; in a population younger than 30, specificity was 97.8%.<sup>12</sup> The lower false-positive rate associated with FITs translates into a lower rate of unnecessary colonoscopy. In addition, the improved sensitivity of the newer tests may compensate for the nonadherence associated with traditional FOBT testing, leading to greater program sensitivity. According to the ACS, immunochemical tests are more patient-friendly, and are likely to be equal or better in sensitivity and specificity than guaiacum-based tests for the detection of occult blood.<sup>13</sup>

**Stool DNA testing** New testing for DNA mutations in stool have the potential to identify cancers and advanced lesions that would not otherwise be identified. DNA has proven to be a potentially good marker, since it is stable in the stool, is shed continuously, and can be detected in small amounts. In addition, the test does not require dietary restrictions or bowel preparation. Although results from early clinical trials were encouraging, a recent study showed that the majority of neoplastic lesions identified by colonoscopy were not detected by either stool DNA testing or the FOBT.<sup>12</sup>

The test is expensive (more than \$750) and requires an entire bowel movement, which may influence adherence. Until more studies are conducted in average-risk patients and the most appropriate markers for DNA detection of cancer are identified, the use of stool DNA mutation testing cannot be recommended. A large National Cancer Institute trial is underway.

**CT colonography** The lack of evidence regarding CT colonography, also known as virtual colonoscopy, precludes its use for general screening for now. The high sensitivity and specificity in research findings (85-90%) do not match real-world outcomes, where results are influenced by the skill of the examiner.<sup>6</sup> Also, only frank colon cancers and larger polyps—not small and flat ones—are well-visualized on CT colonography, and polyps found cannot be removed during the procedure. However, a panel convened by the ACS in 2002 notes that CT colonography may identify cancers located near complex haustral folds and other areas not adequately visualized with conventional colonoscopy (i.e., for polypectomy).<sup>12</sup> If proven viable, CT colonography might be used to determine which patients require therapeutic colonoscopy.<sup>12</sup> Before it can be adopted for general screening, however, further studies are needed. In summary, the key issues are sensitivity, threshold for referral for colonoscopy, and implications of extracolonic findings.



## Cervix

Medical advances such as liquid-based cytology and human papilloma virus (HPV) testing have prompted significant

cervical screening guideline changes within the past few years. According to the ACS, American College of Obstetricians and Gynecologists (ACOG), and USPSTF, an increasing number of women will no longer need annual testing for cervical cancer, and screening can begin later than previously recommended.<sup>4</sup>

## Initial screening

The ACS's guidelines for initiating cervical screening—shared by ACOG and USPSTF—state that screening with either a traditional Pap test or liquid-based cytology should begin approximately three years after first sexual intercourse or by age 21.<sup>14,15</sup> Although testing soon after first sexual intercourse or by age 18 had formerly been recommended, the guideline organizations determined that initiating cervical screening within the first several years of vaginal intercourse is unnecessary. Evidence demonstrates that HPV infection in young women is common and often clears within 1-2 years without causing cancerous changes. Rather, it is the persistence of HPV as well as the long latency period between initial infection and development of high-grade dysplasia or cervical cancer that causes the problem. Women who have never had intercourse have virtually no risk of developing cervical cancer. The guidelines list an age for initial screening to protect patients who are either unaware of or not forthcoming about prior sexual exposures.

## Liquid-based or traditional Pap test?

The traditional Pap test is very effective when done properly, and it is less expensive than liquid-based cytology. No major guideline recommends one test over the other. Although liquid-based tests are considered more sensitive, their specificity is lower than that of Pap tests. They are particularly useful for managing the equivocal Pap test result of atypical squamous cells of undetermined significance (ASCUS). When a Pap test is used, the woman must return for an HPV test. With a liquid-based test, however, resampling the patient is unnecessary before doing an HPV test.

## Screening intervals

The ACS and ACOG concur that annual testing for cervical cancer should be conducted until age 30; after age 30, screening can occur every 2-3 years for women with three negative

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cytology tests.<sup>4,15</sup> Exceptions to extended screening intervals include women who are either immunocompromised or have a history of cervical intraepithelial neoplasia. The USPSTF recommends that Pap testing be performed at least every three years.<sup>14</sup> Among these organizations, only the ACS specifies screening every two years rather than annually for women younger than 30 if liquid-based rather than conventional cytology screening is used.<sup>4</sup> However, ACOG maintains that there are limited data to support this approach and notes that this interval does not take into account potentially false-negative results.<sup>15</sup> Screening intervals for women 30 years and older would change with the use of the HPV test in combination with the Pap test for primary screening.

#### HPV testing

Several options exist for follow-up of ASCUS Pap test results. One is watchful waiting, with follow-up Pap tests every 4-6 months. Minor cervical changes may never progress and resolve on their own about 50% of the time. The second option is to refer the patient for colposcopy. The third is to perform HPV testing to identify the high-risk HPV types. If the woman is positive for high-risk HPV, she will be referred for colposcopy. About 50% of women with ASCUS will test positive for high-risk types of HPV.<sup>16</sup> If a woman tests negative for a high-risk HPV type, she can be screened with Pap test in one year.

The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends "reflex" HPV testing as a convenient and cost-effective approach for follow-up of women of all ages with atypical findings.<sup>2</sup> The ASCCP also has other recommendations on the use of HPV testing for management of other abnormal cytology or documented CIN ([www.asccp.org/](http://www.asccp.org/)).

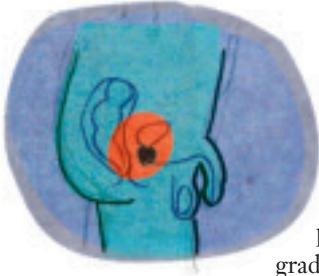
As part of routine cervical cancer screening, along with the Pap test for women aged 30 and older, HPV DNA testing is now an option for primary cervical cancer screening according to the ACS and ACOG.<sup>4,15</sup> In 2003, the FDA approved the use of the HPV DNA test in conjunction with cervical cytology testing as a cervical cancer screen for women aged 30 and older; it is not, however, approved for use as a stand-alone screening test. The test is only appropriate for women in this age subset. Testing in younger women, therefore, would cause unnecessary anxiety.

Both the ACS and ACOG agree on a screening interval of every three years for women aged 30 and older with negative test results on concurrent cervical cytology and HPV DNA tests.<sup>4,15</sup> This recommendation is based on evidence that negative combined test results reflect an extremely low risk for developing neoplasia during the next 3-5 years. For women who have discordant test results, there has been some interim guidance provided.<sup>16</sup>

HPV DNA testing is not indicated for women or men diagnosed with external genital warts or for women or men as a general stand-alone screening test for HPV. This test is also not indicated in general as a follow-up test for women with higher grade cytological results. This is because there is no evidence that it improves clinical management. And for men, test performance is not well-defined.

It is important to note that these gains in sensitivity are somewhat offset by poor specificity; that is to say, both ultrasound and MRI generate a higher rate of false-positive results. In this unique group at appreciably greater risk of breast cancer compared with average-risk women, the higher rate of false-positive results may be an acceptable trade-off, although it is important that women at inherited risk who are considering initiating screening at an earlier age learn about the potential benefits and limitations of current surveillance options. This kind of imaging is not recommended for women at average risk or even at increased risk due to more prevalent variants of family history.

Despite the superiority of MRI in high-risk women, a recent clinical review concluded that such new screening modalities are unlikely to replace mammography in the near future for screening the general population.<sup>27</sup> MRI has a low positive predictive value and low specificity, resulting in many false-positives and unnecessary biopsies when used in the general population. Likewise, ultrasound has not been sufficiently evaluated outside the high-risk population. Thus, neither MRI nor ultrasound is recommended for general screening.



### Prostate

Prostate-specific antigen (PSA) testing and DRE may reduce mortality by detecting prostate cancer in its early stages in some patients with moderate-to high-grade tumors. However, the decision to screen for prostate cancer is confounded by the limitations of these tests. A major risk of PSA screening includes treatment with radiation or prostatectomy for a disease that may have remained inconsequential. Also, because PSA testing has poor specificity, false-positive findings occur, leading to unnecessary ultrasound and biopsies.

No major U.S. medical organization endorses universal or mass screening for average-risk men. Given the limitations of the available evidence, the ACS, American Academy of Family Physicians, the American College of Physicians, American Medical Association, and American Urological Association (AUA) recommend that for men aged 50 and older and for men at higher risk for prostate cancer, clinicians

- Discuss with patients the potential benefits and possible harms of PSA testing
- Consider patient preferences
- Individualize the decision to test.<sup>4,28</sup>

Those in the high-risk category are African American men and men with a first-degree relative with prostate cancer. These men could consider testing beginning at age 40 or 45, but only after going through a process of informed decision making. The CDC offers "Tools to Facilitate Shared Decision Making for Prostate Cancer Screening" ([www.cdc.gov/cancer/prostate/screening/toolkit.htm](http://www.cdc.gov/cancer/prostate/screening/toolkit.htm)).

### DRE: A viable screen?

The AUA states that combining PSA testing and DRE is considered best practice, as this is the most sensitive method for early prostate cancer detection.<sup>28</sup> DRE will detect some tumors in patients who have prostate cancer despite a normal PSA (4 ng/mL or less), and conversely, PSA will detect some abnormalities in patients with normal DRE findings. Furthermore, approximately 20% of aggressive prostate cancers are found in men with PSA levels of less than 4 ng/mL.<sup>28</sup>

Shared decision-making must include a discussion of each test's limitations, such as PSA's poor specificity for prostate cancer and DRE's inaccessibility to areas likely to have cancerous lesions (only 25% to 30% of prostate cancers are found in areas accessible by DRE).<sup>28</sup> Patient preference should be a strong factor in the decision to conduct either test.

### Cutoff value

Although there are no guidelines currently recommending age-specific ranges for PSA cutoff values, many experts consider in making their decision to proceed to biopsy. Baseline PSA is higher in older men (due to enlarged prostate) than in younger men, although the current guidelines do not address this point. Only the AUA specifies a cutoff value; a PSA value that is 4 ng/mL or more warrants a prostate biopsy.<sup>28</sup> Many consider a significant rise in PSA from one test to the next as an indication for the need to perform a biopsy. Cutoff values are receiving increasing scrutiny. New research shows that a cutoff value of 4 ng/mL will miss a significant percentage of occult cancers, but that the lower cutoff values will significantly increase the false-positive rate.

### When to stop screening

Due to the high prevalence of clinically insignificant prostate cancer in older men, it is recommended that screening stop when life expectancy is less than 10 years. ■

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# Nonhormone choices for menopausal symptoms

## Vasomotor hot flashes and flushes

Changing endogenous estrogen concentrations may play a role in the initiation of early menopausal symptoms; however, endogenous estrogen levels are not always predictive of either the hot flash frequency or severity. In many women, a circadian rhythm can be observed: hot flash frequency peaking in the early evening hours, followed in three hours, by a peak in core-body temperature.

Between 68-75% of North American women experience menopausal vascular changes. The majority are mild to moderate in intensity and abate over time; some women experience severe and unremitting symptoms, leading them to seek treatment. African women report hot flashes most frequently, followed by Hispanic, Caucasians, Chinese, and Japanese. Differences in body mass index may be a more important predictor of hot flashes than ethnic differences.

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**suggested reading:** Treatment of Menopausal-Associated Vasomotor Symptoms: Position Statement of the North American Menopause Society. *J N Am Menopause Soc* 2004; 11(1): 11-13.

### Predisposing factors

- Warm, ambient air temperatures increase a woman's core-body temperature, increasing the likelihood of her developing flashes, flushes, and sweats.
- Somewhat surprisingly, women with a high BMI are at increased risk for severe hot flashes compared to those with a low BMI.
- Cigarette smoking is associated with an increased risk of flashes, flushes, and sweats. Among current smokers, the risk of vasomotor symptoms increases with the number of cigarettes smoked.
- Exercise produces variable results. Strenuous exercise may precipitate hot flashes in poorly conditioned women, whereas daily exercise in well-conditioned women is associated with a reduction in flashes.
- Low socioeconomic status is associated with increase of hot flashes.

### Nonhormonal preparations

Since the publication of the Women's Health Initiative (WHI), significant numbers of women have abandoned a highly effective regimen of estrogen, with/without progestin, as the management of choice for their menopausal vasomotor symptoms. Many have solved the problem by learning to tough it out, or through lifestyle modifications and relaxation techniques. Others have sought solace from their severe and disturbing symptoms by turning to over-the-counter (OTC) and health food store preparations.

Evidence is lacking regarding the efficacy and long-term safety of most OTC remedies. Many are categorized as dietary supplements, lacking government and scientific verification and validation of claims purporting efficacy, safety, and uniformity of dosing. Data regarding the interaction of some of these therapies with each other and with other prescription drugs are limited.

### Isoflavones (phytoestrogens)

Isoflavones are plant-derived dyphenolic compounds that exhibit both hormonal and nonhormonal properties. They bind to estrogen-receptor B more than to estrogen-receptor A, and possess both estrogen agonist and antagonist properties.

#### Soy-derived

Approximately 30-50% of women convert daidzein, one of the isoflavones found in soy, to a metabolite known as equol, a nonsteroidal estrogen with estrogenic effects. Most hot flash studies used isoflavones in amounts of 40-80 mg a day. A review of 14 randomized double-blind controlled studies compared soy foods with soy isoflavin to placebo supplements. Of the 14, 11 studies showed no significant differences between active product and placebo in the number, frequency, or intensity of hot flashes.

### Red clover-derived isoflavones

Red clover contains several phytoestrogens including daidzein and genistein.

Three double-blind controlled studies found no benefit for hot flash treatment using standard doses of commercial red clover products (Promensil and Rimostil) when compared to placebo.

Although the studies provide some evidence for a biological effect of red clover, none of the supplements had any clinically significant effect on hot flashes or other menopausal symptoms when compared to placebo.

### Black cohosh

Almost all studies of black cohosh have used the commercial preparation Remifemin, containing a standardized 1 mg of 27-deoxyacetyl. A few randomized double-blind placebo-controlled studies compared black cohosh with estrogens and placebo. In two of the

## Summaries

### Summary of nonprescription OTC preparations

Although individual anecdotal and poorly designed studies proclaim the efficacy of nonprescription, nonhormonal preparations in the management of menopausal vascular symptoms, well-designed double-blind controlled randomized studies show that in almost all cases their effect is not superior to that of placebo. In most well-designed studies, the positive placebo effect runs between 30-35%. As vasomotor symptoms tend to abate with the passage of time from the onset of menopause, it is common for menopausal symptoms to spontaneously improve by the end of a study, whether patients are on active component or in the placebo arm of the trial. The physician who recommends such nonhormonal, nonprescription preparations should understand that the benefits attributable to these preparations is minimal, and the risks to the patient unknown.

### Prescription nonhormonal options

- **Antidepressants** It is reasonable to expect that antidepressant medications, which alter CNS serotonin and norepinephrine concentrations, would have a beneficial effect on menopausal hot flashes.
- **Venlafaxine: a combination serotonin and norepinephrine re-uptake inhibitor (SNRI).** In a randomized double-blind placebo-controlled clinical trial, this preparation, especially in higher doses, demonstrated superior reduction of menopausal flashes when compared to placebo. The effect was noted within 1-2 weeks.

studies, black cohosh provided no benefit over a placebo and was not nearly as effective as estrogen in managing menopausal vascular symptoms. In a third study, beneficial effect was noted.

There is contradictory evidence as to whether or not black cohosh is estrogenic. As a result, most physicians are unwilling to use black cohosh in women with a previous history of, or at significant risk for, postmenopausal breast cancer.

#### **Dong quai**

Dong quai, a Chinese herb, is a common ingredient of a mixed bag of traditional Chinese medicine treatments. Data are inconclusive regarding the estrogenicity of dong quai. Only one randomized double-blind placebo-controlled study evaluated its efficacy. Although dong quai reduced hot flashes by 25-30% from baseline, this was not significantly better than placebo.

#### **Evening primrose oil**

Only one randomized double-blind placebo-controlled clinical trial has been conducted. Evening primrose oil demonstrated no benefit over placebo. There was no significant improvement in the number of hot flashes from baseline in the treated group, whereas the placebo group did demonstrate significant improvement. Important side effects include GI upset.

#### **Ginseng**

Ginseng is another commonly-used preparation found in traditional Chinese medical potions. Many ginseng products contain other contaminants that may be responsible for some of the benefits and side effects. In a randomized double-blind placebo-controlled clinical trial, standardized extracts displayed no benefit over placebo in the management of hot flashes, flushes, and sweats.

#### **Licorice root**

Licorice root is used in many traditional Chinese medical preparations for menopause. There are no clinical data regarding its safety or efficacy in the management of menopausal symptoms.

#### **Chinese herb mixtures**

Only one randomized double-blind placebo-controlled study evaluated this type of mixture when a standardized preparation was given to a group of women. The placebo-controlled group demonstrated better results in the management of menopausal symptoms than did the group receiving the Chinese herb mixture.

#### **Vitamin E**

Doses of 50-100 IU/d are no more effective than placebo in relieving menopausal vascular symptoms. Similar results were obtained when the dose of vitamin E was increased to 400 IU/d. ■

- **Paroxetine (Paxil):** a selective serotonin re-uptake inhibitor (SSRI).

In a double-blind randomized controlled study, in doses of both 12.5 and 25 mg/d for six weeks, paroxetine significantly decreased hot flashes when compared to placebo.

- **Fluoxetine (Prozac) (SSRI):**

In a double-blind placebo-controlled cross-over study, fluoxetine 20 mg/d demonstrated an additional 20% reduction in menopausal symptoms over placebo.

### **Other Drugs**

- **Gabapentin (Neurontin).** The mechanism of action of this anticonvulsant is unknown but thought to be influenced by the modulation of calcium currents. In a randomized double-blind placebo-controlled study, 500 mg/d reduced menopausal flashes, flushes and sweats significantly compared to placebo.
- **Clonidine (Dixarit) (an alpha adrenergic agonist).** In two double-blind randomized controlled studies, oral clonidine 0.1 mg/d significantly reduced hot flashes when compared to placebo.
- **Methyldopa.** Two randomized double-blind placebo-controlled cross-over trials demonstrated that methyldopa in doses of 500-1000 mg/d decreased menopausal-related flashes,

flushes, and sweats.

- **Bellergal spacetabs.** This preparation of a barbiturate, ergotamine and belladonna has been around for decades. In a randomized, double-blind placebo-controlled study, Bellergal significantly reduced hot flashes when compared to placebo.

### **Summary of nonhormonal prescription drugs**

There is good evidence in small well-controlled studies that antidepressants, anticonvulsants, and antihypertensive drugs with well-known and well-established side effect and safety profiles can be used effectively in the management of menopausal symptoms.

Many women are presently experiencing adverse changes in the quality of their lives because of lack of confidence in, and anxiety over, the use of well-studied preparations containing estrogen and progestin. Many, in desperation, have abandoned traditional prescription formulations in favor of untested, unreliable, and possibly unsafe OTC preparations. For those women who are unwilling or unable to safely reconsider hormone therapy, other prescription medications with a long track-record of safety and proven efficacy are available.

Physicians should make every effort to counsel their patients to seek treatment strategies which are both effective and safe.