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Primary Care Reports

The Practical, Peer-Reviewed Journal for Primary C

NEWSLETTER & ELECTRONIC PUBLISHERS FOUNDATION EDITORIAL EXCELLENCE AWARD WINNER

Volume 8, Number 11 **May 27, 2002**

Cancer Screening for Primary Care Physicians: Part II

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Editor's Note—*Cancer is considered a lethal disease, with a 5-year relative survival rate of 60% for all cancers combined. The National Cancer Institute estimates that 8.9 million Americans currently have cancer. The American Cancer Society estimates that approximately 1,284,900 cases of cancer will be diagnosed in 2002.[2] Prevention, early detection, diagnosis, and treatment may prevent premature death or promote decreased incidence of cancer. Primary care physicians (PCPs) are often the first to detect cancer in patients.*

This manuscript is the second in a two-part series reviewing common cancers encountered in primary care practice. We will review risk factors, primary prevention, early recognition, and screening. We will summarize guidelines and recommendations of national major medical organizations as well as specialty societies, related to different types of cancer.

Breast Cancer

Breast cancer is the most common malignancy in women in the United States. A women's lifetime risk of developing breast cancers is about 1 in 8.[1] There will be an estimated 203,500 cases of breast cancer in American women in 2002 with an estimated 39,600 deaths.[2] Caucasian women are more likely to develop breast cancer than African-American women.

Risk Factors

One half of breast cancer cases can be explained by known risk factors. The incidence increases with age, especially older than the age of 50. There is also an increased incidence in women with a positive family history of breast cancer. Obesity after menopause, and having the first child after age 30 increase the risk as well.[3] Early menarche and late menopause, and increased fat intake correlate with a greater incidence of the disease.[4]

About 8% of all breast cancer is hereditary and one half of those are mutations in 2 breast cancer susceptibility genes: BRCA1 and BRCA2.[5]

Presentation and Diagnostic Findings

Women usually seek attention when they feel a palpable mass during breast self-examination. Other presentations are redness, edema, other skin changes (puckering and scaling), and nipple retraction or discharge.[6]

Clinical breast examination may show a solitary, hard, nontender mass, but other findings should be sought during the examination, such as skin or nipple retraction, inflammation, and breast asymmetry. Axillary or other lymphadenopathy should be looked for during the physical examination. Areas of distinct breast thickening should be assessed.[7] Other modes of diagnosis are mammography, which can identify small breast cancers that are still nonpalpable.[8] The sensitivity of mammography is highly dependent upon breast density.

The role of magnetic resonance imaging (MRI) is to evaluate palpable breast masses, but there is no role for screening yet. The primary role of ultrasound is to evaluate palpable or

mammographically diagnosed masses, and not screening.[9]

Primary Prevention

High-risk Patients. Data from the National Surgical Adjuvant Breast and Bowel Project, Breast Cancer Prevention Trial show that the drug tamoxifen reduces the risk of developing breast cancer by 49% in women with increased risk. Tamoxifen, however, does have the potential for vascular and endometrial side effects.[10]

Preventive Mastectomy. Women with an extremely high risk for developing breast cancer will benefit from prophylactic mastectomy. Women with BRCA gene mutations, cancer in the contralateral breast, breast cancer in several close relatives, or lobular carcinoma in situ can expect a 90% reduction in risk. Extensive counseling needs to be conducted before this possibility is considered.[10]

Low-risk Patients. Women should avoid any unnecessary irradiation, even fluoroscopy,[11] decrease their alcohol intake and weight the risks and benefits of hormone replacement therapy (HRT). They should also increase fruits and vegetables in their diets.[12]

Secondary Prevention and Screening

USPSTF:[13] There is insufficient evidence for or against clinical or self-breast examinations alone. Mammography alone, or with clinical breast examination, is recommended every 1-2 years for women aged 40 and older.

CTF:[14] Current evidence does not support the inclusion or exclusion of screening mammography from the periodic health examinations of women between 40 and 49 at average risk of breast cancer. At 40 years old, women should be informed of the potential benefits and risks of mammography and assisted in a decision on the appropriateness of screening. There is good evidence for annual screening of women aged 50-69 by clinical examination and mammography.

ACS:[15] Self-breast exam should be performed once a month starting at 20 years of age. Between 20 and 39, women should have a clinical breast examination by a professional every 3 years. After age 40, an annual mammogram and a clinical examination are recommended.

NCI:[16] For women aged 39 years and younger, there are no study results showing a benefit for screening, nor for performing baseline mammograms in women younger than 40. Between the ages of 40 and 69, screening mammography (with or without clinical breast examination) should be performed every 1-2 years. Women at higher risk for breast cancer should consult with their physicians to determine appropriate screening measures.

AAFP:[17] For women between the ages of 50 and 69, a mammography and a clinical breast exam performed every 1-2 years are strongly recommended. Women between 40 and 49 should be counseled regarding the potential risks and benefits of mammography. Currently, the AAFP is reconsidering age ranges in their screening guidelines.

American College of Radiology (ACR):[18] For women 40 and older, annual mammogram and clinical breast examination are recommended.

Cervical Cancer

It is estimated that approximately 13,000 cases of cervical carcinoma will occur in the United States during 2002, with 4100 deaths.[2] The disease is usually preceded by an asymptomatic phase that is preinvasive, and hence ideal for early detection and screening. Cervical cancer is a preventable disease, with human papilloma virus (HPV) being the primary cause, except for 5% of the cases where other causes are postulated.

Risk Factors

Cervical cancer is highly related to sexual activity and sexually transmitted HPV infections. Multiple sexual partners or partners who have multiple partners increases the risk of cervical cancer. Other independent risk factors are smoking, sexual activity at a young age, and low socioeconomic status.[19,20] Minorities, including African-Americans, Native Americans, and Hispanics (but not Asian-Americans) have a higher risk than Caucasians. The difference mostly can be explained by associated socioeconomic factors.[21]

Presentation and Diagnostic Findings

Precancerous lesions of the cervix usually have no symptoms and are only detected by examination and Pap smear. Cervical cancer, however, may present with abnormal vaginal bleeding, spontaneously or after intercourse. Menorrhagia and increasing vaginal discharge are other symptoms.

Pelvic examination and Pap smear followed by colposcopy are the ideal diagnostic procedures for detection of this cancer. Guided biopsy is the best way to get a tissue diagnosis. HPV testing is also proposed as a secondary test for patients with abnormal Pap smears.

Primary Care Reports™, ISSN 1040-2497, is published biweekly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports™***, P.O. Box 740059, Atlanta, GA 30374.

Periodicals postage paid at Atlanta, GA.
Back issues: $23. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

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$299 per year (Student/Resident rate: $150).

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This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2002. This volume has been approved for up to 50 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief) serves as a consultant to Aventis and Sanofi and does research for Astrazeneca. Dr. Zoorob (author) and the peer reviewer report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Primary Prevention

There is strong evidence to recommend regular gynecologic examinations and Pap smears for women at the start of sexual activity or beginning at 18 years of age. Since cervical cancer is strongly tied to the carcinogen effects of HPV transmitted sexually, barrier methods of contraception that lower such transmission lower the incidence of cancer.[22] Other primary prevention include smoking cessation. Increased carotenoids in the diet may decrease cervical cancer risk.[23]

Secondary Prevention and Screening

USPSTF:[24] Routine screening for cervical cancer is recommended for all sexually active women with a cervix at the onset of sexual activity at least every 3 years. Insufficient evidence exists to recommend for or against on an upper age limit to stop screening. There is also insufficient evidence to screen routinely with cervicography or colposcopy, or to test for HPV in asymptomatic patients.

CTF:[25] Fair evidence exists to include a Pap smear in periodic health examinations of sexually active women. Annual screening is undertaken when sexual activity begins or by age 18. After 2 normal laboratory reports, women should be screening every 3 years until the age of 69. Consider increasing the frequency of Pap smears in women with risk factors such as multiple partners, smoking, low socioeconomic status and sexual intercourse before the age 18.

NCI:[26] The evidence suggests decreasing mortality when women are screened regularly with Pap smears at the start of sexual activity or when they reach age 18. An upper age at which to cease screening has not been determined.

ACS:[27] Annual screening at age 18 or onset of sexual activity, whichever comes first. After 3 normal laboratory reports, the frequency of Pap testing can be decreased, though an annual pelvic examination should be continued. There is no upper age limit recommended by ACS.

AAFP:[17] Women who have had sex and have a cervix should have a complete Pap smear at least every 3 years.

AGS:[28] Pap smear screening for older women is the responsibility of primary care providers, with culturally appropriate programs designed to address barriers identified in the population being served. Regular Pap smear screening at 1- to 3-year intervals until at least the age of 70 seems reasonable. Beyond age 70, there is little evidence for or against screening women who have been regularly screened in previous years. An older woman of any age who has never had a Pap smear may be screened with at least 2 negative Pap smears 1 year apart. Risk factors for the development of cervical carcinoma may be assessed on an ongoing basis and taken into consideration when deciding how often and for how long to screen older women for the development of cervical carcinoma.

ACOG:[29] Women should have their first Pap test by age 18 or when they start having sex with men, whichever comes first, and should continue past menopause. If tests show abnormal results, a doctor may advise more frequent Pap testing. Annual pelvic examinations are still recommended.

Endometrial Cancer

This is the most common gynecologic malignancy in the United States. It is estimated that 39,300 women will develop endometrial cancer in 2002. Mortality is relatively low; hence 6600 deaths are estimated for this year. The incidence is higher in Caucasians compared to African-Americans, but mortality is higher in African-American women. Cases also increase with age, peaking in the seventh decade of life.[2]

Risk Factors

Risk factors are related to increased estrogen levels from, for example, medication (ie, unopposed estrogen or tamoxifen administration) or estrogen-secreting tumors, obesity, chronic anovulation, diabetes, late menopause, or never having had children. Hereditary nonpolyposis colon cancer increases risk; pregnancy and oral contraceptives provide protection.[2]

Presentation and Diagnostic Findings

Endometrial cancer usually presents with postmenopausal uterine bleeding. Endometrial sampling should be performed for diagnosis. Most cancers are confined to the uterus; hence the survival rate is 90% or more. Endometrial sampling can be obtained by curettage, now mostly replaced by a less invasive method: endometrial biopsy accompanied by hysteroscopy. Another diagnostic method is transvaginal ultrasound to evaluate endometrial thickness, but there is no agreed upon endometrial thickness with high diagnostic sensitivity or specificity.[29]

Primary Prevention

Although most cases of endometrial cancer cannot be prevented, there are measures a woman can take to lower her risk of developing this disease. These measures include using oral contraceptives, using progestogens in combination with estrogen during HRT, controlling diabetes and obesity, and prompt treatment of hyperplasia before it becomes cancerous.[30]

Secondary Prevention and Screening

ACS:[31] There is no need to screen asymptomatic women with no risk factors either by biopsy or ultrasound. Women who are between 18 and 39 years old should have a pelvic exam every 3 years; women older than 40 should have 1 annually. Although the pelvic exam can find some female reproductive system cancers, including some advanced uterine cancers, it is not effective in finding early endometrial cancers. The Pap test can find some early endometrial cancers as well, but most cases are not detected by this test.

ACOG: Only annual pelvic examinations are recommended in asymptomatic women.[32]

Ovarian Cancer

Ovarian cancer is the gynecological malignancy with the highest death rate and a 5-year survival rate of 28%.[33] It is estimated that 23,300 cases of ovarian cancer will be diagnosed in 2002 with 13,900 deaths.[2] Epithelial ovarian cancer is responsible for 5.8% of all cancer deaths.[34]

Risk Factors

The most common risk factor is genetic predisposition. Family history of breast or ovarian cancer increases risk. These are families with BRCA1 or BRCA2 mutations.[33,35] The risk of ovarian cancer increases with age. One half of ovarian cancers are found in women older than 65 years of age. Women who

started menstruating at an early age (before age 12), had no children or had their first child after age 30, and/or experienced menopause after age 50, may have an increased risk of ovarian cancer. Use of fertility drugs, HRT, family history of ovarian or breast cancer have also been linked to increased risk.[36]

Diagnosis and Presentation

Presentation is usually made clinically as an ovarian mass or as seen on ultrasound. Although ultrasonographic findings may be able to define a cancerous mass, diagnosis should be made only on pathologic findings.[37] The most common sign is increased abdominal growth due to ascites. Long-term abdominal, pelvic or leg pain, nonspecific digestive symptoms with no gastrointestinal findings, and gas or bloating may sometimes indicate underlying ovarian cancer.[38]

Fine needle aspiration is not recommended for solid or mixed ovarian masses nor for pure cystic lesions (> 5 cm) of postmenopausal women. They need to be surgically excised or followed by ultrasound. Management of postmenopausal cystic lesions < 5 cm or premenopausal cystic lesions is not yet standardized. Some clinicians aspirate premenopausal cysts under vaginal ultrasound guidance.[37]

Primary Prevention

Oral contraceptive use, one live-born child, and breast-feeding are associated with reduced risk of ovarian cancer. Postmenopausal HRT may be associated with an increased risk of developing ovarian cancer. Tubal ligation, decreased dietary fat, and hysterectomy may decrease the incidence of ovarian malignancy. Prophylactic oophorectomy should only be considered in women with inherited ovarian cancer syndrome.[39]

Screening and Secondary Prevention

USPSTF:[40] There is fair evidence to exclude screening for ovarian cancer by any means including ultrasound, C125, pelvic examination or combination of any testing in both pre- and postmenopausal women. There is also insufficient evidence to recommend for or against the screening of asymptomatic women at increased risk of developing ovarian cancer.

CTF:[41] Identical to USPSTF, there is insufficient evidence to recommend for or against screening.

ACS:[42] Transvaginal ultrasound and tumor markers C125 may help in determining a diagnosis but are unnecessary for routine screening women at average risk for ovarian cancer.

NCI:[43] There is insufficient evidence that screening for ovarian cancer with C125 level or other serum markers, transvaginal ultrasound or pelvic examination will result in decreased mortality.

AAFP:[44] For women without a family history of frequent ovarian cancer, there is insufficient evidence to recommend for or against routine screening with ultrasound of the pelvis, and/or serum tumor markers.

Prostate Cancer

Prostate cancer is the most common cancer in men. The ACS estimates 189,000 cases will occur in 2002, with 30,200 deaths.[2] This type of cancer grows slowly and tends to strike later in life. It may take 3-4 years to double in size. The odds of developing prostate cancer in the average American male during his lifetime are 1 in 6. The median age of diagnosis is 71 in Caucasians and 69 in African-Americans.[45]

Risk Factors

Age, especially after the age of 50, increases risk. Seventy-five percent of prostate cancer is diagnosed at 65 years of age or older.[46] A family history of prostate cancer also increases risk. In fact, prostate cancer in a brother or father doubles the risk. Nine percent of all prostate cancer results from an inherited susceptibility gene.[47] A diet that includes a high percentage of fatty food can also be a risk factor, which is why its incidence is higher in the United States than in Eastern Europe.[48] Dietary fat may increase serum androgen levels, which are a key factor in the development of this type of cancer.

African-American men have a higher incidence of prostate cancer as they age compared to other races. According to the NCI, they also have twice the mortality. Prostate cancer risk increases depending on the degree of prostate androgen exposure. Levels of testosterone and dihydrotestosterone are highest in African-Americans, with Caucasians and Japanese males following. Androgen deprivation leads to prostate involution and clinical response of some prostate cancers.

Presentation and Diagnostic Findings

This type of cancer is asymptomatic in its early stages. When symptoms appear, they include:

- Hematuria;
- Dysuria;
- Weak urinary stream;
- Hesitancy in urination;
- Nocturia;
- Increased frequency in urination;
- Straining to start urine stream;
- Pain in the back or pelvis.

Diagnosis of prostate cancer can be made via digital rectal examination (DRE) in conjunction with transrectal ultrasonography (TRUS), which localizes abnormal tissue for needle biopsy. It can also be diagnosed during transurethral resection of the prostate. Identification of lymph node involvement can be made using computed tomography (CT) and MRI testing.[49]

Primary Prevention

According to the NCI, there is no proof that a low-fat diet has any effect on prostate cancer. However, since a high-fat diet is a risk factor and other benefits are derived from low-fat diets, it is sensible advice to follow a low-fat diet.

There is a study in progress that will be concluded in 2004 on the drug finasteride to determine if its use decreases the incidence of prostate cancer.[50] Studies have shown that selenium reduces the risk of a variety of cancers. In a multi-institutional study of skin cancer, 1312 patients with basal or squamous cell cancer were randomized to receive either 200 µg/d of selenium or placebo. A PSA was performed on all participants who were evaluated in a follow-up at 6.4 years. Those treated with selenium had one third less diagnoses of prostate cancer compared to placebo.[51]

In addition, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was conducted in 14 areas in southwest Fin-

land. This randomized, double-blind, placebo-controlled study compared alpha tocopherol (Vitamin E) vs. beta carotene in 29,133 men who were divided into 4 groups to receive a different regimen: 50 mg of alpha tocopherol and placebo; 20 mg of beta carotene plus placebo; 50 mg alpha tocopherol and 20 mg beta carotene; placebo and placebo. Follow-up was conducted at 6.1 years (median). The mean patient age was 57.2 years. Five- to 8-year dietary supplement resulted in a decrease of prostate cancer in the alpha tocopherol group.[52]

There is evidence that a diet high in fruits and vegetables decreases the risk of prostate cancer. It is postulated that lycopene, as a retinoid, produces an antioxidant effect resulting in this decrease. Currently, study results are mixed and cannot differentiate between lycopene and other fruit ingredients that decrease the risk of prostate cancer.

Secondary Prevention and Screening

USPSTF:[53] Routine screening for prostate cancer by DRE, PSA, or transrectal ultrasound are not recommended.

CTF:[54] There is poor evidence to conclude that DRE should be performed during periodic health examinations for men older than the age of 50. While a PSA identifies prostate cancer at an earlier stage, false-positive results occur from 67% to 93% of the time. Hence, the CTF does not recommend routine screening with PSA for asymptomatic men older than 50 years. Due to feasibility and cost concerns, transrectal ultrasound is not recommended for men older than the age of 50 as well.

ACS:[55] DRE and PSA testing should be performed annually beginning at the age of 50 for men with at least a 10-year life expectancy. African-Americans or those with first-degree relatives with prostate cancer should begin testing at the age of 45. Individuals with multiple first-degree relatives with prostate cancer should start testing at 40 years old. If their initial PSA is less than 1 mg/mL, then testing should be repeating at 45; if between 1 and 2.5 mg/mL, annual testing should be performed; greater than 2.5, then biopsy is needed.

NCI:[56] There is insufficient evidence to determine if annual DRE or PSA decrease mortality from prostate cancer. The optimal frequency and age range for conducting DRE and PSA testing are also unknown. Neither is recommended.

AAFP:[57] For men between 50 and 65, the decision to screen should be individualized and determined after a discussion between patient and family practitioner that describes potential benefits and harms of screening techniques.

American Urological Association (AUA):[58] Like the ACS, the AUA recommends PSA and DRE should be offered annually, beginning at age 50 to men who have a life expectancy of at least 10 years. Men at high risk (eg, African-Americans and those with a first-degree relative diagnosed with prostate cancer at a young age) should begin testing at age 45. Patients should be provided information about benefits and limitations of testing.

Testicular Cancer

Testicular cancer is a leading cause of solid tumors in men between the ages of 20 and 34.[59] The estimated incidence in 2002 is 7500 cases, with 400 deaths.[2] Although incidence has increased in the United States and continues to climb in Europe, more effective treatments have led to a decrease in mortality.[60,61] Five-year survival now exceeds 95%.

Risk Factors

Risk factors include undescended testicles, orchitis including mumps, testicular trauma, and race. Caucasians have a higher incidence of this type of cancer.[62] It occurs 4-5 times more often in Caucasians as compared to African-Americans.[63]

Presentation and Diagnostic Findings

The most common presentation is a painless lump. Other symptoms include pain and swelling. Testicular cancer is usually detected by self- or partner-examination or physician examination after reporting another genital compliant. The doubling time of testicular cancer is estimated at 10-30 days, which underscores the need for early detection. All testicular masses require ultrasound screening; if intratesticular masses are detected then biopsy needs to be performed followed by serum tumor markers, chest x-ray, and abdominal CT to rule out metastases.[64] Ninety percent of cancers are germ cell tumors (seminomas and nonseminomas). Seminomas account for 50% of cases while 10% are stromal cell cancers.

Primary Prevention

The primary risk factors, cryptorchidism, white race, and a family history of the disease, are fixed. Consequently, it is not currently possible to prevent most cases of this disease.[65]

Secondary Prevention and Screening

USPSTF:[66] There is insufficient evidence to recommend screening of asymptomatic men in the general population by a health care professional or self-examination. A recommendation to discuss screening options with high-risk patients may be made on other grounds.

CTF:[67] There is insufficient evidence to include or exclude testicular examination by physician or patient self-examination in low- or high-risk patients. It may be prudent to follow high-risk individuals with regular physical examination. There is fair-to-excellent evidence to exclude tumor markers from periodic health examinations.

ACS:[68] For men at average risk of testicular cancer, there is no medical evidence to suggest that monthly examination by a health care professional is any more effective than simple awareness and prompt medical evaluation. However, the choice of whether to perform this examination should be made individually.

Men should be taught testicular self-examination to be performed monthly both in asymptomatic individuals and patients with risk factors.

NCI:[69] There is insufficient evidence to establish that screening decreases mortality from testicular cancer.

American Urologic Association (AUA):[70] The AUA endorses testicular self-examination and supports education for proper examination methods. Frequency of self-examination is not specified.

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Physician CME Questions

52. Which of the following screening tests are universally recommended for breast cancer among women 50-69 years old?
    a. Clinical breast examination, mammography, fine needle aspiration
    b. Mammography with or without clinical breast examination
    c. Mammography and self breast examination
    d. Self breast examination is not indicated

53. According to the American Academy of Family Practice:
    a. Pap smears should be performed only for women at high-risk.
    b. Every sexually active woman with a cervix should be recommended for a Pap smear at least every 3 years.
    c. Women with a positive family history are the only 'high risk' group for cervical cancer.
    d. All women aged 16 and older should have a Pap smear independent of sexual activity.

54. For endometrial cancer, the ACS recommends that women:
    a. between 18 and 39 years old should have a pelvic examination every 3 years.
    b. older than 40 should have a pelvic examination annually.
    c. older than 50 should have a pelvic examination annually.
    d. between 39 and 50 should have a pelvic examination every 5 years.
    e. a and b

55. Risk factors for ovarian cancer include:
    a. family history of breast or ovarian cancer.
    b. late menstruation (beginning after age 12).
    c. use of fertility drugs or HRT.
    d. having first child before the age of 30.
    e. a and c

56. According to the American Cancer Society and the American Urological Association, at what age should you recommend prostate cancer screening to an average-risk man who has at least a 10-year life expectancy ?
    a. 35 years
    b. 40 years
    c. 50 years
    d. 60 years

57. Risk factors for testicular cancer include:
    a. undescended testicles, mumps, testicular trauma.
    b. family history of testicular cancer.
    c. previous prostate cancer.
    d. being a Caucasian.
    e. a and d

In Future Issues:

Management of the Hospitalized Diabetic—Keith R. Doram, MD, MBA, FACP