CEBP Focus: Second Primary Cancers

*Minireview*

# Identifying and Screening Patients at Risk of Second Cancers

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## Abstract

Background: **The average age of the U.S. population is increasing, and cancer incidence increases with age. Both improved early detection of first malignancies and effective primary oncologic therapy have led to prolonged survival, and the risk of secondary malignancies has consequently increased. A few anatomic sites are at increased risk for second malignancies within the same organ: breast, colon and rectum, lung, head and neck (or upper aerodigestive malignancies), prostate, and the uterine cervix. Some of the cancers also incur a risk for a second malignancy at another anatomic site. In addition, there are well-described clinical genetic syndromes that, as unique clinical entities, predispose to second malignant tumors.**

Methods/Results: **In this review, we focus on issues related to the risk of second malignancies among patients with primary breast, colon, lung and head and neck, prostate, and cervical cancers that comprise the most common sites of primary malignancy among patients in the United States. We review recent data related to both established and new screening strategies at these sites.**

Conclusions: **There is some evidence that screening will improve outcomes among patients who may develop second malignancies, although the data are limited. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites.** (Cancer Epidemiol Biomarkers Prev 2006;15(11):2027–32)

## Introduction

The average age of the U.S. population is increasing, and cancer incidence increases with age. Both improved early detection of first malignancies and primary oncologic therapy have led to prolonged survival, and the risk of secondary malignancies has consequently increased (1). We are, in a sense, the fortunate victims of our own success. In this short review, we discuss the issues related to second malignancies that occur among patients with primary cancers. This review will consider a few illustrative examples of who is at risk for second malignancies and what anatomic sites are at risk. It will consider the available screening strategies for individuals who are at risk for second malignancies as well as the techniques that can be used for risk stratification; it will not consider or discuss second malignancies that occur in children.

A few anatomic sites are most at risk for second malignancies within the same organ. These include primary tumors of the breast, colon and rectum, lung, head and neck (or upper aerodigestive malignancies), prostate, and the uterine cervix. Some of the cancers also incur a risk for a second malignancy at another anatomic site. In addition, there are well-described clinical genetic syndromes that, as unique clinical entities, predispose to second malignant tumors. These include various syndromes that lead to an increased risk of second colorectal malignancies as outlined in Table 1: the multiple endocrine neoplasia (MEN) syndromes and the familial medullary thyroid cancer syndromes (Table 2). A detailed discussion of these genetic predisposition syndromes is, however, beyond the scope of this review.

We will focus on issues related to the risk of second malignancies among patients with primary breast, colon, lung and head and neck, prostate, and cervical cancers, as these sites comprise the most common sites of primary malignancy among patients in the United States.

**Breast Cancer: General Considerations.** Breast cancer is most common malignancy and the second most common cause of cancer deaths among U.S. women. A woman's lifetime risk approaches 12% in North American Caucasians, and >200,000 incident cases occur annually (4, 5). As estimated from extensive clinical trial data, the risk of second primary (contralateral) breast tumors is 6 of 1,000 woman-years (6). Whether the risk of colon malignancy following a breast cancer diagnosis is elevated is the subject of some debate. The risk of endometrial malignancy following a primary breast cancer is increased 2- to 4-fold in postmenopausal women who use tamoxifen. The risk of ovarian cancer increases with age and is linked to hereditary/genetic syndromes. The roles of radiation dose, chemotherapy, and hormonal factors in the etiology of breast cancer following Hodgkin's disease are reviewed by Travis in the current minireview (1).

**Breast and Ovarian Cancer Syndromes.** Several well-described genetic syndromes increase the risk for second breast neoplasms, ovarian malignancies, and tumors at other anatomic sites. Clinical features of the breast/ovarian cancer syndromes are shown in Table 3. Although a description of the individual syndromes is beyond the scope of this minireview, it is instructive to examine the clinical investigations that have

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**Table 1. Syndromes leading to an increased risk of second colorectal malignancies**

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| Syndromes with adenomatous polyps |
| *APC* gene mutations (1%) |
| Familial adenomatous polyposis |
| Attenuated adenomatous polyposis coli |
| Turcot's syndrome (two thirds of families) |
| *MMR* gene mutations (3%) |
| Hereditary nonpolyposis colorectal cancer types I and II |
| Muir-Torre syndrome |
| Turcot's syndrome (one third of families) |
| Syndromes with hamartomatous polyps (<1%) |
| Peutz-Jeghers (*LKB1*) |
| Juvenile polyposis (*SMAD4, PTEN*) |
| Cowden (*PTEN*) |
| Bannayan-Ruvalcaba-Riley syndrome |
| Mixed polyposis |
| Other familial causes (up to 20-25%) |
| Family history of adenomatous polyps (*MYH*) |
| Family history of colon cancer |
| Risk >3-fold if two first-degree relatives or one first-degree relative <50 years with colon cancer |
| Risk 2-fold if second-degree relative affected |
| Familial colon-breast cancer |
| Nonfamilial causes |
| Personal history of adenomatous polyps |
| Personal history of colorectal cancer |
| Inflammatory bowel disease (ulcerative colitis, Crohn's colitis) |
| Radiation colitis |
| Ureterosigmoidostomy |
| Acromegaly |
| Cronkhite-Canada syndrome |

NOTE: Modified with permission from Libutti et al. (2).

attempted to improve strategies for detecting second breast cancers in this high-risk population. Among women with *BRCA1*-associated cancers, the lifetime risk of second breast cancers is 40% to 60% and the lifetime risk of ovarian malignancy is 15% to 45%. Similarly, the risk of second breast cancers among women with *BRCA2*-associated cancers is also 40% to 60%, whereas the risk of ovarian cancers is 10% to 20%. The need for early detection of both cancers is high.

**Screening for Second Breast Cancers.** All major U.S. medical organizations recommend screening mammography for women ages ≥40 years. Screening mammography reduces breast cancer mortality by about 20% to 35% in women ages 50 to 69 years and slightly less in women ages 40 to 49 years at 14 years of follow-up (10). Approximately 95% of women with abnormalities on screening mammograms do not have breast cancer with variability based on such factors as age of the woman and assessment category assigned by the radiologist. Computer-aided diagnosis increases cancer detection rates and recall rates. Screening clinical breast examination detects some cancers missed by mammography, but the sensitivity reported in the community is lower (28-36%) than in randomized trials (~54%). Based on expert opinion only, annual screening mammography is recommended for high-risk women beginning at ages 25 to 30 years if childbearing is complete. All women with a diagnosis of breast cancer should undergo annual diagnostic mammography.

Both the American Society of Clinical Oncology and National Comprehensive Cancer Network have published guidelines for follow-up of women following a diagnosis of breast cancer (11, 12). General physical and breast examinations are done every 3 months for 2 years and then every 6 months for a total of 5 years. The routine use of chest X-rays, computed tomography (CT) scans, bone scans, blood tests, and serum tumor markers is recommended neither for detecting recurrences of the first primary tumor nor for screening for new primary malignancies, except where site-specific screening is indicated by age-related guidelines.

**Magnetic Resonance Imaging.** Several published studies have examined the use of breast magnetic resonance imaging (MRI), mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. Few, if any, studies of MRI have been done in women at risk for second breast cancers. Sensitivity of MRI in high-risk women has been found to be much higher than that of mammography, but specificity is generally lower. The effect of the MRI on breast cancer mortality is not known, including among women with prior breast malignancies.

In a small study of 196 women, ages 26 to 59 years, with proven *BRCA1* or *BRCA2* mutations (96 women) or strong family histories of breast or ovarian cancer (100 women), all subjects underwent mammography, ultrasound, MRI, and clinical breast examination on a single day to compare the performance of the imaging modalities (13). A biopsy was done when any of the four investigations was judged to be suspicious for malignancy. Six invasive breast cancers and one noninvasive breast cancer were detected among the 196 high-risk women. Five of the invasive cancers occurred in mutation carriers, and the sixth occurred in a woman with a previous history of breast cancer. The prevalence of invasive or noninvasive breast cancer in the 96 mutation carriers was 6.2%. All six invasive cancers were detected by MRI, all were ≤1.0 cm in diameter, and all were node negative. In contrast, only three invasive cancers were detected by ultrasound, two by mammography, and two by physical examination. The addition of MRI to the more commonly available triad of mammography, ultrasound, and breast examination may identify additional invasive breast cancers that would otherwise have been missed, but confirmation of these results in prospective trials is needed.

A study of MRI and mammography in women with a hereditary risk of breast cancer compared MRI with mammography to determine which modality was more sensitive and whether MRI could play a role in the early detection of breast cancer for these women (14). Receiver-operator

**Table 2. MEN syndromes and familial medullary thyroid cancer**

| Characteristics | MEN 1 | MEN 2A | MEN 2B | Familial medullary thyroid carcinoma |
|---|---|---|---|---|
| Chromosome | 11q12-13 | Pericentromeric 10 | Pericentromeric 10 | Pericentromeric 10 |
| Genetic defect | *MEN1* mutation | RET mutation | RET mutation | RET mutation |
| Medullary thyroid carcinoma | No | Bilateral | Bilateral | Bilateral |
| Pheochromocytoma | No | 70% bilateral | 70% bilateral | No |
| Parathyroid disease | Hyperplasia | Hyperplasia | No | No |
| Pancreatic endocrine tumors | Yes | No | No | No |

NOTE: Reprinted with permission from Doherty and Jensen (3).

**Table 3. Clinical features that indicate an increased likelihood of having *BRCA1* or *BRCA2* mutations**

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|---|
| Multiple cases of early onset breast cancer |
| Ovarian cancer (with family history of breast or ovarian cancer) |
| Breast and ovarian cancer in the same woman |
| Bilateral breast cancer |
| Ashkenazi Jewish heritage |
| Male breast cancer |

NOTE: Refs. 7-9.

characteristic curves were generated for MRI and mammography, and the area under each curve (AUC) was assessed for the entire cohort of 179 women and for a subset of 75 women who had received both a MRI and a mammographic examination within a 4-month period. The investigators detected 13 breast cancers; 7 cancers were not revealed by mammography, but all were detected by MRI. For the entire cohort, the AUC for mammography was 0.74 [95% confidence interval (95% CI), 0.68-0.79] and the AUC for MRI was 0.99 (95% CI, 0.98-1.0). For the subset of women who had both examinations, the AUC for mammography was 0.70 (95% CI, 0.60-0.80) and the AUC for MRI was 0.98 (95% CI, 0.95-1.0). Thus, MRI was more accurate than mammography in annual breast cancer surveillance of women with a hereditary risk of breast cancer.

More recent studies among women suspected or proven to carry a breast cancer susceptibility gene have yielded comparable results (15, 16). One larger study was conducted among 1,909 women, including 358 carriers of germ-line *BRCA* mutations (15). Women who had a cumulative lifetime risk of breast cancer of ≥15% were screened every 6 months with a clinical breast examination and once a year by mammography and MRI, with independent readings. The characteristics of the cancers that were detected were compared with the characteristics of those in two different age-matched control groups. Within a median follow-up period of 2.9 years, 51 tumors and 1 lobular carcinoma *in situ* were detected. The sensitivities of clinical breast examination (17.9%), mammography (33.3%), and MRI (79.5%) for detecting invasive breast cancer differed markedly, whereas the specificities were 98.1%, 95.0%, and 89.8%, respectively. The proportion of invasive tumors that were ≤10 mm in diameter was significantly greater in the MRI group (43.2%) than in either control group [14.0% ($P < 0.001$) and 12.5% ($P = 0.04$), respectively]. The combined incidence of positive axillary nodes and micrometastases in invasive cancers was 21.4% compared with 52.4% ($P < 0.001$) and 56.4% ($P = 0.001$) in the two control groups. These findings suggest that MRI seems to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to breast cancer. Mammography alone, or mammography combined with breast ultrasound, seems to be insufficient for early diagnosis of breast cancer in women who are at increased familial risk with or without a documented *BRCA* mutation.

The American College of Radiology Imaging Network is conducting study American College of Radiology Imaging Network 6666, the ''Screening Breast Ultrasound Trial for High-Risk Women,'' to assess the use of screening sonography in high-risk women (17). In addition to women with a personal history of breast cancer, high risk is defined for this trial as asymptomatic women over age 25 years with heterogeneously or homogeneously dense breasts by mammography who have a known *BRCA1* or *BRCA2* mutation or a prior biopsy showing lobular carcinoma *in situ*, atypical ductal hyperplasia, atypical lobular hyperplasia, or atypical papillary lesion who are not on chemoprevention. The trial also includes those who have a history of chest, mediastinal, or axillary irradiation before age 30 years and at least 8 years before study entry; a lifetime risk of breast cancer by the Gail or Claus models of at least 25%; a 5-year risk by the Gail model of at least 2.5%; or a 5-year risk by the Gail model of at least 1.7% with at least 75% dense breast tissue by a prior mammogram. The trial is currently open to accrual but has not yet reported results. The trial will yield important results that pertain to women with a first breast cancer.

**Management of Women at Risk of Malignancy in the Hereditary Breast-Ovarian Cancer Syndromes.** Clinical management of women with predisposing mutations that increase the risk of breast and ovarian cancer has been reviewed extensively (7-9, 18-20). Women with a *BRCA1* or *BRCA2* mutation may choose to undergo prophylactic bilateral total mastectomy that has been shown to reduce the incidence of breast cancer at 3 years of follow-up (21). Prophylactic bilateral mastectomy virtually eliminates the risk of second breast cancers in mutation carriers, and the risk of primary ovarian malignancy is exceedingly low after prophylactic bilateral salpingo-oophorectomy. Contralateral prophylactic mastectomy may be considered after the diagnosis of a primary breast malignancy. Bilateral salpingo-oophorectomy also reduces the risk of subsequent invasive breast cancers by ~50% and nearly eliminates the risk of ovarian malignancy (22). Transvaginal Doppler ultrasound and CA-125 assays are recommended for women with intact ovaries, but no data validate their use.

**Colorectal Cancer Screening after a First Primary Tumor.** The incidence of second primary colorectal cancer in patients with a history of colon cancer compared with patients with a history of adenomatous polyps is unknown. It is unclear whether guidelines for colonoscopic screening in patients with polyps are appropriate for patients with previous colon cancer. The need for intensive screening immediately following surgical resection of colorectal malignancy is based mainly on a study of 3,278 patients with resected stage II and III colorectal cancer, which found a high rate of recurrence in the first 4 years (23). Forty-two cases of second primary invasive colon cancer were found over 15,345 person-years of follow-up, yielding an incidence rate of 2.74 per 1,000 person-years (95% CI, 1.96-3.69 per 1,000 person-years) and a cumulative incidence of 1.5% (95% CI, 1.1-2.0) at 5 years. Compared with rates of first colon cancer in the general population and in patients who had undergone frequent colonoscopy and polypectomy because of a history of adenomatous polyps, the standardized incidence ratios (SIR) were 1.6 (95% CI, 1.2-2.2) and 6.8 (95% CI, 2.7-22.0), respectively.

Both expert opinion (24, 25) and a recent meta-analysis (26) recognize some benefit to more aggressive screening, but there is no information about which component of the intensive surveillance provides benefit (annual colonoscopy versus occult blood testing). Clinicians should do surveillance in these patients to assess therapeutic complications, discover a curable recurrence, identify new neoplasms at a preinvasive stage, and reassure the patient that no recurrence or new tumor has occurred. The incidence of second primary colorectal cancer remains high, and intensive surveillance strategies are recommended. Current recommendations for patients with a history of colorectal malignancy is to have colonoscopy 1 year after diagnosis and surgery or within 3 to 6 months if there was no or incomplete preoperative colonoscopy. If an adenoma is present, repeat colonoscopy should be done in 1 to 3 years. If the examination is normal, repeat colonoscopy should be done in 2 to 3 years. For patients without residual disease, the National Comprehensive Cancer Network panel recommends a history and physical

examination every 3 months for the first 2 years and then every 6 months for a total of 5 years (27).

### Upper Aerodigestive Cancers

*Lung Cancer.* There is as yet no consensus recommendation for clinical follow-up after a diagnosis of primary lung cancer, although these individuals are at significant risk for second malignancies throughout the entire aerodigestive tract. Pilot trials of spiral CT in lung cancer screening are reported to be promising with >80% frequency of stage I detectable lung cancer in newly diagnosed cases (28). The National Lung Screening Trial (American College of Radiology Imaging Network Protocol A6654) is an ongoing randomized, controlled study involving 50,000 current or former smokers designed to examine the risks and benefits of low-dose, spiral CT scans compared with chest X-rays as primary screening (29). It aims to compare the effectiveness of the two screening tests in reducing lung cancer–specific mortality in persons who are at high risk for developing lung cancer. The trial is sponsored by the National Cancer Institute and conducted within two separate administrative organizations: the Prostate, Lung, Colorectal, and Ovarian (30) cancer screening trial network and American College of Radiology Imaging Network under a harmonized protocol. Recruitment through 10 Prostate, Lung, Colorectal, and Ovarian screening centers began at the end of September 2002 and was completed in January 2004. Total National Lung Screening Trial accrual at Prostate, Lung, Colorectal, and Ovarian screening centers was 34,614. Participants were randomized to CT and chest X-ray groups. No mortality results are yet available in this primary screening trial, and there are no data yet to compare CT scans and chest X-rays as follow-up strategies in patients at risk for recurrent lung cancer.

The National Comprehensive Cancer Network Non–Small Cell Lung Cancer Guidelines Panel recommends participation of persons with high risk of lung cancer in the prospective trials evaluating low-dose, spiral CT and possibly other measures, such as the International Early Lung Cancer Action Program (31) for the screening and early detection of lung cancer. Non–small cell lung cancer patients should undergo routine physical examination and chest X-ray every 4 months in the first 2 years, then every 6 months for 3 years, and then annually. Spiral chest CT scan is recommended at 4 to 6 months and then at 1 year postoperatively and annually thereafter because it is reported to be more effective than the chest X-ray in screening for lung cancer. Smoking cessation counseling should be provided to aid the treatment of lung cancer and improve the quality of life of the patients.

*Head and Neck Malignancies.* Second primary tumors develop at an annual rate of 3% to 7% in patients with head and neck squamous cell cancer (32), a risk that is comparable with the rates seen with predisposing genetic syndromes. Several underlying principles guide the recommendations for individuals with primary malignancy at these sites. The risk of developing a second primary tumor of the upper aerodigestive tract is largely a result of a combination of exposure to carcinogens and genetic predisposition. For the majority of these patients, the carcinogens responsible for induction of a significant proportion of head and neck cancers are tobacco and alcohol. The high risk of developing a second cancer means that any increased probability of curing the index malignancy is offset, in part, by the chance of dying from a subsequent tumor.

**New Approaches Are Needed.** Novel strategies are needed to identify individuals at greatest risk to develop second malignancies. Homann et al. (33) tested whether altered p53 expression in histologically normal epithelia distant from a primary head and neck tumor at the time of diagnosis was of clinical value as a biomarker for second primary carcinoma development. Overexpression of p53 in tumor-distant epithelia that was found in 46.7% of patients was independent of the p53 protein status of the primary tumor and of the tumor site, size, stage, and grading. Mucosal p53 overexpression was not associated with local primary recurrences, lymph node or distant metastases, or overall survival. Mucosal p53 overexpression was significantly associated, however, with an increased incidence of second primary carcinomas ($P = 0.0001$), whereas overexpression in the primary tumors was not. This observation serves as a model for biological markers that are needed to identify individuals at increased risk of second tumors. Many additional investigations are required.

Chemoprevention of second malignancies of the upper aerodigestive tract has been reviewed by Mayne and Cartmel in this volume (34). Surveillance for secondary primary head and neck tumors includes follow-up head and neck examination every 1 to 2 months for 2 years, every 3 months for the 3rd year, every 6 months for the 4th and 5th years, and annually thereafter. Chest radiography and thyroid function tests are done annually. Additional studies (e.g., CT, MRI, and/or positron emission tomography) may be necessary and are currently under extensive evaluation.

**Gynecologic Malignancies.** Studies have suggested that women with previous diagnoses of cervical, endometrial, or ovarian malignancies have an increased risk for colorectal cancer, particularly when diagnosed at an early age (35). A retrospective cohort analysis of the Surveillance, Epidemiology, and End Results program database from 1974 to 1995 examined 21,222 patients with cervical cancer, 51,680 patients with endometrial cancer, and 28,832 patients with ovarian cancer. SIRs were calculated for each gynecologic cancer site and for subgroups to represent the relative risk for colorectal cancer in women with previously diagnosed gynecologic cancer compared with women without gynecologic cancer. Overall, risk for colorectal cancer was elevated among women with previous ovarian cancer [SIR, 1.36 (95% CI, 1.21-1.53)]. Risk was greatest in women who received a diagnosis before 50 years of age [SIR, 3.67 (95% CI, 2.74-4.80)] but was also elevated in women who received a diagnosis between 50 and 64 years of age [SIR, 1.52 (95% CI, 1.25-1.83)]. The risk for colorectal cancer after endometrial cancer was also elevated substantially if endometrial cancer was diagnosed before the age of 50 years [SIR, 3.39 (95% CI, 2.73-4.17)]. No apparent risk elevation was associated with previous cervical cancer, however.

A similar study used the Swedish Family-Cancer Database to analyze 9,426 second primary cancers in 117,830 subjects diagnosed with *in situ* and 17,556 subjects with invasive cervical cancer from the years 1958 to 1996. SIRs were elevated after both *in situ* and invasive cervical cancer for cancers of the upper aerodigestive tract, anus, pancreas, lung, other female genitals, and urinary bladder (36). Anus and other female genitals, known targets of human papillomavirus, showed SIRs exceeding 3.0 and ≥10 within the year of diagnosis of cervical cancer. Among the remaining sites, smoking seemed to be the major cause, but for urinary bladder cancer, it only explained one half of the excess; human papillomavirus infection, possibly through immunosuppression, could account for the remaining excess. Invasive cervical cancer showed a SIR of 2.3 after *in situ* cancer.

No prospective studies have defined validated screening strategies to search for second tumors among women with first gynecologic malignancies.

**Preinvasive and Microinvasive Cervical Carcinoma.** Several anatomic sites are observed to have significantly increased

incidence of new, second primary malignancies after a diagnosis of either grade 3 cervical intraepithelial neoplasia III or cervical cancer: anus (SIR, 5.9 and 6.3, respectively), lung (SIR, 1.8 and 2.5), vulva (SIR, 4.4 and 1.9), vagina (SIR, 18.5 and 8.0), and kidney (SIR, 1.6 and 1.9; ref. 37). In addition, the incidence of cancers of the rectum, bladder, and connective tissue was significantly increased after invasive cervical cancer.

Recurrence rates following treatment of cervical intraepithelial neoplasia are low (10-15%), and progression to invasion occurs in <2% in most series. Lifelong surveillance of these patients must be maintained, and the risk of recurrence may be somewhat increased in women infected with human papillomavirus type 16 or 18 as noted above. The role of vaccination in this population will be under investigation, and vigilant surveillance is required.

**Prostate Cancer.** Approximately 45% of men with prostate cancer experience recurrence within the first 2 years after radical prostatectomy, 77% within the first 5 years, and 96% by 9 years. The data pertaining to new primary prostate cancers are a bit less clear, but the National Comprehensive Cancer Network Prostate Cancer Guidelines Panel recommends that serum PSA levels should be measured every 6 months for the first 5 years and then rechecked annually (38). After radiation therapy, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually. An annual digital rectal examination is also appropriate to monitor for prostate cancer recurrence as well as for new primary colorectal cancer.

**New Approaches to Manage the Risk of Second Tumors.** The first generation of screening strategies is useful but not optimal for detecting new primary malignancies in patients at risk. Clearly, more sensitive and specific screening strategies along with new genomic profiling or other predictors of second primary tumor occurrence are required. Age-specific and risk-appropriate strategies need to be validated in prospective screening trials of persons with first malignancies. Strategies are also needed for informed risk profiling and screening for second primary malignancies. Such a strategy may arise from efforts to identify patients who are at high risk of recurrence of first malignancies.

**Prognostic and Predictive Tumor Profiling.** Investigators in the National Surgical Adjuvant Breast and Bowel Project tested whether the results of a reverse transcription-PCR assay of 21 prospectively selected genes in paraffin-embedded tumor tissue correlated with the likelihood of distant recurrence in patients with node-negative, tamoxifen-treated breast cancer who were enrolled in the National Surgical Adjuvant Breast and Bowel Project clinical trial B-14 (39). The levels of expression of 16 cancer-related genes and 5 reference genes were used in a prospectively defined algorithm to calculate a recurrence score and to determine a risk group (low, intermediate, or high) for each patient. The rate of recurrence in the low-risk group was significantly lower than that in the high-risk group ($P < 0.001$). In a multivariate Cox model, the recurrence score provided significant predictive power that was independent of age and tumor size ($P < 0.001$). The recurrence score was also predictive of overall survival ($P < 0.001$) and could be used as a continuous function to predict distant recurrence in individual patients. Although the recurrence score has been validated as quantifying the likelihood of distant recurrence in tamoxifen-treated patients with node-negative, estrogen receptor–positive breast cancer, no data yet exist using a similar molecular approach to predict the risk of developing second primary breast cancers or second malignancies at other important anatomic sites. This is an urgent need that should be addressed in new, translational research.

**Recommendations for Future Research.** Few, if any, validated, prospective screening trials among individuals who are at risk for second malignancies have been conducted. For example, we should evaluate whether the use of MRI is superior to mammography in the detection of second breast malignancies, particularly among premenopausal women whether they carry a predisposing genetic mutation. Among women with mutations, we need prospective MRI breast screening studies compared with mammography with mortality as the end point. We also need to develop new strategies to screen for ovarian cancer among women with genetic syndromes. A search for serum markers of ovarian malignancy should continue.

The use of virtual colonoscopy with CT imaging and of capsule video endoscopy should be developed among individuals with a first colon malignancy, and mortality end point studies should be conducted among individuals with genetic syndromes that predispose to an increased risk of colon malignancy. Results from studies of spiral (helical) CT imaging of the lung are awaited among individuals at risk of primary lung cancer. If those studies show advantages for CT imaging compared with plain chest radiograms, studies should be conducted among individuals with primary lung cancer to evaluate the role of CT imaging in detecting second tumors. In addition, the development and validation of tissue-based and cytogenetic markers to predict reliably the risk of recurrence of upper aerodigestive malignancies should continue as a high priority.

Educational programs for primary care providers should emphasize the risk of second malignancies in cancer survivors and clarify the role of nononcologists in screening for second cancers. Primary care professional societies should work with oncology groups to develop coordinated and standardized approaches for the identification of high-risk survivors of first cancers along with delineation of screening and detection strategies for these patients.

Finally, additional work should be carried out using the promising techniques of predictive genomic tumor profiling not only to select therapy for primary cancers but also to identify individuals who are at greatest risk for development of second primary tumors. Current technologies make this a reasonable goal.

## Conclusions

We are left, finally, with several caveats: (*a*) there are few (if any) prospective, controlled trials of screening strategies among patients who are at risk for second malignancies that can guide us with objective, evidence-based information about appropriate screening and management for patients with primary malignancies; (*b*) there is very little validated evidence that an increased screening frequency will improve outcomes among patients who develop second malignancies; (*c*) the optimal screening modalities and strategies for patients who are at risk for second malignancies remain to be defined for most tumor sites; and (*d*) no screening strategy is appropriate for or can be expected to reduce the risk of mortality for rare second malignancies (e.g., acute myelogenous leukemia following chemotherapy for Hodgkin's lymphoma). Additional investigative efforts in the future should strive to address these limitations of our current knowledge.

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