Care of Cancer Survivors

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Cancer survivors are at increased risk for recurrence of their original malignancy; development of second primary malignancies; and medical, developmental, and psychologic problems resulting from cancer therapy, genetic predisposition to cancer, and other risk factors. Surveillance following curative cancer treatment generally includes interval history and physical examinations every six months for five years. Thereafter, histories and examinations are recommended annually for breast cancer; every three months for two years, then every six months for three to five years for colorectal cancer; and every six months for five years, then annually for prostate cancer. Recommended laboratory tests and ancillary procedures include annual mammography of preserved breast tissue in breast cancer survivors, carcinoembryonic antigen level monitoring in conjunction with annual colonoscopy in colorectal cancer patients, and prostate-specific antigen measurements every six months for five years and then annually in prostate cancer survivors. In addition, family physicians should be attentive to concerns about altered body image or sexuality issues following curative surgical procedures. Continued emphasis on preventive health practices is encouraged. Physicians should remain alert to nonspecific symptoms or physical findings (e.g., mass, adenopathy) that can indicate cancer recurrence. In childhood cancer survivors, periodic evaluation that includes a plan for surveillance and prevention, incorporating risks based on previous cancer, therapy, genetic predispositions, personal behaviors, and comorbid health conditions, is recommended. (Am Fam Physician 2005;71:699-706,713-4. Copyright© 2005 American Academy of Family Physicians.)

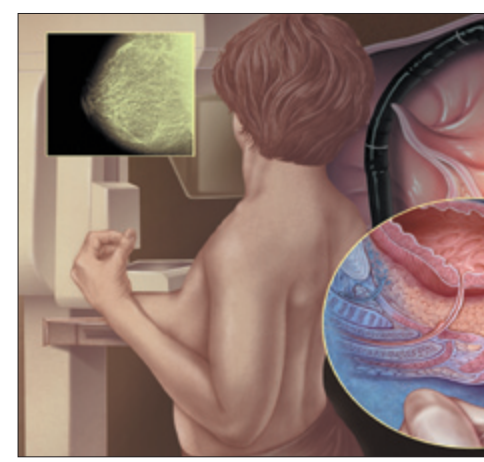

ILLUSTRATION BY STEVE OH

▶ **Patient information:** A handout on care after cancer treatment, written by the authors of this article, is provided on page 713.

See page 639 for definitions of strength-of-recommendation labels.

A cancer survivor is "anyone who has been diagnosed with cancer from the time of diagnosis through the balance of his or her life."[1] Continued advances in cancer treatment have led to marked improvements in cure rates, resulting in almost 10 million U.S. cancer survivors.[2] Nearly two thirds of all cancer patients survive for at least five years, and survival rates are much higher for many common types of cancer *(Table 1)*.[2,3] Cancer survivors are at increased risk for recurrence of the original cancer and development of second primary malignancies as a result of cancer therapy and other risk factors. Prolonged monitoring and treatment are warranted for long-term side effects of surgical, radiation, or cytotoxic therapy.

Approximately 70 percent of cancer patients have comorbid conditions,[4] requiring a comprehensive approach to medical care. Family physicians often have established long-term relationships with these patients and their families, and most cancer patients continue to receive medical care from their family physicians. In addition to overseeing care, acting as a patient advocate, and providing support for family members, the family physician can ensure continued surveillance, provision of preventive care, and management of medical problems.

This article provides an overview of ongoing care and follow-up for cancer survivors. It summarizes surveillance recommendations for the detection of recurrent cancer and second primaries, describes monitoring for potential physical and psychosocial complications of treatment, and addresses other considerations such as genetic risk assessment among survivors of breast, colorectal, and prostate cancers, childhood acute lymphoblastic leukemia, and Hodgkin's disease.

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
Breast cancer patients should be counseled that intensive surveillance using laboratory and imaging tests does not improve overall survival or quality of life. However, monthly self-breast examination, annual mammography of preserved breast tissue, and a careful history and physical examination every six months for five years are recommended.	A	8
Use of carcinoembryonic antigen testing and computed tomographic scanning for follow-up of colorectal cancer patients yields a survival advantage of about 19 percent, but the optimal combination of tests or frequency of clinical follow-up is not known.	A	5, 19
Prostate cancer survivors who received definitive therapy should receive annual digital rectal examination and monitoring of prostate-specific antigen levels every six months for five years, and then annually.	C	7
Survivors of childhood cancers are at increased risk for depression and should be screened and treated, as appropriate.	C	38, 39
Female Hodgkin's disease survivors treated with chest irradiation are at increased risk of developing breast cancer; surveillance should be started at 25 years of age.	C	39, 41, 42

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 639 for more information.

These cancers were selected as examples based on their high prevalence or high rates of survival. *Tables 2*[5,6] *and 3* summarize surveillance information.

Breast Cancer Survivors

More than 2.1 million U.S. women are breast cancer survivors.[2] Current recommendations for surveillance after primary breast cancer include monthly self-examination of the breasts, annual mammography of preserved breast tissue, and a careful history and physical examination every six months for five years, and annually thereafter.[7] Intensive surveillance using laboratory and imaging tests does not improve overall survival or quality of life.[8] Routine surveillance using bone scans, chest radiographs, and blood tests for tumor markers is not recommended.[8]

Breast cancer survivors have an increased risk of second primary cancers involving the ipsilateral and contralateral breast, ovaries, colon, and rectum.[9] Most recurrent breast cancers arise within the first five years following treatment. Recurrence rates are very low in patients with primary tumors smaller than 1 cm and negative axillary nodes.[10] Nonspecific symptoms (e.g., weight loss, persistent cough) or physical findings (e.g., breast or chest wall changes, adenopathy) are common indicators of breast cancer recurrence[11] that should be evaluated thoroughly and specifically sought during regular surveillance.

Appropriate surveillance of survivors of primary breast cancer consists of monthly self-examination of the breasts, annual mammography of preserved breast tissue, and interval history and physical examinations every six months for five years, and then annually.

Breast cancer survivors also may develop physical complications of treatment such as lymphedema, premature menopause, neurocognitive changes, and osteopenia or osteoporosis, as well as psychologic distress related to coping and sexuality changes.[9] Up to 30 percent of breast cancer patients treated with chemotherapy experience cognitive effects, sometimes referred to as "chemo brain."[12] These complications warrant discussion and possible intervention with cognitive-behavior therapy or pharmacotherapy. Studies of various treatment strategies are underway.[12] Lymphedema occurs in 20 to 30 percent of breast cancer patients treated surgically[13] and often responds to early conservative management by physical therapists specializing in this condition.[14] Meticulous skin care is recommended to reduce the risk of local and systemic infection arising from impaired lymphatic return. (Additional information is available online at http://www.cancer.org or through the National Lymphedema Network at 800-541-3259.)

Although tamoxifen (Nolvadex) has been demonstrated to reduce the risk of recurrent breast cancers[15] and maintain bone density,[16] it does increase the risk of uterine cancer. Annual monitoring by pelvic examination is indicated.[7] Recent data suggest that the use of aromatase inhibitors (anastrozole [Arimidex]) in postmenopausal, estrogen receptor–positive breast cancer patients may have greater efficacy and fewer side effects than tamoxifen in the adjuvant setting.[17]

Finally, a review of family history may suggest a hereditary component in breast cancer. Approximately 5 to 10 percent of breast cancers are caused by mutations in cancer-susceptibility genes, most commonly BRCA1

TABLE 1
Incidence, Prevalence, and Survival for Selected Cancer Sites

Cancer type	Age-adjusted incidence per 100,000*	Prevalence*	Five-year relative survival (%)*	10-year relative survival (%)†	15-year relative survival (%)†
All sites					
Women	414.4	5,487,919	64.3	58.0	54.3
Men	554.3	4,321,121	64.0	56.0	51.0
Colon					
Women	34.8	540,103‡	62.2§	55.4§	53.9§
Men	44.3	496,588‡	63.9§	55.4§	53.9§
Rectum					
Women	11.6		65.6§	55.2§	51.8§
Men	19.1		63.2§	55.2§	51.8§
Acute lymphoblastic leukemia					
Women	27.5‖	17,940¶	81.7	NA	NA
Men	—	22,015¶	77.8	NA	NA
Hodgkin's disease					
Women	13.6#	64,354¶	93.7	NA	NA
Men		66,925¶	92.6	NA	NA
Breast (women)	135.2	2,199,394	87.7	78.3	71.3
Prostate (men)	172.3	1,727,847	99.3	95.2	87.1

NA = not available.

**—Incidence rates, prevalence, and five-year relative survival based on Surveillance, Epidemiology, and End Results data (1997-2001).[2]*

†—*Based on period estimates of relative survival. Relative survival considers cancer survival over a specified interval in the absence of other causes of death.[3]*

‡—*Prevalence data for colon and rectal cancers combined.*

§—*Survival data for men and women combined.*

‖—*Incidence data for persons zero to 14 years of age at time of diagnosis, 1975-2000.*

¶— *Survival data includes persons of all ages at time of diagnosis.*

#—*Incidence data for persons zero to 19 years of age at time of diagnosis, 1975-2000.*

Information from references 2 and 3.

and BRCA2.[18] The role of genetics professionals is important in assessing individual genetic risk and the need for specific testing among these patients and their family members. (A directory of professionals can be found online at http://cancer.gov/search/genetics_services/).

Colorectal Cancer Survivors

For the more than 1 million colorectal cancer survivors in the United States,[2] the prompt detection of recurrent disease can result in improved survival and potential cure. The risk of recurrence is highest in the first five years following resection; thus, frequent follow-up and surveillance have been recommended during this time *(Table 2)*.[5,6] Although a recent meta-analysis[5,19] has shown a survival benefit of 19 percent at five years in patients undergoing intensive follow-up, the American Society of Clinical Oncology[20] and the National Comprehensive Care Network (NCCN)[7] guidelines have limited their follow-up recommendations to history taking, physical examination, carcinoembryonic antigen testing, and colonoscopy. Interpretation of the meta-analysis is complicated by the variety of tests and follow-up schedules used in the studies reviewed. While in this meta-analysis more intensive follow-up was associated with an overall survival benefit, it is not possible to infer an optimal combination of tests or frequency of clinical follow-up for intensive colorectal cancer surveillance.[5]

History taking, physical examinations, and carcinoembryonic antigen monitoring are recommended every three months for the first two years following treatment, and then every six months for the next three years[7,20] *(Table 2)*.[5,6] Patients with carcinoembryonic antigen elevations should be investigated with computed tomography (CT), positron-emission tomography, or colonoscopy, as appropriate, to identify the site of recurrence and its potential for resection. Elevated carcinoembryonic antigen levels may precede symptoms by as much as three to eight months.[21] Surveillance colonoscopy is

TABLE 2
Follow-up Care and Surveillance for Cancer Survivors, Selected Cancer Sites

			Treatment complications	
Cancer	*Surveillance for recurrence*	*Second primary*	*Physical*	*Psychosocial*
Breast	Monthly self-examination of the breasts; clinical breast examinations, history, and physical examinations every six months for five years,and then annually; mammography annually	Increased risk of ipsilateral and contralateral breast cancer, ovarian, and colorectal cancers	Lymphedema; premature menopause; osteoporosis; uterine cancer; and medical conditions resulting from tamoxifen (Nolvadex) therapy	Distress about risk of recurrence; sexuality; body image
Colorectal	Carcinoembryonic antigen and clinical examination every three months for two years, and then every six months for three to five years; computed tomographic scanning (optimal interval undetermined); colonoscopy after one year, and then at three years, and then every five years*	Metachronous colorectal cancer	Ostomy care; rectal incontinence; radiation proctitis or diarrhea; adhesions	Sexuality; body image
Prostate	Clinical evaluation, prostate-specific antigen every six months for five years, and then annually; digital rectal examination annually	Bladder cancer	Sexual dysfunction; bowel or urinary incontinence; radiation proctitis or diarrhea	Depression; sexuality

NOTE: *Surveillance recommendations from the National Comprehensive Cancer Network (NCCN) can be accessed online at http://www.nccn.org.*

**—Although a meta-analysis[5] found that more intensive follow-up was associated with an overall survival benefit, it is not possible to infer an optimal combination of tests or frequency of clinical follow-up for colorectal cancer.*

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TABLE 3
Follow-up Care and Surveillance for Childhood Cancer Survivors, Selected Cancer Sites

			Treatment complications	
Cancer	*Surveillance*	*Second primary*	*Physical*	*Psychosocial*
Acute lymphoblastic leukemia	Individualized based on chemoradiation treatment regimen*	Cranial radiotherapy: central nervous system tumors, thyroid tumors (papillary), acute monocytic leukemia Cyclophosphamide (Cytoxan) therapy: bladder cancer	Cranial radiotherapy: cognitive dysfunction, obesity, osteopenia or osteoporosis, periodontal disease, cataracts Anthracycline therapy (doxorubicin [Adriamycin] or daunorubicin): cardiomyopathy, transfusion-acquired hepatitis C (blood products before 1992)	Depression; distress about risk of recurrence; fertility issues; sexuality
Hodgkin's disease	Individualized*	Breast cancer (in women only); lung cancer; colorectal cancer; bone cancer; thyroid cancer; nonmelanoma skin cancer	Hypothyroidism; ovarian failure; late-onset anthracycline-induced cardiomyopathy; osteopenia or osteoporosis	Depression; distress about risk of recurrence; fertility issues; sexuality

**—Derived from guidelines for the long-term follow-up care of survivors of childhood, adolescent, and young adult cancer developed by the Children's Oncology Group. Frequency based on cumulative anthracycline and chest radiation dose and age at treatment. See http://www.survivorshipguidelines.org for specific recommendations.*

Other considerations
Assess age at diagnosis and family cancer history; consider referral for genetic counseling for BRCA1 or BRCA2 mutations; clinical interview to assess for "chemo brain"; annual pelvic examination if patient is taking tamoxifen; screening for colorectal and cervical cancer; pneumococcal and influenza vaccinations; assess psychosocial function
Assess family cancer history for familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, and refer for genetic counseling and assessment, if present; breast and cervical cancer screening; pneumococcal and influenza vaccination; assess psychosocial function
Assess age at diagnosis and family cancer history; consider referral for genetic counseling and assessment if strong family history; colorectal cancer screening; pneumococcal and influenza vaccinations; assess psychosocial function

Other considerations
Monitor school and work performance; consider neurocognitive testing; cardiovascular screening; cancer screening; periodic lipoprotein measurements; counseling on diet, exercise, and body weight; calcium supplementation; avoidance of smoking
Increased risk of sepsis in patients who had splenectomy; pneumococcal and influenza vaccinations in patients who had splenectomy; cardiovascular screening; cancer screening; periodic lipoprotein screening; counseling on diet, exercise, and body weight; calcium supplementation; avoidance of smoking

recommended 12 months postoperatively, provided a full colonoscopy was performed before surgery (at six months if otherwise), and then every three to five years if no abnormalities are detected.[7] Use of routine chest radiographs for annual follow-up is not recommended.[7]

Many survivors of colorectal cancer need to adapt to treatment-associated effects such as fecal incontinence and adhesions. Radiation therapy can cause persistent diarrhea and episodic bleeding resulting from radiation proctitis. This may be treated symptomatically[22] with antimotility agents such as loperamide (Imodium). In severe radiation proctitis, a short course of hydrocortisone foam enemas may be beneficial. Family physicians should be alert to the challenges of ostomy care, including issues of body image and sexuality.[23] Consultation with an ostomy specialist can help family physicians develop individualized treatment recommendations and supportive care.

Colorectal cancer can be organized into three categories based on family history: (1) sporadic (about 60 percent of all cases)—no family history; (2) familial (about 30 percent of cases)—several affected family members; and (3) hereditary (about 10 percent of cases)—mainly genetic syndromes such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).[20] FAP has a classic presentation with the formation of hundreds to thousands of adenomatous polyps within the colon and rectum at an early age. Persons with FAP have a nearly 100 percent chance of developing cancer by age 50.[24] Persons with HNPCC have an increased risk for colorectal cancers, as well as cancers of the endometrium, small bowel, ureter, and renal pelvis.[25] Women with HNPCC have a lifetime risk of 30 to 60 percent of developing endometrial cancer.[26] Genetic counseling can help determine familial risk and the need for regular testing. Nonsteroidal anti-inflammatory drugs such as aspirin and sulindac (Clinoril) have been shown to have a protective effect against colorectal cancers and polyps.[27,28]

Prostate Cancer Survivors

Approximately 98 percent of prostate cancer patients are alive five years after diagnosis, with many men thriving for extended periods *(Table 1)*.[2,3] As a result, the number of prostate cancer survivors is estimated to exceed 1.7 million persons.[2]

Surveillance for prostate cancer survivors includes annual digital rectal examination and monitoring of prostate-specific antigen (PSA) levels every six months for five years, and then annually.[7] The serum PSA declines to undetectable levels following radical pros-

Recommended surveillance for prostate cancer survivors includes annual digital rectal examination and monitoring of prostate-specific antigen levels every six months for five years, and then annually.

tatectomy; a slower decline is noted after radiation therapy.[29] Elevated serum PSA levels following the initial decline attained with definitive therapy indicates disease recurrence. More recently, the concept of PSA velocity, or the change in PSA level over time, is gaining attention. Preoperative PSA velocity during the year before diagnosis has been associated with the risk of death from prostate cancer.[30] Postoperative PSA velocity, along with Gleason score and cancer staging, has been shown to predict disease recurrence.[29]

Although recurrence represents the most serious threat to patients' health, complications resulting from therapy are of greater concern to patients and significantly affect quality of life. A study[31] of patients with localized prostate cancer who were assigned randomly to surgery or watchful waiting noted more erectile dysfunction and urinary leakage in those treated surgically. Phosphodiesterase type 5 inhibitors (tadalafil [Cialis], vardenafil [Levitra], sildenafil [Viagra]) can be used to treat erectile dysfunction in patients who have completed nerve-sparing prostatectomy.[32] These inhibitors can potentiate the hypotensive effects of nitrates and alpha blockers.

Published data on treatment complications in prostate cancer vary depending on the type of therapy, outcome definitions, and study participants. An increased incidence of bladder cancer has been noted among prostate cancer patients treated with radiation therapy, but this could be attributable to increased surveillance.[33]

Many cases of prostate cancer have a familial component. The risk to an individual increases as the number of affected family members increases.[34] In addition, men with family members affected by breast or ovarian cancers may be at increased risk for prostate cancer caused by BRCA1 and BRCA2 mutations.[35] Consultation with a genetics professional for risk assessment and possible testing may be useful.

Childhood Cancer Survivors

Providing risk-based health care for the growing number of survivors of childhood and adolescent cancer (currently 270,000 in the United States) is challenging, given the risk for a variety of late complications associated with therapy. Chemotherapy and radiation therapy administered during years of growth and development significantly influence the aging of various organ systems. Nearly one half of young adult survivors of childhood cancer have at least one major adverse outcome.[35] Later cancer-related effects predominantly increase the risk for early mortality caused by second cancers and cardiac or pulmonary disease.[36] Single-institution studies[37] estimate that two thirds of survivors have at least one chronic or late-occurring complication of cancer therapy, with about one third having serious or life-threatening complications. The incidence of most late effects increases with age, with some effects not becoming apparent clinically until decades after therapy.

With many of these late effects, there is a window of opportunity for surveillance and early diagnosis. Currently, testing for the early detection of cancer in childhood cancer survivors lags below desired levels, despite the increased risk.[38] Periodic evaluation is recommended and should include a systematic plan for surveillance and

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Follow-up of childhood cancer survivors must be individualized on the basis of the type of cancer and the specific therapy used, in addition to other risk factors.

prevention, incorporating risks based on the previous cancer or cancer therapy, genetic predispositions, personal behaviors, and comorbid health conditions.[39]

Assessing and stratifying risks for a heterogeneous population of childhood cancer survivors treated in different eras is difficult. The Children's Oncology Group recently developed a set of guidelines for the long-term follow-up care of survivors of childhood, adolescent, and young adult cancers (http://www.survivorshipguidelines.org). However, the relatively limited size of these populations precludes studies assessing the extent to which surveillance impacts measurable reductions in morbidity or mortality. Two case studies are presented that briefly illustrate risks for late effects faced by survivors.

Illustrative Cases

CASE ONE

A 27-year-old man had been diagnosed in 1980, when he was two years old, with acute lymphoblastic leukemia, the most common childhood cancer. He was treated with 24 Gray (Gy) cranial radiotherapy, methotrexate (Trexall), 6-mercaptopurine (Purinethol), vincristine (Oncovin), prednisone, and asparaginase (Elspar). He has not received any specific follow-up for more than 10 years.

Treatment that occurred during the early 1980s is associated with cognitive dysfunction, growth hormone deficiency, obesity, osteoporosis, and psychosocial problems.[40] In addition to a history and physical examination (including calculation of body mass index), surveillance recommendations include checking thyroid-stimulating hormone and free-thyroxine levels for central hypothyroidism.[40] An assessment for osteoporosis should be considered because treatment with methotrexate and prednisone is associated with early onset of this condition.[40] If the patient is obese, blood pressure, dyslipidemia, and insulin resistance also should be assessed.[40]

Periodontal disease is associated with cranial radiotherapy; therefore, dental cleaning every six months and an annual evaluation by a dentist are recommended.[40] Assessment of educational and vocational progress is important, and neurocognitive testing should be considered if problems are apparent. Patients who received more than 24 Gy of cranial radiotherapy appear to be at increased risk of cognitive dysfunction. All survivors of childhood cancers are at increased risk for depression and should be screened and treated appropriately.[40]

CASE TWO

A 28-year-old woman who had been diagnosed with Hodgkin's disease at age 15 presents with a breast mass. Previously, she had been treated with staging laparotomy and splenectomy followed by radiation therapy (45 Gy to the mediastinum; 36 Gy to periaortic and perisplenic lymph nodes; 21 Gy to the pelvis) and chemotherapy using nitrogen mustard (mechlorethamine [Mustargen]), procarbazine (Matulane), 125 mg per m^2 of doxorubicin (Adriamycin), bleomycin (Blenoxane), vincristine, vinblastine (Velban), and prednisone.

Female Hodgkin's disease survivors treated with mediastinal, mantle, or chest radiation face a significant increase in the risk for breast cancer, which can occur as quickly as six to eight years after radiation therapy. The 30-year cumulative incidence is about 17 percent.[41] Because of a cumulative risk of 35 percent for breast cancer at 40 years, surveillance with clinical breast examinations, beginning at 20 years of age, and mammography, beginning at 25 years of age, has been recommended for female Hodgkin's disease survivors who were treated with chest irradiation.[42] These patients also are at increased risk for second primary cancers (e.g., nonmelanoma skin cancers, soft tissue sarcomas, thyroid cancer), as well as ovarian failure, late-onset anthracycline-induced cardiomyopathy, osteoporosis, and overwhelming sepsis caused by splenectomy. Surveillance recommendations, which are available from the Children's Oncology Group screening guideline, are summarized in *Table 3.*

Final Comments

Definitive recommendations for surveillance of childhood cancer survivors are complicated by published data that generally are limited to cross-sectional studies and cohort studies of limited size.[40] More importantly, the majority of childhood and adolescent survivors present to family physicians at different times in their lives. The intent of the guidelines is to facilitate optimal care of this population and enhance communication between survivors, clinicians, and cancer centers.[43]

Survivors of adult and childhood cancers should be encouraged to engage in preventive health practices, including immunizations, cancer screening, and maintenance of a healthy body weight and balanced nutrition, as well as regular exercise. Physicians should remain alert to nonspecific symptoms or physical findings (e.g., mass, adenopathy) that can indicate cancer recurrence.

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