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Survivorship, Version 2.2020:

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for consequences of adult-onset cancer and its treatment, with the goal of helping healthcare professionals who work with survivors, including those in primary care. The guidelines also provide recommendations to help clinicians promote physical activity, weight management, and proper immunizations in survivors and facilitate care coordination to ensure that all of the survivors' needs are addressed. These NCCN Guidelines Insights summarize additions and changes made to the guidelines in 2020 regarding cardiovascular disease risk assessment and screening for subsequent primary malignancies.

Overview

The number of cancer survivors in the United States increased from approximately 3 million in 1971 to nearly 16.9 million in 2019.[1–3] These numbers are predicted to surpass 22 million by 2030.[3] This striking increase is generally attributed to increasing cancer incidence rates (mainly resulting from an aging population), earlier detection, and better treatment.

Approximately 64% of survivors were aged ≥65 years in 2019, and an estimated 1 of every 5 persons aged >65 years is a cancer survivor.[3] Only 5% are <40 years of age, and survivors of childhood cancer constitute between 0.5% and 3.0% of the survivor population.[4,5] The most common cancers in the survivor population are breast, prostate, colon/rectum, and melanoma, together accounting for approximately 58% of survivors.[4] Approximately 64% of survivors were diagnosed ≥5 years ago, whereas 15% of survivors were diagnosed ≥20 years ago, and approximately 5% have survived ≥30 years.[4]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship provide screening, evaluation, and treatment recommendations for consequences of cancer

and cancer treatment to aid healthcare professionals who work with survivors of adult-onset cancer. Guidance is also provided to help promote physical activity, a healthful diet and weight management, and proper immunizations in survivors and to facilitate care coordination to ensure that all needs are addressed. The NCCN Survivorship Panel is comprised of a multidisciplinary panel of experts that includes at least one of the following: oncologist, bone marrow transplant clinician, gynecologist, urologist, cardiologist, primary care physician, psychologist, nutrition scientist, nurse, epidemiologist, social worker, and cancer survivor. The panel meets annually to discuss the latest data emerging in the field of survivorship and to decide about requested changes to the guidelines that come from panel members or other health professionals at NCCN Member Institutions (internal requests) or from outside individuals or groups (external requests).

Among the changes the panel made this year were the addition of a new section on cardiovascular disease (CVD) risk assessment and changes to the recommendations related to screening for subsequent primary malignancies. These updates are discussed herein. Other updates can be seen in the complete version of these guidelines, available at NCCN.org.

CVD Risk Assessment

After receiving internal requests from the panel members, the panel decided that it was important to review the data on CVD in cancer survivors and to add recommendations to the guidelines related to CVD risk assessment and risk management in this population.

CVD and cancer are the 2 leading causes of death in the United States, together accounting for approximately 44% of deaths in 2017.[6] CVD is also a leading cause of death and the most common cause of noncancer death for survivors of most cancer types.[7] In fact, survivors of most cancers have a markedly increased risk of developing CVD compared with noncancer populations.[8–10] One reason for this increased CVD risk in cancer survivors is that cytotoxic, hormonal, and targeted systemic cancer therapies (eg, HER2-directed therapy, VEGF signaling pathway inhibitors, cisplatin, anthracyclines with or without taxanes, and androgen deprivation therapy) and radiation therapy are associated with cardiovascular toxicities and can result in diverse cardiovascular issues, including cardiomyopathy, hypertension, hyperlipidemia, cardiac arrhythmia, myocardial infarction, and cerebrovascular accidents.[11–17] In addition, shared risk factors for both cancer and CVD likely contribute to the development of CVD and structural heart disease or heart failure in cancer survivors. These risk factors include well-established and well-studied risk factors, such as tobacco use, obesity, and poor health behaviors, as well as recently discovered ones. For example, somatic mutations in blood cells cause clonal hematopoiesis of indeterminate potential (CHIP) and increase the risk of hematologic malignancies, and CHIP is also emerging to be an important causal risk factor for CVD.[18] Other well-defined CVD risk factors (eg, hypertension, hyperlipidemia, diabetes) are more common in cancer than noncancer populations.[19,20] Most CVDs (eg, atherosclerosis) develop over time as a result of these and other risk factors. Thus, the risk of CVD-related death varies with years from cancer diagnosis, with most survivors being at greatest risk ≥5 years after diagnosis and completion of curative therapy.[21]

Control of CVD and shared CVD/cancer risk factors can decrease the risk of subsequent cardiovascular events.[21,22] Data show that attention to and counseling about CVD/cancer risk factors may improve cancer- and cardiovascular-related outcomes.[23] However, data also show that fewer than half of cancer survivors discuss diet, exercise, or smoking or other lifestyle changes with their physician.[19,24]

The panel discussed the possibility of providing recommendations for CVD risk management in cancer survivors based on a CVD risk group assignment. However, the panel concluded that not enough data are available to define CVD risk groups among cancer survivors. Tools exist to help quantify atherosclerotic CVD risk (eg, ASCVD risk score[25]), but these tools do not take into account cancer treatment history (eg, anthracycline exposure, tyrosine kinase inhibitor exposure) and thus may not accurately capture true CVD risk in a given survivor.

Therefore, panel consensus was to recommend that physicians provide CVD risk assessment and counseling on CVD risk factor management to all cancer survivors throughout the survivorship continuum. The assessment should include (1) preexisting and emerging CVD, such as coronary artery disease, congestive heart failure, peripheral vascular disease, and arrhythmias including atrial fibrillation; (2) CVD risk factors, including hypertension, dyslipidemia, obesity, and diabetes mellitus; (3) cancer treatment history, such as systemic therapy regimen and radiation field, including cumulative doses received of applicable cardiotoxic therapies; and (4) diet and exercise habits and cigarette/tobacco use (see SCVD-1, page 1019). Counseling should include discussions of any increased risk of CVD the survivor may have based on prior cancer treatment, comorbidity, or CVD risk factors and on the ABCDEs of CVD prevention (see SCVD-2, above). Interventions for modifiable risk factors should be recommended as appropriate. Cooperation and shared care with primary care providers, and with cardiovascular specialists as needed, is key to optimizing cardiac and vascular outcomes in cancer survivors. Referral to cardio-oncology or a cardiology specialist should be considered for cancer survivors deemed to be at high-risk for the development of CVD.

The “ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors” table that the panel added this year was adapted from a paradigm developed to address CVD risk factors in survivors of breast and prostate cancer (see SCVD-2, above).[26,27] The table includes items such as aspirin use for secondary prevention (with clinician–survivor discussion required for primary prevention with careful weighing of benefits and risks); blood pressure monitoring/management; cholesterol assessment/management; healthy lifestyle recommendations, including diet/weight management, exercise, and tobacco use; and an echocardiogram and/or electrocardiogram based on individual risk.

Subsequent Primary Malignancies

Subsequent primary cancers are new unrelated cancers in an individual with a history of cancer that are not a recurrence or metastasis of the original primary cancer, with some survivors having more than 2 unrelated primary cancers in their lifetime. The overall incidence of subsequent primary cancers in survivors is higher than the incidence of cancer

in the general population because of genetic susceptibilities (eg, hereditary cancer syndromes), shared causative factors (eg, smoking, obesity, environmental exposures, HPV or Epstein-Barr virus infection), and/or the mutagenic effects of cancer treatment.[28–38] In fact, subsequent primary cancers accounted for 18% of all cancers diagnosed in the United States between 2009 and 2013.[39] These subsequent malignancies are especially well studied in long-term survivors of childhood cancers.[40–43] Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.[44–50] Studies by individual cancer type show that the incidence of subsequent unrelated cancers ranges from 2% in survivors of malignant lymphoma to 30% in survivors of small cell lung cancer.[51] Another study of >2 million cancer survivors in the SEER database identified bladder cancer survivors as having the highest risk for subsequent primary cancers (34% at 20 years).[52] Overall, this study found that 8.1% of survivors of cancers diagnosed after age 18 years develop a subsequent malignancy within a mean follow-up of 7.1 years, with 55% of these survivors dying as a result of the subsequent cancer.

With appropriate screening and early detection of subsequent cancers, risk to the cancer survivor can be mitigated. Therefore, the panel has included recommendations for screening for subsequent new primary cancers in survivors in the NCCN Guidelines since 2014.

Role of Genetics

Data suggest that somewhere in the range of 6% to 16% of cancer survivors harbor a germline mutation in a gene associated with oncogenesis,[53–56] making genetic predisposition an important driver of subsequent primary cancers. Identification of a germline mutation in a cancer survivor helps establish their risk of developing a subsequent primary malignancy and their need for screening or other risk-reducing measures (eg, surgical, medical). Genetic testing may also have a cascade effect by providing opportunities to identify and reduce risks in relatives of cancer survivors. Several NCCN Guidelines (available at NCCN.org) include management recommendations for patients with known germline mutations linked to an increased risk for cancer.[57–59]

Based on an external request, the panel reviewed the language in the guidelines regarding hereditary cancer risk assessment and genetic testing in cancer survivors. The panel discussed the fact that not all survivors received a hereditary cancer risk assessment at the time of diagnosis. Furthermore, genetic testing guidelines and knowledge about hereditary cancer risk evolve over time, and new family diagnoses may have occurred since an initial family history evaluation. Therefore, some survivors who previously did not meet criteria for genetic risk assessment may now qualify for genetic testing. Thus, the panel concluded that periodic review of family cancer history in cancer survivors is important to reassess the risk of a hereditary cancer syndrome (see SURV-3, page 1018). The panel consensus was that genetic risk assessment is appropriate for all survivors of breast cancer, epithelial ovarian cancer, high-grade prostate cancer, and pancreatic cancer and for survivors of colorectal or endometrial cancer diagnosed at age ≤50 years. Many other survivors of rare cancers or cancers diagnosed at young ages, those with multiple primary cancers, and those with ≥1 relative with the same or related cancers are also candidates for risk assessment per

guidelines from NCCN and other expert groups.[57–66] When available, genetic testing is recommended for appropriate survivors based on results of the risk assessment to identify those with an increased risk for subsequent malignancies.

Screening for Subsequent Primary Cancers

Overall, the panel consensus is that screening for subsequent primary cancers should be a shared responsibility between primary and oncology care providers (see NCCN Guidelines for Detection, Prevention, and Risk Reduction, available at NCCN.org). In addition, lifestyle modifications that reduce the risk of subsequent primary cancers (eg, smoking cessation, physical activity, weight loss) should be encouraged.[67] As discussed earlier, periodic hereditary cancer assessment, with genetic counseling and testing as appropriate, is also recommended (see SURV-3, page 1018).

Conclusions

Subsequent primary cancers and cardiovascular disease are 2 leading causes of death in cancer survivors. Risk of the former can be mitigated with appropriate cancer screenings and/or cancer risk–reducing measures as informed by treatment exposures and genetic counseling/testing results. Risk of the latter can be reduced by CVD risk assessment and through counseling the survivor on CVD prevention measures, such as lifestyle modification and management of CVD risk factors (eg, blood pressure, cholesterol). The NCCN Survivorship Panel hopes that the guidance added this year will help both oncologic and primary healthcare professionals recognize and optimally manage these risks so that survivors can lead long and rewarding lives.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1:

Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:

Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:

Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:

Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

SCREENING FOR SUBSEQUENT NEW PRIMARY CANCERS

- Subsequent new primary malignant neoplasms may occur in survivors years after treatment when the survivor's oncologist may no longer be involved in the survivor's care.
- The overall cancer rate in survivors is higher than in the general population. This increased risk is due to genetic susceptibilities (eg, hereditary cancer syndromes) and/or family history, shared etiologic exposures (eg, smoking, environmental exposures), and mutagenic effects of cancer treatment.
- Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.
- Screening for subsequent primary cancers should be a shared responsibility between primary and oncology care physicians (See the NCCN Guidelines for Detection, Prevention, and Risk Reduction Table of Contents).
- Evidence suggests that excess lifetime radiation exposure from CT imaging may be associated with a mildly increased risk of developing a radiation-associated cancer. Use of radiologic studies to screen for recurrent cancer should be based on diagnosis and evidence that early detection of recurrence will improve cancer-related outcomes. Recommendations for surveillance imaging modality and frequency can be found in the NCCN Guidelines for Treatment of Cancer by Site.
- Healthy lifestyle and behavioral counseling are important to reduce risk factors that may contribute to subsequent cancers (See HL-1).
- Periodic updating of family cancer history (when known) is recommended to reassess hereditary risk, as it should not be assumed that all cancer survivors were assessed at diagnosis. Genetic testing guidelines and knowledge about hereditary cancer risk evolve over time and new family diagnoses may occur making periodic assessment important.
- Genetic risk assessment is appropriate for all breast cancer survivors, all survivors of epithelial ovarian cancer, survivors of colorectal or endometrial cancer diagnosed at age 50 or younger, high-grade prostate cancer, or pancreatic cancer. Many other survivors of rare cancers, cancers diagnosed at young ages, multiple primary cancers, or those with one or more relatives with the same or related cancers are also candidates for risk assessment per guidelines from NCCN and other expert groups. Genetic testing is recommended for appropriate survivors based on results of the risk assessment.
- Referral to genetic risk assessment and/or testing should be considered for appropriate candidates when available to identify those with an increased risk for subsequent malignancies. Genetic testing may also provide opportunities to identify and reduce risks in relatives of cancer survivors.

- Criteria for genetic risk assessment and testing, and for management of patients with known germline mutations linked to an increased risk for cancer can be found in the following NCCN Guidelines:
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - NCCN Guidelines for Gastric Cancer
  - NCCN Guidelines for Neuroendocrine and Adrenal Tumors
  - NCCN Guidelines for Thyroid Carcinoma
  - NCCN Guidelines for Prostate Cancer
  - NCCN Guidelines for Cutaneous Melanoma

PRINICIPLES OF CARDIOVASCULAR DISEASE RISK ASSESMENT

- Cardiovascular disease (CVD) remains a leading cause of death in cancer survivors. The risk of CVD-related death varies with years from diagnosis, with most survivors being at greatest risk 5 or more years after diagnosis and completion of curative therapy.
- Shared risk factors for both cancer and CVD (ie, smoking, poor health behaviors) contribute to the development of CVD and structural heart disease or heart failure, a concept that becomes especially relevant to cancer survivors. Attention and counseling regarding shared risk factors may improve cancer- and cardiovascular-related outcomes.
- Cancer treatments (cytotoxic and targeted systemic therapies, a radiation therapy) can result in diverse cardiovascular issues, including cardiomyopathy, hypertension, hyperlipidemia, cardiac arrhythmia, myocardial infarction, and cerebrovascular accidents. Survivors treated with anthracyclines may be at increased risk for heart failure. (See SCARDIO-1)
- Most cardiovascular diseases (such as atherosclerosis) develop over time as a result of well-defined risk factors such as hypertension, hyperlipidemia, tobacco abuse, obesity and diabetes. Control of these risk factors can decrease the risk of subsequent cardiovascular events.
- Survivors should be assessed throughout the survivorship continuum for:
  - Pre-existing and emerging CVD (eg, coronary artery disease [CAD], congestive heart failuree [CHF], peripheral vascular disease, arrhythmias including atrial fibrillation) and CVD risk factors (eg, hypertension, dislipidemia, obesity, cigarette/tobacco use, diabetes mellitus), with intervention for modifiable risk factors as necessary
  - Cancer treatment history (eg, regimen/dose,[a] radiation field)
  - Diet and exercise habits, cigarette/tobacco use
- Tools exist to help quantify atherosclerotic CVD (ASCVD) risk (eg, ASCVD risk score[b]).
- Survivors should be counseled on any increased risk of CVD they may have based on prior treatment, comorbidify, or CVD risk factors and on the ABCDEs of CVD Prevention. (See Table 1 on SCVD-2)
- Cooperation and shared care with primary care providers, and cardiovascular specialists as needed, is key to optimizing cardiac and vascular outcomes in cancer survivors.
- Consider referral to cardio-oncology or a cardiology specialist for high-risk survivors.

[a]HER2-directed therapy, VEGF signaling pathway inhibitors, cisplatin, anthracyclines with or without taxanes, and androgen deprivation therapy are CVD risk factors.

[b]The ASCVD Risk Estimator Plus from the American College of Cardiology is available at http://tools.acc.org/ascvd-risk-estimator-plusWi/calculate/estimate/.

PRINICIPLES OF CARDIOVASCULAR DISEASE RISK ASSESMENT

Table 1:

ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors[c]

A	• Awareness of risks and presentation of heart disease • Assessment of cardiovascular disease and cardiovascular risk • Aspirin use as appropriate (indicated for secondary prevention; clinician-survivor discussion required for primary prevention with careful weighing of benefits and risks)
B	• Blood pressure monitoring/management (with clinician-survivor discussion regarding the use of hypertension treatment and blood pressure goals)
C	• Cholesterol assessment/management (with clinician-survivor discussion regarding the use of statin therapy for primary prevention and lipid profile goals) • Cigarette/tobacco cessation (See NCCN Guidelines for Smoking Cessation)
D	• Diet and weight management (See SNWM-1) • Dose (cumulative) of anthracyclines and/or radiation to heart • Diabetes mellitus prevention/treatment
E	• Exercise (See SPA-1) • Echocardiogram and/or EKG based on individual risk

[c]Adapted with permission from Montazeri K, Unitt C, et al. ABCDE Steps to Prevent Heart Disease in Brest cancer Survivors. Circulation 2014:130:e157–e159.