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# Secondary solid cancer screening following hematopoietic cell transplantation

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest

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## Abstract

Hematopoietic stem cell transplant (HCT) recipients have a substantial risk of developing secondary solid cancers, particularly beyond 5 years after HCT and without reaching a plateau overtime. A working group was established through the Center for International Blood and Marrow Transplant Research and the European Group for Blood and Marrow Transplantation with the goal to facilitate implementation of cancer screening appropriate to HCT recipients. The working group reviewed guidelines and methods for cancer screening applicable to the general population and reviewed the incidence and risk factors for secondary cancers after HCT. A consensus approach was used to establish recommendations for individual secondary cancers. The most common sites include oral cavity, skin, breast and thyroid. Risks of cancers are increased after HCT compared with the general population in skin, thyroid, oral cavity, esophagus, liver, nervous system, bone and connective tissues. Myeloablative TBI, young age at HCT, chronic GVHD and prolonged immunosuppressive treatment beyond 24 months were well-documented risk factors for many types of secondary cancers. All HCT recipients should be advised of the risks of secondary cancers annually and encouraged to undergo recommended screening based on their predisposition. Here we propose guidelines to help clinicians in providing screening and preventive care for secondary cancers among HCT recipients.

## INTRODUCTION

Advances in hematopoietic cell transplantation (HCT) and supportive care measures have led to substantial improvements in long-term survival for HCT recipients.[1] Transplant survivors are at considerable risk for developing significant late effects, and general recommendations regarding the multi-faceted approach required in their evaluation and treatment have been recently published.[2] One particular challenge faced in the post-HCT setting is the risk of development of secondary malignancies. There is an increased risk of secondary malignancies following both autologous and allogeneic HCT, which may be further impacted by pretransplant therapies. Secondary malignancies can be grouped into post-transplant lymphoproliferative diseases, leukemia or myelodysplasia and solid cancers. The incidence of secondary solid malignancies can continue to rise over time and studies with follow-up to 20 years have not shown a plateau in their occurence.[3–5]

Several organizations (for example, National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS), United States Preventative Services Task Force) have developed standardized cancer screening methods that are currently implemented as part of a routine general health evaluation for certain malignancies in the general population, but application of these guidelines to HCT recipients have not been reviewed. In acknowledging the increased risk of secondary solid cancers among HCT recipients, a working group was established through the Center for International Blood and Marrow Transplant Research Late Effects and Quality of Life Working Committee and the European Group for Blood and Marrow Transplantation Complications and Quality of Life Working Party with the goal to facilitate implementation of cancer screening appropriate to HCT recipients. As a clinical output of this working group's effort, we offer consensus-based recommendations applicable for screening and prevention of individual secondary solid cancers among HCT recipients.

## METHODS

The goals of this document were to provide an expert review of existing, evidence-based, cancer screening guidelines applicable to the general population and adopt them to the post-HCT setting. In order to integrate the incidence and risk factors of individual secondary cancers after HCT, an incidence rate and a standardized incidence ratio (SIR) (the ratio of observed cancer cases in a HCT cohort to expected cancer cases in the general population of similar age and gender) were summarized from existing literatures (Table 1) and reported risk factors for secondary cancer among HCT recipients were reviewed (Table 2). Cancer screening guidelines for the general population were primarily based on those established by ACS or NCCN, unless otherwise specified (Table 3). Details of screening guidelines and methods in the general population are summarized in the Supplementary Appendix. Adult and pediatric HCT recipients were considered in the development of these guidelines.

### Skin cancer

**Overview—**There are three main types of skin cancer, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. Age-standardized incidence rates of melanoma in men and women were 3.3 and 2.8, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] Age-standardized incidence rates of other skin cancers have not been reported. Incidence varies 100-fold between countries and ethnicities and is the highest in Caucasians. BCC and SCC are the most common and have better prognosis than other skin cancers in the general population. Actinic keratoses have been considered as direct precursors of both BCC and SCC, and the annual rate of transformation is estimated as 0.03–20%.[7] Exposure to UV radiation is a well-known risk factor for melanoma and non-melanoma skin cancers.[8,9] The risk of developing skin cancers is incredibly high after solid organ transplantation owing to the chronic use of potent immunosuppression.[10]

**Incidence and risk factors after transplantation—**The reported incidence rates of skin cancers after HCT were 105 per 100 000 person-years for BCC, 76 for SCC and 18–76 for melanoma.[3,5,11,12] Reports describing skin cancer following HCT are dominated by case reports, but at least five large studies have reported an increased incidence of melanoma after allogeneic HCT compared with the general population (SIR 1.4–8.3).[3,5,11–13] The risk of

developing melanoma was also increased compared with the general population after HCT with reduced-intensity conditioning (RIC) regimens (SIR 3.04 for leukemia or myelodysplastic syndrome patients and SIR 3.52 for lymphoma patients).[13] An Asian study reported an increased incidence of skin cancers without distinguishing cancer subtypes after allogeneic HCT (SIR 7.2).[14] One study reported that the cumulative incidences of BCC and SCC were 6.5% and 3.4% at 20 years after allogeneic HCT in a predominantly Caucasian cohort.[15] Although it is rare, merkel cell carcinoma can occur after HCT,[16] which is fatal in approximately one-third of patients and requires immediate treatment. Chronic GVHD (cGVHD), younger age at HCT and myeloablative TBI (that is, single doses ⩾ 10 Gy or fractionated doses ⩾ 13 Gy) are consistently reported risk factors for secondary skin cancer (Table 2).[4,5,11,14,15,17] Voriconazole might increase the risk of skin cancer in organ transplant recipients, including HCT.[18] The risk of skin cancer for patients who had allogeneic HCT for non-malignant disease remains undefined. A report restricted to autologous HCT demonstrated a SIR of 2.55 for melanoma, and multivariate analysis revealed age ⩾ 45 years, male patients and relapse following HCT as risk factors for melanoma development.[19]

**Recommendation for transplant recipients—**Given the considerations above, HCT recipients should maintain at least annual follow-up with their provider to incorporate skin cancer awareness and early disease recognition into routine late effects management. Photoprotection should be counseled to all HCT recipients as it can reduce the risk of skin cancer.[20–22] Physical examination is the primary method for skin cancer screening. Heightened awareness is warranted for patients who received myeloablative TBI, those who had HCT at ages < 18 years, those with prior or concurrent GVHD of any form and those who had HCT for hereditary disorders, such as Fanconi anemia. Suspicious lesions should be addressed promptly, with management complying with standard practices.[23]

## Thyroid cancer

**Overview—**Thyroid cancer is the most common endocrine cancer. Age-standardized incidence rates in men and women were 1.9 and 6.1, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] The incidence of thyroid cancer has steadily risen over the past decades with no change in mortality rate (0.5 deaths per 100 000 person-years), which has largely been attributed to earlier detection.[24] The incidence in women is approximately three times that in men and the median age at diagnosis is 50 years. Radiation and exposure to radioactive iodine isotopes are known risk factors for the development of thyroid cancer, though the majority of well-differentiated thyroid cancers (that is, papillary and follicular thyroid cancer) are unrelated to radiation exposure.

**Incidence and risk factors after transplantation—**Results have been conflicting in studies investigating the incidence of secondary thyroid cancer after HCT. Although some have found an increased incidence of thyroid cancers (SIR 5.8–6.5),[5,11] others have not found any difference.[12,25] In an attempt to better characterize the risk of secondary thyroid cancer, the European Group for Blood and Marrow Transplantation Late Effect Working Party reviewed data on 68 936 patients undergoing HCT between 1985 and 2003.[26] They found an increased risk of secondary thyroid cancers when compared with the general

population, with a SIR of 3.26. Multivariate analysis revealed that age ⩽ 20 years at HCT was the strongest risk factor for secondary thyroid cancer (relative risk (RR) 24.6 for age 0–10 years; RR 4.80 for age 11–20 years). Other risk factors were irradiation history (RR 3.44), female gender (RR 2.79) and history of cGVHD (RR 2.94). The median interval between HCT and secondary thyroid cancer was 8.5 years.

**Recommendations for transplant recipients—**Physical examination (neck palpation) at least once a year remains the cornerstone of thyroid cancer screening. There is no evidence for routine imaging (for example, thyroid ultrasound) in screening. Heightened awareness is warranted for pediatric long-term survivors, female patients, TBI recipients and patients with cGVHD.

## Oropharyngeal cancer

**Overview—**Age-standardized incidence rates of oropharyngeal cancer in men and women were 5.5 and 2.5, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] Oral squamous cell cancer (SCC) is the most common type and the major risk factors in the general population are tobacco and alcohol use.[27] Human papilloma virus (HPV) and other viruses have also been implicated in the pathogenesis.[28] Other reported risk factors are low socioeconomic status, dietary, tylosis, poor oral hygiene, use of chewing tobacco, betel nut chewing, occupational exposure, radiation and genetic predispositions.

**Incidence and risk factors after transplantation—**Among secondary cancers after HCT, oropharyngeal cancer is the most frequent (Table 1). The incidence rate of oropharyngeal cancer after HCT ranged from 32 to 92 per 100 000 person-years with a 7–16-fold higher risk than the general population.[3,5,11,14] The risk of oropharyngeal cancers was also elevated after HCT with RIC regimens (SIR 46.7).[13] The risk of oral SCC is particularly high in patients with cGVHD receiving long-term immunosuppressive therapy ⩾ 24 months.[4,5,11,13–15,29–31] There was an association between oral cancer and male gender.[5,11] In addition to cGVHD, conditioning regimens with limited field irradiation was associated with an increased risk of SCC of the oral cavity (RR = 4.7).[5,11] A pediatric study showed an increased incidence of pharyngeal cancer after autologous HCT,[32] whereas an adult study did not report oropharyngeal cancer after autologous HCT.[33] Patients with hereditary disorders such as Fanconi anemia are at a significantly increased risk of oropharyngeal cancer. In immunocompromised patients, oncogenic viruses such as HPV may contribute to oropharyngeal SCC.[34]

**Recommendation for transplant recipients—**We recommend that all HCT recipients should be informed about the risks and symptoms of oropharyngeal cancer. Evaluation for premalignant lesions or oral cancer by a dentist or an oral surgeon is recommended annualy.[2] Alternatively, primary care providers can include careful oral examination as part of an annual physical exam. Screening every 6 months may be considered for patients at high risk for developing oropharyngeal cancer (for example, cGVHD; Table 2). No definitive preventive interventions are recommended beyond general lifestyle counseling (for example, smoking cessation). Children who received radiation-containing treatment at a young age may require particular attention to screening for oropharyngeal cancer.

## Esophageal cancer

**Overview—**Age-standardized incidence rates of esophageal cancer in men and women were 9.0 and 3.1, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] Adenocarcinoma is the most common subtype in countries where smoking rate is low, and SCC is the most common subtype in countries where smoking rate is high. Reported risk factors are tobacco use, alcohol use, low socioeconomic status, dietary, other esophageal diseases, previous head and neck cancer, bisphosphonate use, occupational exposure, radiation and genetic predispositions. Barrett's esophagus is the major risk factor for esophageal adenocarcinoma in the general population. Factors known to increase the risk for Barrett's esophagus include White ethnicity, older age, obesity and longstanding gastroesophageal reflux disease symptoms.[35]

**Incidence and risk factors after transplantation—**The incident rate of esophageal cancer after HCT ranges from 4 to 59 per 100 000 person-years and the SIR compared with the general population is 8.5–11-fold.[3,5,14] The risk of secondary esophageal cancer was increased in patients with persistent cGVHD and those receiving long-term immunosuppressive therapy ⩾ 24 months.[4,14] In particular, extensive-type cGVHD was a risk factor for esophageal cancer (RR = 5.3). Information is limited in the pediatric population. An adult study did not show an increased incidence of esophageal cancer after autologous HCT.[33]

**Recommendation for transplant recipients—**HCT recipients should be informed about the risks and symptoms of secondary esophageal cancer. Patients who have persistent gastroesophageal reflux disease symptoms or dysphagia should be evaluated by upper gastrointestinal (GI) endoscopy. Endoscopic screening can be considered in patients receiving prolonged immunosuppressive treatment ⩾ 24 months for cGVHD, especially if symptoms such as dysphagia and persistent heartburn are present. Barium swallow is inexpensive and could be used for screening, but its sensitivity is unknown.[36]

## Gastric cancer

**Overview—**Gastric cancer was the fifth most common cancer worldwide in 2012 and age-standardized incidence rates of gastric cancer in men and women were 17.4 and 7.5, respectively, per 100 000 person-years (Figure 1).[6] Almost three quarters of the new cases occurred in Asia. Incidence varies 10-fold between countries, with the highest incidence in East Asia and central and Eastern Europe. Incidence rates are low in Africa and in North America. *Helicobacter pylori* infection is a well-established carcinogen for gastric cancer and is found in approximately 75% of all cases of gastric cancer.[37]

**Incidence and risk factors after transplantation—**Although GI tract cancers are among the most common cancers worldwide, current data in HCT survivors have not necessarily indicated an increased risk of secondary gastric cancer relative to the general population.[3,11,12,38–41] In the largest study of long-term HCT survivors, no gastric cancers were reported.[5] Although cGVHD has been linked to secondary SCC, cGVHD does not appear to be associated with gastric cancer. Given the long latency of GI cancers, studies with longer-term follow-up are needed to clarify the risk of GI cancers after HCT. Of note,

most secondary cancer studies have included patients from regions with a low prevalence of gastric cancer.

**Recommendation for transplant recipients—**There are currently no data indicating an increased risk of secondary gastric cancers in HCT recipients. Routine screening for gastric cancer in HCT recipients is not recommended, but following local screening recommendations based on geographic location and associated predisposition may be considered.

## Colorectal cancer

**Overview—**Colorectal cancer represents almost 10% of the global cancer incidence burden in 2012 and is the third most common cancer in men and the second most common cancer in women. Age-standardized incidence rates in men and women were 20.6 and 14.3, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] Incidence varies 10-fold between countries in both genders and rates tend to be low in many African countries.

**Incidence and risk factors after transplantation—**Limited data in the post-HCT setting do not indicate a greatly increased risk of secondary colorectal cancers relative to the general population.[3,11,12,38–41] In the largest study of long-term HCT survivors, there were only two cases of colon cancer (observed/expected (O/E), 0.52; 95% confidence interval (CI), 0.06–1.89) and four cases of rectal cancer (O/E, 1.67; 95% CI, 0.46–4.29) described among 28 874 patients.[5] Secondary GI cancers were similarly infrequent in a recent cohort of 4269 long-term survivors of HCT with RIC regimens (1 small intestinal cancer, 3 colon cancers, and 2 rectal cancers).[13] A more recent study that included 17 545 HCT recipients, in contrast to prior reports, did find an increased risk (SIR 1.9) of colon cancer.[14]

**Recommendation for transplant recipients—**The data indicating an increased risk of secondary colorectal cancers in HCT recipients is limited, but has been reported.[14] It is recommended that HCT recipients undergo screening for secondary colorectal cancers according to the current general population guidelines (Table 3). This would include consideration of annual stool guaiac testing, flexible sigmoidoscopy every 5 years or colonoscopy every 10 years, with earlier and more frequent screening in high-risk patients.

## Liver cancer

**Overview—**The annual incidence of hepatocellular carcinoma (HCC) is rising worldwide. Age-standardized incidence rates in men and women were 15.3 and 5.4, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] A history of hepatitis B, hepatitis C, chronic active hepatitis and cirrhosis are potential risk factors for the development of HCC.

**Incidence and risk factors after transplantation—**An increased incidence of liver cancer in long-term survivors of both autologous and myeloablative allogeneic HCT has been reported (6–28-fold increased risk compared with the general population) by some[5,11,25] but not all studies (Table 1).[12] Similarly, a trend towards increased incidence of liver cancer is also noted in recipients of allogeneic HCT with RIC regimens (SIR, 5.96; 95% CI, 0.72–21.54).[13] Risk factors of liver cancer in HCT survivors include younger age

(< 34 years) at HCT (SIR, 200; 95% CI, 18.9–573.2), history of chronic hepatitis C infection, liver cirrhosis and TBI-based conditioning (SIR, 20.0; 95% CI, 1.9–57.3)(Table 2).[42] No data indicate that GVHD increases the risk of liver cancer in allogeneic HCT survivors. An additional consideration in the post-HCT population is the potential for iron overload from prior transfusions.[43,44] Iron overload can contribute to the development of chronic liver disease and/or subsequent HCC in cases of both hereditary[45] and acquired iron overload syndromes,[46] but further studies are needed to determine whether there would be similar implications of iron overload in the post-HCT setting.

**Recommendation for transplant recipients—**General population guidelines can be followed for screening for HCC in HCT survivors (screening liver ultrasound every 6 months in patients at increased risk for developing HCC, as defined in AASLD guidelines).[54]

## Lung cancer

**Overview—**Lung cancer is the most frequent cancer worldwide and is the leading cause of cancer death in men and in women. Age-standardized incidence rates in men and women were 34.2 and 13.6, respectively, per 100 000 person-years worldwide in 2012 (Figure 1).[6] Incidence varies 80-fold between countries, with the highest incidence in North America, Europe and East Asia and relatively low incidence in many African countries. The two main classes of lung cancer are small cell lung carcinoma (SCLC) and non-SCLC. Non-SCLC is further subdivided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma. SCLC is strongly associated with tobacco use in the general population.

**Incidence and risk factors after transplantation—**Reported SIRs for secondary lung cancer in HCT survivors compared with the general population vary among large studies from 0.7 to 2.6.[3,5,11–14] A recent study evaluated the incidence and risk factors for solid cancers after HCT using high-dose BU and CY conditioning in 4318 recipients of first allogeneic HCT. In this study, lung cancer was the most common site ($n$ = 11, including 9 with non-SCLC, among 66 patients with all solid cancers).[3] Median age at HCT for these 11 patients was 48 (range, 24–58) years, and lung cancer occurred at a median of 4.5 years after HCT. The association of radiation (for example, TBI) and lung cancer risk in HCT survivors is not well established, especially when lung shielding is applied. Limited data in the setting of radiation used for the treatment of Hodgkin lymphoma, however, suggest an increase in the risk of lung cancer following radiation therapy.[47,48] Tobacco use prior to HCT was a strong risk factor for developing secondary lung cancer (RR = 11.6, $P$ = 0.02).[3] In other large studies, however, overall SIRs of developing secondary lung cancers were not significantly elevated compared with the general population.[5,11–14]

**Recommendation for transplant recipients—**Patients preparing to undergo HCT who are current smokers should be counseled to quit immediately to avoid the risks of secondary lung cancers and other adverse post-HCT health effects. Past or current smokers who are HCT survivors should be counseled about the risks of secondary lung cancer. Assessment of tobacco use, counseling against smoking and smoking cessation guidance for current smokers should be routinely included as part of post-transplant assessment.[2] Screening with

low-dose computed tomography may be offered to high-risk smokers and former smokers according to general population guidelines.[49]

## Breast cancer

**Overview—**Breast cancer is the most frequently diagnosed and the leading cause of cancer death in women worldwide.[50,51] An age-standardized incidence rate of breast cancer was 43.3 per 100 000 person-years worldwide in 2012 (Figure 1).[6] Introduction of screening programs has reduced breast cancer-related mortality by 20–48%.[52,53]

**Incidence and risk factors after transplantation—**Overall incidence of breast cancer is not increased among HCT survivors as compared with the general population (Table 1). Among HCT survivors, however, patients who had HCT at a younger age have an increased risk of developing breast cancer, with the highest incidence in young females < 18 years at HCT. The risk remains elevated for subsequent age groups.[12,32,54] The incidence of breast cancer was increased markedly from 0.8% at 10 years to 4.6% at 20 years, reaching 11% at 25 years after HCT.[54] Similar results have been observed in other studies.[5,11,32] The use of TBI-based conditioning regimens has been associated with an increased risk of breast cancer after allogeneic HCT.[5,54] The effect of TBI seems to be greater in children irradiated before 10 years of age with a 55-fold increase in the risk of developing solid cancers, including breast cancer. The risk remains elevated at 4–6-fold among recipients irradiated between 10 and 19 years and 20 and 29 years. The incidence of breast cancer was increased among patients > 50 years of age who received BU–CY conditioning regimen,[3] but the incidence was not increased among patients of similar age in another study.[14] Other studies have reported an increased risk of breast cancer associated with antithymocyte globulin[5] or growth factors.[3] One study, in which many patients received radiation therapy before HCT or as part of conditioning, showed a higher risk of developing breast cancer in pediatric patients after autologous HCT.[32] In contrast, none of 1482 adult patients in another large cohort of autologous HCT recipients developed breast cancer.[33]

**Recommendation for transplant recipients—**Breast awareness should be emphasized for all long-term survivors after HCT, with prompt reporting of any new breast symptoms (for example, new nodules) to a health-care professional. Mammograms and clinical breast exam beginning at age 40 years and occurring every 1–2 years are recommended for all HCT recipients. For patients who received chest radiation or TBI, special consideration should be given for annual clinical breast exam, mammography and breast magnetic resonance imaging beginning at age 25 years or 8 years after radiation or TBI, whichever occurs later, but no later than 40 years of age.[2] Screening at an earlier age may also be considered in women at high risk for breast cancer (for example, known *BRCA* mutations) and should follow general population screening guidelines. Breast ultrasound may be considered in addition to mammography for high-risk women, but additional benefits over magnetic resonance imaging are undetermined.[55]

## Cervical and endometrial cancer

**Overview—**Age-standardized incidence rate of cervical cancer was 14.0 per 100 000 person-years worldwide in 2012 (Figure 1).[6] The incidence and mortality rate of cervical

cancer have declined since the introduction of the Papanicolaou (Pap) test. More than 80% cases are SCC and 10–20% are adenocarcinomas. Cervical cancers present with no symptoms in early stages but progresses to abnormal vaginal bleeding, pelvic pain or pain during intercourse in advanced stages. As HPV of high-risk subtypes such as HPV16 and HPV18 causes > 90% of cases, routine HPV vaccination is recommended for females aged 9–26 years.[56,57] The Centers for Disease Control and Prevention recommends HPV vaccination for girls and boys at age 11 or 12 years. Age-standardized incidence rate of endometrial cancer was 8.2 per 100 000 person-years worldwide in 2012 (Figure 1).[6] Endometrial cancers typically occur after menopause, and the first symptom is often vaginal bleeding. Obesity and excessive estrogen exposure are known risk factors.[58] It often develops from endometrial hyperplasia and 80% of cases are endometrioid carcinoma.

**Incidence and risk factors after transplantation—**The reported incidence rates of cervical and endometrial cancers occurring after HCT are 2–67 and 2–7 per 100 000 person-years.[3,5,11,14] Several studies have shown that the overall incidence rates of these cancers did not differ from the general population,[3,5,11,14] but one study reported a 13-fold increased risk of cervical cancer compared with the general population (Table 1).[25] Age > 34 years and systemically treated cGVHD for > 3 years were associated with an increased risk of cervical cancer (Table 2).[25,59] HPV-related cervical dysplasia occurred in more than one-third of long-term survivors after allogeneic HCT, and most cases had high-risk HPV subtypes 16 and 18.[59] Risk factors for endometrial cancer after HCT have not been studied. Information on cervical or endometrial cancer after autologous HCT or in the pediatric population are limited, although some studies have included adult survivors of HCT during childhood.[32]

**Recommendation for transplant recipients—**The screening and preventive practice guidelines for HCT recipients recommend annual pelvic exam for all female HCT survivors, ideally to begin in the year following transplant, as age appropriate.[2,60] Screening methods recommended for the general population by expert societies apply to HCT recipients as well.[61] Although the efficacy of HPV vaccination in HCT recipient remains to be determined, the Centers for Disease Control and Prevention has recommended vaccination in those who are immunocompromised.[57,62] Three doses of HPV vaccination starting at 1 year after allogeneic HCT are provided in some transplant centers for males and females aged 9–26 years. Although there are no clear contraindications to vaccination, studies demonstrating its effectiveness in the post-transplant setting are lacking and clinical studies are needed to evaluate the benefit in this subpopulation. Information about the risks and symptoms of endometrial cancers (any unexpected bleeding or spotting) should be provided to female HCT recipients at the time of menopause. Combination of estrogen and progestogens should be used for HCT recipients who need hormone-replacement therapy,[63,64] as estrogen alone increases risk of endometrial cancer in the general population.[65,66]

## Ovarian cancer

**Overview—**Ovarian cancer is the second most common gynecological cancer in developed countries. Age-standardized incidence rate of ovarian cancer was 6.1 per 100 000 person-

years worldwide in 2012 (Figure 1).[6] The fatality rate of ovarian cancer is higher than other cancers of the female reproductive organs. Ovarian carcinomas are the most common type and nulliparous women are more frequently affected than those with suppressed ovulation typically by pregnancy or oral contraceptives.

**Incidence and risk factors after transplantation—**Few studies have reported on the incidence of ovarian cancer after HCT. In long-term Asian survivors of allogeneic HCT compared with the general population, the incidence of ovarian cancer does not appear to be increased (SIR 0.8; 95% CI 0.2–2.4%; Table 1).[14] No specific risk factors predisposing to secondary ovarian cancer among HCT recipients are known.

**Screening recommendations for transplant recipients—**Routine ovarian cancer screening in average-risk transplant survivors is not recommended. Evaluation should instead focus on early detection in symptomatic patients. Such evaluation includes physical exam, transvaginal ultrasound and serum CA-125 levels.[67]

## Prostate cancer

**Overview—**Prostate cancer is most frequent in men > 65 years but rarely reported as a primary cause of death.[68] Age-standardized incidence rate was 31.1 per 100 000 person-years worldwide in 2012 (Figure 1).[6] In the general population, risk factors for prostate cancer are family history, African American ethnicity, older age and abnormal digital rectal examination.[23]

**Incidence and risk factors after transplantation—**The incidence rate of prostate cancer after HCT is 4–10 per 100 000 patient-years, and the risk has not exceeded the risk in the general population.[3,5,11,12,14,38,69] No specific risk factors predisposing to secondary prostate cancer among HCT recipients are known.

**Recommendation for transplant recipients—**HCT survivors should follow guidelines for the general population. For prostate cancer, after an informed decision-making process for asymptomatic men aged > 50 years with life expectancy of at least 10 years, or for those considered to be at higher risk, consideration should be made for routine digital rectal examination with or without prostate-specific antigen.[23,70–72]

## Testicular cancer

**Overview—**Testicular cancer usually presents between 20 and 30 years of age and represents about 1% of male malignant tumors.[73] Age-standardized incidence rate was 1.5 per 100 000 person-years worldwide in 2012 (Figure 1).[6] Risk factors for testicular cancer include cryptorchidism/hypospadias, a personal or family history of testicular cancer, infertility, tobacco use, increased height or weight, HIV infection, Caucasian or Hispanic ethnicity and exposure to organochlorine compounds.[73–82]

**Incidence and risk factors after transplantation—**The incidence rate of testicular cancer after HCT is 4–5 per 100 000 patient-years, and the risk after HCT does not seem to

exceed the risk in the general population.[3,5,11,12,14,38,69] No specific risk factors predisposing to secondary testicular cancer among HCT recipients are known.

**Recommendation for transplant recipients—**Screening recommendations for testicular cancer among HCT recipients should mirror screening recommendations in the general population, including performance of a testicular exam as part of a routine annual physical exam.

### Other secondary solid cancers

In addition to screening for cancers that the general population is also at risk for, it is notable that patients with history of cancer or who are post-transplant are at higher risk for cancers where there are no routine screening recommendations. These include central nervous system tumors and sarcomas (Table 1).[3] Although there is no evidence to suggest clear recommendations for screening, providers should maintain vigilance and have a high level of suspicion in patients who present with relevant symptoms. Central nervous system tumors may be of particular concern in those who have previously undergone central nervous system irradiation as part of prior therapy or have received TBI.[83]

### Additional considerations

The incidence of secondary solid cancers did not differ according to donor type or HLA matching in many previous studies.[3–5,11,12,14,15,54] As previous studies included few cord blood or haploidentical transplantation, further studies are warranted to characterize outcomes after the use of these new graft sources. One recent study found a similar risk of secondary cancers between RIC and myeloablative conditioning for leukemia or myelodysplastic syndrome patients and a lower risk of secondary cancers after RIC than after myeloablative conditioning for lymphoma patients.[13] Compared with allogeneic HCT, data of secondary solid cancers after autologous HCT are relatively lacking partly because recurrent malignancy occurs frequently after autologous HCT, precluding long-term follow-up to investigate secondary cancers. Some studies found different risks of secondary cancers according to diseases indicated for HCT or recipient genders. The risk of secondary cancers was increased in patients with acute leukemia or chronic myeloid leukemia but not in those with lymphoma or severe aplastic anemia.[25] The risk of skin BCC was higher in patients with hematological malignancies than those with benign diseases.[15] The risk of SCC in the skin and mouth was higher in male recipients than in female recipients.[5,11] The risks of thyroid cancer and melanoma were higher in female recipients than in male recipients.[5,26]

Although the consensus recommendations and this manuscript provide a general overview of risks related to development of secondary solid cancers, a few caveats have to be considered. First, incidence of cancers may differ by race and ethnicity and the practice of cancer screening may differ among countries. As available literature is dominated by studies of Western populations with an overrepresentation of Caucasians, our recommendations would require careful application in other races, ethnicities and regions (for example, risks of gastric cancer in Asian populations). Second, reported incidences of secondary malignancies after HCT rely largely on registry data, which may underestimate the true incidence as transplant centers may not have information on long-term HCT survivors. Hence, we would

emphasize that transplant centers keep in touch with long-term survivors and report events in order to accurately estimate the incidence of secondary cancers. Finally, establishing the appropriate time after transplant to initiate screening for secondary malignancies is not clear, especially given the long latency of certain solid cancers and the steady rise in incidence, which is especially important when considering secondary cancer screening in those who underwent HCT as children. This is demonstrated by a Nordic study consisting of 47 697 patients with childhood cancers followed up to age 79 years.[84] The cumulative risk of a secondary cancer increased substantially at the age of 60–80 years, with a predominance of cancers of the breast, GI, respiratory or genitourinary organs in patients ⩾ 60 years, which was a different distribution compared with secondary cancers seen in younger patients. Certainly, children who undergo HCT will continue to be at increased risk for development of secondary solid cancers over the course of their lifetime, but adopting standard practice guidelines that are applicable in the general adult population may be neither feasible nor reliable in a younger population. Hence, for children it will be even more imperative to rely on clinical signs/symptoms that would prompt early initiation of screening as opposed to only that which would be initiated solely based on age.

## CONCLUSION

In conclusion, we provide our consensus recommendations for secondary solid cancer screening in Table 3. As risks of cancers in the skin, thyroid, oral cavity, esophagus, liver, brain/nervous system, bone and connective tissues are increased after HCT compared with the general population, heightened awareness is warranted for these sites. These recommendations will inform future iterations of screening and preventive practice guidelines for HCT survivors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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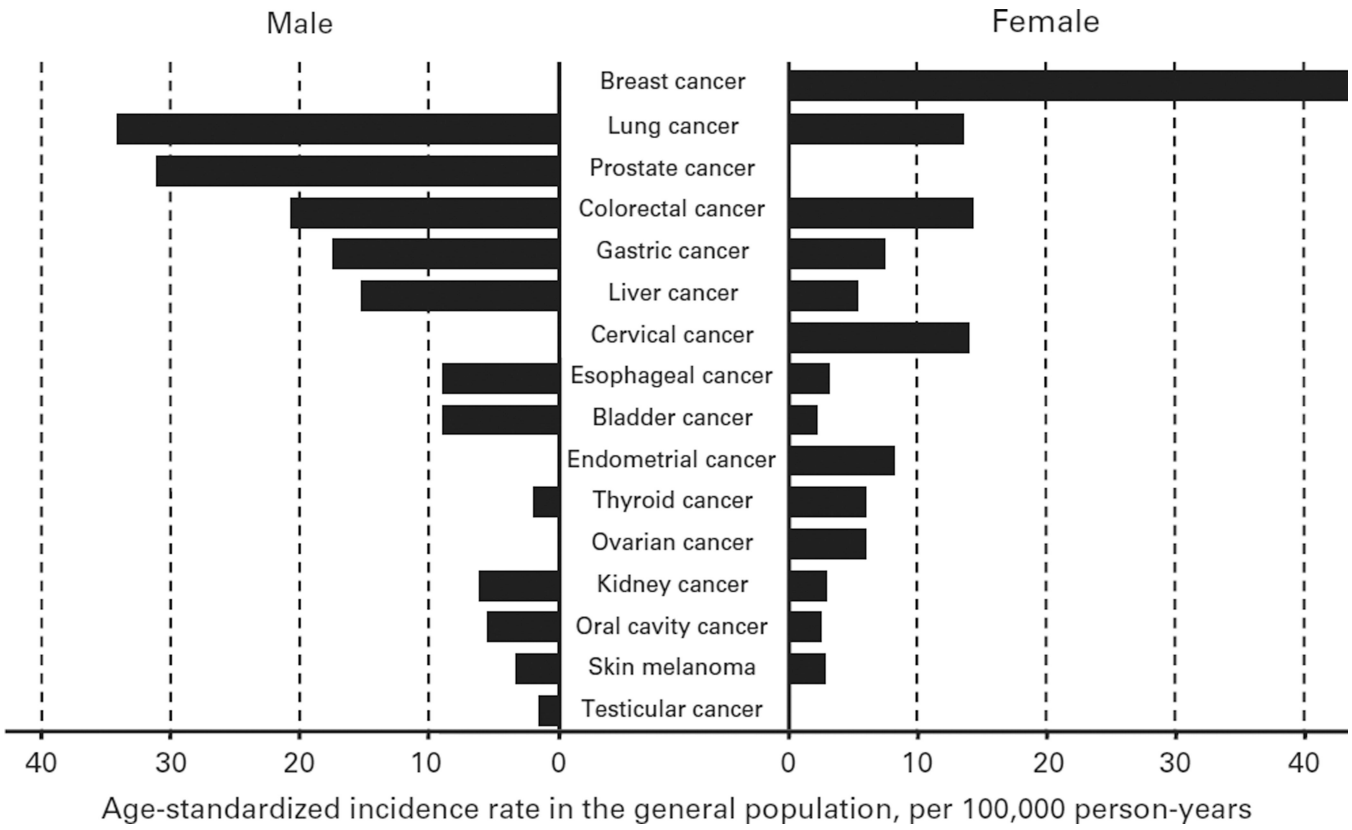


**Figure 1.**

Age-standardized cancer incidence rate in the general population. Data were based on Cancer Incidence in Five Continents Time Trends in 2012.[85]

**Table 1**

Incidence rate of secondary cancers according to time after transplantation

| Site | Incidence rate per 100 000 person-years according to time after transplantation | | | | | SIR | Reference |
|---|---|---|---|---|---|---|---|
| | < 1 years | 1–4 years | 5–9 years | ⩾ 10 years | Total | | |
| Any skin | 16 | 20 | 16 | 28 | 19[a] | **7.2** | 19 |
| Melanoma | 0–21 | 10–31 | 10–30 | 50–58 | 18–76 | **1.4–8.3** | 3, 5, 16, 17 |
| Thyroid | 8–16 | 9–10 | 20–24 | 83–170 | 6–34 | **5.8–6.6**[b] | 5, 16, 19, 32 |
| Female breast | 0–8 | 10–51 | 5–60 | 0–83 | 10–41 | 0.3–2.0 | 3, 5, 16, 17, 19, 31 |
| Lung | 5–57 | 4–40 | 0–48 | 0–150 | 4–50 | 0.7–2.6[c] | 3, 5, 16, 17, 19 |
| Mouth/pharynx | 0 | 10–52 | 76–140 | 130–290 | 32–92 | **7.0–16** | 5, 16, 19 |
| Lip | 0 | 4–30 | 10–15 | 0–33 | 4–18 | **19–27** | 3, 5, 16 |
| Tongue | 0 | 3–20 | 25–30 | 0–170 | 12–18 | **9.3–20** | 3, 5, 16 |
| Oral cavity | 0 | 0 | 30 | 50 | 14–100 | **7.3–17** | 3, 17, 31 |
| Salivary gland | 0 | 0 | 20–36 | 0 | 5–7 | **14–23** | 3, 16 |
| Gum or other | 0 | 3–4 | 10–24 | 33–120 | 6–11 | **5.1–13** | 3, 16 |
| Pharynx | 0 | 0 | 10–15 | 0 | 2 | 1.2–5.4[d] | 3, 5, 16 |
| Esophagus | 0 | 20–43 | 60–90 | 0–150 | 4–59 | **8.5–11**[e] | 3, 5, 19 |
| Stomach | 16 | 23 | 32 | 14 | 23[a] | 0.6 | 19 |
| Colon | 0 | 0–5 | 0–15 | 0–100 | 2–39 | 0.5–1.2[f] | 3, 5, 16, 17, 19 |
| Rectum | 0 | 3–7 | 0 | 17–69 | 4–9 | 0.6–2.2 | 5, 16, 19 |
| Liver | 5–8 | 4–5 | 0–5 | 50–58 | 7–34 | **6.3–28**[b] | 5, 16, 19, 31 |
| Gallbladder | 16 | 7 | 11 | 0 | 9[a] | 2.6 | 19 |
| Pancreas | 0 | 7 | 32 | 14 | 13[a] | 1.9 | 19 |
| Adrenal gland | 29 | 0 | 0 | 0 | 5 | 23.2 | 3 |
| Kidney | 0–29 | 0–3 | 0–5 | 0 | 3–10 | 0.5–2.5 | 3, 17, 19 |
| Bladder | 8–29 | 0–10 | 0 | 0 | 5–6 | 0.8–1.4 | 3, 19 |
| Cervix | 0–29 | 4–13 | 0–15 | 0–17 | 2–67 | 0.7–2.3[g] | 3, 5, 16, 19 |
| Endometrium | 0–16 | 0–3 | 10–12 | 0 | 2–7 | 1.1–1.4 | 5, 16, 19 |
| Ovary | 0 | 3 | 5 | 14 | 4[a] | 0.8 | 19 |

| Site | Incidence rate per 100 000 person-years according to time after transplantation | | | | | SIR | Reference |
|---|---|---|---|---|---|---|---|
| | < 1 years | 1–4 years | 5–9 years | ⩾ 10 years | Total | | |
| Prostate | 0–8 | 0–10 | 0–5 | 14–50 | 4–10 | 0.5–0.7 | 3, 17, 19 |
| Testis | 0 | 0–9 | 0–15 | 0–17 | 4–5 | 0.9–1.2 | 3, 5, 16 |
| Brain/nervous system | 0–16 | 3–20 | 5–84 | 0–55 | 10–38 | **3.8–9.5** | 3, 5, 16, 17, 19 |
| Bone | 0 | 7–13 | 10–12 | 17–58 | 7–11 | **8.5–13** | 3,16 |
| Connective tissue | 5–29 | 5–10 | 15–20 | 0 | 8–14 | **6.5–8.0** | 3, 5, 16 |

Abbreviation: SIR = standardized incidence ratio. The values in bold indicate increased risk of cancer at *P*-values < 0.05.

[a] Report from an Asian population.[19]

[b] Two studies did not show statistically increased risk.[17,19]

[c] One study showed increased risk.[3]

[d] One study showed increased risk after reduced-intensity conditioning (SIR 46.7).[18]

[e] One study did not show statistically increased risk.[5]

[f] One study showed increased risk.[19]

[g] One study observed increased risk (SIR=13).[31] One study showed increased risk after TBI conditioning.[31]

## Table 2

Reported risk factors for individual secondary cancers among HCT population

| Site | Risk factor |
|---|---|
| Skin | Chronic GVHD[19] |
| SCC | Acute GVHD,[20] chronic GVHD,[4,5,20] male,[5] age < 18 years at transplantation[20] |
| BCC | Age < 18 years at transplantation,[20] myeloablative TBI conditioning,[20,22] white,[20,22] chronic GVHD,[19,20] attained age[22] |
| Melanoma | Myeloablative TBI conditioning,[5,16] T-cell depletion,[5] female[5] |
| Thyroid | Radiation conditioning,[5,32] female,[32] age ⩽ 20 years at transplantation,[32] chronic GVHD[32] |
| Oral | Persistent chronic GVHD,[4,5,16,18–20,36–38] cumulative duration of immunosuppressive therapy, including prophylaxis > 24 months,[4] history of localized field irradiation,[5,16] ages < 10 y.o. at the time of transplant,[5] male gender[5,16] |
| Esophagus | Persistent chronic GVHD,[4,19] prolonged immunosuppressive therapy > 24 months[4] |
| Stomach | None reported |
| Colorectal | None reported |
| Liver | TBI-based conditioning, younger age (< 34 years) at HCT, liver cirrhosis, chronic hepatitis C infection[54] |
| Lung | Tobacco use prior to transplantation[3] |
| Breast | History of myeloablative TBI or radiation treatment,[5,74] longer time since HCT,[5,16,39,74] age < 18 years at HCT,[17,39,74] use of growth factors,[3] antithymocyte globulin[5] |
| Cervix | Chronic GVHD with systemic immunosuppressive therapy > 3 years,[83] age > 34 years[31] |
| Endometrial | None reported |
| Ovary | None reported |
| Prostate | None reported |
| Testis | None reported |
| Brain/CNS | None reported, prior history of CNS irradiation may increase risk.[115] |
| Sarcoma | None reported |

Abbreviations: BCC = basal cell carcinoma; CNS = central nervous system; HCT = hematopoietic stem cell transplant; SCC = squamous cell carcinoma.

**Table 3**

Cancer screening guidelines for the general and HCT populations

| Site | American Cancer Society (ACS) | National Comprehensive Cancer Network (NCCN) | Consensus recommendations for post-HCT screening |
|---|---|---|---|
| Skin | General cancer-related checkup for men and women ⩾ 20 years[a] | No specific guidelines | Routine skin examination in all transplant survivors, particularly for patients who had myeloablative TBI, HCT at ages < 18 years or GVHD |
| Thyroid | General cancer-related checkup for men and women ⩾ 20 years[a] | No specific guidelines | Annual physical examination. Heightened awareness for patients aged ⩽ 20 years at HCT, female patients, those receiving TBI-containing conditioning regimens and those who develop chronic GVHD |
| Oropharyngeal | General cancer-related checkup for men and women ⩾ 20 years[a] | No specific guidelines | Screening every 12 months. Screening every 6 months may be considered for patients with risk factors summarized in Table 2 |
| Esophagus | No specific guidelines | Surveillance upper endoscopies with biopsies for patients with certain hereditary predisposition cancer syndromes (for example, Familial Barrett's, Bloom syndrome and Fanconi anemia) | Upper GI endoscopy for patients who have persistent GERD symptoms or dysphagia. Endoscopic screening may be considered for patients with prolonged immunosuppressive treatment (> 24 months) for chronic GVHD |
| Stomach | No specific guidelines | No specific guidelines | Follow guidelines for the general population |
| Colorectal | Starting at ⩾ 50 years for average risk. Sigmoidoscopy: every 5 years. Colonoscopy: every 10 years. Barium enema: every 5 years. CT colonography: every 5 years. More frequent screening guidelines available for those at increased risk | Starting at ⩾ 50 years for those with average risk. Sigmoidoscopy: every 5 years with or without stool testing at year 3.[b] Colonoscopy: every 10 years.[c] Guaiac-based or immunochemical-based stool testing (multitarget stool DNA testing: Cologuard[52]): annually.[d] More frequent screening guidelines available for those at increased risk | Follow guidelines for the general population |
| Liver | No screening recommendations for those at low risk. For those at risk for hepatocellular carcinoma, including those with cirrhosis or chronic hepatitis B, consider alfa-fetoprotein (AFP) and ultrasound every 6–12 months | No screening recommendations for those at low risk, without cirrhosis or chronic hepatitis. For those at risk for hepatocellular carcinoma, including those with cirrhosis or chronic hepatitis B, consider AFP and ultrasound every 6–12 months | Follow guidelines for the general populations. Consider liver ultrasound every 6 months in HBV seropositive recipients or in patients with history of cirrhosis |
| Lung | Consider screening in patients aged 55–74 years who have at least a 30 pack-year smoking history and who currently smoke | Screening with low-dose CT recommended for two high-risk groups: | Follow guidelines for the general population. Encourage smoking cessation. |

| Site | American Cancer Society (ACS) | National Comprehensive Cancer Network (NCCN) | Consensus recommendations for post-HCT screening |
|---|---|---|---|
| | or have quit within the past 15 years.<br>Discuss risk/benefits prior to any screening for lung cancer with low-dose CT scan.<br>Encourage smoking cessation | • > 55 years and ⩾ 30 pack-year smoking history (those who quit smoking > 15 years ago are excluded)<br>• ⩾ 50 and have ⩾ 20 pack-year smoking history with one additional risk factor (for example, radon, asbestos, family history of lung cancer, second-hand smoke exposure) | Consider screening if there are additional risk factors (for example, smoking history) |
| Breast | Average risk:<br>• age 20–40 years:<br>- Clinical breast exam every 3 years<br>• age > 40 years:<br>- Annual mammography and clinical breast exam.<br>High risk,[e] including women treated for Hodgkin lymphoma:<br>• Annual mammogram and MRI starting at age 30 years | Breast awareness for all risk groups which can be attained by periodic, consistent breast self-exams.<br>Average risk:<br>• age 25–40 years:<br>- Clinical breast exam every 1–3 years<br>• age > 40 years<br>- Annual clinical breast exam<br>- Annual mammogram<br>Increased risk,[g] including prior thoracic radiation therapy between 10 and 30 years (for example, mantle):<br>• age < 25 years:<br>- Annual clinical breast exam from 8 to 10 years after radiation therapy<br>• age ⩾ 25 years:<br>- Annual mammogram + clinical breast exam every 6–12 months from 8 to 10 years after radiation or age 40 years, whichever comes first + annual breast MRI | Breast awareness for all patients<br>Average risk:<br>• age 20–40 years:<br>- Clinical breast exam every 1–3 years<br>• age > 40 years:<br>- Annual clinical breast exam<br>- Annual mammogram<br>Prior radiation therapy or TBI:<br>• age 25 years or 8 years after radiation therapy/TBI, whichever comes first, but no later than age 40 years:<br>- Annual clinical breast exam<br>- Annual mammogram<br>- Annual breast MRI |
| Cervix | Pap test is recommended for women aged | Pap test is recommended for women aged | Annual Pap test and HPV DNA test |

| Site | American Cancer Society (ACS) | National Comprehensive Cancer Network (NCCN) | Consensus recommendations for post-HCT screening |
|---|---|---|---|
| | 21–29 years every 3 years. Both Pap test and HPV DNA test are recommended for women aged 30–65 years every 5 years. Annual screening is recommended for immunocompromised women | 21–29 years every 3 years. Both Pap test and HPV DNA test are recommended for women aged 30–65 years every 5 years. Annual screening is recommended for immunocompromised women | |
| Endometrial | Information about the risks (for example, replacement of estrogen alone) and symptoms (unexpected bleeding or spotting) of endometrial cancers should be provided to women at average risk at the time of menopause | No specific guidelines | Follow guidelines for the general population |
| Ovary | No recommended specific screening guidelines in average-risk women. General cancer-related checkup for men and women ⩾ 20 years.[a] In those with a hereditary bilateral ovarian cancer syndrome (*BRCA1/2* mutation or history of Lynch syndrome), do annual pelvic exam, CA-125 and transvaginal ultrasounds until childbearing is complete or until age 35 years, at which prophylactic bilateral oophorectomy is recommended[f] | No recommended specific screening guidelines in average-risk women. General cancer-related checkup for men and women ⩾ 20 years.[a] In those with a hereditary bilateral ovarian cancer syndrome (*BRCA1/2* mutation or history), consider screening every 6 months with CA-125 and transvaginal ultrasound starting at age 30 years or 5–10 years earlier than the earliest diagnosis of ovarian cancer in the family[f] | Follow guidelines for the general population |
| Prostate | PSA ± digital rectal examination after informed decision-making | PSA ± digital rectal examination after informed decision-making | Follow guidelines for the general population |
| Testis | General cancer-related checkup for men ⩾ 20 years[a] | No specific guidelines | Follow guidelines for the general population |
| Brain/CNS | No specific guidelines | No specific guidelines | No specific guidelines |
| Sarcoma | No specific guidelines | No specific guidelines | No specific guidelines |

Abbreviations: CNS = central nervous system; CT = computed tomographic; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HBV = hepatitis B virus; HCT = hematopoietic cell transplantation; HPV = human papillomavirus; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

[a] On the occasion of a periodic health examination, the cancer-related checkup should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity and skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, risk factors, sexual practices and environmental and occupational exposures.[14]

[b] Colonoscopy is recommended if polyps with higher malignant potential are identified.

[c] Repeat more frequently if polyps with higher malignant potential are identified.

[d] Colonoscopy is recommended if stool tests are positive.

[e] Women with a known *BRCA* mutation, women who are untested but have a first-degree relative with a *BRCA* mutation or women with an approximately 20–25% or greater lifetime risk of breast cancer based upon specialized breast cancer risk estimation models capable of pedigree analysis of first- and second-degree relatives on both the maternal and paternal side.[117]

[f] In women with a known hereditary breast ovarian cancer syndrome, such as mutations on *BRCA1* and *BRCA2*, site-specific ovarian cancer syndrome and hereditary nonpolyposis colon cancer, should receive annual pelvic exam, CA-125 determinations and transvaginal ultrasound until childbearing is completed or until age 35 years, at which time prophylactic bilateral oophorectomy is recommended.

[g] Prior history of breast cancer: annual mammogram + clinical breast exam every 4–6 months for the first 5 years after primary therapy and annually thereafter. Women ⩾ 35 years with 5-year risk of invasive breast cancer ⩾ 1.7%, with lobular carcinoma *in situ* or with atypical ductal or lobular hyperplasia: annual mammogram + clinical breast exam every 6–12 months. Women who have a lifetime risk > 20% according to family history: annual mammogram + clinical breast exam every 6–12 months from the age of 30 years + annual breast MRI from the age of 30 years. Prior thoracic radiation between ages 10 and 30 years (for example, mantle): age < 25 years, annual clinical breast exam from 8 to 10 years after radiation; age ⩾ 25 years, annual mammogram + clinical breast exam every 6–12 months from 8 to 10 years after radiation or age 40 years, whichever comes first + annual breast MRI.