Second Malignancies Among Elderly Survivors of Cancer

ARI M. VANDERWALDE,^{a,b} ARTI HURRIA^b

^aDepartment of Hematology and Hematopoietic Cell Transplantation and ^bDepartment of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, California, USA

Key Words. Neoplasms • Second primary • Geriatrics • Antineoplastic agents • Neoplasms • Radiation induced • Lymphoma • Carcinoma

Disclosures: Ari M. VanderWalde: Amgen (E, OI); Arti Hurria: GTX (C/A); GlaxoSmithKline, Celgene (prior Abraxis) (R/F).

(C/A), consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder

ABSTRACT

The U.S. population is aging, life expectancy is increasing, and cancer is a disease associated with aging. Advances in screening and therapeutics have led to a growing number of cancer survivors who are at risk for the development of secondary malignancies. Although the risks for the development of second malignancies following a first diagnosis of cancer are well described for survivors of childhood malignancies, there are fewer data for malignancies common in older adults. With the aging of the U.S. population, and with improving survival statistics in many adult malignancies, there is an increasing need to identify those second malignancies that might develop in

the older adult survivor of cancer. In this paper, we describe the types and rates of second malignancies following cancers commonly seen in older adults and review the literature on these malignancies. Comparisons are made between older and younger adults with regard to the risks for developing treatment-related cancers with different modalities. Recommendations for early detection of second malignancies are summarized, though there remains an unmet need for evidence-based guidelines for screening for second malignancies in the older adult in particular. *The Oncologist* 2011;16:1572–1581

INTRODUCTION

The number of cases of cancer in the U.S. is increasing, with >1.5 million estimated new cases in 2010, compared with 1.3 million cases estimated in 2005 [1]. This is a result, for the most part, of the aging of the population. The absolute number of cases diagnosed in those individuals aged ≥65 years is expected to double by 2030 [2]. Approximately 21% of men and 15% of women will develop cancer at some time between their 50th and 70th birthdays [3]. Both the increase in number of cases and the increase in survival rates are expected to contribute to a growing number of cancer survivors in the coming decades.

It is well established that the risk for a new malignancy is higher in those who have already survived one or more cancers than in the general population [4–7]. Second cancers make up as many as 14% of all incident malignancies in the U.S. [5, 7, 8]. Adult survivors of childhood cancer have up to six times the life-

time risk of developing a new malignancy than the general population [9, 10]. However, the overall frequency of second cancers is highest among those diagnosed with their first cancer at the age of 50–69 years (16.4% by 25 years of follow-up) [10].

Although adults who develop a first cancer at age ≥70 years have not been shown to be at higher risk, on average, than the general population for the development of a new cancer, it is thought that the lack of a higher risk seen among adults with a first diagnosis at age ≥70 years may be a result of underreporting of second malignancies in older patients, who may be suboptimally followed after first diagnosis [10, 11]. Additional possible reasons for equivalent or lower rates of second cancers in older adults may include a lesser susceptibility to the mutagenic effect of radiation, a lower likelihood of association with a genetic cancer syndrome, more competing causes of mortality, generally fewer remaining years to develop a second

Correspondence: Ari VanderWalde, M.D., M.P.H., Department of Hematology and Hematopoietic Cell Transplantation and Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, California 91010, USA. Telephone: 626-471-9200; Fax: 626-301-8233; e-mail: arivanderw@gmail.com Received June 28, 2011; accepted for publication August 29, 2011; first published online in *The Oncologist Express* on October 31, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0214>

cancer, and more indolent sporadic cancers than in the younger adult population requiring less aggressive treatment. Another possibility is that age is occasionally a surrogate for era of treatment. Older adults who are long-term survivors of cancer were generally treated in an earlier time period with different survival rates, which could affect perceived second malignancy rates. Parsing out to what extent these factors play a role has rarely been done and makes it difficult to examine the impact of second malignancies among older adults.

Genetic cancer syndromes, shared risk factors, and treatment of the first cancer may predispose to second malignancies [12]. Below we describe second malignancies that are common among older adults.

OVERVIEW OF TREATMENT-RELATED SECOND MALIGNANCIES IN OLDER ADULTS

Second malignancies may be related to prior chemotherapy, radiation therapy, hormonal therapy, or a combination of effects of more than one of these modalities. For a patient to be susceptible to a second malignancy, that patient needs to survive long enough following diagnosis and treatment of the first cancer for new carcinogenesis to take place. Hence, second malignancies are best reported for cancers and/or treatment modalities that have high long-term survivorship numbers and rates, such as breast and prostate cancers. Conversely, patients with aggressive cancers such as lung cancer have poor survival rates, leading to a small relative number of survivors of lung cancer among the population of cancer survivors, despite the high incidence of lung cancer in the population [13]. Furthermore, less common cancers, such as Hodgkin's lymphoma (HL) and testicular cancer, are associated with the development of second malignancies largely because of the high curability of these diseases and relatively young age of many patients at diagnosis, and hence the large number of person-years of follow-up [8].

Solid tumors, as a whole, are more common sequelae of cancer treatment than hematologic malignancies. There are some cancers that are particularly prone to develop after certain types of primary cancer. Examples of these include breast cancer following HL, bladder cancer following prostate cancer, and sarcoma following breast cancer. An abridged list of new malignancies associated with specific primary cancers can be seen in Table 1 [14–45].

Importantly, treatment-related second malignancies are often more aggressive and less responsive to treatment than malignancies not related to treatment, even in older adults. For example, the median survival time of patients with therapy-related acute myeloid leukemia (AML) is only 8–10 months, with a 5-year survival rate <10% [46]. This is compared with a 5-year relative survival rate of 23% in all adult patients with AML [47].

BREAST CANCER SURVIVORS

In survivors of a first breast cancer, the risk for a subsequent contralateral breast cancer is approximately two- to fivefold greater [15, 16]. Some of the greater risk is a result of pre-existing risk factors, and radiation therapy may also contribute,

though results of trials are conflicting. In a study by Boice et al. [15], the overall relative risk (RR) for contralateral breast cancer was not greater in women treated with radiation therapy than in women with breast cancer who did not receive radiation. However, in women aged <45 years at the time of radiation therapy, the RR was significantly higher (RR, 1.59; 95% confidence interval [CI], 1.07–2.36), consistent with the hypothesis that older women are not as likely to develop radiation-associated breast cancer [15]. In a large Danish case-control study, there was no significant difference in the risk for contralateral breast cancer in women who were irradiated versus those who were not, regardless of age at treatment, and the locations of second cancers were evenly distributed across the breast. Areas of the contralateral breast near the radiation field would be more likely to develop a tumor if there had been a true radiation effect [16]. In an Early Breast Cancer Trialists' Collaborative Group report, which combined 42,000 women from 78 clinical trials and reported on 15-year survival outcomes, there was a significantly higher risk for contralateral breast cancer (rate ratio, 1.18; standard error, 0.06; $p = .002$) in those who were irradiated, even among women aged ≥ 50 years at the time of randomization [17]. And in a study by Gao et al. [18], women aged >55 years at the time of initial diagnosis of breast cancer had a significantly higher risk for developing contralateral breast cancer than women aged 45–55 years (RR, 1.15; $p = .04$). Additionally, the risk associated with radiation therapy was apparent in both younger (age <45 years) and older (age ≥ 55 years) women, with women aged ≥ 55 years 15% more likely to develop contralateral breast cancer if they received radiation than if they did not [18].

Other solid malignancies are also more likely following radiation treatment for breast cancer. Women who received radiation treatment for breast cancer in one population-based study were found to have a significantly greater risk for developing lung cancer after 10 years (RR, 1.62; 95% CI, 1.05–2.54) and a higher risk for esophageal cancer after 15 years (RR, 2.19; 95% CI, 1.10–4.62) than those who did not receive radiation, although no breakdown of risk by age was performed [23]. The risk for second cancers appears higher with radiation given postmastectomy, wherein the irradiated field is more extensive, where radiation given postlumpectomy has less certain effects [48]. Sarcoma risk is higher in survivors of breast cancer, though the overall risk remains low, and these cancers appear to be related to prior radiation because the tumors occur most often in the irradiated field [21, 22].

In survivors of breast cancer, alkylating agents have been associated with a higher risk for subsequent leukemia. In one study, those who received alkylating agents had a 10-fold higher risk for subsequent AML than those who received neither chemotherapy nor radiation [19]. The dose intensity of alkylating agents, specifically cyclophosphamide, is an independent determinant of future hematologic malignancy risk. In a study of patients with breast cancer that combined results from multiple National Surgical Adjuvant Breast and Bowel Project (NSABP) studies, a dose-intense arm of cyclophosphamide (2,400 mg/m² every 3 weeks for either two or four cycles) when combined with standard-dose doxorubicin

Table 1. Primary malignancies and association with second cancers [14]

Primary cancers	Associated second cancers	Probable precipitating factors
Breast cancer	Contralateral breast Leukemia Sarcoma Lung Uterus Melanoma Ovary	Genetic predisposition, chest irradiation [15–17], shared risk factors (late and low parity, high BMI) [18] Alkylating agents, anthracyclines, irradiation [19, 20] Chest/axillary irradiation [21, 22] Chest irradiation [23] Tamoxifen [24] Genetic predisposition, possible shared hormonal mechanisms, chemotherapy [25] Genetic predisposition, shared risk factors [26]
Ovarian cancer	Breast Colon Biliary tract Ocular melanoma Sarcoma Bladder Acute leukemia	Genetic factors [27, 28], nutritional and hormonal influences [29] Abdominal–pelvic irradiation, cytotoxic chemotherapy [30] Alkylating agents, platinum compounds [31, 32]
Prostate cancer	Bladder Rectum Thyroid Small bowel (carcinoid)	Prostate irradiation [33–35] Possible shared hormonal risk factors [36, 37]
Colorectal cancer	Second primary colorectal Small intestine Stomach Uterus Ovary Cervix	Genetic susceptibility, shared risk factors [38, 39] Shared lifestyle factors (diet, obesity, physical inactivity); genetic susceptibility (cancer syndromes) [39], rectal irradiation [40]
HL	Leukemia (AML) Non-HL Lung Breast Thyroid Salivary glands Uterus GI tract (stomach, esophagus, small bowel, colon/rectum)	Alkylating agents [41] Cellular immune dysfunction persisting after HL, misclassification [42] Alkylating agents, radiation [43] Chest wall irradiation before the age of 40 yrs [44] Neck irradiation [42, 45] Pelvic irradiation [42, 45] Abdominal irradiation [42, 45]

Abbreviations: AML, acute myeloid leukemia; BMI, body mass index; GI, gastrointestinal; HL, Hodgkin's lymphoma.

(60 mg/m²) was associated with a 5-year risk for the development of AML of 1.01% (95% CI, 0.63%–1.62%), compared with a risk of 0.21% in those who received standard dosing of each agent (cyclophosphamide, 600 mg/m²; doxorubicin, 60 mg/m²; every 21 days for four cycles) [20].

Older age may predispose to a higher risk for hematologic malignancy following treatment for breast cancer. In a study by Patt et al. [49], women aged ≥66 years at the time of a breast cancer diagnosis showed a 10-year absolute risk for developing AML after adjuvant chemotherapy of 1.8%, versus a 1.2% 10-year risk if they did not receive chemotherapy (hazard

ratio, 1.53; 95% CI, 1.14–2.06). Myeloid growth factors are increasingly being used as supportive medications in the treatment of many primary malignancies. Whether or not these factors have a contributory role to the development of secondary myeloid malignancies remains a topic of some debate. Hershman et al. [50] recently performed a population-based study of 5,510 women aged ≥65 years treated with chemotherapy for breast cancer. Those authors found that the use of G-CSF was associated with a risk for subsequent myelodysplastic syndrome (MDS) or AML that was double that of those who did not receive the growth factor [50]. However, Patt et al. [49]

found that G-CSF use within the first year of diagnosis did not convey a greater risk for subsequent AML in older women. In addition, in a randomized trial of dose-dense chemotherapy (doxorubicin and cyclophosphamide followed by docetaxel [AC-T] or doxorubicin, docetaxel, and cyclophosphamide [ATC] given every 2 weeks with G-CSF support) in comparison with conventional chemotherapy (the same doses of AC-T or ATC given every 3 weeks without G-CSF support), there was no difference in the risk for AML or MDS after a median follow-up of 36 months [51].

Endocrine therapy with tamoxifen for breast cancer has a protective effect against contralateral breast cancer, with a 32% lower 5-year risk for patients with hormone-positive or unknown hormone status cancers, as calculated in one meta-analysis [52]. However, tamoxifen conveys a higher risk for subsequent endometrial cancer, as confirmed in the NSABP P-1 study (RR for tamoxifen versus placebo, 2.53; 95% CI, 1.35–4.97). Those authors noted that the greater risk occurred predominantly in women aged ≥ 50 years [24]. There has been debate over whether tamoxifen-related endometrial cancers are more or less aggressive than those unrelated to tamoxifen [8]. In a study comparing women with breast cancer who developed endometrial cancer with or without prior tamoxifen use, Saadat et al. [53] found that, although tamoxifen use was associated with more aggressive tissue subtypes, there was no difference in histologic grade or stage, and there was no difference in the endometrial cancer-related survival outcome because most cases were amenable to surgery. This finding mirrored the result in the NSABP P-1 study [24].

There are limitations in interpreting the relevance of the aforementioned studies to older adults because there is heterogeneity in how patient ages are reported, and multivariate analyses taking into account age and other potential risk factors are rarely possible with small sample sizes. Table 2 provides a summary of how studies evaluating second malignancies in breast cancer may be applied to older adult populations.

OVARIAN CANCER SURVIVORS

Most ovarian cancer patients present with relatively late stage disease, and thus the overall 5-year survival rate is only 46% [1]. However, in women who survive ≥ 5 years following ovarian cancer, the risk for developing a second malignancy is high, with a 31% higher risk than in the general population [54]. The cancers most often seen after ovarian cancer are breast, colorectal, and bladder cancer and leukemia [55]. Breast and colon cancer are most often seen after ovarian cancer in younger women, largely because of the prevalence of genetic syndromes, such as *BRCA* mutation and hereditary nonpolyposis colorectal cancer, that predispose to these tumors and ovarian cancer [27, 29, 55]. Some rare tumors have also been associated with ovarian cancer, including biliary tract cancer and both the ocular and skin variants of malignant melanoma, and are also thought to be a result of genetic syndromes such as *BRCA-2* mutation [26, 54, 56].

However, an excess risk for second malignancies has been

seen in women diagnosed with primary cancer of the ovary at age 50–69 years as well, and these second cancers appear more likely to be a result of treatment. In particular, the risks for bladder, soft tissue, and bone cancers are substantially higher in women who received radiation, and these risks become most apparent ≥ 10 years following the initial radiation therapy [54, 57].

The risk with chemotherapy in the development of second cancers is also apparent across all age groups. The risk for the subsequent development of both AML and acute lymphocytic leukemia have been shown to be significantly higher in women following a primary diagnosis of ovarian cancer, even in women aged ≥ 70 years at the time of their primary diagnosis and in women who did not receive radiation [54]. Historically, this greater risk was attributed to alkylating chemotherapeutic agents, such as melphalan and chlorambucil [32], but these agents have largely fallen out of use in the treatment of ovarian cancer. More recently, platinum-based chemotherapy, which is routinely used in ovarian cancer treatment, has also been associated with a higher late risk for leukemia. This was demonstrated in a large registry case-control study of women who developed leukemia after ovarian cancer. Of note, 71% of patients who developed leukemia were aged ≥ 60 years at the time of their ovarian cancer diagnosis, whereas 29% were aged ≥ 70 years [31].

PROSTATE CANCER SURVIVORS

There is an elevated risk for a second cancer after pelvic irradiation for prostate cancer, but the attributable magnitude of the radiation-related risk remains a topic of debate. In a population-based study using Surveillance, Epidemiology, and End Results (SEER) data, Neugut et al. [33] found that there was a slightly, but statistically significant, higher risk for bladder cancer among prostate cancer survivors treated with radiotherapy (RR, 1.5; 95% CI, 1.1–2.0), but there was no difference in the risk for rectal cancer or hematologic malignancies. The median age at diagnosis of prostate cancer was 69.2 years in the radiation group and 73.2 years in the unirradiated group [33]. Chrouser et al. [34], in a retrospective review of the Mayo Clinic Cancer Registry, did not find a higher risk for bladder cancer after radiation for prostate cancer (mean age at diagnosis of prostate cancer, 70.5 years). However, in men who received adjuvant radiation after radical prostatectomy, there was a statistically significant greater risk (RR, 5.01; 95% CI, 1.04–14.61), likely because of more of the bladder being exposed to radiation in the postoperative setting [34]. In a population-based study using SEER data, Brenner et al. [35] compared men with prostate cancer treated with radiation therapy alone with men treated using surgery alone. They found that those who received external-beam radiation had a slightly, but significantly, higher risk for solid tumors on the whole, with the excess risk largely a result of more cases of bladder, rectum, lung, and connective tissue cancers. The men studied had a mean age of 71 years at the time of diagnosis of prostate cancer, and a mean age of 75.3–77.0 years at the time of diagnosis of the second malignancy [35]. Moon et al. [58], using a more recent SEER database search, found that there was a sig-

Table 2. Second malignancies in patients with breast cancer: Relevance to older adults

Study	Second malignancy studied	Age distribution	Setting	Population of interest compared	Length of follow-up	Conclusion	Relevance to older patients
Boice et al. (1992) [15]	Contralateral breast cancer	At time of first cancer: median age, 51.7 yrs; 38% age ≥ 55	Case-control state registry trial; 655 patients with second cancer, 1,197 controls; all patients had primary tumors in 1935–1982	Incidence of CBC in women with breast cancer who received radiation versus women with breast cancer who did not	NA (average time to CBC, 10–14 yrs)	Women age ≤ 45 yrs have higher risk for CBC following radiation, but women aged ≥ 45 yrs do not	Radiation treatment for breast cancer does not appear to put older adults at a higher risk for developing CBC
EBCTCG (2005) [17]	CBC	~4,000 (~10%) aged ≥ 70 yrs	Meta-analysis of randomized trials; 42,000 patients from 78 trials	Incidence of CBC in women with breast cancer who received radiation versus women with breast cancer who did not receive radiation	NR	Higher risk for development of CBC in those who received radiation therapy (RR, 1.18; $p = .002$)	In patients aged ≥ 50 yrs at time of diagnosis, there is a higher risk for developing CBC associated with radiation (RR, 1.25; $p = .002$); however, no further age stratification was reported
Gao et al. (2003) [18]	CBC	63% age ≥ 55 yrs	Retrospective cohort SEER registry trial; 134,501 women surviving ≥ 3 mos from diagnosis	Incidence of CBC in women aged ≥ 55 yrs versus women aged < 55 yrs	Patients with CBC: mean, 82.1 mos; patients without CBC: mean, 68.2 mos	Age > 55 yrs associated with higher risk for development of CBC (RR, 1.15; 95% CI, 1.08–1.22)	Patients aged ≥ 55 yrs are more likely than younger patients to develop CBC; radiation therapy associated with higher risk in this age group as well; however, no further age stratification was reported
Kirova et al. (2005) [21]	Sarcoma	Age at breast cancer diagnosis: total population, 56.2 yrs; patients who ultimately developed sarcoma, 57 yrs (range, 36–74 yrs); age at sarcoma diagnosis, 63 yrs (41% aged ≥ 70 yrs)	Retrospective single-institute chart review; 35 sarcomas among 16,705 patients treated for breast cancer in 1981–1997	Incidence of sarcoma in patients with breast cancer	9.3 yrs (range, 1–22.4 yrs); latency period range, 3–20.3 yrs	Rates of sarcoma development after RT for breast cancer are low; however, survival rates after diagnosis of sarcoma as SMN are also lower than might be otherwise expected (5-yr survival rate, 36% versus $> 55\%$ in sporadic cases [SEER])	n of cases too small to compare incidence of sarcoma in older versus younger adults; however, age at diagnosis of all at-risk patients similar to age of patients who went on to develop sarcoma, leading to inference that sarcoma is not more common in patients with a younger age at diagnosis
Smith et al. (2003) [20]	AML/MDS	Mean age at diagnosis, 49 yrs; age < 50 yrs, 54%; no ranges reported	Retrospective review of 6 NSABP trials; 43 cases of AML/MDS in 8,563 patients followed up after regimens containing AC	Incidence of AML/MDS in patients treated with AC for breast cancer	Mean, 7.2 yrs (61,810 patient-years/8,563 patients)	Age at breast cancer diagnosis ≥ 50 yrs have higher risk for AML/MDS than those aged < 50 yrs at diagnosis (RR, 2.37; $p = .008$)	5% higher incidence of AML per yr of age at diagnosis; however, likely very few patients aged ≥ 70 yrs
Patt et al. (2007) [49]	AML, adjuvant chemotherapy	Median age, 75.6 yrs (range, 66–104 yrs)	Retrospective SEER–Medicare study; 64,715 women with early-stage breast cancer in 1992–2002	Rates of AML in older women who received adjuvant chemotherapy for breast CA versus those who did not	54.8 mos (range, 66–144 mos)	Adjuvant chemotherapy associated with higher risk for AML in older adults (HR, 1.53; 95% CI, 1.14–2.06)	Older adults may have higher risk for developing AML after adjuvant chemotherapy; absolute 10-yr risk for AML, 1.8% versus 1.2% for chemotherapy versus no chemotherapy

Abbreviations: AC, doxorubicin and cyclophosphamide; AML, acute myeloid leukemia; CBC, contralateral breast cancer; CI, confidence interval; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; HR, hazard ratio; MDS, myelodysplastic syndrome; NA, not applicable; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; RR, relative risk; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results; SMN, second malignancy neoplasm.

nificantly higher risk for developing second cancers at several sites following external-beam radiation for prostate cancer, including the bladder, rectum, colon, brain, and lung. The greater risk at sites distant from the radiation field was thought to be a result of radiation scatter. However, the risk difference was small, with odds ratios of 1.25 for lung to 1.85 for colon. Age at diagnosis was not associated with any difference in the odds ratio on multivariate analysis. Additionally, men who received radiation in the form of radioactive isotopes or implants did not have a higher risk for second cancers [58].

COLORECTAL CANCER SURVIVORS

In a large SEER study, it was found that adults diagnosed with colon cancer at age ≥ 70 years did not have a higher risk for developing new malignancies as a whole when compared with an age-matched general population [38]. This is in contrast to younger adults, who had higher absolute risks for second malignancies that were higher the younger the age at diagnosis. On the other hand, adults aged > 70 years did have a significantly higher risk than the age-matched general population of developing cancer of the small intestine (observed/expected ratio [O/E], 2.42) or rectum (O/E, 1.2) or a new colon primary

(O/E, 1.33) [38]. Adults diagnosed with colon cancer at age 60–69 years additionally had elevated risks for developing new cancers of the esophagus, stomach, kidney, and oropharynx [38]. The higher risk for digestive system cancer following colon cancer is not likely a result of radiation treatment because colon cancer is rarely treated with radiation. The most likely cause for the higher risk for digestive cancer is shared risk factors, such as obesity, diet, and low activity levels [39].

Rectal cancer was also not associated with higher rates of most second malignancies in older adults in the largest SEER study done to date. Although adults diagnosed with rectal cancer at age 50–69 years had higher risks for lung, kidney, and digestive system cancers, adults aged >70 years only had a higher risk for colon cancer, and this excess risk was lower in magnitude than in younger adults (O/E, 1.58 versus 1.29 for age 50–69 years versus age >70 years) [38]. However, patients with rectal cancer who received radiation had higher risks for bladder, uterine, and lung cancers, particularly ≥ 10 years after the initial cancer diagnosis [38]. Studies using other cancer registries have shown greater risks for prostate cancer following a diagnosis of rectal cancer as well [59, 60]. Radiation is a less likely cause because the effect was seen prior to the routine adoption of radiation for rectal cancer. The higher risk is rather thought to be a result of greater cancer surveillance, causing discovery of cancers that might otherwise have remained occult [60].

SURVIVORS OF HL

In a retrospective analysis, second malignancies were the most common cause of death by 15 years after treatment in long-term survivors of HL [61]. At a median of 12 years, survivors of HL had a 4.6-fold higher risk for developing a new cancer than in the general population, and an excess risk of 1% per year [8]. Although HL is most common in younger adults, it is often overlooked that there is a bimodal age distribution, with a peak incidence again emerging at ages >55 years. A review of 1,319 consecutive patients with HL showed that patients aged <20 years at diagnosis had an RR of 10.7 for developing a second cancer (95% CI, 7.8–14.4), compared with those aged ≥ 50 years at diagnosis, who only had an RR of 2.4 (95% CI, 1.6–3.4) [62]. Adults diagnosed with HL at age >60 years have a higher risk for developing a second malignancy than the age-matched general population, particularly, lung cancer and leukemia [42].

In all age groups, solid tumors account for $\sim 75\%$ of second malignancies following HL [62]. In one large registry case-control study of patients treated with alkylating agents for HL, there was a higher risk for lung cancer even from chemotherapy alone, with an RR of 4.2 (95% CI, 2.1–8.8). Of note, 51% of patients who went on to develop lung cancer were aged >50 years at the time of the HL diagnosis, with 20% aged >60 years. Patients aged ≥ 55 years at diagnosis, in particular, had a stronger association of lung cancer with alkylating chemotherapy as well as radiation (RR for alkylating agents, 6.5; 95% CI, 2.3–22; RR for radiation ≥ 5 Gy, 10.2; 95% CI, 2.9–43) [43].

Radiation-associated solid tumors after HL are well stud-

ied. These tend to develop 5–9 years after initial exposure, with a higher risk persisting for ≥ 30 years [45]. Tumors usually develop within or around the edges of prior radiation fields [8]. There is a significant radiation dose–response relationship in the development of lung and breast cancer after radiation for HL [43, 44].

Development of breast cancer is relatively common after chest or mediastinal radiation therapy. The risk in young female survivors of HL also persists into older age. In a study on subsequent malignancies after childhood HL (median age at diagnosis, 11 years), the 30-year cumulative incidence of female breast cancer was 16.9% (95% CI, 9.4%–24.5%), which represented a >50-fold higher risk over the age-matched general population [63]. Other studies have demonstrated an absolute 20- to 25-year risk of 4.2%–34% [64]. However, the risk for breast cancer decreases with increasing age at the time of radiation, because of age-related lesser susceptibility of tissues to the effects of radiation. Women diagnosed with HL at age >50 years have much lower rates of second breast or thyroid cancer than younger survivors of HL [7].

Alkylating agents tend to *decrease* the risk for subsequent breast neoplasms after HL. In a large, international, case-control study, patients who received both chemotherapy and radiation therapy had only about half the risk for later developing breast cancer of those who received radiation alone [44]. The lower risk is likely associated with the high frequency of premature menopause after receiving alkylating agents, implying that ovarian hormones play a role in breast tumorigenesis [44].

Hematologic malignancies such as MDS and AML occur in survivors of HL in particular. One study of 1,939 patients with a history of HL showed a 20-year risk for the development of MDS or AML of 6% in a predominantly younger cohort (11.6% of patients aged ≥ 60 years) [41]. This high risk is likely primarily a result of the high cumulative doses of alkylating agents used in most regimens until recently [41]. Although not demonstrated as such in HL patients, data from breast cancer suggest that the risk for AML or MDS increases with age at initial treatment with alkylating agents, which could make the risk seen in HL even higher in patients diagnosed at older ages. With the replacement of alkylating regimens by other regimens, however, the leukemogenic risk associated with HL treatment has been substantially reduced, though the effect on risk in older adults has not been well studied [65].

SURVIVORS OF NON-HL

The effect of radiation on second malignancies in non-HL (NHL) is not as well defined as in HL. In one population-based cohort study using data from the SEER database, there was no difference in the overall risk for second malignancies between patients who received radiation and those who did not; however, there was a higher risk for sarcoma, breast cancer, and mesothelioma in patients who received radiation. The average age at NHL diagnosis was 61 years and the average follow-up was 60 months. Patients who developed second malignancies tended to be older, with a mean age at NHL diagnosis of 65

years and an average age at second tumor diagnosis of 70 years. The authors noted that the patients who did not receive radiation had a *lower* risk for developing breast cancer than the general population, possibly because of the protective effects of alkylating chemotherapy, whereas those who were irradiated approached the endemic rate [66].

Greater risks for specific solid tumors after chemotherapy alone for NHL have been reported. In one case-control study, patients with NHL treated with cyclophosphamide had a 4.5-fold higher risk for developing bladder and kidney cancer than those who did not receive the drug, and the risk was dependent on the cumulative dose [30]. In a retrospective cohort study conducted by the British Collaborative Group, 1,274 patients treated with chemotherapy alone (usually with cyclophosphamide, doxorubicin, vincristine, and prednisone, the CHOP regimen) had greater risks for lung cancer (RR, 1.9; 95% CI, 1.1–3.3) and colorectal cancer (RR, 2.1; 95% CI, 1.1–3.6) over the median follow-up of 5 years [67]. A large European prospective cohort trial followed patients who received doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (the ACVBP regimen) for NHL for a median of 72 months. The RR for lung cancer was significantly greater than the age-matched general population for men (RR, 2.45; 95% CI, 1.48–3.83) but not for women [68]. However, both the European and British trials did not show a higher risk for all solid tumors taken as a whole [67, 68].

The risk for hematologic malignancies following chemotherapy for NHL remains higher than that of the general population, especially when the regimen includes an alkylating agent. The European trial above showed an RR for MDS or AML after ACVBP over the 72 month follow-up of 5.65 (95% CI, 1.54–14.5) in men, and among women, it was even higher at 19.9 (95% CI, 7.98–41.0) [68]. In the British study, the RR for leukemia was 10.5 (95% CI, 5.0–19.3) after chemotherapy alone, compared with estimated rates in the general population [67].

SCREENING FOR SECOND MALIGNANCIES IN OLDER ADULTS

A number of screening recommendations exist for the development of second malignancies after a wide variety of cancers commonly seen in older adults. The most comprehensive guidelines for screening exist among cancer survivors with a higher risk for developing breast cancer. Additional screening recommendations exist for survivors of cancers of the breast, prostate, colon, and lung and HL, but these guidelines remain incomplete, are generally not based on consistent evidence, and do not take age into account [13].

The National Comprehensive Cancer Network (NCCN) recommends that any woman who has had thoracic irradiation for any malignancy undergo annual mammography and biannual to annual clinical breast exams, and suggests annual breast magnetic resonance imaging as an adjunct to these tests [69]. Additionally, any woman with a history of breast cancer is recommended to undergo a history and physical exam every 3–6 months for 5 years, and then annually, accompanied by an annual mammogram. It is recommended that any woman on

tamoxifen therapy undergo a yearly gynecologic exam [70]. The American Society of Clinical Oncology (ASCO) echoes the NCCN in the need for regular breast exams and mammography. ASCO guidelines recommend that all women with a history of breast cancer undergo annual gynecologic examinations and women taking tamoxifen are recommended to report any vaginal bleeding to their gynecologist. ASCO guidelines do *not* recommend routine blood tests or other forms of imaging as part of routine monitoring following breast cancer [71].

The NCCN additionally has specific guidelines for screening following HL. The NCCN recommends a yearly complete blood count, yearly thyroid function tests if patients received neck irradiation, yearly chest imaging (x-ray or computed tomography scan) for patients at risk for lung cancer, and yearly breast exams as above [72]. For survivors of colorectal cancer, the NCCN recommends colonoscopy at 1 year and then age-appropriate screening for breast, cervical, and prostate cancer, with no changes particular to colon cancer survivors [73]. While the NCCN does not give recommendations regarding surveillance for second cancers following prostate cancer, some authors recommend that all patients receiving prostate irradiation undergo endoscopic evaluation for rectal cancer starting 5 years later [74].

Notably, age and frailty are not taken into account in the above recommendations. Hence, we propose a rational approach to determine whether or not there exists a benefit to screening for a given patient following any particular malignancy. Walter and Covinsky propose a guide for primary cancer screening in older adults that takes into account life expectancy, the risk for a cancer death, and the benefits of early detection using screening. The authors suggest in-depth use of life-expectancy tables, including physician assessment of the relative health of the patient, in the determination of life expectancy. For example, 25% of 75-year-old women will live >17 additional years, 50% will live at least 11.9 years, and 25% will live <6.8 years. By assigning patients to quartiles using functional status, comorbidities, frailty, and other factors, a physician could better predict life expectancy and hence better predict whether or not a patient is likely to benefit from screening [75]. Although developed for primary screening in older adults, this guide may be applied to screening for second cancers as well, though the ability to quantify the benefits of screening may be less well established and thus more difficult for the clinician to estimate. We suggest that, in screening for second cancers in older adults, clinicians attempt to quantify each of the following for the second malignancy for which the patient is at risk: (a) the risk for developing the cancer, (b) the risk for death from the second cancer, (c) the likely benefit of screening to the risk for death from the cancer, (d) the life expectancy of the patient based on quartile assignment, and (e) the values and preferences of the individual patient.

Regardless, it remains critical that primary care physicians and geriatricians have as much specific cancer history and cancer treatment history as possible when caring for older adults with a history of cancer and determining screening and prevention strategies because they may be more involved in the patient's daily care than the treating oncologist.

CONCLUSIONS

The risks for both hematologic and solid malignancies are significantly greater following a wide variety of primary tumors even among older adults. The higher risk may be a result of a genetic predisposition to multiple cancers or shared risk factors such as tobacco, or be related to the treatment of the original cancer. Radiation therapy seems to confer higher risks for both solid and hematologic malignancies after many primary cancers, particularly in organs near and around the original radiation field, though the risks appear to be lower in patients radiated at older ages. Chemotherapy may confer a higher future risk for leukemia, particularly when alkylating agents are used, though platinum agents have also been implicated, and these risks may be higher in older adults. The combination of radiation and chemotherapy often increases the risk for solid tumors more than either modality alone, with the notable exception that alkylating agents actually decrease the risk for the future development of breast cancer likely because of their ovarian suppressive function. The association of myeloid growth factors with future hematologic malignancies remains a topic of dispute; however, there is no definitive evidence of an associ-

ation from randomized trials. Tamoxifen, even while decreasing the risk for contralateral breast cancer, increases the risk for subsequent endometrial cancer. Screening recommendations for second malignancies exist following some cancers, but remain incomplete and are not specific for older adults. Further evidence-based guidelines are needed for early detection and treatment of second malignancies in older adults, and physicians caring for this population should integrate age, health status, projected life expectancy, and patient preferences when deciding upon screening and prevention measures.

ACKNOWLEDGMENTS

The authors would like to thank Smita Bhatia, M.D., M.P.H., for her guidance and help in the review of earlier versions of the manuscript.

AUTHOR CONTRIBUTIONS

Conception/Design: Ari M. VanderWalde, Arti Hurria
Provision of study material or patients: Arti Hurria
Collection and/or assembly of data: Ari M. VanderWalde, Arti Hurria
Data analysis and interpretation: Ari M. VanderWalde, Arti Hurria
Manuscript writing: Ari M. VanderWalde, Arti Hurria
Final approval of manuscript: Ari M. VanderWalde, Arti Hurria

REFERENCES

- Jemal A, Siegel R, Xu J et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
- Edwards BK, Howe HL, Ries LA et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. *Cancer* 2002;94:2766–2792.
- Ries LAG, Melbert D, Krapcho M et al., eds. *SEER Cancer Statistics Review 1975–2005*. Bethesda, MD: National Cancer Institute, 2008;31. Based on November 2007 SEER data submission, posted to the SEER Web site, 2008. Available at http://seer.cancer.gov/csr/1975_2005, accessed September 9, 2008.
- Dong C, Hemminki K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958–1996. *Int J Cancer* 2001;93:155–161.
- Travis LB. The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev* 2006;15:2020–2026.
- Ghelani D, Saliba R, Lima M. Secondary malignancies after hematopoietic stem cell transplantation. *Crit Rev Oncol Hematol* 2005;56:115–126.
- Allan JM, Travis LB. Mechanisms of therapy-related carcinogenesis. *Nat Rev Cancer* 2005;5:943–955.
- Ng AV, Travis LB. Second primary cancers: An overview. *Hematol Oncol Clin North Am* 2008;22:271–289.
- Landier W, Bhatia S. Cancer survivorship: A pediatric perspective. *The Oncologist* 2008;13:1181–1192.
- Fraumeni JF Jr, Curtis RE, Edwards BK et al. Chapter 1: Introduction. In: Curtis R, Freedman D, Ron E et al., eds. *New Malignancies Among Cancer Survivors: SEER Cancer Regis-*
- tries, 1973–2000. Bethesda, MD: National Cancer Institute, 2006:1–9. NIH Publ. No. 05–5302.
- Mauch PM, Kalish LA, Marcus KC et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am* 1995;1:33–42.
- Travis LB, Rabkin CS, Brown LM et al. Cancer survivorship—genetic susceptibility and second primary cancers: Research strategies and recommendations. *J Natl Cancer Inst* 2006;98:15–25.
- Hewitt M, Greenfield S, Stovall G, eds. *From Cancer Patient to Cancer Survivor: Lost in Transition*. National Cancer Policy Board Institute of Medicine and National Research Council of the National Academies Press, 2006:23–65.
- Curtis R, Freedman D, Ron E et al., eds. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. NIH Publ. No. 05–5302. Bethesda, MD: National Cancer Institute, 2006:1–482.
- Boice JD Jr, Harvey EB, Blettner M et al. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med* 1992;326:781–785.
- Storm HH, Andersson M, Boice JD Jr et al. Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst* 1992;84:1245–1250.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;366:2087–2106.
- Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: A population-based study. *Int J Radiat Oncol Biol Phys* 2003;56:1038–1045.
- Curtis RE, Boice JD Jr, Stovall M et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* 1992;326:1745–1751.
- Smith RE, Bryant J, DeCillis A et al. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: The National Surgical Adjuvant Breast and Bowel Project Experience. *J Clin Oncol* 2003;21:1195–1204.
- Kirova YM, Vilcoq JR, Asselain B et al. Radiation-induced sarcomas after radiotherapy for breast carcinoma: A large-scale single-institution review. *Cancer* 2005;104:856–863.
- Rubino C, de Vathaire F, Shamsaldin A et al. Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment. *Br J Cancer* 2003;89:840–846.
- Roychoudhuri R, Evans H, Robinson D et al. Radiation-induced malignancies following radiotherapy for breast cancer. *Br J Cancer* 2004;91:868–872.
- Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371–1388.
- Schaapveld M, Visser O, Louwman MJ et al. Risk of new primary nonbreast cancers after breast cancer treatment: A Dutch population-based study. *J Clin Oncol* 2008;26:1239–1246.
- The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst* 1999;91:1310–1316.
- Li AJ, Karlan BY. Genetic factors in ovarian carcinoma. *Curr Oncol Rep* 2001;3:27–32.
- Lynch HT, Lanspa S, Smyrk T et al. Hereditary nonpolyposis colorectal cancer (Lynch syn-

dromes I & II). Genetics, pathology, natural history, and cancer control, Part I. *Cancer Genet Cytogenet* 1991;53:143–160.

29. Weinberg DS, Newschaffer CJ, Topham A. Risk for colorectal cancer after gynecologic cancer. *Ann Intern Med* 1999;131:189–193.

30. Travis LB, Curtis RE, Glimelius B et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst* 1995;87:524–530.

31. Travis LB, Holowaty EJ, Bergfeldt K et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999;340:351–357.

32. Kaldor JM, Day NE, Pettersson F et al. Leukemia following chemotherapy for ovarian cancer. *N Engl J Med* 1990;322:1–6.

33. Neugut AI, Ahsan H, Robinson E et al. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer* 1997;79:1600–1604.

34. Chrouser K, Leibovich B, Bergstralh E et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol* 2005;174:107–110; discussion 110–111.

35. Brenner DJ, Curtis RE, Hall EJ et al. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000;88:398–406.

36. Scélo G, Boffetta P, Hemminki K et al. Associations between small intestine cancer and other primary cancers: An international population-based study. *Int J Cancer* 2006;118:189–196.

37. Ronckers CM, McCarron P, Ron E. Thyroid cancer and multiple primary tumors in the SEER cancer registries. *Int J Cancer* 2005;117:281–288.

38. Mysliwiec PA, Cronin KA, Schatzkin A. Chapter 5: New malignancies following cancer of the colon, rectum, and anus. In: Curtis R, Freedman D, Ron E et al., eds. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. NIH Publ No 05–5302. Bethesda, MD: National Cancer Institute, 2006:111–144.

39. Giovannucci E. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* 2002;31:925–943.

40. Kendal WS, Nicholas G. A population-based analysis of second primary cancers after irradiation for rectal cancer. *Am J Clin Oncol* 2007;30:333–339.

41. van Leeuwen FE, Klokman WJ, Hagenbeek A et al. Second cancer risk following Hodgkin's disease: A 20-year follow-up study. *J Clin Oncol* 1994;12:312–325.

42. Dores GM, Coté TR, Travis LB. Chapter 16: New malignancies following Hodgkin lymphoma, non-Hodgkin lymphoma, and myeloma. In: Curtis R, Freedman D, Ron E et al., eds. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. NIH Publ No 05–5302. Bethesda, MD: National Cancer Institute, 2006:397–436.

43. Travis LB, Gospodarowicz M, Curtis RE et al. Lung cancer following chemotherapy and radio-

therapy for Hodgkin's disease. *J Natl Cancer Inst* 2002;94:182–192.

44. Travis LB, Hill DA, Dores GM et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003;290:465–475.

45. Hodgson DC, Gilbert ES, Dores GM et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol* 2007;25:1489–1497.

46. Rund D, Krichevsky S, Bar-Cohen S et al. Therapy-related leukemia: Clinical characteristics and analysis of new molecular risk factors in 96 adult patients. *Leukemia* 2005;19:1919–1928.

47. Howlader N, Noone A, Krapcho M et al., eds. *SEER Cancer Statistics Review, 1975–2008*. Bethesda, MD: National Cancer Institute. Based on November 2010 SEER data submission, posted to the SEER Web site, 2011. Available at http://seer.cancer.gov/csr/1975_2008, accessed August 23, 2011.

48. Deutsch M, Land SR, Begovic M et al. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials B-04 and B-06. *Cancer* 2003;98:1362–1368.

49. Patt DA, Duan Z, Fang S et al. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: Understanding risk. *J Clin Oncol* 2007;25:3871–3876.

50. Hershman D, Neugut AI, Jacobson JS et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. *J Natl Cancer Inst* 2007;99:196–205.

51. Citron ML, Berry DA, Cirincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21:1431–1439.

52. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;365:1687–1717.

53. Saadat M, Truong PT, Kader HA et al. Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer: Comparison of cohorts treated with and without tamoxifen. *Cancer* 2008;110:31–37.

54. Freedman DM, Curtis RE, Travis LB et al. Chapter 9: New malignancies following cancer of the uterine corpus or ovary. In: Curtis R, Freedman D, Ron E et al., eds. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. NIH Publ No 05–5302. Bethesda, MD: National Cancer Institute, 2006:231–256.

55. Travis LB, Curtis RE, Boice JD Jr et al. Second malignant neoplasms among long-term survi-

vors of ovarian cancer. *Cancer Res* 1996;56:1564–1570.

56. Houlston RS, Damato BE. Genetic predisposition to ocular melanoma. *Eye (Lond)* 1999;13:43–46.

57. Kaldor JM, Day NE, Kittelmann B et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: A case-control study. *Int J Cancer* 1995;63:1–6.

58. Moon K, Stukenborg GJ, Keim J et al. Cancer incidence after localized therapy for prostate cancer. *Cancer* 2006;107:991–998.

59. McCredie M, Macfarlane GJ, Bell J et al. Second primary cancers after cancers of the colon and rectum in New South Wales, Australia, 1972–1991. *Cancer Epidemiol Biomarkers Prev* 1997;6:155–160.

60. Hoar SK, Wilson J, Blot WJ et al. Second cancer following cancer of the digestive system in Connecticut, 1935–82. *Natl Cancer Inst Monogr* 1985;68:49–82.

61. Hoppe RT. Hodgkin's disease: Complications of therapy and excess mortality. *Ann Oncol* 1997;8(suppl 1):115–118.

62. Ng AK, Bernardo MV, Weller E et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: Long-term risks and risk factors. *Blood* 2002;100:1989–1996.

63. Bhatia S, Yasui Y, Robison LL et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. *J Clin Oncol* 2003;21:4386–4394.

64. Travis LB, Fossa SD, Schonfeld SJ et al. Second cancers among 40,576 testicular cancer patients: Focus on long-term survivors. *J Natl Cancer Inst* 2005;97:1354–1365.

65. Brusamolino E, Baio A, Orlandi E et al. Long-term events in adult patients with clinical stage IA–IIA nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: A single-institution 15-year follow-up. *Clin Cancer Res* 2006;12:6487–6493.

66. Tward JD, Wendland MM, Shrieve DC et al. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer* 2006;107:108–115.

67. Mudie NY, Swerdlow AJ, Higgins CD et al. Risk of second malignancy after non-Hodgkin's lymphoma: A British Cohort Study. *J Clin Oncol* 2006;24:1568–1574.

68. André M, Mounier N, Leleu X et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: A GELA cohort study on 2837 patients. *Blood* 2004;103:1222–1228.

69. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, Version Available at http://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf, accessed April 12, 2011.

70. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology.

Breast Cancer, Version 2.2011. Available at http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, accessed April 12, 2011.

71. Khatcheressian JL, Wolff AC, Smith TJ et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006;24:5091–5097.

72. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma, Version 2.2011. Available at http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf, accessed May 6, 2011.

73. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon Cancer, Version 3.2011. Available at http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf, accessed May 6, 2011.

www.nccn.org/professionals/physician_gls/pdf/colon.pdf, accessed May 6, 2011.)

74. Grady WM, Russell K. Ionizing radiation and rectal cancer: Victims of our own success. *Gastroenterology* 2005;128:1114–1117.

75. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. *JAMA* 2001;2750–2756.