VOLUME 33 · NUMBER 4 · FEBRUARY 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk of Marrow Neoplasms After Adjuvant Breast Cancer Therapy: The National Comprehensive Cancer Network Experience

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Published online ahead of print at www.jco.org on December 22, 2014.

Support information appears at the end of this article.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

This article is dedicated to the memory of Jane C. Weeks, MD, MSc, who established and led the National Comprehensive Cancer Network Breast Cancer Outcomes Database. She prematurely died September 10, 2013, after a long illness.

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0732-183X/15/3304w-340w/$20.00

DOI: 10.1200/JCO.2013.54.6119

ABSTRACT

Purpose
Outcomes for early-stage breast cancer have improved. First-generation adjuvant chemotherapy trials reported a 0.27% 8-year cumulative incidence of myelodysplastic syndrome/acute myelogenous leukemia. Incomplete ascertainment and follow-up may have underestimated subsequent risk of treatment-associated marrow neoplasm (MN).

Patients and Methods
We examined the MN frequency in 20,063 patients with stage I to III breast cancer treated at US academic centers between 1998 and 2007. Time-to-event analyses were censored at first date of new cancer event, last contact date, or death and considered competing risks. Cumulative incidence, hazard ratios (HRs), and comparisons with Surveillance, Epidemiology, and End Results estimates were obtained. Marrow cytogenetics data were reviewed.

Results
Fifty patients developed MN (myeloid, n = 42; lymphoid, n = 8) after breast cancer (median follow-up, 5.1 years). Patients who developed MN had similar breast cancer stage distribution, race, and chemotherapy exposure but were older compared with patients who did not develop MN (median age, 59.1 *v* 53.9 years, respectively; $P = .03$). Two thirds of patients had complex MN cytogenetics. Risk of MN was significantly increased after surgery plus chemotherapy (HR, 6.8; 95% CI, 1.3 to 36.1) or after all modalities (surgery, chemotherapy, and radiation; HR, 7.6; 95% CI, 1.6 to 35.8), compared with no treatment with chemotherapy. MN rates per 1,000 person-years were 0.16 (surgery), 0.43 (plus radiation), 0.46 (plus chemotherapy), and 0.54 (all three modalities). Cumulative incidence of MN doubled between years 5 and 10 (0.24% to 0.48%); 9% of patients were alive at 10 years.

Conclusion
In this large early-stage breast cancer cohort, MN risk after radiation and/or adjuvant chemotherapy was low but higher than previously described. Risk continued to increase beyond 5 years. Individual risk of MN must be balanced against the absolute survival benefit of adjuvant chemotherapy.

J Clin Oncol 33:340-348. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Adjuvant therapy has played a significant role in improving survival outcomes of patients with early-stage breast cancer.[1] Although any negative impact on survival from therapy-related complications is already accounted for in the observed average improvements in disease-free survival (DFS) and overall survival (OS) after adjuvant therapy,[1] less common short- and long-term complications may still adversely affect individual patients.[2] Therefore, more precise estimates of serious therapy-related complications may better inform treatment decision making, especially for patients with early-stage disease who have a lower risk of recurrence and are treated with curative intent.

Reports of leukemia after breast cancer therapy date back to the 1980s. Case-control studies in the early 1990s indicated an increased risk in nonlymphocytic neoplasms after regional radiotherapy alone, after chemotherapy with alkylating agents (particularly with melphalan and cyclophosphamide), and after combined chemotherapy and radiation.[3] In 2003, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported a 0.27% 8-year cumulative incidence of

myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) among patients with breast cancer treated with the topoisomerase II–targeting drug doxorubicin and the DNA alkylating agent cyclophosphamide.[4] An increased risk was also observed in patients treated with breast radiotherapy and with granulocyte colony-stimulating factors (G-CSFs) to support higher chemotherapy doses.[4] However, thus far, the Early Breast Cancer Trialists' Collaborative Group has reported limited data on leukemia incidence and mortality.[1]

AML and MDS are considered prototypical environmental neoplasms, with as many as 15% to 20% of cases secondary to exposure to diverse toxins including chemotherapeutic agents.[2-8] Two predominant genetic variants of therapy-related AML have been described—one after anthracyclines and/or topoisomerase inhibitors (median latency of 1 to 3 year without prodrome) and another after alkylating agents (median latency of 4 to 6 years often preceded by MDS).[4,9]

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program also suggested an increased risk of a subsequent diagnosis of AML in survivors of breast cancer younger than age 50 years, possibly made worse by exposure to chemotherapy.[7] However, the true incidence of MDS may have been under-reported in SEER because the diagnosis of MDS is often missed in the outpatient setting.[10]

In recent years, the Johns Hopkins Leukemia Program anecdotally observed an increasing number of newly diagnosed acute leukemias in patients with a personal history of breast cancer and/or a family history of cancer. This led to the current study, where we examined the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database to describe the incidence of subsequent marrow neoplasms (MNs), not limited to MDS/AML, among women previously diagnosed with breast cancer and the clinical characteristics of these patients, including molecular cytogenetics.

PATIENTS AND METHODS

Source Population

In 1997, the NCCN Breast Cancer Outcomes Database began prospectively collecting patient and tumor characteristics and initial treatment of all newly diagnosed patients with breast cancer who received some or all primary oncology treatment at an NCCN institution. Patients were observed at baseline; at 4, 9, and 18 months after the first visit to an NCCN site; and then annually for subsequent treatment and outcomes (eg, recurrence, contralateral breast cancer, other cancer by type) if care continued at the NCCN site. Data collected via medical record review by trained abstractors included demographics (age and race/ethnicity), tumor stage and phenotype (based on expression of the estrogen and progesterone receptors and of the human epidermal growth factor receptor 2), and therapy (types of surgery and radiation and names of drugs with start and end dates). Vital status and cause of death for those lost to follow-up or who died from unknown causes were reviewed biannually through the National Death Index. Institutional review boards (IRBs) from each center approved the study, data collection, transmission, and

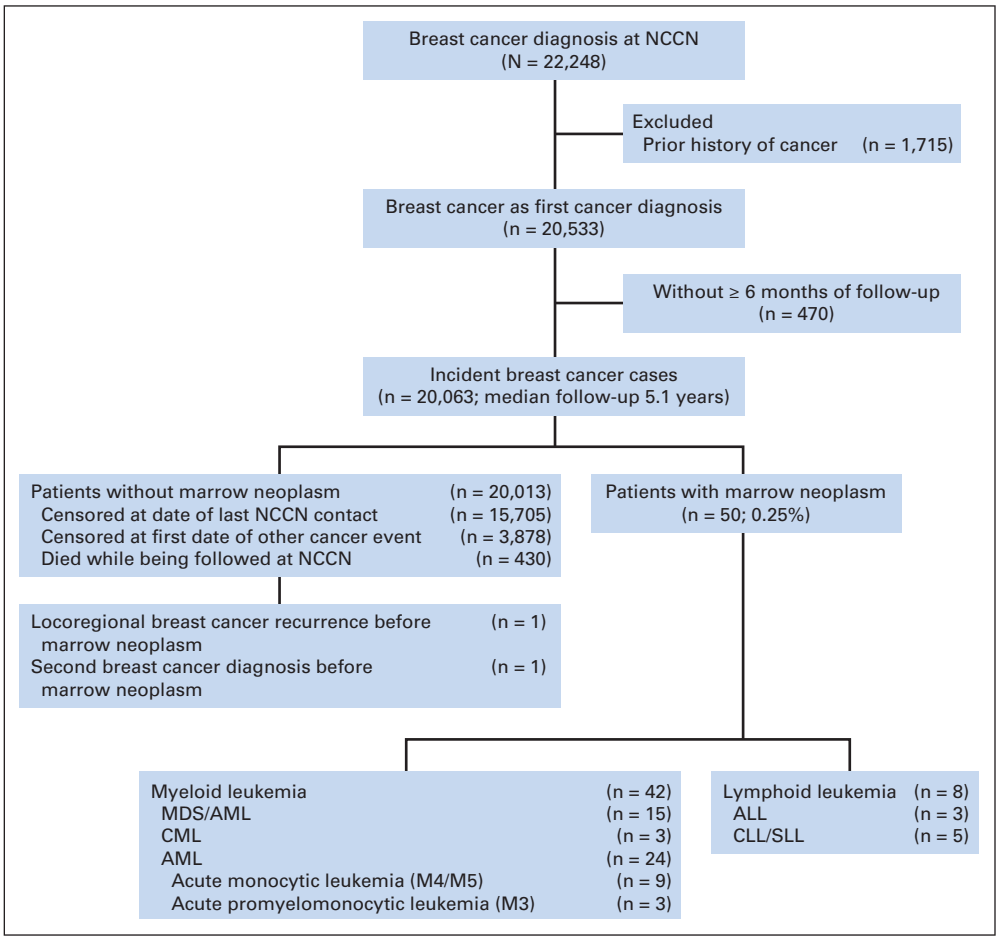

Fig 1. Patient flow diagram. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network; SLL, small lymphocytic lymphoma.

storage protocols. At centers where IRBs required signed informed consent for data collection, only patients who consented were included.

Analytic Cohort

Women with incident stage I, II, or III breast cancer who presented between July 1997 and December 2007 were included. The database was locked in April 2012. Analyses were restricted to eight of the 18 NCCN institutions that initiated data collection before 2000 to allow for sufficient follow-up among incident patients. Patients had to have no prior cancer diagnosis except nonmelanoma skin cancer and at least 6 months of follow-up from their first breast cancer visit date (Fig 1).

Identification of MNs

Patients with lymphoid and myeloid neoplasms after the incident breast cancer were identified in the analytic cohort using International Classification of Diseases, Ninth Revision, codes 202.8 (lymphoma unspecified), 204 to 208 (including 204.1, lymphoma leukemia chronic, and 208, leukemia unspecified), and 238.7 (n = 50). Drug terms suggesting treatment for MN were searched. Retrospective review in accordance with local IRB rules was conducted at institutions with identified patients with MN in the database, including manual records review (standardized case report form) for any family history of cancer, MN diagnosis date, cytogenetics, and MN therapy. Data on available family history of any cancers (dates and type) were retrospectively

Table 1. Patient Demographic, Disease, and Treatment Characteristics

Characteristic	Breast Cancer Only (n = 20,013)		Marrow Neoplasm After Breast Cancer (n = 50)		*P*
	No. of Patients	%	No. of Patients	%	
Age, years					
Median	53.9		59.1		.03
Range	18.4-97.9		32.5-89		
< 50	7,579	38	11	22	.02
≥ 50	12,434	62	39	78	
Race					.85
White	17,514	88	46	92	
African American	1,562	8	3	6	
Other	937	5	1	2	
TNM stage					.84
I	9,070	45	25	50	
II	8,292	41	19	38	
III	2,651	13	6	12	
Histology					.23
Invasive ductal	17,254	86	41	82	
Invasive lobular	1,858	9	8	16	
Other histologies	901	5	1	2	
Phenotype					.65
ER or PgR positive/HER2 negative	11,245	56	32	64	
HER2 positive (any ER/PgR)	3,699	18	7	14	
Triple negative	2,737	14	4	14	
HER2 unknown (before year 2000)	2,332	12	4	8	
Surgery					.92
None	156	1		0	
Lumpectomy	11,394	57	28	56	
Mastectomy	8,463	42	22	44	
Radiation therapy					.24
None	5,767	29	10	20	
After lumpectomy or no surgery	10,847	54	28	56	
After mastectomy	3,399	17	12	24	
Chemotherapy* (anthracycline and/or cyclophosphamide)					.35
None or only endocrine therapy	7,569	38	14	28	
4 cycles	10,269	51	30	60	
6 cycles	2,175	11	6	12	
Local/systemic therapy					.23
None	2,548	13	2	4	
Radiation but no chemotherapy	5,021	25	12	24	
Chemotherapy but no radiation	3,219	16	8	16	
Chemotherapy and radiation	9,225	46	28	56	

NOTE. Median follow-up time was 5.1 years.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.
*Patients were grouped according to the number of cycles (four or six) of chemotherapy that contained the combination of an anthracycline (doxorubicin or epirubicin) with the alkylating agent cyclophosphamide. Most of these patients also received a taxane drug as part of the adjuvant systemic chemotherapy regimen (63% among 12,444 of the patients with breast cancer only and 55% among 36 of the patients with marrow neoplasm after breast cancer who received four or six cycles of chemotherapy). Patients with ER-positive disease also received tamoxifen and/or an aromatase inhibitor. Because only 11% of all 20,013 patients with breast cancer only and 12% of all 50 patients with marrow neoplasm were treated with six cycles of an anthracycline/cyclophosphamide-containing regimen, all subsequent analyses examining the effect of chemotherapy on the risk of marrow neoplasm combined patients treated with four or six cycles into one group.

obtained from any medical records around the time of breast cancer diagnosis and around the time of MN diagnosis.

Statistical Analysis

Patient characteristics, including demographics, breast cancer characteristics, and therapy, were compared among women with breast cancer who did and did not subsequently develop MN using Wilcoxon rank sum tests and Fisher's exact tests. We combined all myeloid and lymphoid marrow disorders to estimate individual hazards for MN risk. Primary analysis was time from breast cancer to diagnosis of MN. Patients who did not develop MN were censored at the first date of another cancer event or at the date of their last NCCN contact. Patients who died before developing an MN or another cancer were considered as having a competing event. Comparisons of time to MN with three mutually exclusive treatment groups (surgery with radiation, surgery with chemotherapy, and all three modalities) to a control group of surgery alone were summarized with cumulative incidence curves and proportional subdistribution hazards calculated using Fine and Gray's method.[11] All reported hazard ratios (HRs) are adjusted for age at breast cancer diagnosis, NCCN site, and race.

Incidence rates per 1,000 person-years at risk were calculated for the whole cohort, by treatment modality group, and over time (5- and 10-year incidence). The corresponding 95% CIs were calculated assuming that MN events followed a Poisson distribution.

The number of MNs observed during the postdiagnosis follow-up period among the final cohort of patients with breast cancer was compared with the number of expected MNs calculated using SEER data. SEER*Stat statistical software version 8.0.1 (http://seer.cancer.gov/seerstat/) was used to calculate age-adjusted incidence rates of MN separately by race (white, black, and other) and by year (1973 through 2009), whereas rates for the 2010 to 2012 period were extrapolated using a regression model. For each patient analyzed, the cumulative sum of the yearly incidence rate was calculated beginning with the patient's year of breast cancer diagnosis up through the year of last known follow-up or year of diagnosis of MN, if affected. The sum of these values across all individuals was taken as the expected number of MNs in this cohort. Ninety-five percent CIs were calculated using a bootstrap approach.

DFS was calculated as the time from breast cancer diagnosis to first date of another cancer event (including MN), death, or last date of NCCN follow-up. OS was calculated as the time from breast cancer diagnosis to death or last NCCN follow-up date. DFS and OS were estimated using the Kaplan-Meier method. Analyses were completed using SAS software version 9.3 of the SAS system for Windows (SAS Institute, Cary, NC) and R version 2.15.1 (http://www.r-project.org/).

RESULTS

Patient Characteristics

Between July 1997 and December 2007, 20,063 patients with incident stage I, II, or III breast cancer were identified (Fig 1). The median follow-up time of the cohort was 5.1 years. Appendix Figure A1 (online only) describes individual times from breast cancer diagnosis to last follow-up. Appendix Figure A2 (online only) describes the dates when patients in our analytic cohort presented with breast cancer. The 10-year DFS rate was 78% (86% for stage I; 72% for stages II and III), and the 10-year OS was 80% (88% for stage I; 74% for stages II and III). Fifty patients (0.25%) who were diagnosed with MN after adjuvant therapy were identified (42 myeloid neoplasms and eight lymphoid neoplasms). The median time from breast cancer to MN was 4.9 years, and the OS after breast cancer diagnosis of these 50 patients was shorter (62% at 5 years and 9% at 10 years) than for patients without MN. The median length of follow-up after MN diagnosis for these 50 patients was 241 days, and the median OS time was 409 days. The OS probability after MN diagnosis was 50% at 1 year and 30% at 2 years.

Among the 42 survivors of breast cancer who subsequently developed myeloid MN, 24 patients developed AML, 15 developed MDS/AML, and three developed chronic myelogenous leukemia. Among the eight patients who developed lymphoid neoplasia, three had acute lymphocytic leukemia (ALL) and five had chronic lymphocytic leukemia (CLL, n = 4)/small lymphocytic lymphoma (SLL, n = 1).

Survivors of breast cancer diagnosed with MN, compared with those who did not develop an MN, were significantly older (median age, 59.1 *v* 53.9 years, respectively, $P = .03$) but of similar race (Table 1). There was no significant difference in the stage distribution, breast tumor characteristics, and adjuvant treatment received between breast

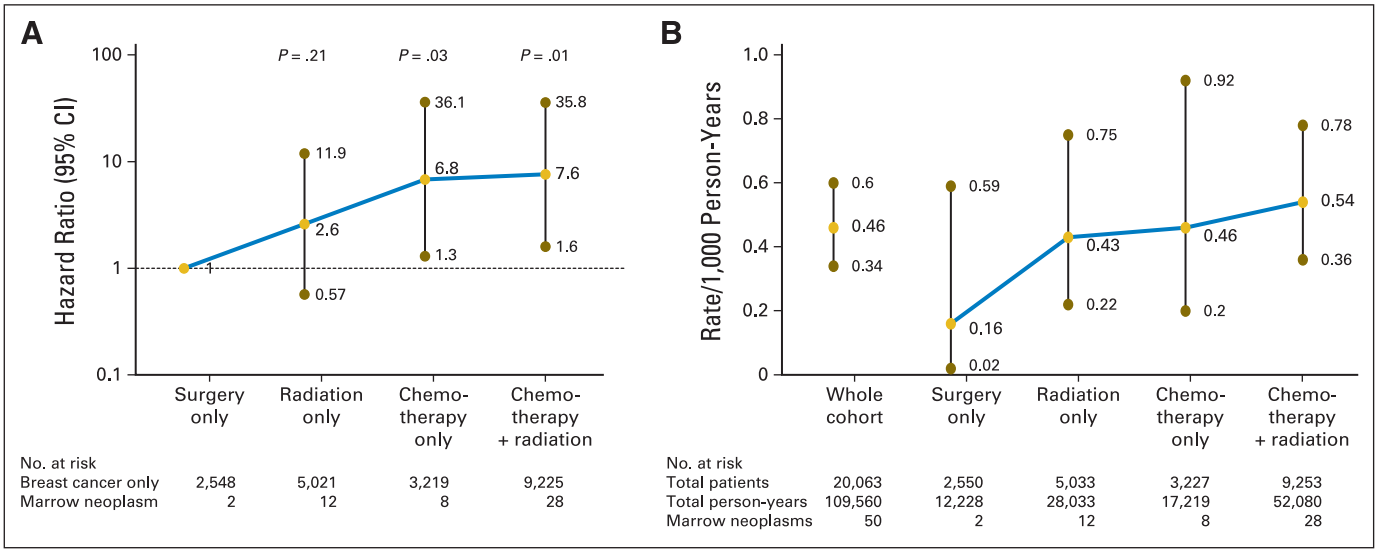

Fig 2. (A) Hazard ratios for risk of marrow neoplasm and (B) incidence rates of marrow neoplasm per 1,000 person-years.

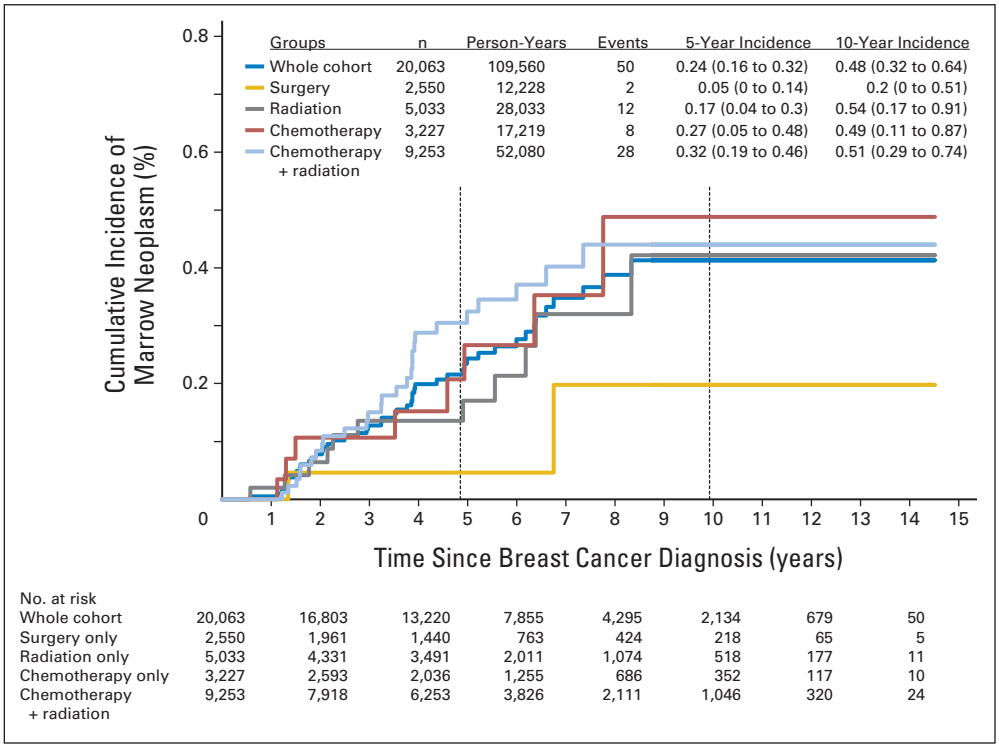

Fig 3. Cumulative incidence of marrow neoplasm. The numbers in parentheses under 5-year incidence and 10-year incidence represent 95% CIs.

cancer patients who developed MN and those who did not. Within each group, those treated with four to six cycles of an anthracycline/cyclophosphamide-containing regimen (Table 1) were combined for the analyses because of the small percentage of patients (12%) treated with more than four cycles.

Risk of MNs Stratified by Treatment Modality

The combined analyses of all myeloid (n = 42) and lymphoid (n = 8) neoplasms are reported (n = 50) because the individual hazards for MN risk were comparable. A multivariable analysis (Fig 2A) compared the risk of developing an MN among three mutually exclusive treatment groups with the risk of breast cancer survivors treated with surgery alone, adjusting for NCCN site, age at breast cancer diagnosis, stage, and race. A nonsignificant increase in MN risk was observed in those treated with surgery plus radiation compared with surgery alone (HR, 2.6; 95% CI, 0.57 to 11.9; $P = .21$). However, there was a significant risk among patients treated with both surgery and chemotherapy (HR, 6.8; 95% CI, 1.3 to 36.1; $P = .03$) and those treated with all three modalities (HR, 7.6; 95% CI, 1.6 to 35.8; $P = .01$). Consistent with prior reports,[12,13] MN risk was not increased for patients also treated with a taxane versus patients not treated with a taxane (HR, 1.46; 95% CI, 0.74 to 2.87; $P = .27$).

After 109,560 person-years of follow-up, the overall rate of MN was 0.46 per 1,000 person-years (Fig 2B). Similar rates were observed in the subsets treated with surgery and radiation (n = 12; rate, 0.43 per 1,000 person-years), surgery and chemotherapy (n = 8; rate, 0.46 per 1,000 person-years), or all three modalities (n = 28; rate, 0.54 per 1,000 person-years), in contrast with surgery alone (n = 2; rate, 0.16 per 1,000 person-years). There was a continuous increase in the cumulative incidence of MN, with half of the 50 MNs occurring between years 6 and 10. The cumulative frequency after 10 years (0.48%) was twice the cumulative frequency observed after 5 years (0.24%; Fig 3).

The expected number of MNs was also calculated using SEER-derived incidence data over the postdiagnosis follow-up period, from age at diagnosis of incident breast cancer to date of last follow-up, death, or diagnosis of MN or other cancer. Matching for race, we obtained an observed-to-expected ratio (n = 50) of 3.6 (95% CI, 2.6 to 4.6; $P < .001$), which suggests that the risk of MN in survivors of breast cancer may be greater than that observed in the general SEER population after accounting for age and race (Table 2).

Table 2. Observed Versus Expected Risk of Developing Marrow Neoplasm Based on SEER-Derived Incidence Data

Cohort	No. of Observed Events	No. of Expected Events	O:E Ratio	95% CI	*P*
Whole cohort	50	14.1	3.6	2.6 to 4.6	< .001
Surgery only	2	1.6	1.3	0 to 3.2	.17
Radiation only	12	3.5	3.4	1.4 to 5.1	< .001
Chemotherapy only	8	2.2	3.6	1.3 to 6.3	.005
Chemotherapy plus radiation	28	6.7	4.2	2.7 to 5.6	< .001

Abbreviations: O:E, observed to expected ratio; SEER, Surveillance, Epidemiology, and End Results.

Table 3. Individual Cytogenetic Karyotypes, Prior Exposure to Adjuvant Chemotherapy, and Family History of Cancer in 41 Women With MN

Patient Characteristics	No. of Patients	Individual Karyotypes
Myeloid MN (n = 36)		
Received chemotherapy for breast cancer (n = 23)		
Positive family history (n = 18)		
Diploid	5	NA
Translocations	6 (4 MLL*)	46XX, t(9;11)(p22;q23) 46XX, t(9;11)(p22;q23) 46XX, t(11;19)(q23;p13.3) 45-46X, −X, t(9;11)(p22;q23) 46XX, t(8;16)(p11.2,p13.3) 45X, −X, t(8;21)(q22;q22)
MDS related	7 (6 complex)	44XX, −5q, −7, −17p, der(5;17), dic(9;11), +12p11.2, +mar 44-53XX, −5, −7q, +12p11.2, der(17)t(5;17), −20, +8, +10, +11, +11, +13, +13, +15, +18, +18, +21, +22 44XX, −5q, −7, −7, +12p13, −20 40-43X, −X, −4, −5q, t(5;15), −17, t(7;17), +mar 44-46XX, −2q, −5, +6, −7, +8, −10, t(11;13) −13, −14, −16, +19p13.3, +21, +3mar 46XX, −5q31-35, t(20;21)(q11.2,q22), −21,+mar 46XX, −7, +mar
Negative family history (n = 5)		
Diploid	1	NA
Translocations	3 (1 MLL, 2 CML)	46XX, t(11;19)(q23;p13.3) 46XX, t(9;22)(q34;q11) 46XX, t(9;22)(q34;q11)
MDS related	1 (1 complex)	41-48XX −5, −7q, +18q, +18, +20q11.2, +mar
No chemotherapy received for breast cancer (n = 13)		
Positive family history (n = 10)		
Diploid	5	NA
Translocations	2 (1 APL, 1 CML)	46XX, t(15;17)(q22;q21) 46XX, t(9;22)(q34;q11)
MDS related	3 (2 complex)	44X, −X, −5q, −13q, −15, −16, −17, −18, −20, +21, +mar 43XX, −5, −7q, −12 46XX, −5q31-35
Negative family history (n = 3)		
Diploid	1	NA
Translocations	2 (1 APL)	46XX, t(15;17)(q22;q21) 46XX, t(3;5)(q21;q31)
MDS related	0	
Lymphoid MN (n = 5)		
Received chemotherapy for breast cancer (n = 4)		
Positive family history (n = 3)		
Diploid	1 (1 CLL)	NA
Translocations	2 ALL (2 MLL*)	t(4;11)(q21;q23) t(4;11)(q21;q23)
MDS related	0	
Negative family history (n = 1)		
Diploid	1 (1 ALL)	NA
Translocations	0	
MDS related	0	
No chemotherapy received for breast cancer (n = 1)		
Positive family history (n = 1)		
Diploid	1 (CLL)	
Translocations	0	
MDS related	0	

(continued on following page)

Table 3. Individual Cytogenetic Karyotypes, Prior Exposure to Adjuvant Chemotherapy, and Family History of Cancer in 41 Women With MN (continued)

Patient Characteristics	No. of Patients	Individual Karyotypes
All patients (n = 41)		
Received chemotherapy for breast cancer (n = 27)		†
Positive family history (n = 21)		
Diploid	6	
Translocations	8 (6 MLL)	
MDS related	7	
Negative family history (n = 6)		
Diploid	2	
Translocations	3 (1 MLL)	
MDS related	1	
No chemotherapy received for breast cancer (n = 14)		†
Positive family history (n = 11)		
Diploid	6	
Translocations	2	
MDS related	3	
Negative family history (n = 3)		
Diploid	1	
Translocations	2	
MDS related	0	

NOTE. Cytogenetics and family history were available and retrospectively obtained in 41 of 50 patients who developed a marrow neoplasm after breast cancer. Right column contains individual karyotypes. At least one of these three data elements was not available for eight of the 50 patients, six of whom developed myeloid leukemia (AML, n = 1; MDS/AML, n = 3, including one with complex cytogenetics; APL, n = 1; t[9;11], n = 1) and two who developed lymphoid leukemia (both CLL).

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; MDS, myelodysplastic syndrome; MLL, translocation involving the mixed lineage leukemia gene; MN, marrow neoplasm; NA, not applicable.

*Seven (26%) of 27 patients who received chemotherapy had leukemia associated with *MLL* gene translocations, five in patients with AML (three with t[9;11] and two with t[11;19]) and two in patients with ALL (both t[4;11]). No *MLL* gene translocations were observed among the 14 patients with leukemia who did not receive adjuvant chemotherapy for breast cancer ($P = .07$). Six of the seven patients whose marrow neoplasm had an *MLL* gene translocation had a family history of cancer. Ten of 11 patients with MDS-related cytogenetics had a family history of cancer.

†See karyotypes listed for myeloid MN and lymphoid MN.

Characteristics of Patients With Observed MNs

In an exploratory analysis, family history of cancer and marrow cytogenetics were available for 41 (82%) of 50 patients with MN (Table 3). Abnormal cytogenetics were detected in two thirds of patients (26 of 41 patients), including 24 (67%) of 36 patients with myeloid disorders and two of (40%) five patients with lymphoid disorders.

Of the 27 patients (66% of 41 patients) who received adjuvant chemotherapy, 19 (70% of 27 patients) had abnormal marrow cytogenetics. In contrast, among the 14 patients with no prior exposure to chemotherapy, abnormal cytogenetics were observed in seven patients (50%), all of whom had myeloid neoplasms. Three of these seven patients had cytogenetic abnormalities associated with MDS, including monosomies of chromosomes 5 and/or 7 and complex karyotypes.

Translocations in the mixed-lineage leukemia (*MLL*) gene were observed in seven (26%) of 27 patients with prior exposure to adjuvant chemotherapy (five patients with AML and two patients with ALL). In contrast, no *MLL* translocations were observed among the 14 patients with available cytogenetics and no prior adjuvant chemotherapy ($P = .07$). Other translocations like those associated with APL and chronic myelogenous leukemia were infrequent and not associated with specific patient subgroups.

A family history of at least one cancer in a first- or second-degree relative was retrospectively observed in 32 (78%) of 41 patients with available cytogenetics. Nineteen (59%) of 32 patients with a family history of cancer had at least one first- or second-degree relative with breast or ovarian cancer.

Among 36 patients with myeloid neoplasms, a family history of cancer was observed in 28 patients (78%), of whom 10 had MDS-related cytogenetics. Of these 10 patients, eight had a family history of breast and/or ovarian cancer and six had complex marrow cytogenetics. Only one of the 11 patients with MDS-related cytogenetics did not have a family history of cancer. Six of seven patients with *MLL* translocations (AML, n = 4; ALL, n = 2) were among the 21 patients who received adjuvant chemotherapy and had a family history of cancer (Table 3).

DISCUSSION

We examined the observed frequency of MN after a diagnosis of early-stage breast cancer in an analytic cohort of 20,063 patients after a median follow-up of 5.1 years. There was a modest nonsignificant increase in MN risk if radiotherapy was added to surgery but a marked significant increase if chemotherapy with or without radiation was added to surgery. These risks were greater than the general population estimates of AML based on SEER-derived incidence data after accounting for age and race. Although radiation alone seems to be a risk factor,[14] it did not increase the risk attributable to chemotherapy in our data set. Most patients received four cycles of an anthracycline and cyclophosphamide as part of their adjuvant chemotherapy regimen, and few received docetaxel/cyclophosphamide. Use of G-CSFs was not prospectively captured, and its impact on the risk of MN could not be examined properly,[15] whereas taxane use did not increase the risk of MN.

To place this risk in perspective, a 60-year-old woman with average comorbidities diagnosed with a 1.1- to 2.0-cm, high-grade, estrogen receptor–positive, node-negative breast cancer has a 12.3% risk of dying of breast cancer after 10 years based on Adjuvant! Online (http://www.adjuvantonline.com/index.jsp) risk estimates.[16] Although four cycles of adjuvant doxorubicin/cyclophosphamide given before endocrine therapy would improve her 10-year OS on average by 1.8% (absolute improvement), our findings suggest that the patient's 10-year cumulative risk of MN is approximately 0.5%.

The cumulative frequency of MN doubled between years 5 (0.24%) and 10 (0.48%). When indirectly compared with the subset of NSABP patients treated with a standard four cycles of doxorubicin/cyclophosphamide who subsequently developed MDS and/or AML,[4] the cumulative incidence of MN observed in our cohort seems to be twice as large (0.27% at 8 years in NSABP *v* 0.48% at 10 years in NCCN). Of clinical importance, our data include both myeloid and lymphoid neoplasms and indicate that the MN risk extends to at least 10 years.

In this data set, we retrospectively observed a high frequency of abnormal marrow cytogenetics among the 50 patients with MN. Although translocations of the *MLL* gene are uncommon in de novo adult AML and ALL,[3,9,17] there was a trend toward an association between *MLL* gene translocations and chemotherapy exposure ($P = .07$). MDS-related cytogenetics (especially complex variants) seemed to be associated with a family history of cancer, particularly breast and/or ovarian. Of possible interest, only one of the seven patients with *MLL* translocations was a patient without a family history of cancer. These observations must be considered exploratory and hypothesis generating and must now be prospectively confirmed in other data sets, including familial breast cancer registries.

Strengths of the NCCN Breast Cancer Database include the geographic distribution of the cancer centers, longer term follow-up with linkage to the National Death Index, availability of specific information on therapy and duration (including drugs), and information on cytogenetics from most patients. Our prospective data collection on second cancers may also have allowed greater ascertainment of MN events. Specific case report forms were not used by the NSABP before 1996, and this may partly explain the observed differences. Our study also has limitations, such as lack of prospective collection of family history, use of G-CSFs, and actual doses of chemotherapy and radiation delivered.

Various studies (including two Institute of Medicine reports in 2002[18] and 2008[19]) have suggested an association between exposure to DNA-damaging chemicals or radiation and CLL.[20,21] CLL and SLL represent spectrums of the same disease (CLL/SLL), and we identified four CLLs and one SLL in our database. In view of the limited published evidence and the few observed cases in our data set, any potential association must be viewed with caution, and we expect many to question our inclusion of CLL/SLL as an MN of potential interest after adjuvant breast cancer therapy. Therefore, we hope that others will now examine the frequency of CLL/SLL in their own data sets.

The Breast Cancer Outcomes Database was the largest disease-specific project among the NCCN Database Projects. This rich database has allowed investigators to ask clinical questions involving rare outcomes that are of direct interest to patients, practicing oncologists, cancer researchers, and policy makers. This study may not be generalizable to all patients with breast cancer given that patients treated at NCCN institutions in the US tend to be of younger age. However, this cohort is likely to be representative of patients treated in most large cancer centers. Although the risk of MN after breast cancer therapy we report is small, it is not zero, and it is not short-lived. Our findings highlight the challenges of studying infrequent but important clinical events and demonstrate the potential benefits of prospective, well-annotated, large, longitudinal databases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** Richard L. Theriault, UpToDate

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Support

Supported in part by National Cancer Institute Grants No. CA89393 to Dana-Farber Cancer Institute, CA006973 to the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, and Susan G. Komen for the Cure Grant No. SAC110053 (A.C.W).

GLOSSARY TERMS

alkylating agents: common antineoplastic alkylating agents include ifosfamide, cyclophosphamide, busulfan, melphalan, carmustine, and chlorambucil. They attach to an alkyl group, which is connected to the guanine base of DNA at the number 7 nitrogen atom of the purine ring.

MLL (myeloid/lymphoid or mixed-lineage leukemia): a protein with two DNA-binding motifs, a DNA methyl transferase motif, a bromodomain, and segments of homology with trithorax, in particular in the C-terminal SET domain.

molecular cytogenetics: cytogenetic studies that probe the molecular makeup of chromosomes. Several techniques have been developed that have advanced the field of molecular cytogenetics, including fluorescent in situ hybridization and array-based comparative genomic hybridization.

topoisomerase II: an enzyme that catalyzes the ATP-dependent transport of one segment of DNA duplex through another DNA duplex. Topoisomerases change the topology of DNA by controlling the essential functions of separating intertwined daughter chromosomes.

Acknowledgment

We thank the study coordinators and principal investigators of the sites that contributed patients for this study: City of Hope National Medical Center (Duarte, CA), Dana-Farber Cancer Institute (Boston, MA), Fox Chase Cancer Center (Philadelphia, PA), The University of Texas MD Anderson Cancer Center (Houston, TX), University of Michigan Cancer Center (Ann Arbor, MI), Moffitt Cancer Center (Tampa, FL), Ohio State University (Columbus, OH), and Roswell Park Cancer Institute (Buffalo, NY). We thank Rebecca A. Ottesen with the Data Coordinating Center at the City of Hope for her efforts with acquisition of data. We acknowledge the support of NCCN and its Member Institutions in the development and maintenance of the NCCN Outcomes Database used for this analysis.

Presented at the 2012 San Antonio Breast Cancer Symposium, December 4-8, 2012, San Antonio, TX.

Appendix

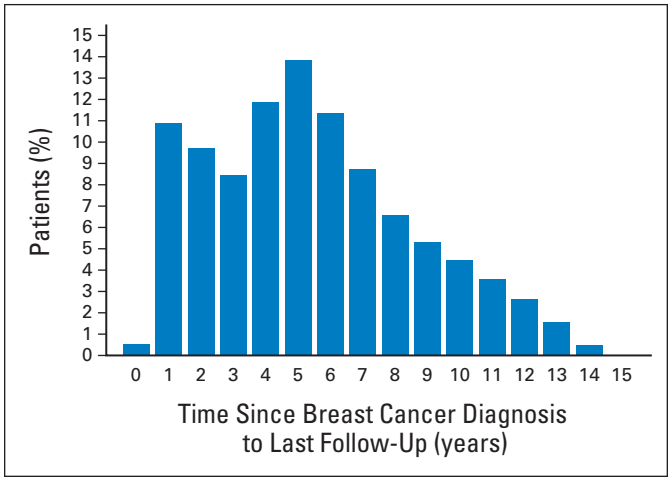

Fig A1. Histogram describing individual times (years) from diagnosis of breast cancer to last follow-up (defined as death, marrow neoplasm [MN] diagnosis, other cancer diagnosis, or last follow-up date at National Comprehensive Cancer Network) of patients in our analytic cohort (N = 20,063). Times were rounded to integer years, so the bars represent values 6 months before and after the given number (eg, patients with times between 1.5 and 2.49 years are included in the bar labeled 2). Most patients (> 12%) have at least 1.5 years of follow-up. However, because the median time from breast cancer to MN was 4.9 years, this longer incubation period suggests that more patients from our study may eventually be diagnosed with an MN, and our current findings may underestimate the true incidence. The latest update on patient follow-up occurred in April 2012 when the database was locked.

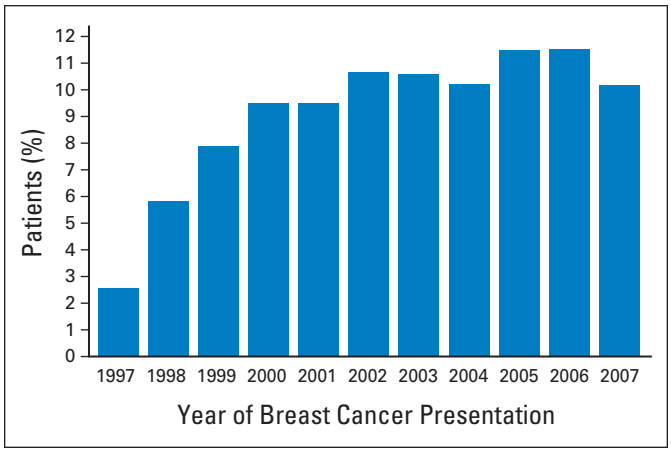

Fig A2. Histogram describing the dates when patients in our analytic cohort presented with breast cancer (N = 20,063).

ERRATUM

The February 1, 2015, article by Wolff et al, entitled, "Risk of Marrow Neoplasms After Adjuvant Breast Cancer Therapy: The National Comprehensive Cancer Network Experience" (J Clin Oncol 33:340-348, 2015), contained an error.

In the acknowledgement section, NCCN support of the Breast Cancer Outcomes Database was incompletely acknowledged. The sentence "We acknowledge the support of NCCN and its Member Institutions in the development and maintenance of the NCCN Outcomes Database used for this analysis, " should have been included as the last sentence to the acknowledgement so it reads as follows:

We thank the study coordinators and principal investigators of the sites that contributed patients for this study: City of Hope National Medical Center (Duarte, CA), Dana-Farber Cancer Institute (Boston, MA), Fox Chase Cancer Center (Philadelphia, PA), The University of Texas MD Anderson Cancer Center (Houston, TX), University of Michigan Cancer Center (Ann Arbor, MI), Moffitt Cancer Center (Tampa, FL), Ohio State University (Columbus, OH), and Roswell Park Cancer Institute (Buffalo, NY). We thank Rebecca A. Ottesen with the Data Coordinating Center at the City of Hope for her efforts with acquisition of data. We acknowledge the support of NCCN and its Member Institutions in the development and maintenance of the NCCN Outcomes Database used for this analysis.

The online version has been corrected in departure from the print. The authors apologize for the error.

DOI: 10.1200/JCO.2015.61.6656; published April 1, 2015

