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ORIGINAL REPORT

Risk of Hematologic Malignancies After Radioiodine Treatment of Well-Differentiated Thyroid Cancer

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ABSTRACT

Purpose
To investigate the risk and outcomes of second hematologic malignancies (SHMs) in a population-based cohort of patients with well-differentiated thyroid cancer (WDTC) treated or not with radioactive iodine (RAI).

Methods
Patients with WDTC were identified from SEER registries. Competing risk regression analysis was performed to calculate the risks of SHMs that occurred after WDTC treatment and outcomes after SHM development were assessed.

Results
Of 148,215 patients with WDTC, 53% received surgery alone and 47% received RAI. In total, 783 patients developed an SHM after a median interval of 6.5 years (interquartile range, 3.3 to 11.2 years) from WDTC diagnosis. In multivariable analysis, compared with those undergoing thyroidectomy alone, RAI treatment was associated with an increased early risk of developing acute myeloid leukemia (AML; hazard ratio, 1.79; 95% CI, 1.13 to 2.82; $P = .01$) and chronic myeloid leukemia (CML; hazard ratio, 3.44; 95% CI, 1.87 to 6.36; $P < .001$). This increased risk of AML and CML after RAI treatment was seen even in low-risk and intermediate-risk WDTC tumors. Occurrence of AML but not CML in patients with WDTC was associated with shorter median overall survival compared with matched controls (8.0 years *v* 31.0 years; $P = .001$). In addition, AML developing after RAI trended toward inferior survival compared with matched controls with de novo AML (median overall survival, 1.2 years *v* 2.9 years; $P = .06$).

Conclusion
Patients with WDTC treated with RAI had an increased early risk of developing AML and CML but no other hematologic malignancies. AML that arises after RAI treatment has a poor prognosis. RAI use in patients with WDTC should be limited to patients with high-risk disease features, and patients with WDTC treated with adjuvant RAI should be monitored for myeloid malignancies as part of cancer surveillance.

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INTRODUCTION

Papillary and follicular thyroid carcinomas are well differentiated thyroid cancers (WDTCs) and comprise > 90% of all thyroid cancer cases in the United States.[1] Definitive therapy for WDTC is thyroidectomy with adjuvant radioactive iodine (RAI) to ablate residual or unresectable disease.[2] In the last three decades, the incidence of WDTC increased four-fold, with the majority of the increase attributed to improved detection of small, low-risk tumors.[1,9] Although adjuvant RAI improves overall and disease-free survival in advanced-stage WDTC, most studies report little or no benefit from RAI in low-risk and intermediate-risk tumors,[2] where 5-year recurrence-free survival is already > 97% without RAI.[4] Because the widespread use of adjuvant RAI has not improved survival,[1] its clinical benefit in the treatment of WDTC is controversial.[5] Furthermore, several meta-analyses have reported an increase in the incidence of second primary malignancies in patients with WDTC treated with RAI.[6,7]

Second hematologic malignancies (SHMs) occurring in patients treated for first cancers are

ASSOCIATED CONTENT

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a rare and devastating complication. In addition, the determination of whether acute myeloid leukemia (AML) is treatment related or not has significant prognostic and treatment implications.[8,9] Although prior studies have shown an increased risk of SHMs in RAI-treated patients with WDTC, these analyses grouped all types of leukemia under one broad category.[3,7,8,10-15] This approach oversimplifies risk estimation, considering the biologic heterogeneity among and within SHM entities, their disparate natural histories, and variable prognosis. Acknowledging the differences in pathogenesis and risk factors of different SHMs, we investigated the risk of developing acute and chronic leukemias of both myeloid and lymphoid lineage, lymphomas, and multiple myeloma in patients with WDTC treated with RAI and assessed outcomes.

METHODS

Study Design and Participants

The study cohort was assembled using the April 2017 release of all 18 registries of the SEER program of the National Cancer Institute. SEER provides data from population-based cancer registries, which cover approximately 28% of the US population. Patients were excluded from analysis if their thyroid malignancy was not of follicular or papillary histology (Data Supplement); if they received treatment with chemotherapy or tyrosine kinase inhibitors; if WDTC was not their first cancer; if their hematologic malignancy (HM) was a first, third, or higher order primary cancer; if they received external-beam radiotherapy; and if radiation or survival status was unknown. The primary outcome of interest was the development of SHM, defined as a nonsynchronous HM occurring ≥ 1 year after treatment of WDTC. SHMs included in this study were AML, chronic myeloid leukemia (CML), acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma (MM), as defined by International Classification of Diseases for Oncology (3rd edition) histology codes and International Classification of Diseases (9th and 10th revision) codes (Data Supplement). Myelodysplastic syndromes (MDS) and Philadelphia chromosome-negative myeloproliferative neoplasms were excluded because of SEER-related differences between the reporting of MDS and Philadelphia chromosome-negative myeloproliferative neoplasms ALL, AML, CLL, CML, Hodgkin lymphoma, non-Hodgkin lymphoma, and MM (Data Supplement). SHMs occurring < 1 year after WDTC diagnosis were also excluded.[16] Low-/intermediate-risk patients with WDTC were defined per the latest American Thyroid Association guidelines as T1-2N0 tumors ≤ 4 cm in size or T1-3N1 tumors in patients older than 45 years of age.[2]

Procedures

A previously validated R program, SEERaBomb,[17] was used to assess risks of SHM after WDTC treatment in the SEER cohort and a subset of low-/intermediate-risk WDTCs. SEERaBomb was preferred over SEER*Stat MP-SIR (Multiple Primary-Standardized Incidence Ratio), a statistical companion tool developed by the National Cancer Institute, because SEERaBomb captures more patients with second primary cancer (Data Supplement). SHM risk dynamics after diagnosis of WDTC treated with surgery alone or surgery plus RAI were estimated using methodology previously published.[17] SEERaBomb was used to calculate relative risk (RR) time courses for developing SHM after WDTC treatment on the basis of the ratio of the observed and expected patients with SHM for each WDTC treatment group. The expected number of patients with SHM was calculated using the background incidence rates of HMs in the US population and the person-years at risk for an SHM after treatment of WDTC as first cancer. RRs were adjusted for age at diagnosis, sex, and year of diagnosis. Additional potential covariables of interest analyzed are

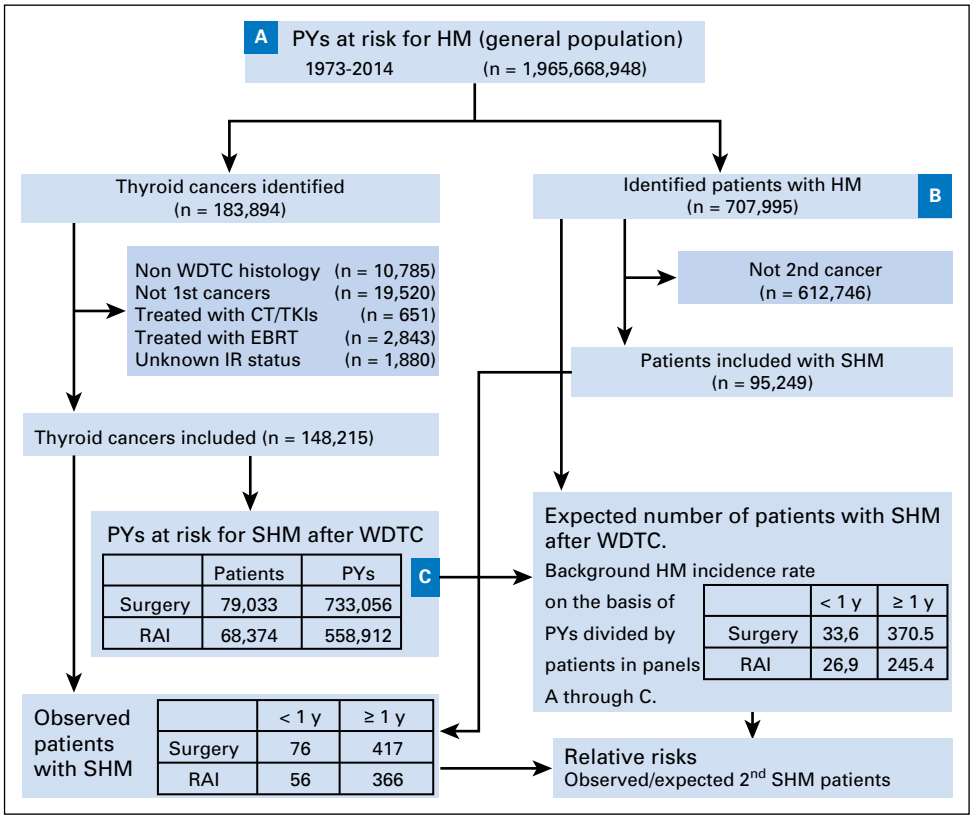

Fig 1. Population-based assessments of second hematologic malignancy (SHM) risks after well-differentiated thyroid cancers (WDTCs). SEER covers an increasing proportion of the US population, 1.97 billion person-years (PYs) since 1973. Shown is a flowchart of the inclusion of patients with WDTC and SHM and their use in calculations of relative risks (RRs) of SHM occurrence after WDTC. RRs are the number of observed patients with SHM after WDTCs divided by the number of expected patients with SHM after WDTCs. The latter is the background incidence rate of SHM per PY, which is calculated by dividing the number of hematologic malignancy (HM) patients by (B) the number of PYs at risk in the general population (A). Separate calculations were performed for each year of age, sex, and year of diagnosis. This was then multiplied by (C), the PYs at risk among WDTC survivors in these demographic cohorts to obtain the expected number of patients with SHMs after WDTCs. In the boxes entitled, "Expected patients with SHM after WDTC. Background on the basis of PYs divided by patients in panels A though C," the numbers in the boxes represent the expected numbers of patients with SHM diagnosed <1 year or <1 year after WDTC diagnosis, separated by treatment (surgery or surgery+RAI). In box "PYs at risk for SHM after WDTC," the total number of patients excludes 808 patients with insufficient follow-up. AML, acute myeloid leukemia; CML. chronic myeloid leukemia; CT, chemotherapy; IR, ionizing radiation; EBRT, external beam radiotherapy; int, intermediate; RAI, radioactive iodine; TKI, tyrosine kinase inhibitor; y, year.

described in the Data Supplement. To assess outcomes of patients with WDTC who developed an SHM, we performed survival analyses using two separate case-control designs, in which each patient with WDTC who developed SHM was compared with either five patients with WDTC who did not develop SHM or with five patients whose HM occurred de novo. Cases and controls were matched by histology, type of treatment received, tumor stage, tumor size, age at diagnosis, sex, year of WDTC/HM diagnosis, and race, in that order of priority.

Statistical Analysis

RRs and RAI-attributable RR ratios with 95% CIs and *P* values were calculated as described in the Data Supplement and explained previously.[18] Because of the low event rate of SHMs, Fine-Gray competing risk regression analyses[19] were performed with SHM as a time-dependent end point and death from all causes or development of non-SHM malignancy were treated as competing events to calculate hazard ratios (HRs) with 95% CIs of developing an SHM after WDTC. Censoring occurred at follow-up cutoff defined by the April 2017 SEER release (January 1, 2015), death, development of a second primary cancer other than the HM of interest, or when 20 years of follow-up after WDTC treatment were reached, whichever occurred first. Cox regression and standardized incidence ratio (SIR) calculations were performed to compare our results with previous studies that used these procedures to assess hazards of developing an SHM after WDTC treatment. Variables significant at an alpha level of .05 (two-sided) in univariable analyses were included in multivariable analyses. The final multivariable models were built using a backward selection procedure. For regression analyses and SIR calculations, the follow-up period was limited to 20 years to focus on early-onset SHMs because SHMs occurring in relatively young survivors of WDTC have treatment implications. Survival plots were made using the Kaplan-Meier method, and *P* values for overall survival (OS) comparisons were calculated using the Gehan-Breslow-Wilcoxon test to provide extra weight to early outcomes. All statistical analyses were performed using R software, and all scripts used to produce the results of this study are provided in the Data Supplement.

RESULTS

Patient Characteristics

Of the 183,894 patients with thyroid cancer identified from the SEER database, 148,215 patients met the inclusion criteria (Fig 1). Baseline demographic and disease characteristics of patients with WDTC by treatment modality are listed in Table 1. A total of 79,033 patients (53%) received surgery alone, and 68,374 patients (47%) received surgery plus RAI. Among the survivors of WDTC, a total of 783 nonsynchronous SHMs were identified, 417 (53%) after surgery alone and 366 (47%) after surgery plus RAI (Data Supplement). Comparisons of characteristics of patients with WDTC on the basis of RAI treatment status who later developed SHM versus those who did not are shown in the Data Supplement.

Risk of SHMs by Treatment Modality

All patient characteristics listed in Table 1 were tested for associations with SHMs as the outcome of interest in univariable (Data Supplement) and multivariable Fine-Gray competing risk regression analysis (Table 2). In multivariable analysis, surgery plus RAI was associated with a significant increase in the risk of developing SHMs (pooled as a group) compared with surgery alone (HR, 1.43; 95% CI, 1.20 to 1.69; $P < .001$). When analyzed by SHM type, the elevated risk was significant for AML (HR, 1.79; 95% CI, 1.13 to 2.82; $P = .01$) and CML (HR, 3.44; 95% CI, 1.87 to 6.36; $P < .001$), but no other SHMs (Table 2). The cumulative risk of any SHM in the first 10 years after WDTC treatment was 0.40% after surgery alone and 0.54% after surgery plus RAI. Cumulative risks of AML and CML during the same time period were 0.08% and 0.01% after surgery alone and 0.12% and 0.06% after surgery plus

Table 1. Baseline Characteristics of Patients With WDTC by Treatment Type, 1973-2014

Characteristic	Surgery Alone (n = 79,033)	Surgery and RAI (n = 68,374)	*P*
Female sex	62,804 (79)	51,657 (76)	< .001[X]
Median age at WDTC diagnosis, (IQR), years	48 (37-59)	45 (35-56)	< .001[M]
Median year of WDTC diagnosis (IQR)	2007 (2000-2011)	2007 (2002-2011)	< .001[M]
Race			
White	64,347 (81)	55,642 (81)	< .001[X]
Black	5,493 (7)	3,714 (5)	
Other	9,093 (12)	9,018 (13)	
Tumor stage			
Localized	58,237 (74)	33,212 (49)	< .001[X]
Regional	17,036 (22)	32,010 (47)	
Distant	1,411 (2)	2,662 (4)	
Unknown	2,343 (3)	488 (1)	
Histology			
Papillary	71,494 (90)	61,456 (90)	.001[X]
Follicular	7,539 (10)	6,918 (10)	
Tumor size			
< 2 cm	47,458 (60)	31,267 (46)	< .001[X]
≥ 2 cm	19,687 (25)	32,826 (48)	
Unknown	12,276 (15)	4,281 (6)	
Median follow-up time of WDTC, (IQR), years	6.6 (2.6-12.7)	6.6 (3.1-11.4)	.009[M]
Total person-years at risk	733,056	558,912	

NOTE. Data presented as No. (%) unless otherwise stated where percentages were calculated within rows. *P* values were calculated using the χ^2 test ([X]) and Mann-Whitney *U* tests ([M]). The total number of patients excludes 808 patients with unknown follow-up, all in the "Surgery Alone" column.
Abbreviations: IQR, interquartile ratio; RAI, radioactive iodine; WDTC, well-differentiated thyroid cancer.

Table 2. Multivariable Competing Risk Regression Analysis of Risk of Developing Hematologic Malignancies in Patients with WDTC

	ALL		AML		CLL		CML		HL		MM		NHL		SHMs Combined	
Covariable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, per year	**1.03 (1.01 to 1.04)**	**.007**	**1.02 (1.01 to 1.04)**	**.001**	**1.05 (1.04 to 1.06)**	**< .001**	**1.02 (1.01 to 1.03)**	**.004**	NS		**1.06 (1.05 to 1.07)**	**< .001**	**1.04 (1.04 to 1.05)**	**< .001**	**1.04 (1.04 to 1.05)**	**< .001**
Race																
Black *v* white	NS		NS		NS	NS	NS		NS		**2.48 (1.48-4.15)**	**.0005**	NS		0.97 (0.68 to 1.38)	.87
Other *v* white	NS		NS		**0.30 (0.09 to 0.93)**	**.04**	NS		NS		NS		**0.65 (0.43 to 0.98)**	**.04**	**0.59 (0.43 to 0.80)**	**.001**
Sex: male *v* female	**2.68 (1.25 to 5.77)**	**.01**	1.29 (0.82 to 2.02)	.26	**1.61 (1.01 to 2.56)**	**.05**	NS		NS		**1.50 (1.01 to 2.21)**	**.04**	**1.51 (1.18 to 1.92)**	**.001**	**1.53 (1.28 to 1.84)**	**< .001**
Year of diagnosis, per year	NS		1.02 (0.99 to 1.05)	.17	NS		NS		**0.95 (0.91 to 0.99)**	**.006**	NS		1.01 (1.00 to 1.02)	.11	**0.93 (0.92 to 0.93)**	**< .001**
Stage, regional *v* localized	NS		**1.92 (1.23 to 2.98)**	**.004**	NS		1.56 (0.89 to 2.74)	.12	2.11 (0.96 to 4.62)	.06	0.78 (0.49 to 1.21)	.27	NS		1.16 (0.96 to 1.39)	.12
Stage, metastasized *v* localized	NS		NS		NS		NS		4.19 (0.90 to 19.40)	.07	NS		NS		1.11 (0.66 to 1.85)	.70
Tumor size, > 2 cm *v* < 2 cm	NS		NS		NS		NS		NS		NS		NS		**0.81 (0.68 to 0.97)**	**.02**
Treatment, RAI *v* no radiation	NS		**1.79 (1.13 to 2.82)**	**.012**	NS		**3.44 (1.87 to 6.36)**	**< .001**	NS		**0.65 (0.44 to 0.97)**	**.04**	NS		**1.43 (1.20 to 1.69)**	**.001**

NOTE. Shown are HRs and 95% CIs for developing a nonsynchronous (≥ 1 year after WDTC diagnosis) SHM in patients with WDTC, calculated using Fine-Gray competing risk regression analyses. Covariables that were significant in univariable analyses ($P < .05$) were included in the multivariable analysis, which was subjected to the backward selection procedure to generate the final model. The large sample size of the SHMs combined analysis allowed for inclusion of all covariables in the multivariable model, which was also subjected to a backward selection procedure. Univariable regression analyses are shown in the Data Supplement. Bold type indicates the numbers that remained significant in multivariate analysis.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; HR, hazard ratio; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NS, not significant in univariable analysis; SHM, second hematologic malignancy; WDTC, well-differentiated thyroid cancer.

RAI, respectively. SIR calculations were used to compare the incidence of SHMs among survivors of WDTC with the incidence rates of these HMs in the US population, adjusted for age, sex, and year of WDTC diagnosis. SIRs for the development of all SHMs combined were higher after both surgery alone (SIR, 119; 95% CI, 107 to 132; $P = .001$) and surgery plus RAI (SIR, 155; 95% CI, 140 to 173; $P < .001$; Table 3 and Data Supplement). When analyzed by specific SHM, SIRs after surgery plus RAI were significantly higher for ALL, AML, CLL, CML, and non-Hodgkin lymphoma. Excess risk attributable to RAI was observed for all SHMs combined (SIR, 130; 95% CI, 112 to 151; $P = .001$), and individually for AML (SIR, 211; 95% CI, 142 to 330; $P = .001$), CLL (SIR, 170; 95% CI, 108 to 269; $P = .02$), and CML (SIR, 387; 95% CI, 210 to 780; $P < .001$; Table 3). Conversely, RAI treatment was associated with decreased risk of developing MM (HR, 0.65; 95% CI, 0.44 to 0.97; $P = .04$; Table 2) and lower SIR (SIR, 68; 95% CI, 45 to 98; $P = .05$; Table 3).

Risk Dynamics of SHMs After WDTC Treatment

RR time courses and time-to-event courses of developing SHMs after WDTC are shown in Figures 2A, 2B, 2C, and 2D and the Data Supplement. Compared with the background incidence rate of AML, an early increase in the risk of AML was observed in patients with WDTC treated with surgery and RAI that peaked in the second year after treatment (RR, 7.1; 95% CI, 4.3 to 11.2; $P < .001$; Fig 2A). Beyond 2 years, the risk of AML declined, reaching baseline rates within 6 years after WDTC diagnosis. A similar significant increase in risk of CML was observed in the second year after RAI exposure compared with the background rates; however, this risk remained elevated up to 10 years after WDTC diagnosis (RR for years 2 to 10, 6.3; 95% CI, 4.4 to 8.8; $P < .001$; Fig 2C). In time-to-event analyses, surgery plus RAI was significantly associated with an increased risk of developing AML compared with surgery alone (HR, 1.6; 95% CI, 1.1 to 2.4; $P = .01$; Fig 2B) and CML (HR, 2.9; 95% CI, 1.7 to 5.2; $P = .001$; Fig 2D) but no other SHMs in patients with WDTC treated with adjuvant RAI compared with thyroidectomy alone (Data Supplement). When the RRs of the surgery alone and surgery plus RAI groups were directly compared using radiation-related RR ratios, we observed increased radiation-related RR ratios for AML and CML but no other SHMs (Data Supplement).

Risk of SHMs in Low-/Intermediate-Risk WDTCs

In a subset analysis among patients with low-risk or intermediate-risk WDTCs, where adjuvant RAI carries no or questionable clinical benefit,[2] RAI treatment was the only factor in Fine-Gray competing risk regression analyses that was significantly associated with the development of AML (HR, 2.87; 95% CI, 1.46 to 5.63; $P = .002$) and CML (HR, 3.94; 95% CI, 1.58 to 9.82; $P = .003$; Data Supplement). RAI treatment was also associated with increased RRs and decreased SHM-free survival for AML and CML in patients with low-risk or intermediate-risk WDTCs (Figs 2E, 2F, 2G, and 2H and Data Supplement).

Outcomes After Development of AML and CML

Regardless of the type of treatment received, patients with WDTC who developed AML had shorter OS compared with matched patients with WDTC who did not (median OS, 8.0 years *v* 31.0 years; $P = .001$; Fig 3A and Data Supplement). Between the WDTC treatment groups, there was a trend toward truncated OS in those who developed AML after surgery plus RAI compared with patients who developed AML after surgery alone (median OS, 6.7 years *v* 9.4 years; $P = .12$). Consistent with a good prognosis of CML, the OS of patients with WDTC who developed CML after surgery alone or surgery plus RAI was not significantly different from matched controls (Fig 3B). Compared with matched population controls with de novo AML, there was no difference in the OS of patients with WDTC who developed AML after surgery, and there was a trend toward decreased OS in patients with AML after RAI treatment (median OS, 1.2 years *v* 2.9 years; $P = .06$; Fig 3C and Data Supplement). We observed no differences in OS on the basis of whether CML occurred after WDTC treatment or de novo (Fig 3D).

DISCUSSION

With rising incidence rates of WDTC[20] and a growing population of long-term survivors of WDTC who received prior RAI, there is a clinical concern regarding the risks of adverse effects from this treatment.[3,5] This concern is particularly heightened because population-level data show that a majority of patients with WDTC treated with RAI have low-risk tumors, a scenario where patients

Table 3. SIRs of SHMs in Patients With WDTC

	Surgery Alone		Surgery and RAI		Additional Risk From RAI	
SHMs	SIR (95% CI)	*P*	SIR (95% CI)	*P*	SIR (95% CI)	*P*
SHMs combined	119 (107 to 132)	.001	155 (140 to 173)	< .001	130 (112 to 151)	.001
ALL	196 (101 to 343)	.03	282 (154 to 473)	.001	143 (61 to 338)	.41
AML	118 (83 to 162)	.35	250 (190 to 322)	< .001	211 (142 to 330)	.001
CLL	91 (63 to 127)	.61	153 (112 to 206)	.006	170 (108 to 269)	.02
CML	141 (77 to 236)	.24	533 (381 to 726)	< .001	387 (210 to 780)	.001
HL	88 (46 to 151)	.69	99 (51 to 173)	.97	112 (47 to 243)	.80
MM	150 (119 to 187)	.001	102 (73 to 138)	.91	68 (45 to 98)	.05
NHL	114 (97 to 133)	.10	130 (109 to 153)	.003	113 (90 to 142)	.28

NOTE. Not including second malignant neoplasms that occurred in the first year after WDTC diagnosis. An SIR of 100 indicates a similar ratio as the background population.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; HR, hazard ratio; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; RAI, radioactive iodine; SHM, second hematologic malignancy; SIR, standardized incidence ratio; WDTC, well-differentiated thyroid cancer.

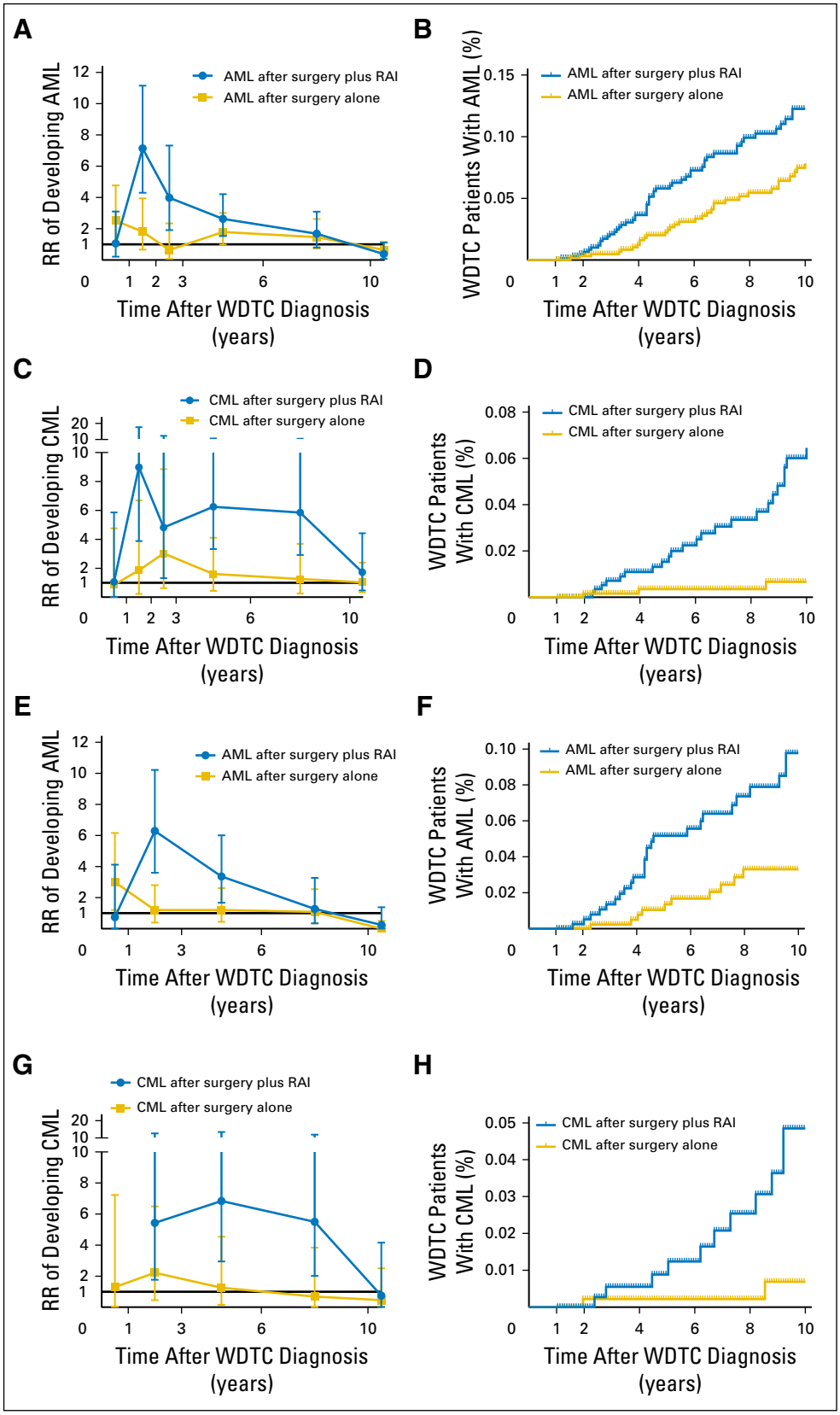

Fig 2. Risk time courses for developing second hematologic malignancy (SHM) after well-differentiated thyroid cancer (WDTC) diagnosis. (A to D) Data for all patients with WDTC; (E to H) data for patients with low-/intermediate-risk WDTC (as defined by the American Tumor Association).[2] (A, C, E, G) Plotted are mean relative risks (RRs) ± 95% CIs of developing (A, E) acute myeloid leukemia (AML) or (C, G) chronic myeloid leukemia (CML) as second cancer, on the basis of WDTC treatment type compared with the background US population, which is represented by the black line at y = 1. The number of person-years at risk, expected and observed patients, RRs, and 95% CIs for each RR time course graph are shown in the Data Supplement. Risk-time courses for SHMs other than AML or CML are shown in the Data Supplement. (B, D, F. H) Plotted are the percentage of patients with WDTC diagnosed with (B, F) AML or (D, H) CML as function of the years after WDTC diagnosis. Patients were censored at death, when they were alive at January 1, 2015, or when they developed a non-SHM second cancer. Additional hazard curves are shown in the Data Supplement. *P* values were calculated using the Gehan-Breslow-Wilcoxon test. RAI, radioactive iodine.

likely do not derive therapeutic benefit from adjuvant RAI but are exposed to its carcinogenic effects.[11] In this population-based study, we performed a comprehensive evaluation of the risk dynamics for development of SHMs in patients with WDTC and the clinical outcome of WDTC patients who developed SHM. The main findings include that (1) patients with WDTC exposed to RAI

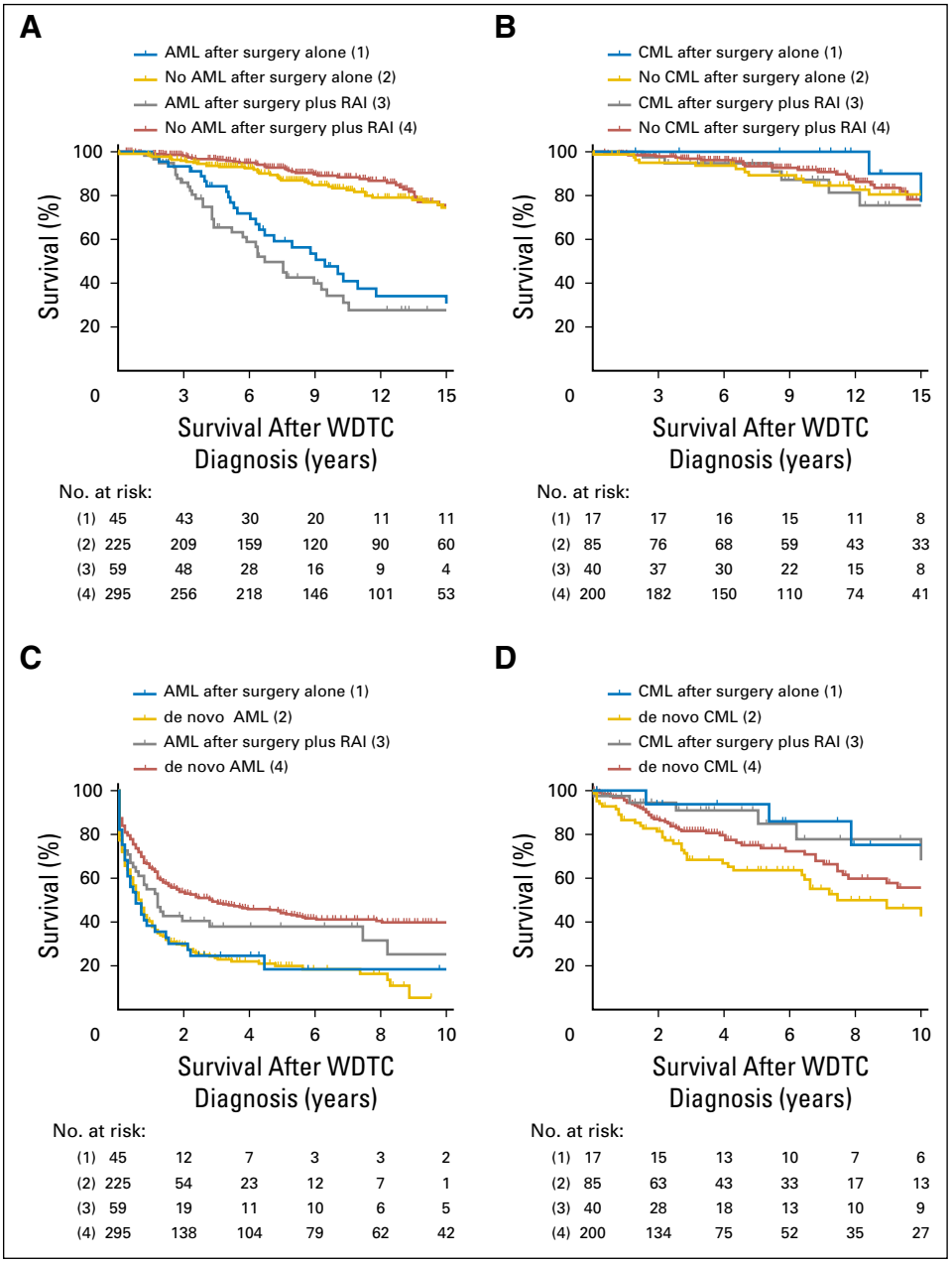

Fig 3. Survival curves of patients with well-differentiated thyroid cancer (WDTC) by development of acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) and by treatment type. Shown are Kaplan-Meier plots of case-control studies wherein the following groups were compared: patients with WDTC who developed (A) AML or (B) CML after WDTC treatment (cases) versus those who did not (controls); (C) patients with AML and (D) CML who were diagnosed with these diseases after treatment of WDTC (cases) versus those who developed AML or CML de novo (controls). In all figures, (2) are matched controls for (1), and (4) are matched controls for (2). *P* values were calculated using the Gehan-Breslow-Wilcoxon test. RAI, radioactive iodine.

have a significantly increased risk of AML and CML compared with background incidence rates in the US population; (2) increased risk for AML and CML is seen even in low-/intermediate-risk patients with WDTC treated with RAI; (3) the latency period for AML and CML after RAI therapy is short; (4) although the risk of AML declines quickly to baseline rates by 3 years, the risk of CML remains elevated for up to 10 years after RAI treatment; and (5) development of AML in patients with WDTC predicted for truncated survival compared with de novo AML.

Comparison of SHM risk attributable to RAI across different studies is challenging for several reasons, because of varying definitions of WDTC and SHM nomenclature, including grouping of disparate SHM histologies under broad leukemia and lymphoma categories, differences in methodologic and statistical considerations, and length of follow-up duration—all affecting the interpretation of results.[3,6,7,10-15] On one hand, our RR time plots show that the median follow-up of 6.5 years after WDTC diagnosis is adequate for SHM risk assessments; on the other hand, a proportion of SHMs developing in atomic bomb survivors occurred at even later time points[21] and these late occurrences may not have been captured by our analysis. We chose to use Fine-Gray competing risk regressions because this approach adequately corrects the risk of developing SHM against the competing risks of occurrence of a nonhematologic second primary malignancy or death, either WDTC-related or WDTC-unrelated. This is a critical consideration because most patients with WDTC are long-term survivors who continue to be at risk for developing solid tumor malignancies and have increased treatment-related cardiovascular mortality.[22] Although the occurrence of AML[23-26] and CML[27] after RAI treatment of WDTC has been previously reported, to our knowledge, this is the

first comprehensive report of risk dynamics of individual SHM entities over time after RAI treatment of WDTC. Furthermore, our analyses did not show increased hazards for the development of other SHMs among WDTC survivors previously treated with RAI. Although SIRs yield interesting data on the frequency of SHMs in RAI-treated WDTC survivors compared with the background population (2.5 times higher for AML and 5.3 times higher for CML), SIRs were only corrected for age, sex, and year of diagnosis, but not for other possible confounders. Whereas the Cox regression is inferior for situations where competing risks are at play, they were the preferred approach in previous studies that described second primary cancer risk after RAI treatment of WDTC.[10] Therefore, we also performed Cox regression analysis to compare our results with those of previous studies and arrived at the same conclusions resulting from our competing risk regressions (Data Supplement). In conclusion, our findings clearly demonstrate increased hazards of developing myeloid leukemias but no other type of SHMs with adjuvant RAI use. An interesting finding in our study was lower risks of MM after RAI treatment compared with thyroidectomy, the possible mechanism of which needs further investigation.

This study has certain limitations. The decision to use RAI is contingent on several covariables of interest that are not captured in the SEER cohort, such as completeness of resection, tumor multicentricity, and findings from postoperative radiologic scans.[2] The SEER database does not record the RAI doses administered to patients; hence, it is not possible to determine the leukemogenic dose-response effect of RAI that some non-SEER studies have shown.[10,12] Another drawback is that SEER only captures radiation data during initial treatment and not if patients received delayed radiation or radiation for recurrent disease. Although this can potentially lead to misclassification of patients with RAI-positive disease into the RAI-negative cohort, this is unlikely to affect our conclusions and if at all present, might reflect an underestimation of the elevated risk attributable to RAI. Another limitation of a retrospective study such as ours is that it may be vulnerable to overascertainment bias, a possible explanation of more recorded occurrences of myeloid leukemias after RAI treatment. However, such assumptions are incompatible with the quick rise and fall in AML risk dynamics that we observed. To further address the issue of latency impacting risk estimates, we re-ran the SHM risk analysis using a 2-year cut-off that excluded all SHMs occurring within 24 months from the diagnosis of WDTC. Our repeat analysis showed that the risk of AML and CML following RAI exposure in WDTC patients continued to be significantly elevated even with 2-year cut-off (Data Supplement 2 [http://ascopubs.org/doi/suppl/10.1200/JCO.2017.75.0232/suppl_file/ds_2017.75.0232.pdf]). The strengths of this study include a large population with relatively homogenous treatment exposure; a novel methodology to maximize capture of patients with SHM across all 18 SEER registries, adjusting for competing risk in statistical analysis; and information on post-SHM outcomes.

Development of therapy-related AML is a devastating complication because of its dismal prognosis.[8,9] Although patients with WDTC who developed an RAI-related AML had a worse prognosis than matched patients with de novo AML, outcomes for AML that arose after thyroidectomy were comparable to matched de novo controls. This suggests that AML that occurs after RAI treatment of WDTC resembles a treatment-related AML (*t*-AML) phenotype, which is characterized by inherent refractoriness to conventional chemotherapies.[8,9] Our findings corroborate a previous comparison of patients with AML after RAI administration for thyroid cancer or hyperthyroidism and patients with de novo AML.[25] A higher proportion of patients with AML with an antecedent history of RAI therapy harbored high-risk cytogenetic abnormalities similar to *t*-AML/treatment-related MDS arising after other cytotoxic anticancer treatments.[25] Unfortunately, SEER does not carry genomic information to facilitate interrogation of molecular and cytogenetic features of SHM arising after RAI treatment.

Our results demonstrate the importance of avoiding treatment with RAI in patients with low-risk or intermediate-risk disease, in whom RAI has shown no or questionable benefit.[2] Furthermore, our results support using the least effective dose to treat patients who have high-risk features to avoid excess bone marrow exposure, because the risk of SHM is dose dependent.[10,12] These results should also be incorporated in the surveillance strategies for patients who receive high doses of RAI to appropriately monitor blood counts to detect development of myeloid malignancies. It is encouraging to see that after the 2009 release of guidelines from American Thyroid Association, there has been a modest decrease in the use of RAI.[28] Strict adherence to these guidelines is essential to decrease the catastrophic consequence of inducing *t*-AML with RAI in a group of cancers with high cure rates affecting a relatively young patient population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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