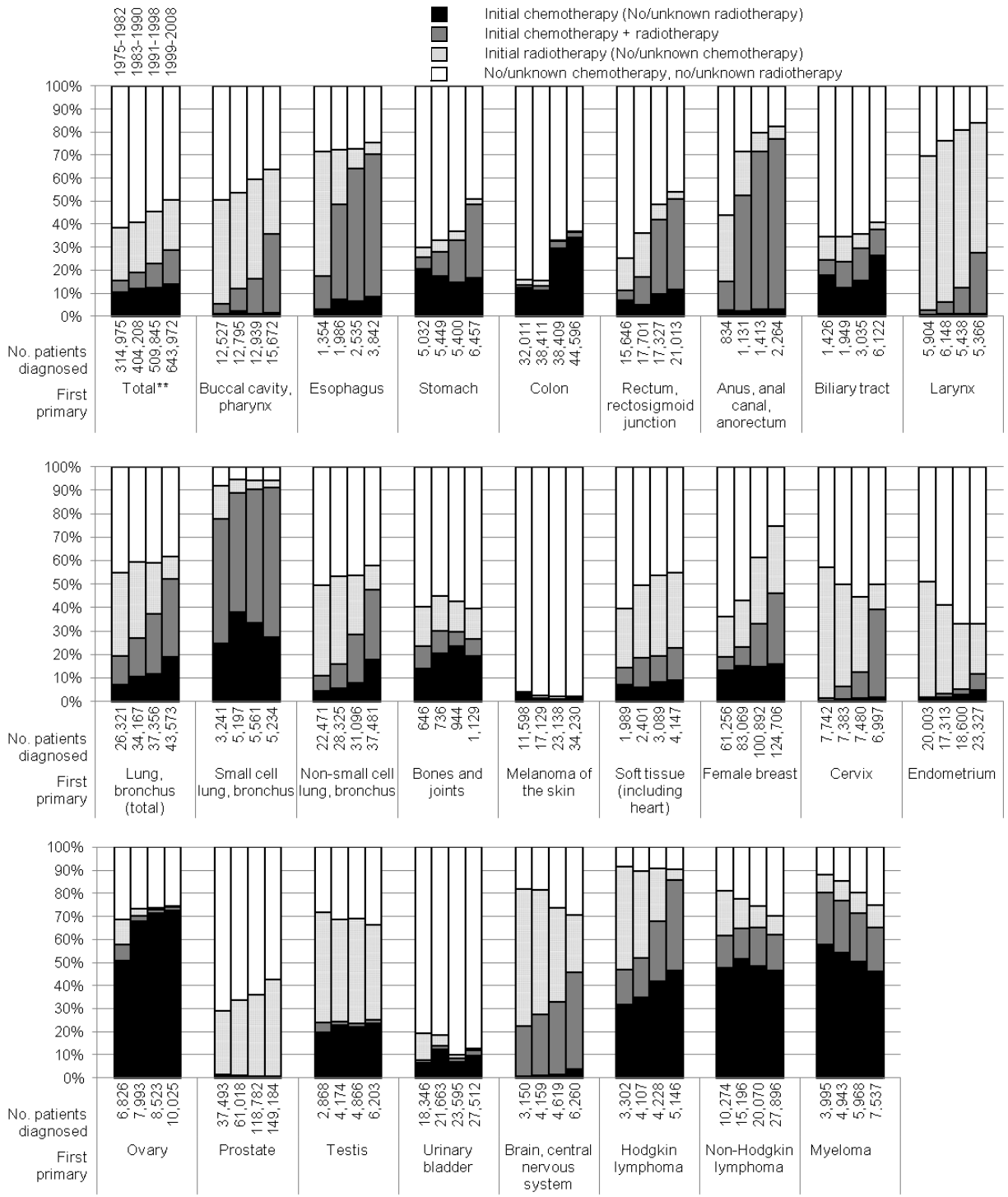**Supplementary Materials: Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008**

Lindsay M. Morton, Graça M. Dores, Margaret A. Tucker, Clara J. Kim, Kenan Onel, Ethel S. Gilbert, Joseph F. Fraumeni, Jr., and Rochelle E. Curtis

Figure S1. Percentage of patients* by calendar period and type of initial treatment for first primary malignancy in adulthood, 9 SEER registries, 1975-2008

Abbreviation: Surveillance, Epidemiology and End Results (SEER).
* The study population was restricted to patients who were diagnosed with a first primary malignancy between ages 20-84 years during 1975-2008 and who survived at least one year following diagnosis. The reported percentages are minimum estimates of the total number of patients who received chemotherapy because of under-ascertainment of initial chemotherapy treatment by the SEER cancer registries and because some patients may receive subsequent chemotherapy. Although initial chemotherapy, particularly treatments received in the outpatient setting, is known to be under-ascertained and the degree of under-ascertainment may vary by calendar period and first primary malignancy, observed trends in chemotherapy use generally are consistent with more detailed patterns of care studies based on medical record re-abstraction and physician verification of treatment.[1-10]
** All first primary malignancies excluding leukemia and non-melanoma skin cancer.

Figure S1 references:

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Table S1. Standardized incidence ratios for tAML, overall and for latency <5 years, by calendar period after initial chemotherapy treatment for selected* first primary malignancies in adulthood, 9 SEER registries, 1975-2008

First primary malignancy Calendar year period	N	SIR**	ERR ratio (95% CI)†		N	SIR**	ERR ratio (95% CI)†	
			Overall				**Latency <5 years**	
Lung, bronchus								
1975-1982	7	9.75#	1.00	(referent)	5	11.93#	1.00	(referent)
1983-1990	12	7.15#	0.83	(0.30 − 2.62)	11	11.72#	0.99	(0.33 − 3.42)
1991-1998	23	6.70#	0.69	(0.28 − 2.06)	19	8.89#	0.72	(0.27 − 2.39)
1999-2008	23	6.20#	0.54	(0.21 − 1.62)	19	5.78#	0.54	(0.20 − 1.80)
			$P_\text{homogeneity}$>0.500				$P_\text{homogeneity}$>0.500	
			P_trend=0.183				P_trend=0.139	
Female breast								
1975-1978	19	6.18#	1.00	(referent)	10	15.16#	1.00	(referent)
1979-1982	9	1.95	0.21	(0.05 − 0.61)	5	5.08#	0.30	(0.06 − 1.00)
1983-1986	16	2.98#	0.22	(0.06 − 0.61)	3	2.42	0.13	(0.01 − 0.53)
1987-1990	23	3.47#	0.38	(0.17 − 0.85)	11	7.24#	0.41	(0.15 − 1.12)
1991-1994	39	4.86#	0.54	(0.28 − 1.01)	30	13.11#	0.81	(0.38 − 1.96)
1995-1998	43	4.97#	0.42	(0.22 − 0.87)	32	9.42#	0.58	(0.27 − 1.41)
1999-2002	34	4.09#	0.27	(0.13 − 0.57)	30	6.14#	0.40	(0.18 − 0.98)
2003-2008	40	10.61#	0.56	(0.29 − 1.14)	39	10.76#	0.65	(0.31 − 1.56)
			$P_\text{homogeneity}$=0.005				$P_\text{homogeneity}$=0.011	
			P_trend>0.500				P_trend>0.500	
Ovary								
1975-1982	31	17.30#	1.00	(referent)	18	39.72#	1.00	(referent)
1983-1990	18	7.04#	0.30	(0.14 − 0.60)	10	12.73#	0.36	(0.14 − 0.81)
1991-1998	11	4.49#	0.15	(0.06 − 0.32)	7	5.82#	0.15	(0.04 − 0.40)
1999-2008	12	8.03#	0.24	(0.10 − 0.49)	9	7.47#	0.22	(0.08 − 0.52)
			$P_\text{homogeneity}$<0.001				$P_\text{homogeneity}$<0.001	
			P_trend<0.001				P_trend<0.001	
Hodgkin lymphoma								
1975-1982	14	16.56#	1.00	(referent)	4	23.07#	1.00	(referent)
1983-1990	22	21.91#	1.14	(0.57 − 2.38)	10	42.85#	1.84	(0.59 − 7.19)
1991-1998	11	10.53#	0.32	(0.11 − 0.80)	4	11.20#	0.44	(0.09 − 2.07)
1999-2008	11	18.68#	0.49	(0.20 − 1.16)	11	25.73#	1.11	(0.36 − 4.32)
			$P_\text{homogeneity}$=0.007				$P_\text{homogeneity}$=0.117	
			P_trend=0.012				P_trend >0.500	
Non-Hodgkin lymphoma								
1975-1978	6	2.97#	1.00	(referent)	<3	3.07	1.00	(referent)
1979-1982	8	2.86#	0.99	(0.24 − 5.31)	<3	1.20	0.49	(0.02 − 16.00)
1983-1986	15	4.29#	1.64	(0.53 − 8.28)	3	2.66	1.10	(0.06 − 13.78)
1987-1990	22	5.34#	2.06	(0.73 − 10.20)	10	6.88#	3.27	(0.62 − 28.02)
1991-1994	28	6.20#	2.42	(0.90 − 11.87)	9	4.92#	1.90	(0.29 − 17.16)
1995-1998	31	7.05#	2.65	(0.98 − 13.02)	10	4.62#	2.02	(0.36 − 17.61)
1999-2002	27	7.38#	2.85	(1.03 − 14.08)	20	8.34#	3.88	(0.82 − 31.36)
2003-2008	21	10.47#	4.69	(1.63 − 23.59)	21	10.81#	5.23	(1.12 − 42.00)
			$P_\text{homogeneity}$=0.028				$P_\text{homogeneity}$=0.016	
			P_trend<0.001				P_trend <0.001	

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Myeloma

1975-1982	20	16.58#	1.00	(referent)	11	13.98#	1.00	(referent)	
1983-1990	19	12.57#	0.75	(0.38 − 1.48)	10	9.98#	0.69	(0.25 − 1.78)	
1991-1998	10	5.36#	0.26	(0.09 − 0.62)	6	4.74#	0.30	(0.08 − 0.89)	
1999-2008	13	9.54#	0.58	(0.26 − 1.25)	10	8.50#	0.64	(0.24 − 1.66)	
			$P_{homogeneity}$=0.014				$P_{homogeneity}$=0.182		
			P_{trend}=0.023				P_{trend}=0.181		

Abbreviations: confidence interval (CI); therapy-related acute myeloid leukemia (tAML); standardized incidence ratio (SIR); Surveillance, Epidemiology and End Results (SEER).

Exact cell counts with <3 patients are suppressed to protect patient confidentiality.

# indicates P<0.05.

* Includes first primary malignancies after which at least 50 tAMLs were reported.

** SIRs are unadjusted.

[†] Derived from Poisson regression models adjusted for age at first primary malignancy diagnosis, receipt of initial radiotherapy, sex (for lung and bronchus, Hodgkin lymphoma, non-Hodgkin lymphoma, and myeloma), stage (for lung and bronchus, female breast, ovary), and latency (overall: 1.0-4.9, 5.0-9.9, 10+ years, except for lung and bronchus: 1-4.9, 5+ years; <5 years: 1.0-2.9, 3.0-4.9 years).

Table S2. Standardized incidence ratios and excess absolute risks for tAML by age after initial chemotherapy treatment for selected* first primary malignancies in adulthood, 9 SEER registries, 1975-2008

First primary malignancy Age at diagnosis (years)	N	SIR (95% CI)**			ERR ratio (95% CI)†				EAR (95% CI) /10,000 **			EAR ratio (95% CI)†			
Lung, bronchus															
<50	8	18.87#	(8.15	– 37.19)	1.00	(referent)			5.88	(2.53	– 11.19)	1.00	(referent)		
50-59	21	12.39#	(7.67	– 18.94)	0.61	(0.27	– 1.56)		7.65	(4.61	– 11.69)	1.25	(0.55	– 3.20)	
60-69	22	5.63#	(3.53	– 8.52)	0.22	(0.09	– 0.58)		6.01	(3.40	– 9.47)	0.94	(0.39	– 2.46)	
≥70	14	3.99#	(2.18	– 6.69)	0.12	(0.03	– 0.36)		6.20	(2.53	– 11.42)	0.89	(0.26	– 2.68)	
					$P_{homogeneity}$<0.001							$P_{homogeneity}$ >0.500			
					P_{trend}<0.001							P_{trend}>0.500			
Female breast															
<40	27	9.98#	(6.57	– 14.52)	1.00	(referent)			1.97	(1.26	– 2.88)	1.00	(referent)		
40-49	63	5.95#	(4.58	– 7.62)	0.55	(0.34	– 0.92)		1.92	(1.42	– 2.52)	0.93	(0.57	– 1.57)	
50-59	62	4.21#	(3.23	– 5.39)	0.29	(0.17	– 0.49)		2.11	(1.50	– 2.82)	0.87	(0.52	– 1.49)	
60-69	57	4.07#	(3.08	– 5.27)	0.22	(0.13	– 0.38)		3.44	(2.38	– 4.69)	1.29	(0.75	– 2.25)	
≥70	14	2.18#	(1.19	– 3.66)	0.06	(0.01	– 0.14)		1.85	(0.36	– 3.97)	0.58	(0.13	– 1.43)	
					$P_{homogeneity}$<0.001							$P_{homogeneity}$=0.378			
					P_{trend}<0.001							P_{trend}>0.500			
Ovary															
<50	13	9.31#	(4.96	– 15.93)	1.00	(referent)			2.70	(1.36	– 4.64)	1.00	(referent)		
50-59	23	10.84#	(6.87	– 16.27)	1.00	(0.48	– 2.22)		6.83	(4.19	– 10.30)	2.24	(1.07	– 5.04)	
60-69	24	8.65#	(5.54	– 12.87)	0.61	(0.28	– 1.39)		8.40	(5.11	– 12.69)	2.54	(1.16	– 5.85)	
≥70	12	6.00#	(3.10	– 10.48)	0.37	(0.14	– 0.94)		8.05	(3.68	– 14.41)	2.59	(1.00	– 6.55)	
					$P_{homogeneity}$=0.0505							$P_{homogeneity}$=0.058			
					P_{trend}=0.009							P_{trend}=0.024			
Hodgkin lymphoma															
<30	16	27.73#	(15.85	– 45.03)	1.00	(referent)			3.90	(2.24	– 6.20)	1.00	(referent)		
30-39	11	18.73#	(9.35	– 33.51)	0.65	(0.27	– 1.45)		4.01	(1.99	– 7.00)	0.99	(0.42	– 2.21)	
40-49	14	25.63#	(14.01	– 43.00)	0.85	(0.39	– 1.83)		9.93	(5.45	– 16.27)	2.37	(1.08	– 5.07)	
≥50	17	9.59#	(5.59	– 15.35)	0.22	(0.10	– 0.46)		10.72	(5.97	– 17.26)	2.29	(1.08	– 4.83)	
					$P_{homogeneity}$<0.001							$P_{homogeneity}$=0.034			
					P_{trend}<0.001							p_{trend}=0.009			

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Non-Hodgkin lymphoma

Age	N	EAR	(95% CI)			SIR	(95% CI)		
<40	19	17.62#	(10.61 – 27.51)	1.00	(referent)	3.42	(2.01 – 5.32)	1.00	(referent)
40-49	28	13.24#	(8.80 – 19.14)	0.64	(0.34 – 1.22)	5.22	(3.39 – 7.56)	1.36	(0.73 – 2.62)
50-59	33	6.05#	(4.16 – 8.49)	0.26	(0.14 – 0.50)	4.27	(2.74 – 6.20)	1.12	(0.59 – 2.17)
60-69	43	4.55#	(3.29 – 6.13)	0.16	(0.09 – 0.30)	5.41	(3.62 – 7.63)	1.41	(0.77 – 2.68)
≥70	35	3.93#	(2.73 – 5.46)	0.10	(0.05 – 0.20)	6.28	(3.82 – 9.37)	1.47	(0.75 – 2.91)
				$P_{homogeneity}<0.001$				$P_{homogeneity}>0.500$	
				$P_{trend}<0.001$				$P_{trend}=0.277$	

Myeloma

Age	N	EAR	(95% CI)			SIR	(95% CI)		
<50	3	12.88#	(2.66 – 37.65)	1.00	(referent)	3.64	(0.62 – 10.04)	1.00	(referent)
50-59	16	17.62#	(10.07 – 28.62)	1.23	(0.39 – 6.24)	11.24	(6.31 – 18.08)	2.77	(0.88 – 14.20)
60-69	27	13.06#	(8.61 – 19.00)	0.88	(0.29 – 4.44)	15.59	(10.00 – 22.79)	3.93	(1.31 – 19.88)
≥70	16	5.84#	(3.34 – 9.49)	0.36	(0.10 – 1.87)	9.95	(5.02 – 16.80)	2.69	(0.79 – 14.20)
				$P_{homogeneity}=0.012$				$P_{homogeneity}=0.093$	
				$P_{trend}=0.004$				$P_{trend}=0.177$	

Abbreviations: confidence interval (CI); excess absolute risk (EAR); therapy-related acute myeloid leukemia (tAML); standardized incidence ratio (SIR); Surveillance, Epidemiology and End Results (SEER).

# indicates $P<0.05$.

* Includes first primary malignancies after which at least 50 tAMLs were reported.

** SIRs and EARs are unadjusted.

† Derived from Poisson regression models adjusted for year of first primary malignancy diagnosis, receipt of initial radiotherapy, sex (for lung and bronchus, Hodgkin lymphoma, non-Hodgkin lymphoma, and myeloma), stage (for lung and bronchus, female breast, ovary), and latency (overall: 1.0-4.9, 5.0-9.9, 10+ years, except for lung and bronchus 1-4.9, 5+ years).