

Supplementary materials for:

Role of Cancer History in Cardiovascular Mortality among Different Age-group

Patients with Differentiated Thyroid Cancer

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Running Head: INCREASED RISK OF CARDIOVASCULAR MORTALITY FOR DTC-2

Key words: Differentiated thyroid cancer; Cardiovascular disease; Mortality risk; Second primary neoplasm; Cancer treatment

Number of supplementary tables: 8

Number of supplementary figures: 4

Fig. S1. Trends of proportion of cases diagnosed as second primary differentiated thyroid cancer (DTC-2) in new differentiated thyroid cancers (DTC) cases.

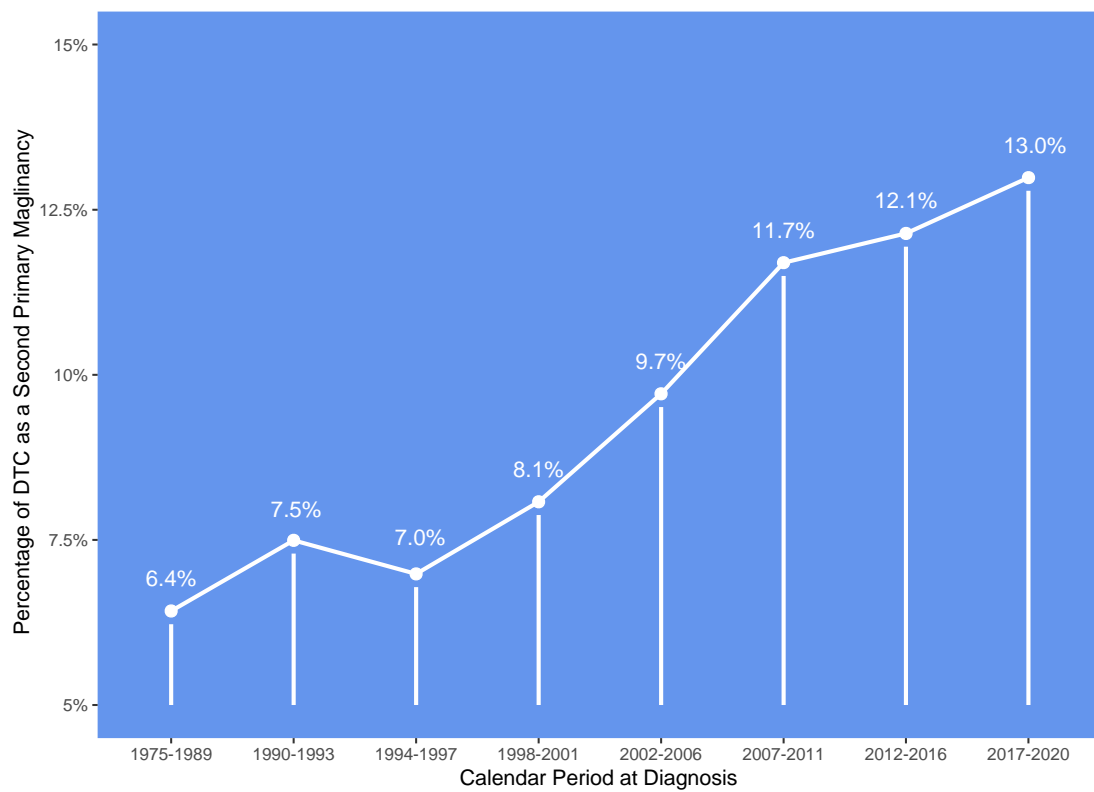


Fig. S2. The distribution of sites of first malignancy, for second primary differentiated thyroid cancer patients with information on previous malignancy diagnosis (N=12889).

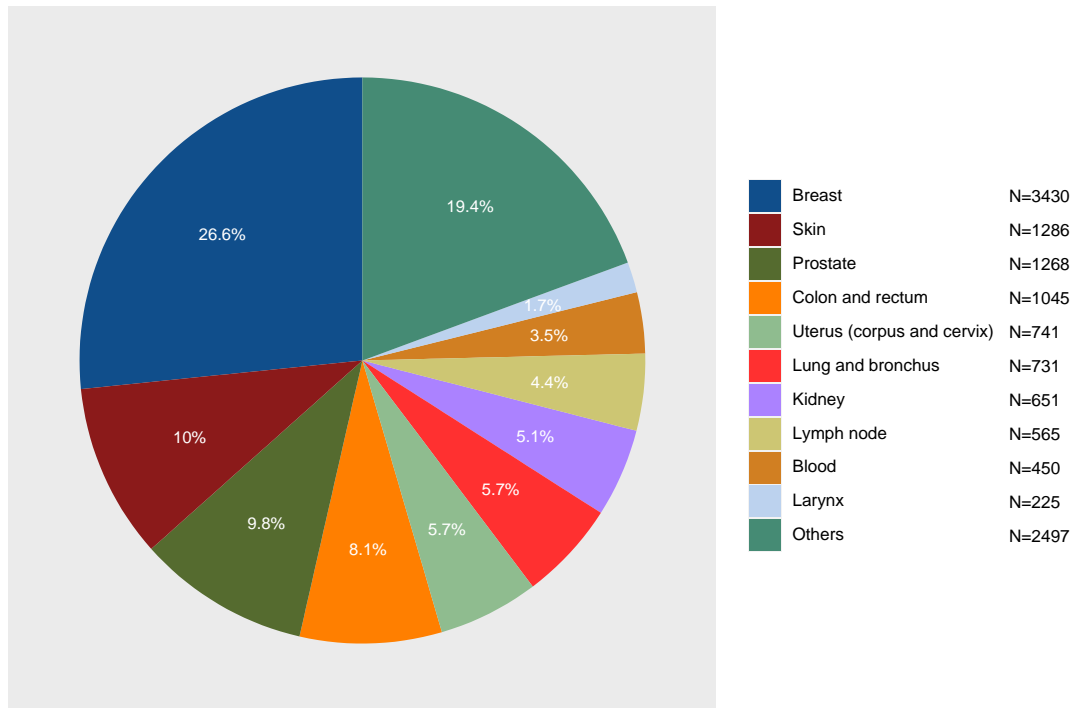


Fig. S3. Cumulative mortality rates of thyroid-cancer specific (A) and cardiovascular (B) causes of death among patients with differentiated thyroid cancer as the first (DTC-1) and second (DTC-2) malignancy from cancer diagnosis to 40 years afterwards using a competing risk model (Fine-Gray model): a population-based cohort study in the U.S., 1975-2020.

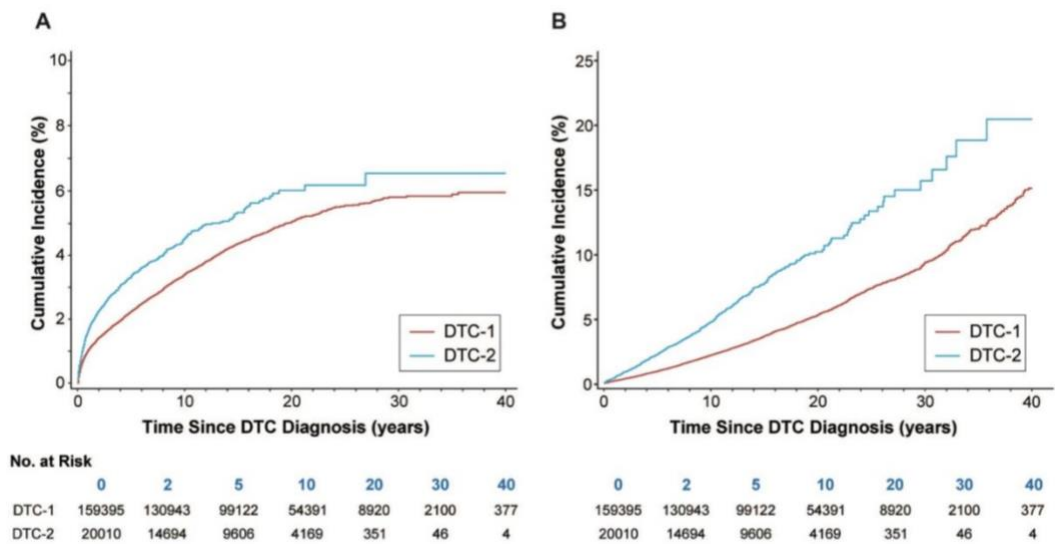


Fig. S4. The stacked area chart which shows cumulative mortality rates by causes of death among patients with first and second primary differentiated thyroid cancer from cancer diagnosis to 20 years afterwards without considering competing risks: a population-based cohort study in the U.S., 1975-2020.

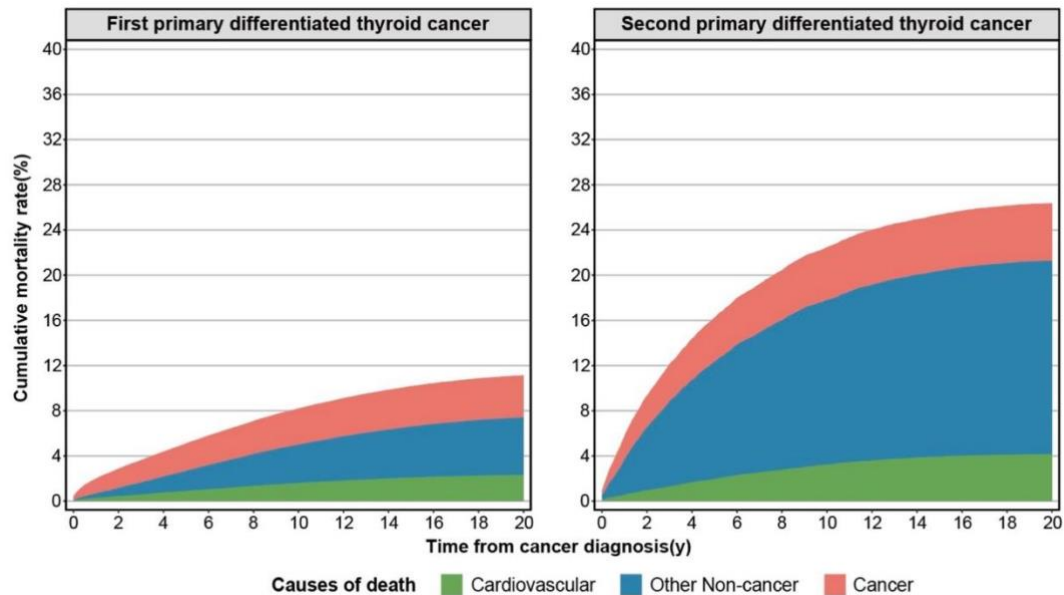


Table S1. International Classification of Diseases (ICD) codes identifying deaths from cardiovascular disease including disease of the heart, cerebrovascular disease, or other cardiovascular disease.

Death of cardiovascular disease	ICD-8 (1968-1978)	ICD-9 (1979-1998)	ICD-10 (1999-present)
Cardiovascular disease	390-448	390-448	I00–I78
Disease of the heart	390-398, 402, 404, 410-429	390-398, 402, 404, 410-429	I00-I09, I11, I13, I20-I51
Cerebrovascular disease	430-438	430-438	I60-I69
Other cardiovascular disease	The remaining codes		

Table S2. Characteristics of patients with differentiated thyroid cancer as the first (DTC-1) and second (DTC-2) malignancy and the U.S. population: a population-based study in the U.S., 1975-2020.

Variables	Population	DTC-1	DTC-2
	Per 100 PYs (%)	N (%)	N (%)
Total	71214642 (100.00)	159395 (100.00)	20010 (100.00)
Gender			
Female	37424739 (52.6)	120604 (75.7)	13572 (67.8)
Male	33789903 (47.4)	38791(24.3)	6438 (32.2)
Calendar year at follow-up			
1975-1989	5672474 (8.0)	4938 (3.1)	339 (1.7)
1990-1993	17746045 (24.9)	2975 (1.9)	241 (1.2)
1994-1997	6110862 (8.6)	4421 (2.8)	332 (1.7)
1998-2001	6480734 (9.1)	10095 (6.3)	887 (4.4)
2002-2006	8558599 (12)	25770 (16.2)	2772 (13.9)
2007-2011	9053738 (12.7)	38574 (24.2)	5110 (25.5)
2012-2016	9572534 (13.4)	46013 (28.9)	6358 (31.8)
2017-2021	8019656 (11.3)	26609 (16.7)	3971 (19.8)
Attained age, years			
30-44	26669217 (37.4)	23995 (15.1)	1037 (5.2)
45-54	15446813 (21.7)	36174 (22.7)	2548 (12.7)
55-64	12818492 (18.0)	43019 (27.0)	4914 (24.6)
65-74	9185027 (12.9)	33240 (20.9)	5783 (28.9)
75+	7095093 (10.0)	22967 (14.4)	5728 (28.6)

Variables	Population	DTC-1	DTC-2
	Per 100 PYs (%)	N (%)	N (%)
Race			
White	59770682 (83.9)	128972 (80.9)	16870 (84.3)
Black	7939453 (11.1)	10725 (6.7)	1274 (6.4)
Others ^a	3504506 (4.9)	19698 (12.4)	1866 (9.3)
Region of residence ^b			
Midwest	3889837 (5.5)	4098 (2.6)	645 (3.2)
Northeast	9777712 (13.7)	30987 (19.4)	4155 (20.8)
South	10763648 (15.2)	35428 (22.2)	4571 (22.9)
West	10365726 (14.6)	73951 (46.4)	9513 (47.5)
Unknown	36417720 (51.1)	14931 (9.4)	1126 (5.6)
Age at diagnosis, years			
30-44	-	55303 (34.7)	2368 (11.8)
45-54	-	41983 (26.3)	3894 (19.5)
55-64	-	33058 (20.7)	5459 (27.3)
65-74	-	19993 (12.5)	5125 (25.6)
75+	-	9058 (5.7)	3164 (15.8)
Time since diagnosis			
0 to <1 month	-	2282 (1.4)	291 (1.5)
1 to <6 month	-	6508 (4.1)	1064 (5.3)
6 to <12 month	-	6143 (3.9)	1129 (5.6)
1 to <2 years	-	10854 (6.8)	2102 (10.5)

Variables	Population	DTC-1	DTC-2
	Per 100 PYs (%)	N (%)	N (%)
2 to <5 years	-	30149 (18.9)	4778 (23.9)
5 to <10 years	-	44644 (28.0)	5762 (28.8)
≥10 years	-	58815 (36.9)	4884 (24.4)
Rural-urban continuum			
Counties in metropolitan areas of lt 250 thousand pop	-	10471 (6.6)	1370 (6.8)
Counties in metropolitan areas of 250,000 to1 million pop	-	33934 (21.3)	4312 (21.5)
Counties in metropolitan areas ge 1 million pop	-	94492 (59.3)	11922 (59.6)
Nonmetropolitan counties adjacent to a metropolitan area	-	8432 (5.3)	1105 (5.5)
Nonmetropolitan counties not adjacent to a metropolitan area	-	6227 (3.9)	892 (4.5)
Unknown/missing/no match/Not 1990-2018	-	5839 (3.7)	409 (2.0)
Median household income in the county of residence			
<\$35,000	-	1815 (1.1)	266 (1.3)
\$35,000-\$54,999	-	25316 (15.9)	3359 (16.8)
\$55,000-\$74,999	-	72758 (45.6)	9107 (45.5)
\$75,000+	-	54545 (34.2)	6937 (34.7)
Unknown/missing/no match/Not 1990-2018	-	4961 (3.1)	341 (1.7)
Marital status			
Married (including common law)	-	103888 (65.2)	12359 (61.8)
Divorced	-	12011 (7.5)	1710 (8.5)
Separated	-	1517 (1.0)	186 (0.9)
Single (never married)	-	24966 (15.7)	2641 (13.2)

Variables	Population	DTC-1	DTC-2
	Per 100 PYs (%)	N (%)	N (%)
Unmarried or Domestic Partner	-	378 (0.2)	41 (0.2)
Widowed	-	8584 (5.4)	1941 (9.7)
Unknown	-	8051 (5.1)	1132 (5.7)
Histology			
Papillary	-	140579 (88.2)	17331 (86.6)
Follicular	-	18816 (11.8)	2679 (13.4)
Tumor grade			
Well differentiated	-	21699 (13.6)	2560 (12.8)
Moderately differentiated	-	4973 (3.1)	556 (2.8)
Undefined	-	132723 (83.3)	16894 (84.4)
Tumor stage			
Localized	-	100874 (63.3)	12390 (61.9)
Regional	-	48923 (30.7)	6041 (30.2)
Distant	-	6818 (4.3)	1093 (5.5)
Unknown	-	2780 (1.7)	486 (2.4)
Surgery			
No/unknown	-	245 (0.2)	41 (0.2)
Yes	-	159150 (99.8)	19969 (99.8)
Radiotherapy for DTC			
No/unknown	-	89453 (56.1)	12478 (62.4)
Radioactive iodine treatment		64135 (40.2)	6697 (33.4)

Variables	Population		DTC-1		DTC-2	
	Per 100 PYs (%)		N (%)		N (%)	
External radiotherapy			5807 (3.6)		835 (4.2)	
Chemotherapy for DTC						
No/unknown	-		158235 (99.3)		19738 (98.6)	
Yes	-		1160 (0.7)		272 (1.4)	
Radiotherapy for the first malignancy						
No/unknown	-		-		8560 (42.8)	
Yes	-		-		4329 (21.6)	
No any information on the first malignancy	-		-		7121 (35.6)	
Chemotherapy for the first malignancy						
No/unknown	-		-		8577 (42.9)	
Yes	-		-		4321 (21.6)	
No any information on the first malignancy	-		-		7121 (35.6)	
	N of deaths	MR	N of deaths	MR	N of deaths	MR
Cardiovascular mortality	41420893	0.58	3612	0.29	737	0.70

Abbreviations: CI, confidence interval; HR+, hormone-receptor positive; HR-, hormone-receptor negative; HER2, human epidermal growth factor receptor 2; PYs, person-years.

^aThe other included American Indian/Alaska Native, Asian, and Pacific Islander.

^bThe Northeast included Connecticut, Massachusetts, New Jersey and New York. The Midwest included Iowa and Illinois. The South included Atlanta, Georgia, Kentucky, Texas, and Louisiana. The West included Alaska, California, Arizona, Hawaii, Idaho, New Mexico, Utah, and Washington. Race other than white and black in the population was grouped at the national level given small numbers of cardiovascular deaths.

Table S3. The sites as well as the corresponding codes of the smoking-related cancers and the thoracic cancers according to ICD-10.

Sites of neoplasms	ICD-10
Smoking-related cancers	
Lip, oral cavity or pharynx	C00-C14
Esophagus	C15
Stomach	C16
Colorectum	C18-C21
Liver	C22
Pancreas	C25
Lung, bronchus or trachea	C33-C34
Cervix	C53
Bladder	C67
Blood	C91-C95
Thoracic cancers	
Esophagus	C15
Lung, bronchus or trachea	C33-C34
Mediastinum and pleura	C38
Breast	C50

Table S4. Incidence rate ratios (IRRs) of cardiovascular deaths among patients with the primary differentiated thyroid cancer (DTC-2) developed from non-thyroidal malignancy, compared with the population and patients with primary differentiated thyroid cancer (DTC-1): without censoring follow-up at the occurrence of a subsequent malignancy.

	References		DTC-2 N (MR)	DTC-2 vs. Population	DTC-2 vs. DTC-1		
	Population N (MR)	DTC-1 N (MR)		IRR (95% CI) ^a	IRR (95% CI) ^b	IRR (95% CI) ^c	IRR (95% CI) ^d
Overall	41420893 (0.58)	4155 (0.32)	860 (0.78)	1.08 (0.94-1.19)	1.33 (1.24-1.44)	1.34 (1.24-1.44)	1.33 (1.24-1.43)
By attained age, yr							
30-44	812453 (0.03)	73 (0.07)	9 (0.27)	14.10 (10.29-19.32)	3.27 (1.54-6.95)	3.86 (2.00-7.44)	3.84 (2.02-7.30)
45-54	2012101 (0.13)	261 (0.10)	32 (0.27)	3.55 (2.63-4.79)	2.73 (1.92-3.87)	2.77 (1.95-3.93)	2.73 (1.89-3.94)
55-64	4467967 (0.35)	544 (0.15)	79 (0.30)	1.51 (1.12-2.05)	1.80 (1.43-2.25)	1.90 (1.52-2.38)	1.87 (1.49-2.33)
65-74	8079918 (0.88)	886 (0.28)	186 (0.57)	0.91 (0.68-1.23)	1.40 (1.19-1.64)	1.43 (1.22-1.67)	1.42 (1.21-1.66)
≥75	26048454 (3.67)	2391 (1.06)	554 (1.56)	0.34 (0.25-0.45)	1.19 (1.10-1.29)	1.20 (1.10-1.29)	1.20 (1.11-1.29)
<i>P</i> for interaction ^e				<0.001	<0.001	<0.001	<0.001

Abbreviations: CI confidence interval, IRR incidence rate ratio, MR mortality rate per 10–0 person-years, N number of deaths.

^aIRRs were adjusted for sex (female or male), attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years), race (white, black or other), and calendar year at follow-up (1975–1989, 1990–1993, 1994–1997, 1998–2001, 2002–2006, 2007–2011, 2012–2016, or 2017–2020). Patients who were not white/black were grouped at the national level when comparing DTC-2 with the population.

^bIRRs were additionally adjusted for time since diagnosis (0 to <1 month, 1 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <10 years or ≥10 years).

^cIRRs were additionally adjusted for tumor stage (localized, regional, distant or unknown), histology (follicular or papillary), and grade (well differentiation, moderate differentiation, poor differentiation, undifferentiation or unknown)

^dIRRs were additionally adjusted for surgery (yes or no/unknown), radiotherapy (yes or no/unknown), and chemotherapy (yes or no/unknown).

^eWe added an interaction term between DTC-2 and attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years) and reported the significance level of the term as *P* for interaction

Table S5. Incidence rate ratios (IRRs) of cardiovascular deaths among patients with the primary differentiated thyroid cancer (DTC-2) developed from non-thyroidal malignancy, compared with the population and patients with primary differentiated thyroid cancer (DTC-1): a population-based study in the U.S., 1975-2020.

	References		DTC-2 N (MR)	DTC-2 vs. Population	DTC-2 vs. DTC-1		
	Population N (MR)	DTC-1 N (MR)		IRR (95% CI) ^a	IRR (95% CI) ^b	IRR (95% CI) ^c	IRR (95% CI) ^d
Overall	41420893(0.58)	3612 (0.29)	737 (0.70)	0.97 (0.81-1.16)	1.12 (1.04-1.22)	1.12 (1.03-1.21)	1.12 (1.03-1.21)
By age at diagnosis, yr							
30-74	2115103 (0.2)	2486 (0.20)	405 (0.42)	1.24 (1.02-1.47)	1.16 (1.04-1.28)	1.16 (1.04-1.29)	1.15 (1.03-1.27)
≥75	3288448 (5.1)	1126 (3.40)	332 (3.51)	0.72 (0.55-0.95)	1.05 (0.95-1.16)	1.04 (0.94-1.16)	1.04 (0.94-1.15)
By age at diagnosis, yr							
30-44	812453 (0.03)	284 (0.05)	26 (0.15)	8.59 (6.56-11.26)	2.22 (1.43-3.46)	2.25 (1.45-3.51)	2.38 (1.56-3.63)
45-54	2012101 (0.13)	492 (0.14)	44 (0.17)	1.67 (1.24-2.25)	1.24 (1.11-1.38)	1.25 (1.13-1.39)	1.24 (1.11-1.38)
55-64	4467967 (0.35)	737 (0.33)	113 (0.38)	1.48 (1.10-2.00)	1.17 (1.09-1.26)	1.19 (1.10-1.27)	1.17 (1.09-1.26)
65-74	8079918 (0.88)	973 (0.90)	222 (0.98)	1.30 (0.96-1.74)	1.15 (1.05-1.25)	1.15 (1.06-1.26)	1.14 (1.04-1.24)
≥75	26048454 (3.67)	1126 (3.40)	332 (3.51)	0.72 (0.55-0.95)	1.05 (0.95-1.16)	1.04 (0.94-1.16)	1.04 (0.94-1.15)
<i>P</i> for interaction ^e				<0.001	<0.001	<0.001	<0.001

^aIRRs were adjusted for sex (female or male), attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years), race (white, black or other), and calendar year at follow-up (1975–1989, 1990–1993, 1994–1997, 1998–2001, 2002–2006, 2007–2011, 2012–2016, or 2017–2020). Patients who were not white/black were grouped at the national level when comparing DTC-2 with the population.

^bIRRs were additionally adjusted for time since diagnosis (0 to <1 month, 1 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <10 years or ≥10 years).

^cIRRs were additionally adjusted for tumor stage (localized, regional, distant or unknown), histology (follicular or papillary), and grade (well differentiation, moderate differentiation, poor differentiation, undifferentiation or unknown)

^dIRRs were additionally adjusted for surgery (yes or no/unknown), radiotherapy (yes or no/unknown), and chemotherapy (yes or no/unknown).

^eWe added an interaction term between DTC-2 and attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years) and reported the significance level of the term as *P* for interaction

Table S6. Incidence rate ratios (IRRs) of cardiovascular deaths among patients with the primary differentiated thyroid cancer (DTC-2) developed from non-mammary malignancy, compared with population and patients with differentiated thyroid cancer (DTC-1): a population-based study in the U.S., 1975–2020, stratified by sex and attained age (30–74 or ≥ 75 years).

	References		DTC-2 N (MR)	DTC-2 vs. Population	DTC-2 vs. DTC-1		
	Population N (MR)	DTC-1 N (MR)		IRR (95% CI) ^a	IRR (95% CI) ^b	IRR (95% CI) ^c	IRR (95% CI) ^d
Overall	41420893 (0.58)	3612 (0.29)	737 (0.70)	1.01 (0.94-1.26)	1.27 (1.18-1.38)	1.27 (1.18-1.38)	1.26 (1.17-1.37)
Female							
30-74	5500815 (0.14)	915 (0.11)	148 (0.29)	2.19 (1.06-4.53)	2.18 (1.84-2.59)	2.20 (1.85-2.61)	2.13 (1.79-2.53)
≥75	15535569 (3.52)	1420 (0.85)	270 (1.28)	0.32 (0.13-0.82)	1.22 (1.08-1.36)	1.22 (1.09-1.37)	1.22 (1.08-1.37)
P for interaction ^e				<0.001	<0.001	<0.001	<0.001
Male							
30-74	9871615 (0.35)	651 (0.27)	115 (0.64)	1.83 (0.94-3.56)	1.41 (1.16-1.72)	1.43 (1.18-1.74)	1.38 (1.13-1.68)
≥75	10512894 (3.92)	626 (1.12)	204 (1.72)	0.43 (0.15-1.24)	1.13 (0.98-1.30)	1.12 (0.97-1.29)	1.12 (0.97-1.29)
P for interaction				<0.001	<0.001	<0.001	<0.001

Abbreviations: CI confidence interval, IRR incidence rate ratio, MR mortality rate per 100 person-years, N number of deaths.

^aIRRs were adjusted for race (white, black or other), and calendar year at follow-up (1975–1989, 1990–1993, 1994–1997, 1998–2001, 2002–2006, 2007–2011, 2012–2016, or 2017–2020). Patients who were not white/black were grouped at the national level when comparing DTC-2 with the population.

^bIRRs were additionally adjusted for time since diagnosis (0 to <1 month, 1 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <10 years or ≥10 years).

^cIRRs were additionally adjusted for tumor stage (localized, regional, distant or unknown), histology (follicular or papillary), and grade (well differentiation, moderate differentiation, poor differentiation, undifferentiation or unknown)

^dIRRs were additionally adjusted for surgery (yes or no/unknown), radiotherapy (yes or no/unknown), and chemotherapy (yes or no/unknown).

^eWe added an interaction term between DTC-2 and attained age (30–74 or ≥ 75 years) and reported the significance level of the term as **P** for interaction

Table S7. Incidence rate ratios (IRRs) of cardiovascular deaths among patients with second primary differentiated thyroid cancer (DTC-2) by time since cancer diagnosis, compared with the population and patients with first differentiated thyroid cancer (DTC-1): a population-based study in the U.S., 1975-2020.

	DTC-1 N (MR)	DTC-2 N (MR)	DTC-2 vs. Population IRR (95% CI) ^a	DTC-2 vs. DTC-1 IRR (95% CI) ^b
Attained age 30 to 74 years				
By time since diagnosis				
0 to <1 month	85 (61.08)	11 (128.16)	21.56 (19.11-24.32)	2.41 (1.37-4.23)
1 to <6 months	84 (6.87)	20 (14.57)	15.79 (13.74-18.14)	3.19 (2.03-5)
6 to <12 months	79 (2.24)	19 (4.44)	15.09 (13.29-17.14)	1.57 (0.92-2.67)
1 to <2 years	144 (1.10)	43 (2.49)	3.86 (3.28-4.54)	1.83 (1.32-2.55)
2 to <5 years	353 (0.41)	73 (0.76)	4.15 (3.44-5.01)	1.42 (1.11-1.81)
5 to <10 years	438 (0.17)	64 (0.26)	1.04 (0.84-1.29)	1.34 (1.04-1.73)
≥10 years	419 (0.06)	42 (0.12)	0.38 (0.33-0.44)	2.09 (1.54-2.83)
Attained age ≥75 years				
By time since diagnosis				
0 to <1 month	36(275.38)	10(400.00)	14.13 (12.37-16.14)	1.57 (0.89-2.76)
1 to <6 months	55(44.61)	20(80.00)	8.20 (7.18-9.37)	1.89 (1.27-2.82)
6 to <12 months	53(23.87)	10(11.42)	1.25 (0.89-1.58)	0.49 (0.28-0.87)
1 to <2 years	94(9.41)	42(10.63)	0.84 (0.64-1.11)	1.12 (0.85-1.48)
2 to <5 years	324(3.96)	107(3.81)	1.13 (0.87-1.48)	1.01 (0.84-1.21)
5 to <10 years	556(1.60)	147(1.53)	0.37 (0.26-0.52)	1.04 (0.88-1.22)
≥10 years	892(0.51)	129(0.62)	0.12 (0.09-0.16)	1.3 (1.09-1.55)

Abbreviations: CI, confidence interval; IRR, incidence-rate ratio; MR, mortality rate per 100 person-years; N, number of deaths.

^aIRRs were adjusted for sex (female or male), attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years), race (white, black or other), and calendar year at follow-up (1975–1989, 1990–1993, 1994–1997, 1998–2001, 2002–2006, 2007–2011, 2012–2016, or 2017–2020). Patients who were not white/black were grouped at the national level when comparing DTC-2 with the population.

^bIRRs were additionally adjusted for time since diagnosis(0 to <1 month, 1 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <10 years, and ≥10 years), tumour stage (localized, regional, distant, or unknown), histology (follicular or papillary), grade (well differentiation, moderate differentiation, poor differentiation, undifferentiation, or unknown), surgery (no surgery, yes surgery, or unknown), radiotherapy (yes or no/unknown), and chemotherapy(yes or no/unknown).

Table S8. Incidence rate ratios (IRRs) of cardiovascular deaths at attained age of 30 to 74 years patients with second primary differentiated thyroid cancer (DTC-2), stratified by demographic and clinical characteristics, compared with the population and patients with first primary differentiated thyroid cancer (DTC-1).

	Population		DTC-1		DTC-2		DTC-2 vs. Population IRR (95% CI) ^a	DTC-2 vs. DTC-1 IRR (95% CI) ^b
	100 PYs	N (MR)	100 PYs	N (MR)	100 PYs	N (MR)		
Tumor stage								
Local	64119548	15372470 (0.24)	7145	957 (0.13)	516	150 (0.29)	0.84 (0.47-1.50) ^c	1.27 (1.05-1.53)
Regional			3538	476 (0.13)	247	89 (0.36)	1.05 (0.59-1.88) ^c	1.56 (1.23-1.97)
Distant			205	99 (0.48)	15	10 (0.67)	1.90 (0.76-4.72) ^c	0.87 (0.46-1.64)
Unstaged			178	34 (0.19)	15	14 (0.94)	3.62 (1.67-7.84) ^c	2.64 (1.17-5.97)
P for difference							<0.001	0.190
Histology								
Papillary	64119548	15372470 (0.24)	9917	1282 (0.13)	718	232 (0.32)	0.94 (0.53-1.64) ^c	1.46 (1.26-1.68)
Follicular			1149	284 (0.25)	76	31 (0.41)	1.03 (0.53-1.98) ^c	1.03 (0.70-1.50)
P for difference							0.218	0.232
Radiotherapy for DTC								
No/unknown	64119548	15372470 (0.24)	5812	1001 (0.17)	452	185 (0.41)	1.13 (0.64-2.01) ^c	1.45 (1.23-1.71)
Radioactive iodine treatment			4869	514 (0.11)	316	72 (0.23)	0.71 (0.39-1.30) ^c	1.32 (1.02-1.72)
External radiotherapy			385	51 (0.13)	25	6 (0.24)	0.80 (0.36-1.79) ^c	1.74 (0.38-1.43)
P for difference							0.013	0.216

Abbreviations: CI, confidence interval; HR+, hormone-receptor positive; HR-, hormone-receptor negative; HER2, human epidermal growth factor receptor 2; PYs, person-years; N, number of death.

^aIRRs were adjusted for sex (female or male), attained age (30–44, 45–54, 55–64, 65–74 or ≥ 75 years), race (white, black or other), and calendar year at follow-up (1975–1989, 1990–1993, 1994–1997, 1998–2001, 2002–2006, 2007–2011, 2012–2016, or 2017–2020). Patients who were not white/black were grouped at the national level when comparing DTC-2 with the population.

^bIRRs were additionally adjusted for time since diagnosis (0 to <1 month, 1 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <10 years, and ≥10 years), tumour stage (localized, regional, distant, or unknown), histology (follicular or papillary), grade (well differentiation, moderate differentiation, poor differentiation, un-differentiation, or unknown), surgery (no surgery, yes surgery, or unknown), radiotherapy (yes or no/unknown), and chemotherapy (yes or no/unknown).

^cThese IRRs were estimated by comparing DTC-2 of different tumor and treatment characteristics with the general population as the reference. When comparing with the general population, we tested the difference of IRRs across characteristics using Wald test and reported the P value for significance; when comparing with patients with DTC-1, we added an interaction term with the characteristic and tested the significant level of the interaction term for difference.