

Table S1 Site-specific observation of first primary malignancy receiving radiation treatment

Site	No. of patients	No. of patients treated with beam radiation	No. of patients treated with combination of beam with implants or isotopes	No. of patients treated with radioactive implants	No. of patients treated with radioisotopes	No. of patients treated with all kinds of radiation	Proportion of patients treated with radiotherapy (%)
Esophagus	17099	10939	106	16	4	11065	64.71
Lung and bronchus	127925	54078	390	121	30	54619	42.69
Breast	478701	211505	2738	4803	153	219199	45.79
Tongue	17465	9491	692	70	9	10262	58.75
Salivary gland	7045	3818	25	7	2	3852	54.67
Floor of mouth	6496	2627	225	10	1	2863	44.07
Gum and other mouth	10344	4736	130	12	7	4885	47.22
Tonsil	9568	7997	162	36	6	8201	85.71
Nasopharynx	2862	2527	95	2		2624	91.68
Oropharynx	1837	1462	29	3	1	1495	81.38
Hypopharynx	4959	3999	39	2		4040	81.46
Nose, nasal cavity, and middle ear	3265	2093	24	7	1	2125	65.08
Larynx	21391	15880	61	11	8	15960	74.61
Eye and orbit	3646	451	14	230	74	769	21.09
Thyroid	65823	1431	340	659	26653	29083	44.18
Bones and joints	3981	804	7	4	3	818	20.54
Rectosigmoid junction	21254	4739	8	0	4	4751	22.35
Rectum	49507	20328	94	19	7	20448	41.31
Anus, anal canal, and anorectum	6709	4901	76	7	1	4985	74.3
Cervix uteri	34108	5725	10510	654	31	16920	49.6
Corpus uteri	115811	17719	17034	6273	295	41321	35.67
Vagina	734	183	276	27	2	488	66.48
Prostate	318280	74051	19006	28069	593	121719	38.24
Testis	21504	8686	14	7	67	8774	40.8
Stomach	32843	7086	19	9	4	7118	21.67
Intrahepatic bile duct	1958	355	42	34	22	453	23.13
Pancreas	25285	8726	50	16	6	8798	34.79
Retroperitoneum	1960	560	10	3	2	575	29.33
Liver	17561	593	17	203	184	997	5.68
Gallbladder	5003	980	7	1	1	989	19.76
Lip	8250	433	26	5		464	5.62
Small intestine	7876	334	1	2	2	339	4.3
Colon	190383	4318	9	7	2	4336	2.27
Peritoneum, omentum, and mesentery	952	41	4	3	NA	48	5.04
Ovary	16798	828	29	23	36	916	5.45
Vulva	5582	1028	51	5		1084	19.41
Penis	2334	188	5	1		194	8.31
Urinary bladder	131097	7963	31	7	3	8004	6.1
Kidney and renal pelvis	63871	1265	7	9	6	1287	2.01
Ureter	2637	253	NA	1	NA	254	9.63

Both description of tumor site and the modalities of radiotherapy in the SEER Program were derived from the SEER official website (<https://seer.cancer.gov/>). NA, not available; No., number; SEER, Surveillance, Epidemiology, and End Results

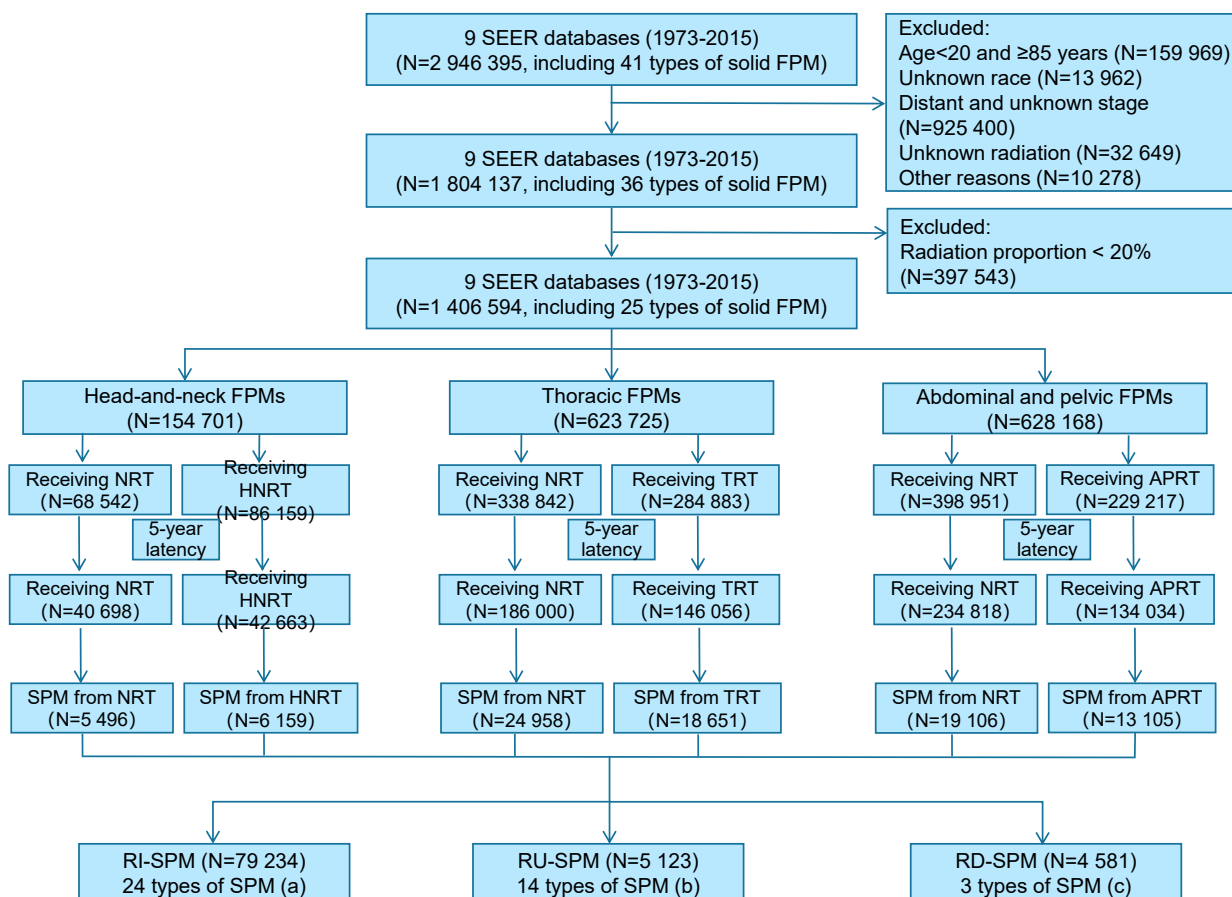


Figure S1 Flow diagram. The risk of SPMs after RT was estimated by dividing the SPMs in patients who received RT by the SPMs in patients who did not receive RT, which was assessed by the HR from multivariable Cox regression analysis. The HRs were adjusted for potential confounding factors, including race, sex, age at FPM diagnosis, and calendar year of FPM diagnosis. (a) RI-SPM was defined as the risk of SPM occurrence increase after HNRT, TRT, or APRT, with HR >1 and P value <0.05. (b) RU-SPM was defined as a risk of SPM occurrence that was unchanged after HNRT, TRT, and APRT, with a statistically nonsignificant HR and a P value ≥ 0.05 . (c) RD-SPM was defined as the risk of SPM occurrence decreasing after HNRT, TRT, or APRT, with HR <1 and a P value <0.05. HR, hazard ratio; FPM, first primary malignancy; RT, radiation therapy; NRT, no radiation therapy; SEER, Surveillance, Epidemiology, and End Results; SPM, second primary malignancy; RI-SPM, risk-increased SPM; RD-SPM, risk-decreased SPM; RU-SPM, risk-unaaffected SPM; HNRT, head-and-neck radiotherapy; TRT, thoracic radiotherapy; APRT, abdominal-and-pelvic radiotherapy.

Table S2 Descriptive statistics of the 5-year survivors according to the site of the first primary malignancy

Site of FPM	No. of patients	Follow-up for patients after RT (months)	Follow-up for patients after NRT (months)	No. of patients treated with RT by age at diagnosis			No. of patients treated with RT by year at diagnosis				No. of patients treated with RT by stage	
				20–49 (years)	50–69 (years)	70–84 (years)	1975-1984	1985-1994	1995-2004	2005+	Local	Regional
Larynx	10913	149 (98-212)*	161 (101-231)	1084	5363	1690	2695	2971	2471	NA	5596	2541
Floor of mouth	2510	117 (83-170)*	124 (87-184)	130	583	108	282	246	186	107	270	551
Gum and mouth	4348	115 (82-176)*	141 (94-217)	302	873	351	385	413	440	288	512	1014
Nasopharynx	1369	176 (105-243)*	192 (129-250)	601	601	85	279	433	575	NA	276	1011
Nose, nasal cavity, and middle ear	1341	132 (91-187)*	139 (94-201)	246	385	159	33	248	282	227	222	568
Oropharynx	488	105 (79-159)*	136 (92-195)	85	274	46	68	81	128	128	73	332
Eye and orbit	2003	119 (85-178)*	151 (94-238)	125	182	69	37	92	121	126	323	53
Hypopharynx	1068	107 (81-156)*	124 (78-184)	112	640	172	229	298	254	143	197	727
Salivary gland	4019	139 (93-218) *	174 (111-269)	701	869	424	278	525	655	537	1123	871
Thyroid	44360	134 (93-197)*	169 (104-277)	12574	5774	944	172	2642	7111	9367	10178	9114
Tongue	7008	114 (83-166)*	127 (88-190)	832	2365	452	466	616	1183	1384	830	2819
Tonsil	3934	117 (83-168)*	120 (84-175)	966	2229	267	348	510	1132	1472	467	2995
Breast	301457	139 (95-199)*	157 (101-239)	38956	72304	26789	9070	25548	57054	46377	94762	43287
Esophagus	2534	102 (76-144)*	110 (82-160)	149	863	328	88	237	516	499	637	703
Lung and bronchus	28066	95(73-135)*	109 (81-158)	777	4048	1842	NA	1745	2755	2167	1454	5213
Intrahepatic bile duct	118	99 (79-133) *	86 (67-119)	8	24	4	5	8	7	16	21	15
Stomach	8376	110 (81-157)*	126 (86-194)	276	735	325	61	188	542	545	367	969
Pancreas	1762	100 (75-147)*	104 (78-160)	75	342	123	24	75	216	225	113	427
Rectum and rectosigmoid junction	44039	142 (94-213)*	125 (86-186)	2631	8071	3043	1244	3092	5076	4333	4787	8958
Anus, anal canal, and anorectum	3753	127 (88-184)*	139 (94-211)	736	1514	488	226	490	983	1039	1699	1039
Corpus uteri	63453	165 (102-254)*	229 (143-325)	1917	10950	4539	4697	4424	4447	3838	12444	4962
Vagina	442	166 (101-228)*	194 (136-277)	57	134	93	102	88	94	NA	165	119
Cervix uteri	20443	173 (106-263)*	263 (150-331)	3703	3165	913	2305	2020	2059	1397	3237	4543
Prostate	209829	123 (91-164)	122 (89-170)	1519	46388	34677	NA	NA	46 314	36 270	82584	NA
Testis	16636	221 (150-309)*	194 (296-117)	6834	711	39	1382	2235	2701	1266	6507	1077

*, P<0.05. FPM, first primary malignancy; RT, radiation therapy; NRT, no radiation therapy; NA, not available.

Table S3 Comparisons of baseline characteristics of patients with head and neck cancer by treatment modality

Characteristic	NRT for FPM (n=40698)	RT for FPM (n=42663)	P value
Median age at first primary cancer diagnosis, (IQR), years	50 (38-62)	53 (42-62)	<0.001 ^a
Age at FPM diagnosis, n (%)			<0.001 ^b
20-49	19590 (48.1)	17758 (41.6)	
50-69	16421 (40.3)	20138 (47.2)	
70-84	4687 (11.5)	4767 (11.2)	
Gender, n (%)			<0.001 ^b
Female	26273 (64.6)	20914 (49)	
Male	14425 (35.4)	21749 (51)	
Year at FPM diagnosis, n (%)			<0.001 ^b
1975-1984	9404 (23.1)	5272 (12.4)	
1985-1994	9057 (22.3)	9074 (21.3)	
1995-2004	11157 (27.4)	14538 (34.1)	
2005+	11080 (27.2)	13779 (32.3)	
Race, n (%)			<0.001 ^b
White	34750 (85.4)	35232 (82.6)	
Black	2656 (6.5)	2993 (7)	
Other	3292 (8.1)	4438 (10.4)	
Grade of FPM, n (%)			<0.001 ^b
Grade I/II	13090 (32.2)	14532 (34.1)	
Grade III/IV	1602 (3.9)	6754 (15.8)	
Unknown	26006 (63.9)	21377 (50.1)	
Stage of FPM, n (%)			<0.001 ^b
Localized	31061 (76.3)	20067 (47)	
Regional	9637 (23.7)	22596 (53)	
Tumor size (cm) of FPM, n (%)			<0.001 ^b
<2	8290 (20.4)	6470 (15.2)	
≥2	3126 (7.7)	7744 (18.2)	
Unknown	29282 (71.9)	28449 (66.7)	
Treatment strategy for FPM, n (%)			<0.001 ^b
Surgery alone	40378 (99.2)	36770 (86.2)	
Surgery with chemotherapy	320 (0.8)	5893 (13.8)	
Median follow-up time of first primary cancer, (IQR), months	158 (100-252)	132 (91-195)	<0.001 ^a
Median follow-up time between FPM and SPM, (IQR), months	135 (91-207)	118 (84-168)	<0.001 ^a
Person with the SPM diagnosis	5496	6159	
Total person-years at risk	639218	539922	

P values were calculated using the Mann-Whitney U test (a) for continuous variables and χ^2 test (b) for categorical variables. RT, radiation therapy; NRT, no radiation therapy; IQR, interquartile range; FPM, first primary malignancy; SPM, second primary malignancy.

Table S4 Comparisons of baseline characteristics of patients with thoracic cancer by treatment modality

Characteristic	NRT for FPM (n=186000)	RT for FPM (n=146056)	P value
Median age at FPM diagnosis, (IQR), years	60 (50-70)	58 (49-67)	<0.001 ^a
Age at FPM diagnosis, n (%)			<0.001 ^b
20-49	45818 (24.6)	39882 (27.3)	
50-69	90452 (48.6)	77215 (52.9)	
70-84	49730 (26.7)	28959 (19.8)	
Sex, n (%)			<0.001 ^b
Female	174027 (93.6)	141304 (96.7)	
Male	11973 (6.4)	4752 (3.3)	
Year at FPM diagnosis, n (%)			<0.001 ^b
1975-1984	40627 (21.8)	9158 (6.3)	
1985-1994	57141 (30.7)	27530 (18.8)	
1995-2004	52236 (28.1)	60325 (41.3)	
2005+	35996 (19.4)	49043 (33.6)	
Race, n (%)			<0.001 ^b
White	159624 (85.8)	122092 (83.6)	
Black	13775 (7.4)	11697 (8)	
Other	12601 (6.8)	12267 (8.4)	
Grade of FPM, n (%)			<0.001 ^b
Grade I/II	70183 (37.7)	78309 (53.6)	
Grade III/IV	46079 (24.8)	41776 (28.6)	
Unknown	69738 (37.5)	25971 (17.8)	
Stage of FPM, n (%)			<0.001 ^b
Localized	127570 (68.6)	96853 (66.3)	
Regional	58430 (31.4)	49203 (33.7)	
Tumor size (cm) of FPM, n (%)			<0.001 ^b
<2	20754 (11.2)	33674 (23.1)	
≥2	18718 (10.1)	21014 (14.4)	
Unknown	146528 (78.8)	91368 (62.6)	
Treatment strategy for FPM, n (%)			<0.001 ^b
Surgery alone	144931 (77.9)	85649 (58.6)	
Surgery with chemotherapy	41069 (22.1)	60407 (41.4)	
Median follow-up time of first primary cancer, (IQR), months	149 (97-229)	136 (93-196)	<0.001 ^a
Median follow-up time between FPM and SPM, (IQR), months	131 (91-193)	126 (89-179)	<0.001 ^a
Individuals with SPM diagnosis	24958	18651	
Total person-years at risk	2697338.8	1861050.3	

P values were calculated using the Mann-Whitney U test (a) for continuous variables and χ^2 test (b) for categorical variables. RT, radiation therapy; NRT, no radiation therapy; IQR, interquartile range; FPM, first primary malignancy; SPM, second primary malignancy.

Table S5 Comparisons of baseline characteristics of patients with abdominal and pelvic cancer by treatment modality

Characteristic	NRT (n=234818)	RT (n=134034)	P value
Median age at first primary cancer diagnosis, (IQR), years	62 (54-69)	65 (56-72)	<0.001 ^a
Age at FPM diagnosis, n (%)			<0.001 ^b
20–49	37756 (16.1)	17756 (13.2)	
50–69	140857 (60)	72034 (53.7)	
70–84	56205 (23.9)	44244 (33)	
Gender, n (%)			<0.001 ^b
Female	77534 (33)	33369 (24.9)	
Male	157284 (67)	100665 (75.1)	
Year at FPM diagnosis, n (%)			<0.001 ^b
1975–1984	24528 (10.4)	10046 (7.5)	
1985–1994	27247 (11.6)	12620 (9.4)	
1995–2004	97892 (41.7)	62439 (46.6)	
2005+	85151 (36.3)	48929 (36.5)	
Race, n (%)			<0.001 ^b
White	195754 (83.4)	108075 (80.6)	
Black	22697 (9.7)	15944 (11.9)	
Other	16367 (7)	10015 (7.5)	
Grade of FPM, n (%)			<0.001 ^b
Grade I/II	142406 (60.6)	76112 (56.8)	
Grade III/IV	56236 (23.9)	42188 (31.5)	
Unknown	36176 (15.4)	15734 (11.7)	
Stage of FPM, n (%)			<0.001 ^b
Localized	92027 (39.2)	29341 (21.9)	
Regional	15546 (6.6)	22109 (16.5)	
Localized/regional (prostate cases)	127245 (54.2)	82584 (61.6)	
Tumor size (cm) of FPM, n (%)			<0.001 ^b
<2	16439 (7)	2463 (1.8)	
≥2	18269 (7.8)	10850 (8.1)	
Unknown	200110 (85.2)	120721 (90.1)	
Treatment strategy for FPM, n (%)			<0.001 ^b
Surgery alone	227488 (96.9)	114751 (85.6)	
Surgery with chemotherapy	7330 (3.1)	19283 (14.4)	
Median follow-up time of first primary cancer, (IQR), months	136 (93-199)	131 (93-183)	<0.001 ^a
Median follow-up time of between FPM and SPM, (IQR), months	123 (87-178)	117 (86-165)	<0.001 ^a
Person with the SPM diagnosis	19106	13105	
Total person-years at risk	3072157.3	1650377.7	

P values were calculated using the Mann-Whitney U test (a) for continuous variables and χ^2 test (b) for categorical variables. RT, radiation therapy; NRT, no radiation therapy; IQR, interquartile range; FPM, first primary malignancy; SPM, second primary malignancy.

Table S6 Univariable and multivariable Cox regression analysis of risk of developing second primary malignancy in all site primary cancer patients

Site	Univariable Cox regression			Multivariable Cox regression		
	HR (95% CI)	β	P value	HR (95% CI)	β	P value
Lip	1.01 (0.75-1.35)	0.014	0.92	1.02 (0.76-1.37)	0.025	0.87
Tongue	1.48 (1.32-1.66)	0.394	<0.001	1.44 (1.28-1.62)	0.369	<0.001
Salivary gland	1.49 (1.21-1.84)	0.403	<0.001	1.39 (1.13-1.73)	0.335	<0.001
Floor of mouth	1.27 (1.08-1.62)	0.244	0.048	1.38 (1.08-1.76)	0.324	0.009
Gum and other mouth	1.23 (1.07-1.43)	0.214	0.003	1.31 (1.13-1.51)	0.27	0.001
Tonsil	1.25 (0.97-1.49)	0.186	0.09	1.22 (0.98-1.52)	0.206	0.06
Nasopharynx	1.59 (1.07-2.35)	0.463	0.03	1.51 (1.01-2.25)	0.414	0.04
Oropharynx	2.72 (1.93-3.88)	1.001	<0.001	2.68 (1.87-3.84)	0.988	<0.001
Hypopharynx	2.11 (1.69-2.63)	0.748	<0.001	2.16 (1.73-2.69)	0.77	<0.001
Esophagus	1.75 (1.57-1.95)	0.562	<0.001	1.75 (1.57-1.95)	0.561	<0.001
Stomach	1.07 (0.97-1.17)	0.069	0.14	1.03 (0.94-1.13)	0.036	0.45
Small intestine	1.12 (0.94-1.33)	0.117	0.18	1.06 (0.89-1.26)	0.065	0.46
Colon	1.01 (0.96-1.05)	0.016	0.64	1.08 (1.04-1.14)	0.085	<0.001
Rectum	1.12 (1.03-1.21)	0.115	0.003	1.16 (1.07-1.26)	0.154	<0.001
Anus, anal canal, and anorectum	1.11 (0.89-1.38)	0.107	0.33	1.09 (0.87-1.35)	0.086	0.44
Liver	1.41 (1.24-1.66)	0.345	<0.001	1.27 (1.12-1.44)	0.241	0.001
Gallbladder	0.93 (0.77-1.15)	-0.125	0.41	0.87 (0.68-1.12)	-0.13	0.31
Intrahepatic bile duct	1.32 (1.02-1.71)	0.278	0.03	1.21 (0.93-1.57)	0.192	0.15
Pancreas	1.19 (1.11-1.28)	0.178	0.001	1.13 (1.06-1.21)	0.128	0.001
Nose, nasal cavity, and middle ear	1.39 (1.05-1.85)	0.333	0.02	1.38 (1.03-1.84)	0.322	0.03
Larynx	1.48 (1.29-1.72)	0.393	<0.001	1.45 (1.26-1.67)	0.374	<0.001
Lung	1.29 (1.25-1.33)	0.256	<0.001	1.29 (1.26-1.33)	0.261	<0.001
Breast	1.37 (1.34-1.41)	0.319	<0.001	1.43 (1.39-1.47)	0.362	<0.001
Cervix uteri	0.89 (0.71-1.12)	-0.191	0.34	1.01 (0.81-1.26)	0.006	0.95
Corpus and uterus	1.19 (1.11-1.27)	0.175	<0.001	1.23 (1.15-1.32)	0.213	0.001
Ovary	1.04 (0.94-1.15)	0.045	0.37	1.16 (1.05-1.28)	0.15	0.003
Vagina	1.66 (1.25-2.22)	0.511	<0.001	1.85 (1.38-2.49)	0.617	0.001
Vulva	0.95 (0.79-1.14)	-0.047	0.62	0.93 (0.77-1.12)	-0.07	0.47
Prostate	1.09 (1.02-1.16)	0.087	0.007	1.01 (0.94-1.07)	0.005	0.86
Testis	1.48 (1.13-1.94)	0.396	0.003	1.23 (0.94-1.61)	0.212	0.12
Penis	2.07 (1.26-3.41)	0.734	0.003	1.68 (1.03-2.76)	0.522	0.04
Urinary bladder	1.63 (1.55-1.71)	0.488	<0.001	1.53 (1.45-1.61)	0.427	0.001
Kidney and renal pelvis	1.08 (1.03-1.16)	0.079	0.04	1.02 (0.94-1.11)	0.02	0.60
Ureter	1.57 (1.13-2.18)	0.451	0.007	1.58 (1.14-2.21)	0.463	0.006
Eye and orbit	1.21 (0.89-1.66)	0.198	0.22	1.21 (0.87-1.65)	0.185	0.25
Brain	0.97 (0.84-1.12)	-0.026	0.72	0.96 (0.83-1.11)	-0.03	0.64
Cranial nerves, other nervous system	1.01 (0.58-1.75)	0.017	0.95	0.98 (0.56-1.71)	-0.02	0.95
Thyroid	0.91 (0.81-1.03)	-0.085	0.15	0.82 (0.73-0.92)	-0.19	<0.001
Thymus	1.03 (0.59-1.81)	0.036	0.90	0.97 (0.55-1.71)	-0.03	0.92
Adrenal gland	0.96 (0.41-1.97)	-0.098	0.80	0.97 (0.44-2.13)	-0.03	0.95
Trachea	1.34 (1.15-1.57)	0.295	0.001	1.21 (1.03-1.41)	0.196	0.02

Cox regression analyses were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SPM in all site primary cancer patients treated with RT versus patients not treated with RT. Multivariable Cox regression was stratified by age at primary cancer diagnosis, calendar year of primary cancer diagnosis, sex, and race. HR, hazard ratio; CI, confidence interval; SPM, second primary malignancy; RT, radiation therapy; NRT, no radiation therapy.

Table S7 Univariable and multivariable Cox regression analysis of risk of developing second primary malignancy in head and neck primary cancer patients

Site	Univariable Cox regression			Multivariable Cox regression		
	HR (95% CI)	β	P value	HR (95% CI)	β	P value
Lip	0.61 (0.32-1.13)	-0.497	0.12	0.48 (0.25-0.91)	-0.725	0.03
Tongue	1.23 (1.05-1.43)	0.208	0.007	0.92 (0.78-1.07)	-0.089	0.30
Salivary gland	1.62 (1.02-2.58)	0.484	0.04	1.39 (0.86-2.25)	0.331	0.18
Floor of mouth	1.03 (0.75-1.42)	0.033	0.84	0.91 (0.65-1.24)	-0.104	0.53
Gum and other mouth	1.09 (0.91-1.32)	0.091	0.36	0.95 (0.78-1.16)	-0.045	0.65
Tonsil	1.47 (1.05-2.05)	0.388	0.02	1.22 (0.87-1.73)	0.205	0.24
Nasopharynx	5.11 (2.34-11.11)	1.631	<0.001	4.49 (2.02-9.96)	1.502	<0.001
Oropharynx	2.82 (1.71-4.63)	1.037	<0.001	2.23 (1.34-3.72)	0.805	0.001
Hypopharynx	2.81 (2.07-3.81)	1.033	<0.001	2.18 (1.61-2.98)	0.782	<0.001
Esophagus	2.28 (1.84-2.82)	0.824	<0.001	1.95 (1.57-2.43)	0.671	<0.001
Stomach	1.39 (1.03-1.89)	0.335	0.03	1.04 (0.76-1.42)	0.044	0.78
Small intestine	1.19 (0.64-2.21)	0.177	0.57	0.98 (0.52-1.85)	-0.013	0.97
Colon	1.26 (1.08-1.45)	0.231	<0.001	1.13 (0.97-1.32)	0.128	0.09
Rectum	1.04 (0.81-1.33)	0.039	0.76	0.94 (0.73-1.22)	-0.052	0.69
Anus, anal canal, and anorectum	1.49 (0.69-3.21)	0.404	0.30	1.57 (0.71-3.44)	0.451	0.26
Liver	1.98 (1.43-2.74)	0.686	<0.001	1.43 (1.02-1.99)	0.359	0.03
Gallbladder	2.76 (1.16-6.55)	1.016	0.02	2.21 (0.92-5.31)	0.795	0.07
Intrahepatic bile duct	1.17 (0.54-2.49)	0.158	0.68	0.87 (0.41-1.91)	-0.129	0.74
Pancreas	1.19 (0.92-1.54)	0.177	0.18	1.03 (0.79-1.35)	0.033	0.81
Nose, nasal cavity, and middle ear	1.51 (0.91-2.51)	0.408	0.12	1.13 (0.67-1.91)	0.124	0.64
Larynx	1.83 (1.42-2.35)	0.604	<0.001	1.38 (1.07-1.79)	0.328	0.01
Lung	1.93 (1.79-2.08)	0.659	<0.001	1.72 (1.59-1.86)	0.545	<0.001
Breast	0.76 (0.68-0.85)	-0.269	<0.001	1.01 (0.89-1.13)	0.009	0.87
Cervix uteri	0.57 (0.28-1.15)	-0.549	0.12	1.01 (0.49-2.07)	0.009	0.98
Corpus and uterus	0.78 (0.61-1.01)	-0.247	0.06	1.05 (0.81-1.37)	0.051	0.70
Ovary	0.61 (0.42-0.89)	-0.483	0.01	0.78 (0.61-1.01)	-0.247	0.06
Vagina	0.86 (0.07-9.71)	-0.139	0.91	1.08 (0.09-12.51)	0.082	0.95
Vulva	1.73 (0.74-4.03)	0.551	0.20	2.32 (0.98-5.48)	0.845	0.053
Prostate	1.67 (1.52-1.85)	0.517	<0.001	1.05 (0.95-1.16)	0.055	0.27
Testis	0.64 (0.16-2.58)	-0.438	0.54	0.49 (0.11-2.07)	-0.701	0.34
Penis	3.15 (0.26-36.81)	1.147	0.36	1.49 (0.12-17.31)	0.401	0.75
Urinary bladder	1.69 (1.41-2.02)	0.525	<0.001	1.21 (1.01-1.43)	0.183	0.046
Kidney and renal pelvis	1.31 (1.06-1.64)	0.277	0.01	1.04 (0.83-1.31)	0.043	0.70
Ureter	0.67 (0.19-2.32)	-0.391	0.54	0.52 (0.14-1.81)	-0.651	0.31
Eye and orbit	0.91 (0.41-1.97)	-0.105	0.79	0.74 (0.33-1.66)	-0.296	0.47
Brain	1.11 (0.73-1.71)	0.112	0.60	1.02 (0.66-1.57)	0.02	0.93
Cranial nerves, other nervous system	0.58 (0.14-2.35)	-0.537	0.45	0.51 (0.12-2.17)	-0.663	0.37
Thyroid	0.41 (0.28-0.59)	-0.888	<0.001	0.36 (0.25-0.52)	-1.014	<0.001
Thymus	2.51 (0.49-12.5)	0.918	0.26	1.85 (0.36-9.37)	0.616	0.46
Adrenal gland	0.43 (0.04-4.26)	-0.829	0.48	0.44 (0.04-4.76)	-0.802	0.51
Trachea	4.08 (0.81-20.61)	1.407	0.09	5.08 (0.93-27.51)	1.625	0.06

Cox regression analyses were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SPM in head and neck primary cancer patients treated with RT versus patients not treated with RT. Multivariable Cox regression was stratified by age at primary cancer diagnosis, calendar year of primary cancer diagnosis, sex, and race. HR, hazard ratio; CI, confidence interval; SPM, second primary malignancy; RT, radiation therapy; NRT, no radiation therapy.

Table S8 Univariable and multivariable Cox regression analysis of risk of developing second primary malignancy in thoracic primary cancer patients

Site of SPM	Univariable Cox regression			Multivariable Cox regression		
	HR (95% CI)	β	P value	HR (95% CI)	β	P value
Lip	0.63 (0.31-1.28)	-0.454	0.21	0.75 (0.36-1.57)	-0.278	0.46
Tongue	1.02 (0.77-1.36)	0.028	0.84	0.99 (0.74-1.33)	-0.003	0.98
Salivary gland	1.36 (0.73-0.98)	0.314	0.06	1.19 (0.84-1.69)	0.178	0.32
Floor of mouth	0.62 (0.34-1.12)	-0.474	0.11	0.78 (0.42-1.45)	-0.238	0.45
Gum and other mouth	1.01 (0.74-1.36)	0.009	0.95	1.21 (0.88-1.67)	0.195	0.23
Tonsil	0.71 (0.42-1.15)	-0.352	0.17	0.98 (0.58-1.65)	-0.016	0.95
Nasopharynx	0.49 (0.19-1.25)	-0.699	0.14	0.45 (0.17-1.17)	-0.797	0.10
Oropharynx	0.78 (0.33-1.85)	-0.241	0.58	1.12 (0.46-2.75)	0.119	0.79
Hypopharynx	1.15 (0.68-1.94)	0.139	0.60	1.61 (0.93-2.79)	0.478	0.09
Esophagus	1.49 (1.22-1.82)	0.401	<0.001	1.98 (1.61-2.44)	0.685	<0.001
Stomach	0.78 (0.66-0.92)	-0.247	0.003	0.93 (0.78-1.11)	-0.062	0.48
Small intestine	0.81 (0.59-1.09)	-0.216	0.17	0.76 (0.55-1.05)	-0.271	0.10
Colon	0.77 (0.71-0.82)	-0.261	<0.001	0.95 (0.88-1.02)	-0.046	0.23
Rectum	0.77 (0.67-0.88)	-0.265	<0.001	0.99 (0.86-1.14)	-0.005	0.94
Anus, anal canal, and anorectum	0.92 (0.65-1.31)	-0.077	0.66	0.82 (0.57-1.17)	-0.194	0.28
Liver	0.98 (0.76-1.26)	-0.016	0.90	0.93 (0.71-1.21)	-0.071	0.60
Gallbladder	0.76 (0.53-1.09)	-0.266	0.15	0.75 (0.52-1.11)	-0.277	0.15
Intrahepatic bile duct	1.48 (0.97-2.26)	0.396	0.06	1.31 (0.85-2.04)	0.277	0.22
Pancreas	1.06 (0.95-1.18)	0.061	0.26	1.04 (0.93-1.17)	0.047	0.41
Nose, nasal cavity, and middle ear	0.97 (0.56-1.68)	-0.027	0.92	1.17 (0.66-2.11)	0.165	0.58
Larynx	0.81 (0.58-1.09)	-0.222	0.17	1.08 (0.78-1.51)	0.084	0.62
Lung	0.97 (0.92-1.01)	-0.029	0.20	1.01 (0.97-1.06)	0.018	0.45
Breast	1.51 (1.47-1.55)	0.415	<0.001	1.51 (1.45-1.55)	0.408	<0.001
Cervix uteri	0.84 (0.63-1.11)	-0.171	0.21	0.96 (0.72-1.29)	-0.031	0.84
Corpus and uterus	1.03 (0.96-1.11)	0.038	0.31	1.04 (0.97-1.13)	0.046	0.24
Ovary	0.96 (0.86-1.08)	-0.031	0.59	1.06 (0.94-1.19)	0.064	0.28
Vagina	1.36 (0.77-2.41)	0.314	0.28	1.66 (0.91-3.03)	0.511	0.09
Vulva	0.96 (0.72-1.29)	-0.031	0.83	0.94 (0.71-1.27)	-0.042	0.72
Prostate	0.41 (0.33-0.49)	-0.901	<0.001	0.91 (0.75-1.11)	-0.091	0.33
Testis	–	–	–	–	–	–
Penis	0.65 (0.05-7.26)	-0.418	0.73	1.39 (0.12-15.41)	0.331	0.79
Urinary bladder	0.83 (0.74-0.93)	-0.181	<0.001	0.99 (0.88-1.11)	-0.005	0.92
Kidney and renal pelvis	1.11 (0.95-1.26)	0.098	0.17	1.16 (1.01-1.34)	0.149	0.045
Ureter	0.83 (0.45-1.51)	-0.184	0.54	0.93 (0.51-1.75)	-0.063	0.84
Eye and orbit	1.61 (0.96-2.71)	0.481	0.07	1.86 (1.08-3.21)	0.623	0.02
Brain	1.08 (0.85-1.36)	0.079	0.51	1.13 (0.89-1.45)	0.131	0.30
Cranial nerves, other nervous system	1.31 (0.51-3.34)	0.264	0.58	1.61 (0.59-4.32)	0.472	0.351
Thyroid	1.21 (1.02-1.41)	0.185	0.02	0.98 (0.83-1.15)	-0.016	0.85
Thymus	1.41 (0.57-3.49)	0.349	0.45	1.46 (0.57-3.73)	0.379	0.43
Adrenal gland	0.48 (0.12-1.83)	-0.719	0.29	0.55 (0.13-2.22)	-0.584	0.41
Trachea	1.21 (1.02-1.41)	0.185	0.02	0.98 (0.83-1.15)	-0.016	0.85

Cox regression analyses were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SPM in thoracic primary cancer treated with RT versus patients not treated with RT. Multivariable Cox regression was stratified by age at primary cancer diagnosis, calendar year of primary cancer diagnosis, sex, and race. HR, hazard ratio; CI, confidence interval; SPM, second primary malignancy; RT, radiation therapy; NRT, no radiation therapy.

Table S9 Univariable and multivariable Cox regression analysis of risk of developing second primary malignancy in abdominal and pelvic primary cancer patients

SPM site	Univariable Cox regression			Multivariable Cox regression		
	HR (95% CI)	β	P value	HR (95% CI)	β	P value
Lip	1.46 (1.01-2.13)	0.382	0.046	1.26 (0.86-1.84)	0.232	0.23
Tongue	1.53 (1.19-1.97)	0.431	<0.001	1.39 (1.08-1.81)	0.335	0.009
Salivary gland	1.46 (1.04-2.06)	0.383	0.03	1.27 (0.91-1.81)	0.245	0.16
Floor of mouth	1.89 (1.12-3.19)	0.637	0.02	1.83 (1.08-3.11)	0.608	0.02
Gum and other mouth	0.95 (0.67-1.34)	-0.049	0.78	0.88 (0.62-1.25)	-0.125	0.48
Tonsil	0.98 (0.68-1.43)	-0.011	0.95	0.91 (0.63-1.33)	-0.085	0.66
Nasopharynx	0.98 (0.51-1.93)	-0.014	0.98	0.88 (0.44-1.73)	-0.128	0.71
Oropharynx	4.15 (1.96-8.77)	1.423	<0.001	3.93 (1.85-8.36)	1.373	<0.001
Hypopharynx	0.86 (0.52-1.41)	-0.144	0.57	0.77 (0.46-1.26)	-0.259	0.31
Esophagus	1.54 (1.31-1.81)	0.437	<0.001	1.28 (1.09-1.51)	0.255	0.002
Stomach	1.31 (1.16-1.48)	0.275	<0.001	1.14 (1.01-1.29)	0.135	0.03
Small intestine	1.43 (1.15-1.78)	0.364	0.001	1.32 (1.06-1.65)	0.283	0.01
Colon	1.25 (1.17-1.33)	0.227	<0.001	1.21 (1.12-1.28)	0.185	<0.001
Rectum	1.51 (1.36-1.67)	0.411	<0.001	1.43 (1.29-1.58)	0.363	<0.001
Anus, anal canal, and anorectum	1.27 (0.94-1.71)	0.238	0.12	1.31 (0.96-1.76)	0.264	0.09
Liver	1.59 (1.34-1.89)	0.467	<0.001	1.36 (1.14-1.61)	0.308	<0.001
Gallbladder	0.88 (0.61-1.29)	-0.122	0.53	0.85 (0.57-1.24)	-0.161	0.41
Intrahepatic bile duct	1.26 (0.87-1.82)	0.237	0.21	1.12 (0.77-1.62)	0.113	0.55
Pancreas	1.39 (1.26-1.53)	0.336	<0.001	1.23 (1.12-1.36)	0.212	<0.001
Nose, nasal cavity, and middle ear	1.55 (0.99-2.43)	0.443	0.051	1.45 (0.92-2.28)	0.375	0.10
Larynx	1.59 (1.31-1.94)	0.466	<0.001	1.35 (1.11-1.66)	0.305	<0.001
Lung	1.43 (1.36-1.51)	0.359	<0.001	1.31 (1.24-1.37)	0.268	<0.001
Breast	0.73 (0.68-0.78)	-0.349	<0.001	0.95 (0.89-1.02)	-0.042	0.23
Cervix uteri	1.01 (0.63-1.61)	0.019	0.97	1.41 (0.88-2.25)	0.345	0.15
Corpus and uterus	2.19 (1.78-2.68)	0.783	<0.001	2.93 (2.39-3.61)	1.078	<0.001
Ovary	1.27 (0.97-1.66)	0.241	0.08	1.71 (1.31-2.23)	0.536	<0.001
Vagina	2.02 (1.45-2.83)	0.707	<0.001	2.73 (1.95-3.83)	1.007	<0.001
Vulva	0.95 (0.73-1.22)	-0.049	0.70	1.25 (0.97-1.62)	0.226	0.08
Prostate	0.78 (0.71-0.87)	-0.236	<0.001	0.73 (0.66-0.82)	-0.304	<0.001
Testis	1.81 (1.37-2.38)	0.594	<0.001	1.34 (1.01-1.76)	0.292	0.04
Penis	2.48 (1.48-4.15)	0.909	<0.001	1.77 (1.05-2.99)	0.576	0.03
Urinary bladder	2.25 (2.12-2.39)	0.813	<0.001	1.86 (1.75-1.98)	0.625	<0.001
Kidney and renal pelvis	1.09 (0.98-1.21)	0.091	0.08	0.95 (0.86-1.06)	-0.043	0.41
Ureter	2.57 (1.68-3.94)	0.946	<0.001	2.29 (1.49-3.53)	0.837	<0.001
Eye and orbit	1.11 (0.69-1.75)	0.094	0.69	0.96 (0.61-1.54)	-0.035	0.89
Brain	0.93 (0.77-1.13)	-0.066	0.51	0.87 (0.71-1.06)	-0.133	0.19
Cranial nerves, other nervous system	1.05 (0.48-2.29)	0.055	0.89	1.01 (0.46-2.21)	0.009	0.98
Thyroid	0.77 (0.63-0.94)	-0.255	0.01	0.81 (0.65-0.97)	-0.222	0.03
Thymus	0.68 (0.28-1.61)	-0.385	0.39	0.61 (0.25-1.44)	-0.508	0.26
Adrenal gland	1.74 (0.58-5.22)	0.559	0.32	1.68 (0.55-5.11)	0.522	0.36
Trachea	3.61 (0.32-39.81)	1.284	0.30	3.71 (0.32-42.41)	1.309	0.29

Cox regression analyses were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SPM in abdominal and pelvic primary cancer patients treated with RT versus patients not treated with RT. Multivariable Cox regression was stratified by age at first primary cancer diagnosis, calendar year of first primary cancer diagnosis, sex, and race. HR, hazard ratio; CI, confidence interval; RT, radiation therapy; NRT, no radiation therapy; SPM, second primary malignancy.

Table S10 Radiation-attributed risk of RI-SPMs by age at all site primary cancer diagnosis, latency, and year of all site primary cancer diagnosis

Characteristic	Univariable Poisson regression		Multivariable Poisson regression	
	RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age at all site primary cancer diagnosis, years				
20–49	1.33 (1.29-1.38)	<0.001	1.52 (1.47-1.57)	<0.001
50–69	1.21 (1.18-1.22)	<0.001	1.31 (1.28-1.33)	<0.001
≥70	1.14 (1.11-1.18)	<0.001	1.21 (1.17-1.25)	<0.001
Latency between all site primary cancer and RI-SPMs, months				
60–119	1.09 (1.07-1.11)	<0.001	1.28 (1.25-1.31)	<0.001
120–239	1.04 (1.01-1.06)	<0.001	1.24 (1.22-1.27)	<0.001
240–360	1.31 (1.24-1.36)	<0.001	1.46 (1.39-1.53)	<0.001
Year of all site primary cancer diagnosis				
1975–1984	1.28 (1.24-1.33)	<0.001	1.28 (1.23-1.32)	<0.001
1985–1994	1.31 (1.27-1.34)	<0.001	1.34 (1.31-1.38)	<0.001
1995–2004	1.28 (1.25-1.31)	<0.001	1.26 (1.23-1.29)	<0.001
≥2005	1.29 (1.23-1.35)	<0.001	1.24 (1.19-1.31)	<0.001
Sex				
Female	1.17 (1.15-1.19)	<0.001	1.29 (1.27-1.31)	<0.001
Male	1.33 (1.31-1.36)	<0.001	1.31 (1.28-1.34)	<0.001
All	1.21 (1.21-1.23)	<0.001	1.32 (1.31-1.34)	<0.001

Poisson regression analyses were used to calculate the radiation-attributed risk (RR) and 95% confidence intervals (CIs) of RI-SPMs for all site primary cancer patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at first primary cancer diagnosis, calendar year of first primary cancer diagnosis, sex, and race. A determination of statistical significance of RRs was based on $P < 0.05$ (2-sided). RR, radiation-attributed risk; SPM, second primary malignancy; CI, confidence interval; RI-SPMs, risk increased-SPMs.

Table S11 Radiation-attributed risk of RI-SPMs by age at head and neck primary cancer diagnosis, latency, and year of head and neck cancer diagnosis

Characteristic	Univariable Poisson regression		Multivariable Poisson regression	
	RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age at head and neck primary cancer diagnosis, years				
20–49	1.38 (1.32-1.43)	<0.001	1.61 (1.53-1.67)	<0.001
50–69	1.23 (1.21-1.26)	<0.001	1.26 (1.23-1.29)	<0.001
≥70	1.13 (1.11-1.17)	<0.001	1.12 (1.08-1.16)	<0.001
Latency between head and neck primary cancer and RI-SPM, months				
60–119	1.11 (1.08-1.14)	<0.001	1.11 (1.08-1.14)	<0.001
120–239	1.02 (0.99-1.04)	0.08	1.09 (1.06-1.11)	<0.001
240–360	1.38 (1.31-1.44)	<0.001	1.28 (1.22-1.35)	<0.001
Year of head and neck primary cancer diagnosis				
1975–1984	2.07 (2.01-2.13)	<0.001	1.37 (1.33-1.42)	<0.001
1985–1994	1.54 (1.51-1.59)	<0.001	1.25 (1.22-1.29)	<0.001
1995–2004	1.39 (1.34-1.44)	<0.001	1.25 (1.21-1.29)	<0.001
≥2005	1.02 (0.95-1.09)	0.55	1.03 (0.96-1.11)	0.41
Sex				
Female	1.23 (1.21-1.27)	<0.001	1.43 (1.39-1.47)	<0.001
Male	1.19 (1.17-1.22)	<0.001	1.21 (1.18-1.23)	<0.001
All	1.38 (1.36-1.41)	<0.001	1.28 (1.26-1.31)	<0.001

Poisson regression analyses were used to calculate the radiation-attributed risk (RR) and 95% confidence intervals (CIs) of RI-SPMs for head and neck cancer patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at first primary cancer diagnosis, calendar year of first primary cancer diagnosis, sex, and race. A determination of statistical significance of RRs was based on $P < 0.05$ (2-sided). RR, radiation-attributed risk; CI, confidence interval; SPM, second primary malignancy; RI-SPMs, risk increased-SPMs.

Table S12 Radiation-attributed risk of RI-SPMs by age at thoracic primary cancer diagnosis, latency, and year of thoracic cancer diagnosis

Characteristic	Univariable Poisson regression		Multivariable Poisson regression	
	RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age at thoracic primary cancer diagnosis, years				
20–49	1.29 (1.24-1.34)	<0.001	1.48 (1.42-1.54)	<0.001
50–69	1.01 (0.99-1.04)	0.16	1.15 (1.12-1.18)	<0.001
≥70	1.07 (1.02-1.12)	0.002	1.13 (1.08-1.19)	<0.001
Latency between thoracic primary cancer and RI-SPMs, months				
60–119	0.91 (0.87-0.93)	<0.001	1.21 (1.17-1.24)	<0.001
120–239	0.88 (0.86-0.91)	<0.001	1.21 (1.16-1.23)	<0.001
240–360	1.29 (1.21-1.37)	<0.001	1.51 (1.41-1.61)	<0.001
Year of thoracic primary cancer diagnosis				
1975–1984	1.19 (1.12-1.25)	<0.001	1.21 (1.14-1.27)	<0.001
1985–1994	1.28 (1.24-1.33)	<0.001	1.31 (1.27-1.36)	<0.001
1995–2004	1.09 (1.05-1.12)	<0.001	1.14 (1.11-1.17)	<0.001
≥2005	1.01 (0.94-1.08)	0.74	1.09 (1.02-1.16)	0.01
Sex				
Female	1.09 (1.07-1.12)	<0.001	1.24 (1.21-1.26)	<0.001
Male	1.11 (1.02-1.22)	<0.001	1.14 (1.04-1.25)	<0.001
All	1.08 (1.06-1.11)	<0.001	1.23 (1.21-1.26)	<0.001

Poisson regression analyses were used to calculate the radiation-attributed risk (RR) and 95% confidence intervals (CIs) of RI-SPMs for thoracic cancer patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at first primary cancer diagnosis, calendar year of first primary cancer diagnosis, sex, and race. A determination of statistical significance of RRs was based on $P < 0.05$ (2-sided). RR, radiation-attributed risk; CI, confidence interval; SPM, second primary malignancy; RI-SPMs, risk increased-SPMs.

Table S13 Radiation-attributed risk of RI-SPMs by age at abdominal and pelvic primary cancer diagnosis, latency, and year of abdominal and pelvic cancer diagnosis

Characteristic	Univariable Poisson regression		Multivariable Poisson regression	
	RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age at abdominal and pelvic primary cancer diagnosis, years				
20–49	1.35 (1.26-1.45)	<0.001	1.46 (1.36-1.57)	<0.001
50–69	1.31 (1.26-1.34)	<0.001	1.34 (1.31-1.38)	<0.001
≥70	1.24 (1.19-1.31)	<0.001	1.28 (1.22-1.34)	<0.001
Latency between abdominal and pelvic primary cancer and RI-SPMs, months				
60–119	1.29 (1.25-1.33)	<0.001	1.33 (1.29-1.38)	<0.001
120–239	1.17 (1.13-1.21)	<0.001	1.26 (1.22-1.31)	<0.001
240–360	1.51 (1.25-1.83)	<0.001	1.57 (1.29-1.92)	<0.001
Year of abdominal and pelvic primary cancer diagnosis				
1975–1984	1.21 (1.15-1.29)	<0.001	1.24 (1.17-1.31)	<0.001
1985–1994	1.27 (1.21-1.35)	<0.001	1.31 (1.24-1.39)	<0.001
1995–2004	1.39 (1.35-1.44)	<0.001	1.31 (1.27-1.35)	<0.001
≥2005	1.51 (1.41-1.61)	<0.001	1.39 (1.31-1.48)	<0.001
Sex				
			(-)	
Female	1.33 (1.27-1.38)	<0.001	1.31 (1.25-1.35)	<0.001
Male	1.37 (1.33-1.41)	<0.001	1.33 (1.29-1.37)	<0.001
All	1.33 (1.31-1.36)	<0.001	1.32 (1.29-1.35)	<0.001

Poisson regression analyses were used to calculate the radiation-attributed risk (RR) and 95% CIs of RI-SPMs for abdominal and pelvic cancer patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at primary cancer diagnosis, calendar year of primary cancer diagnosis, sex, and race. A determination of statistical significance of RRs was based on $P < 0.05$ (2-sided). RR, radiation-attributed risk; CI, confidence interval; SPM, second primary malignancy; RI-SPMs, risk increased-SPMs.

Table S14 Standardized incidence ratio of RI-SPMs by age at all site cancer diagnosis, latency, and year of all site cancer diagnosis

Characteristic	RT vs. US general population		NRT vs. US general population	
	SIR (95% CI)	P value	SIR (95% CI)	P value
All	1.31 (1.29-1.32)	0.01	1.01 (0.99-1.03)	0.11
Latency between all site primary cancer and RI-SPMs, months				
60–119	1.29 (1.27-1.31)	0.002	1.08 (1.06-1.09)	0.003
120–239	1.32 (1.31-1.34)	0.005	0.98 (0.96-0.99)	0.001
240–359	1.31 (1.26-1.35)	0.01	0.85 (0.83-0.87)	0.02
Age at all site cancer diagnosis, years				
20–49	1.77 (1.73-1.81)	0.002	1.13 (1.11-1.15)	0.008
50–69	1.26 (1.25-1.28)	0.03	0.97 (0.95-0.98)	0.03
≥70	1.12 (1.11-1.15)	0.02	0.97 (0.95-0.99)	0.01
Year of first primary malignancy diagnosis				
1975–1984	1.31 (1.27-1.35)	0.007	0.96 (0.95-0.98)	0.009
1985–1994	1.43 (1.41-1.46)	0.003	1.04 (1.02-1.06)	0.04
1995–2004	1.25 (1.23-1.27)	0.02	0.97 (0.96-0.99)	0.03
≥2005	1.26 (1.22-1.31)	0.02	1.03 (1.01-1.06)	0.01

SIR was defined as the ratio of the observed cases of RI-SPMs among all site cancer survivors to the expected number of cases in the US general population and was stratified by age at all site cancer diagnosis, latency, and year of all site cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of RI-SPMs was derived from data provided by the SEER database. RT, radiation therapy; NRT, no radiation therapy; SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; US, United States; SEER, Surveillance, Epidemiology, and End Results.

Table S15 Standardized incidence ratio of RI-SPMs by age at head and neck cancer diagnosis, latency, and year of head and neck cancer diagnosis

Characteristic	(RT vs. US general population)		(NRT vs. US general population)	
	SIR (95% CI)	P value	SIR (95% CI)	P value
All	1.75 (1.71-1.81)	0.002	1.23 (1.19-1.26)	0.004
Latency between head and neck primary cancer and RI-SPMs, months				
60–119	1.98 (1.91-2.06)	0.01	1.56 (1.49-1.64)	0.02
120–239	1.61 (1.54-1.68)	0.02	1.21 (1.14-1.25)	0.01
240–359	1.34 (1.21-1.49)	0.01	0.91 (0.83-0.97)	0.02
Age at head and neck primary cancer diagnosis, years				
20–49	1.55 (1.45-1.65)	0.004	1.08 (1.02-1.13)	0.005
50–69	1.86 (1.79-1.92)	0.005	1.32 (1.27-1.38)	0.002
≥70	1.58 (1.46-1.72)	0.02	1.27 (1.16-1.38)	0.01
Year of head and neck primary cancer diagnosis				
1975–1984	1.89 (1.79-2.01)	0.01	1.11 (1.06-1.16)	0.01
1985–1994	1.74 (1.66-1.83)	0.002	1.22 (1.15-1.29)	0.03
1995–2004	1.68 (1.59-1.76)	0.002	1.39 (1.31-1.48)	0.01
≥2005	1.62 (1.47-1.79)	0.003	1.48 (1.32-1.65)	0.009

SIR was defined as the ratio of the observed cases of RI-SPMs among head and neck cancer survivors to the expected number of cases in the US general population and was stratified by age at all site cancer diagnosis, latency, and year of all site cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of RI-SPMs was derived from data provided by the SEER database. RT, radiation therapy; NRT, no radiation therapy; SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; US, United States; SEER, Surveillance, Epidemiology, and End Results.

Table S16 Standardized incidence ratio of RI-SPMs by age at thoracic cancer diagnosis, latency, and year of thoracic cancer diagnosis

Characteristic	RT vs. US general population		NRT vs. US general population	
	SIR (95% CI)	P value	SIR (95% CI)	P value
All	1.45 (1.43-1.47)	<0.001	1.16 (1.14-1.17)	<0.001
Latency between thoracic primary cancer and RI-SPMs, months				
60–119	1.42 (1.39-1.45)	<0.001	1.31 (1.28-1.33)	<0.001
120–239	1.49 (1.46-1.52)	<0.001	1.15 (1.13-1.17)	<0.001
240–359	1.45 (1.37-1.52)	<0.001	0.89 (0.86-0.93)	<0.001
Age at thoracic primary cancer diagnosis, years				
20–49	2.02 (1.96-2.07)	<0.001	1.28 (1.25-1.32)	<0.001
50–69	1.34 (1.31-1.37)	<0.001	1.14 (1.12-1.16)	<0.001
≥70	1.23 (1.19-1.28)	<0.001	1.11 (1.07-1.13)	<0.001
Year of thoracic primary cancer diagnosis				
1975–1984	1.34 (1.28-1.41)	<0.001	1.04 (1.01-1.06)	<0.001
1985–1994	1.47 (1.44-1.51)	<0.001	1.12 (1.11-1.14)	<0.001
1995–2004	1.45 (1.42-1.49)	<0.001	1.33 (1.29-1.36)	<0.001
≥2005	1.47 (1.41-1.54)	<0.001	1.48 (1.41-1.56)	<0.001

SIR was defined as the ratio of the observed cases of RI-SPMs among thoracic cancer survivors to the expected number of cases in the US general population and was stratified by age at all site cancer diagnosis, latency, and year of all site cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of RI-SPMs was derived from data provided by the SEER database. RT, radiation therapy; NRT, no radiation therapy; SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; US, United States; SEER, Surveillance, Epidemiology, and End Results.

Table S17 Standardized incidence ratio of RI-SPMs by age at abdominal and pelvic cancer diagnosis, latency, and year of abdominal and pelvic cancer diagnosis

Characteristic	RT vs. US general population		NRT vs. US general population	
	SIR (95% CI)	P value	SIR (95% CI)	P value
All	0.81 (0.79-0.81)	<0.001	1.04 (1.03-1.06)	<0.001
Latency between abdominal and pelvic primary cancer and RI-SPMs, months				
60–119	0.84 (0.82-0.85)	<0.001	1.03 (1.01-1.06)	<0.001
120–239	0.77 (0.75-0.79)	<0.001	1.05 (1.03-1.09)	<0.001
240–359	0.76 (0.72-0.81)	<0.001	1.08 (1.01-1.16)	<0.001
Age at abdominal and pelvic primary cancer diagnosis, years				
20–49	0.88 (0.84-0.92)	<0.001	1.32 (1.25-1.41)	<0.001
50–69	0.77 (0.76-0.79)	<0.001	1.02 (1.01-1.05)	<0.001
≥70	0.83 (0.81-0.86)	<0.001	1.01 (0.98-1.04)	0.12
Year of abdominal and pelvic primary cancer diagnosis				
1975–1984	0.81 (0.78-0.84)	<0.001	1.06 (1.01-1.11)	<0.001
1985–1994	0.83 (0.81-0.86)	<0.001	1.13 (1.08-1.19)	<0.001
1995–2004	0.78 (0.76-0.81)	<0.001	1.02 (1.01-1.05)	<0.001
≥2005	0.81 (0.78-0.85)	<0.001	1.03 (0.99-1.08)	0.09

SIR was defined as the ratio of the observed cases of RI-SPMs among abdominal and pelvic cancer survivors to the expected number of cases in the US general population and was stratified by age at all site cancer diagnosis, latency, and year of all site cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of RI-SPMs was derived from data provided by the SEER database. RT, radiation therapy; NRT, no radiation therapy; SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; US, United States; SEER, Surveillance, Epidemiology, and End Results.

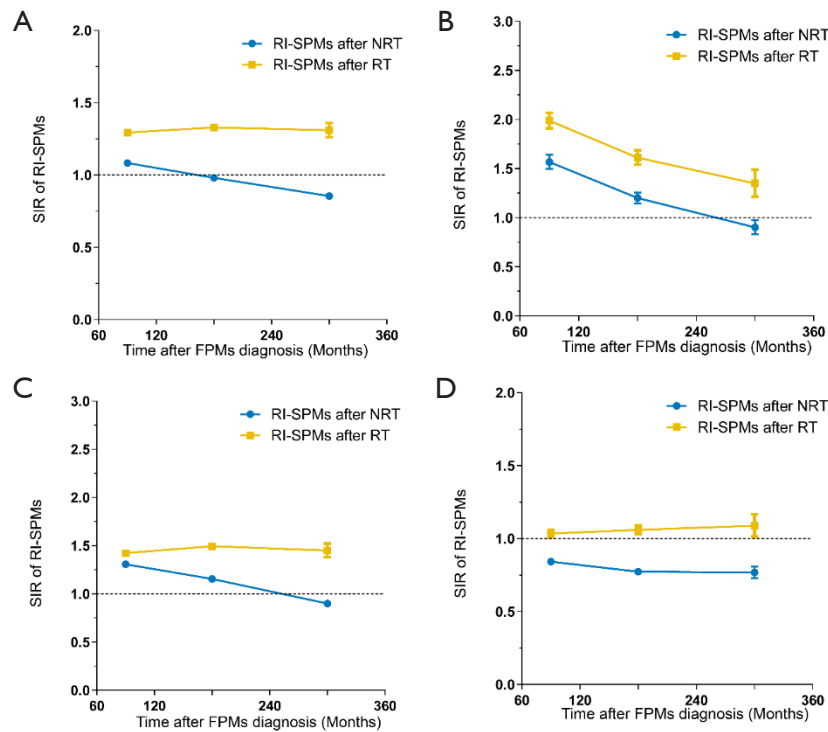


Figure S2 Dynamic standardized incidence ratio (SIR) plots for risk-increased SPM (RI-SPM) for patients in the latency-SIR plot. (A) Patients with cancers from all sites. (B) Patients with head-and-neck radiotherapy (HNRT). (C) Patients with thoracic radiotherapy (TRT). (D) Patients with abdominal-and-pelvic radiotherapy (APRT). (A-D) Adjusted SIRs and 95% CIs of the development of RI-SPMs in patients treated with RT versus those of the US general population are plotted. Comparisons were made with patients treated with NRT, including those with cancers from all sites, head-and-neck cancer, thoracic cancer, and abdominal-and-pelvic cancer, with the US general population, and the incidence in the background US population is represented by the gray line (at $y=1$). The detailed data of RRs and SIRs are provided in the supplementary data. RI-SPM, risk-increased second primary malignancy; RT, radiation therapy; CI, confidence interval.

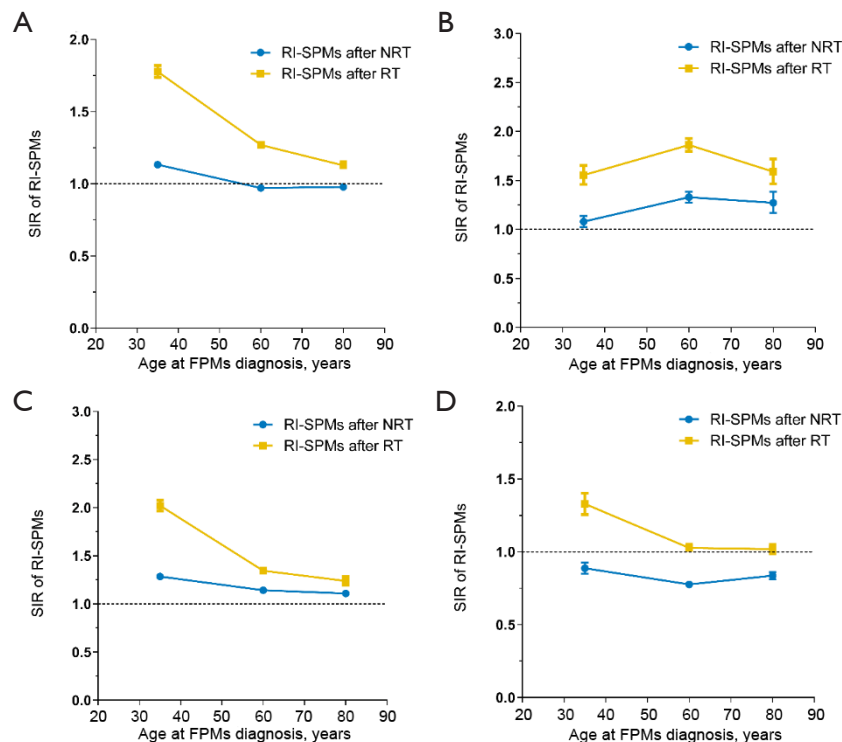


Figure S3 Dynamic standardized incidence ratio (SIR) plots for risk increased SPM (RI-SPM) for patients in the age-SIR plot. (A) Patients with cancer from all sites. (B) Patients with head-and-neck radiotherapy (HNRT). (C) Patients with thoracic radiotherapy (TRT). (D) Patients with abdominal-and-pelvic radiotherapy (APRT). (A-D) Adjusted SIRs and 95% CIs of the development of RI-SPMs in patients treated with RT versus those of the US general population are plotted. Comparisons were made with patients treated with NRT, including those with all-site cancers, head-and-neck cancer, thoracic cancer, and abdominal-and-pelvic cancer, and the US general population, and the incidence in the background US population is represented by the gray line (at $y=1$). The detailed data of RRs and SIRs are provided in the supplementary data. RI-SPM, risk-increased second primary malignancy; RT, radiation therapy; CI, confidence interval.

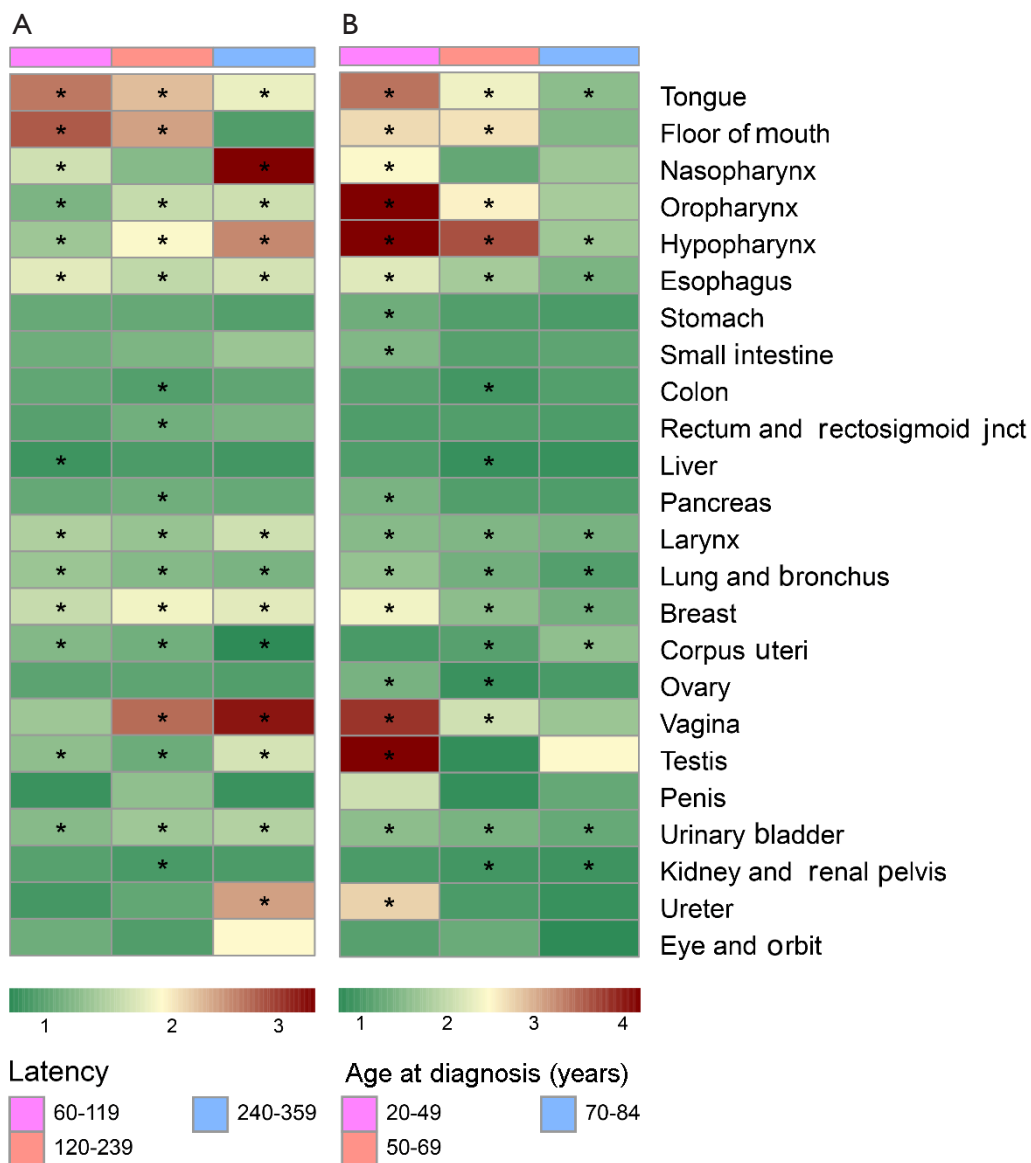


Figure S4 Standardized incidence ratios (SIRs) for each type of risk-increased second primary malignancy (RI-SPM). (A) SIRs for each type of RI-SPMs in different latency period. (B) SIRs for each type of RI-SPM in the different age groups. SIR was calculated by dividing the observed number of RI-SPMs of each cell by the expected number of RI-SPMs in the general population. SIRs were adjusted for sex, age at SPM diagnosis, and the calendar year of SPM diagnosis in our analysis. *, indicates statistically significant SIRs, with $P < 0.05$. The color scale shows the range of SIR values. The detailed data of SIRs are provided in the supplementary data. Jnct, junction.

Table S18 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by latency of all site cancer diagnosis

Site	Latency between all site primary cancer and RI-SPMs							
	All		60–119 months		120–239 months		240–360 months	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	2.35 (2.16-2.55)	<0.001	2.53 (2.25-2.83)	<0.001	2.21 (1.91-2.53)	<0.001	1.79 (1.21-2.57)	<0.001
Floor of mouth	2.41 (1.99-2.88)	<0.001	2.67 (2.08-3.38)	<0.001	2.34 (1.71-3.14)	<0.001	0.93 (0.19-2.71)	0.14
Nasopharynx	1.56 (1.15-2.06)	<0.001	1.64 (1.09-2.38)	<0.001	1.23 (0.69-2.03)	0.34	3.11 (1.14-6.77)	<0.001
Oropharynx	2.77 (2.19-3.45)	<0.001	2.34 (1.64-3.25)	<0.001	3.18 (2.21-4.42)	<0.001	3.26 (1.19-7.11)	<0.001
Hypopharynx	3.27 (2.81-3.77)	<0.001	2.72 (2.18-3.37)	<0.001	3.78 (2.99-4.71)	<0.001	4.91 (2.75-8.11)	<0.001
Esophagus	1.67 (1.55-1.79)	<0.001	1.74 (1.58-1.93)	<0.001	1.56 (1.38-1.76)	<0.001	1.66 (1.21-2.24)	<0.001
Stomach	1.05 (0.97-1.13)	0.07	1.05 (0.95-1.17)	0.23	1.04 (0.93-1.17)	0.08	0.95 (0.69-1.26)	0.07
Small intestine	1.14 (1.01-1.31)	<0.001	1.09 (0.89-1.32)	0.14	1.18 (0.96-1.43)	0.21	1.35 (0.83-2.09)	0.15
Colon excluding rectum	0.98 (0.95-1.02)	0.01	1.02 (0.97-1.07)	0.11	0.94 (0.89-0.99)	<0.001	1.01 (0.89-1.14)	<0.001
Rectum, rectosigmoid junction, anus, anal canal, and anorectum	1.03 (0.98-1.09)	0.02	0.96 (0.88-1.04)	0.08	1.11 (1.02-1.21)	<0.001	1.16 (0.94-1.41)	<0.001
Liver	0.86 (0.78-0.94)	<0.001	0.82 (0.71-0.94)	<0.001	0.91 (0.78-1.05)	0.11	0.85 (0.57-1.22)	0.09
Pancreas	1.07 (1.01-1.13)	<0.001	1.04 (0.96-1.12)	0.31	1.11 (1.02-1.19)	0.01	1.05 (0.87-1.26)	0.33
Larynx	1.41 (1.27-1.56)	<0.001	1.46 (1.27-1.66)	<0.001	1.33 (1.12-1.57)	<0.001	1.64 (1.04-2.47)	<0.001
Lung and bronchus	1.27 (1.25-1.31)	<0.001	1.35 (1.31-1.39)	<0.001	1.22 (1.18-1.26)	<0.001	1.16 (1.06-1.26)	<0.001
Breast	1.71 (1.67-1.74)	<0.001	1.59 (1.54-1.64)	<0.001	1.83 (1.78-1.88)	<0.001	1.75 (1.65-1.86)	<0.001
Corpus and uterus, NOS	1.11 (1.06-1.17)	<0.001	1.21 (1.12-1.30)	<0.001	1.11 (1.03-1.21)	<0.001	0.72 (0.58-0.89)	<0.001
Ovary	0.98 (0.91-1.06)	0.08	0.98 (0.87-1.11)	0.18	1.01 (0.89-1.13)	0.34	0.93 (0.71-1.19)	0.23
Vagina	2.27 (1.83-2.81)	<0.001	1.36 (0.86-2.05)	0.13	2.59 (1.89-3.47)	<0.001	4.71 (2.87-7.26)	<0.001
Testis	4.97 (4.05-6.03)	<0.001	5.11 (3.89-6.60)	<0.001	4.34 (3.01-6.06)	<0.001	6.69 (2.89-13.19)	<0.001
Penis	1.05 (0.73-1.45)	0.12	0.81 (0.44-1.32)	0.16	1.29 (0.76-2.04)	0.69	0.81 (0.02-4.47)	0.67
Urinary bladder	1.31 (1.26-1.36)	<0.001	1.23 (1.17-1.30)	<0.001	1.37 (1.31-1.45)	<0.001	1.49 (1.29-1.71)	<0.001
Kidney and renal pelvis	0.92 (0.87-0.98)	<0.001	0.96 (0.88-1.05)	0.09	0.89 (0.81-0.98)	0.12	0.91 (0.71-1.14)	0.09
Ureter	1.04 (0.81-1.31)	0.33	0.86 (0.57-1.24)	0.34	1.03 (0.69-1.48)	0.11	2.34 (1.17-4.19)	0.03
Eye and orbit	1.08 (0.84-1.37)	0.21	1.09 (0.75-1.52)	0.26	0.93 (0.59-1.38)	0.24	1.91 (0.87-3.62)	0.21

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among all site cancer survivors to the expected number of cases in the US general population and was stratified by latency. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S19 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by age at all site cancer diagnosis

Site	Age at all site primary cancer diagnosis					
	20–49 years		50–69 years		70–84 years	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	3.39 (2.85-4.01)	<0.001	2.34 (2.09-2.61)	<0.001	1.52 (1.21-1.91)	<0.001
Floor of mouth	2.68 (1.71-4.03)	<0.001	2.63 (2.09-3.27)	<0.001	1.44 (0.78-2.41)	0.14
Nasopharynx	2.43 (1.41-3.91)	<0.001	1.19 (0.74-1.81)	0.12	1.67 (0.81-3.07)	0.22
Oropharynx	4.99 (3.16-7.49)	<0.001	2.53 (1.85-3.38)	<0.001	1.74 (0.83-3.21)	0.24
Hypopharynx	4.28 (2.91-6.09)	<0.001	3.64 (3.04-4.32)	<0.001	1.68 (1.05-2.54)	<0.001
Esophagus	2.21 (1.77-2.73)	<0.001	1.73 (1.57-1.91)	<0.001	1.39 (1.21-1.61)	<0.001
Stomach	1.28 (1.02-1.61)	<0.001	1.04 (0.95-1.16)	0.09	0.99 (0.87-1.12)	0.16
Small intestine	1.43 (1.02-1.96)	<0.001	1.07 (0.89-1.28)	0.11	1.14 (0.88-1.46)	0.19
Colon excluding rectum	1.08 (0.97-1.21)	0.18	0.92 (0.88-0.97)	<0.001	1.05 (0.99-1.11)	0.09
Rectum, rectosigmoid junction, anus, anal canal, and anorectum	1.02 (0.88-1.19)	0.11	1.05 (0.97-1.13)	0.19	1.01 (0.91-1.13)	0.14
Liver	1.02 (0.81-1.31)	0.13	0.83 (0.73-0.95)	<0.001	0.84 (0.69-1.01)	0.18
Pancreas	1.37 (1.17-1.59)	<0.001	1.05 (0.97-1.13)	0.12	1.02 (0.93-1.12)	0.15
Larynx	1.48 (1.11-1.95)	<0.001	1.42 (1.25-1.62)	<0.001	1.35 (1.09-1.66)	<0.001
Lung and bronchus	1.61 (1.51-1.71)	<0.001	1.32 (1.28-1.36)	<0.001	1.07 (1.02-1.12)	<0.001
Breast	2.35 (2.28-2.44)	<0.001	1.53 (1.49-1.57)	<0.001	1.32 (1.25-1.39)	<0.001
Corpus and uterus, NOS	0.98 (0.88-1.09)	0.08	1.08 (1.01-1.15)	<0.001	1.55 (1.37-1.75)	<0.001
Ovary	1.36 (1.17-1.57)	<0.001	0.85 (0.76-0.95)	<0.001	0.98 (0.81-1.17)	0.13
Vagina	3.83 (2.51-5.62)	<0.001	2.08 (1.52-2.77)	<0.001	1.65 (0.94-2.68)	0.11
Testis	7.51 (6.06-9.21)	<0.001	0.79 (0.25-1.85)	0.21	2.45 (0.79-5.72)	0.26
Penis	2.06 (0.56-5.29)	0.33	0.81 (0.44-1.36)	0.17	1.21 (0.71-1.91)	0.21
Urinary bladder	1.53 (1.34-1.74)	<0.001	1.36 (1.31-1.43)	<0.001	1.21 (1.14-1.28)	<0.001
Kidney and renal pelvis	0.99 (0.84-1.16)	0.12	0.92 (0.85-0.99)	<0.001	0.88 (0.78-0.99)	<0.001
Ureter	2.74 (1.36-4.91)	<0.001	0.99 (0.71-1.37)	0.14	0.84 (0.52-1.27)	0.19
Eye and orbit	1.08 (0.54-1.94)	0.12	1.24 (0.91-1.66)	0.17	0.74 (0.38-1.29)	0.22

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among all site cancer survivors to the expected number of cases in the US general population and was stratified by age at all site cancer diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S20 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by year of all site cancer diagnosis

Site	Year of all site primary cancer diagnosis							
	1975–1984		1985–1994		1995–2004		2005–2015	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	3.27 (2.59-4.08)	<0.001	2.92 (2.44-3.47)	<0.001	2.01 (1.76-2.27)	<0.001	2.21 (1.78-2.72)	<0.001
Floor of mouth	2.74 (1.77-4.06)	<0.001	2.62 (1.78-3.72)	<0.001	2.18 (1.61-2.89)	<0.001	2.27 (1.21-3.88)	<0.001
Nasopharynx	1.71 (0.68-3.53)	0.23	2.05 (1.12-3.44)	<0.001	1.27 (0.77-1.96)	0.14	1.68 (0.72-3.32)	0.17
Oropharynx	4.15 (2.14-7.27)	<0.001	4.26 (2.64-6.52)	<0.001	2.33 (1.63-3.23)	<0.001	1.89 (0.91-3.49)	0.11
Hypopharynx	5.17 (3.73-6.99)	<0.001	5.35 (4.05-6.94)	<0.001	2.15 (1.65-2.74)	<0.001	2.73 (1.71-4.14)	<0.001
Esophagus	3.11 (2.61-3.67)	<0.001	2.35 (2.01-2.73)	<0.001	1.27 (1.13-1.42)	<0.001	1.42 (1.15-1.75)	<0.001
Stomach	1.15 (0.94-1.39)	0.12	1.13 (0.96-1.32)	0.14	1.01 (0.91-1.11)	0.09	1.01 (0.81-1.23)	0.13
Small intestine	0.95 (0.56-1.51)	0.18	1.24 (0.92-1.65)	0.22	1.08 (0.89-1.29)	0.19	1.34 (0.97-1.81)	0.16
Colon excluding rectum	1.13 (1.04-1.22)	<0.001	0.99 (0.92-1.07)	0.07	0.93 (0.89-0.98)	<0.001	0.96 (0.86-1.08)	0.15
Rectum, rectosigmoid junction, anus, anal canal, and anorectum	1.08 (0.93-1.24)	0.09	1.02 (0.91-1.15)	0.08	1.03 (0.95-1.12)	0.08	1.01 (0.86-1.19)	0.10
Liver	0.88 (0.61-1.23)	0.12	1.09 (0.88-1.34)	0.11	0.81 (0.69-0.91)	<0.001	0.84 (0.66-1.05)	0.17
Pancreas	1.01 (0.85-1.18)	0.22	1.05 (0.93-1.18)	0.29	1.07 (0.99-1.15)	0.19	1.14 (1.01-1.31)	<0.001
Larynx	1.85 (1.42-2.38)	<0.001	1.71 (1.35-2.12)	<0.001	1.23 (1.06-1.41)	<0.001	1.41 (1.06-1.81)	<0.001
Lung and bronchus	1.61 (1.51-1.69)	<0.001	1.44 (1.38-1.51)	<0.001	1.13 (1.11-1.17)	<0.001	1.26 (1.19-1.35)	<0.001
Breast	1.28 (1.21-1.35)	<0.001	1.81 (1.75-1.87)	<0.001	1.81 (1.76-1.86)	<0.001	1.63 (1.54-1.73)	<0.001
Corpus and uterus, NOS	0.63 (0.53-0.75)	<0.001	1.24 (1.13-1.36)	<0.001	1.21 (1.12-1.31)	<0.001	1.11 (0.94-1.28)	0.17
Ovary	0.76 (0.62-0.94)	<0.001	1.11 (0.97-1.26)	0.16	1.01 (0.88-1.13)	0.17	0.94 (0.72-1.22)	0.19
Vagina	4.04 (2.68-5.84)	<0.001	2.47 (1.67-3.51)	<0.001	1.52 (0.97-2.27)	0.24	1.55 (0.56-3.38)	0.31
Testis	7.19 (4.39-11.11)	<0.001	6.79 (4.71-9.49)	<0.001	4.31 (3.11-5.81)	<0.001	2.21 (0.88-4.56)	0.35
Penis	1.89 (0.51-4.85)	0.47	0.32 (0.01-1.81)	0.19	1.19 (0.78-1.73)	0.16	0.63 (0.17-1.62)	0.14
Urinary bladder	1.64 (1.47-1.83)	<0.001	1.21 (1.11-1.33)	<0.001	1.31 (1.24-1.36)	<0.001	1.26 (1.15-1.39)	<0.001
Kidney and renal pelvis	0.73 (0.58-0.91)	<0.001	0.88 (0.76-1.01)	0.09	0.96 (0.89-1.04)	0.07	0.93 (0.81-1.08)	0.08
Ureter	2.14 (1.22-3.49)	<0.001	1.03 (0.54-1.76)	0.16	0.95 (0.66-1.31)	0.13	0.53 (0.17-1.24)	0.11
Eye and orbit	1.21 (0.55-2.31)	0.22	1.02 (0.56-1.72)	0.15	1.11 (0.77-1.53)	0.13	0.99 (0.45-1.89)	0.17

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among all site cancer survivors to the expected number of cases in the US general population and was stratified by year of all site cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S21 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by latency of head and neck cancer diagnosis

Site	Latency between head and neck primary cancer and RI-SPMs							
	All		60–119 months		120–239 months		240–360 months	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	11.21(10.11-12.52)	<0.001	14.25(12.36-16.34)	<0.001	9.23(7.67-11.02)	<0.001	6.16(3.71-9.62)	<0.001
Floor of mouth	9.71(7.62-12.11)	<0.001	10.57(7.62-14.29)	<0.001	10.17(6.91-14.44)	<0.001	1.79(0.05-9.98)	0.58
Nasopharynx	5.91(3.99-8.44)	<0.001	6.49(3.71-10.55)	<0.001	3.74(1.62-7.37)	<0.001	13.93(5.12-30.34)	<0.001
Oropharynx	12.31(9.17-16.38)	<0.001	9.68(5.74-15.31)	<0.001	14.28(9.15-21.25)	<0.001	13.28(4.31-31.01)	<0.001
Hypopharynx	15.21(12.81-18.06)	<0.001	13.72(10.52-17.59)	<0.001	16.67(12.75-21.41)	<0.001	16.68(8.62-29.14)	<0.001
Esophagus	4.59(4.04-5.19)	<0.001	5.73(4.82-6.76)	<0.001	3.84(3.09-4.72)	<0.001	2.95(1.72-4.72)	<0.001
Stomach	1.07(0.86-1.31)	0.11	1.21(0.89-1.62)	0.12	1.01(0.71-1.39)	0.15	0.35(0.07-1.01)	0.09
Small intestine	1.03(0.64-1.58)	0.11	0.68(0.25-1.49)	0.18	1.57(0.86-2.64)	0.22	0.43(0.01-2.41)	0.20
Colon excluding rectum	1.03(0.93-1.15)	0.23	1.12(0.96-1.30)	0.10	0.95(0.81-1.12)	0.17	1.05(0.74-1.45)	0.19
Rectum	0.91(0.72-1.11)	0.15	0.99(0.73-1.33)	0.12	0.77(0.53-1.09)	0.07	0.98(0.45-1.86)	0.22
Liver	1.52(1.23-1.87)	<0.001	1.37(0.96-1.89)	0.31	1.82(1.35-2.39)	<0.001	1.17(0.51-2.29)	0.19
Pancreas	0.87(0.72-1.05)	0.16	1.09(0.83-1.41)	0.22	0.75(0.54-1.02)	0.11	0.61(0.28-1.16)	0.14
Larynx	3.51(2.97-4.12)	<0.001	3.11(2.41-3.97)	<0.001	3.88(3.02-4.92)	<0.05	4.11(2.29-6.78)	<0.001
Lung and bronchus	2.59(2.47-2.72)	<0.001	3.07(2.87-3.27)	<0.001	2.39(2.22-2.58)	<0.05	1.57(1.29-1.89)	<0.001
Breast	1.01(0.92-1.11)	0.13	1.07(0.94-1.22)	0.11	0.94(0.82-1.08)	0.18	1.06(0.79-1.39)	0.22
Corpus and uterus, NOS	0.87(0.71-1.06)	0.07	0.77(0.54-1.07)	0.18	0.87(0.62-1.19)	0.10	1.29(0.71-2.16)	0.23
Ovary	0.87(0.63-1.18)	0.22	1.04(0.66-1.57)	0.16	0.68(0.37-1.14)	0.13	1.07(0.35-2.49)	0.11
Vagina	0.38(0.01-2.12)	0.23	0(0-3.19)	0.21	0.87(0.02-4.86)	0.19	0(0-12.96)	0.88
Testis	0.61(0.12-1.81)	0.34	0(0-1.34)	0.28	1.64(0.34-4.81)	0.77	0(0-13.93)	0.97
Penis	0.42(0.05-1.54)	0.11	0.48(0.01-2.73)	0.27	0(0-1.83)	0.18	1.86(0.05-10.34)	0.68
Urinary bladder	1.07(0.95-1.21)	0.10	1.29(1.09-1.52)	0.12	0.93(0.77-1.12)	0.09	0.79(0.51-1.17)	0.11
Kidney and renal pelvis	1.22(1.04-1.42)	<0.001	1.27(1.01-1.60)	<0.001	1.11(0.85-1.39)	0.22	1.62(1.04-2.41)	<0.001
Ureter	0.56(0.15-1.44)	0.14	0.32(0.08-1.81)	0.12	0.97(0.19-2.83)	0.35	0(0-4.41)	0.41
Eye and orbit	1.52(0.76-2.73)	0.16	1.82(0.67-3.98)	0.23	1.29(0.35-3.31)	0.44	1.34(0.03-7.49)	0.65

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among head and neck cancer survivors to the expected number of cases in the US general population and was stratified by latency of head and neck cancer diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S22 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by age at head and neck cancer diagnosis

SPM site	Age at head and neck primary cancer diagnosis					
	20–49 years		50–69 years		70–84 years	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	10.22 (8.28-12.49)	<0.001	11.43 (9.97-13.05)	<0.001	13.99 (9.81-19.37)	<0.001
Floor of mouth	7.82 (4.38-12.91)	<0.001	10.91 (8.21-14.19)	<0.001	6.01 (1.63-15.37)	<0.001
Nasopharynx	7.95 (4.45-13.12)	<0.001	3.91 (1.94-6.99)	<0.001	10.88 (2.96-27.85)	<0.001
Oropharynx	13.71 (7.67-22.61)	<0.001	12.52 (8.56-17.68)	<0.001	6.59 (0.79-23.82)	0.87
Hypopharynx	15.36 (10.26-22.21)	<0.001	15.55 (12.61-18.95)	<0.001	13.01 (6.52-23.43)	<0.001
Esophagus	4.21 (3.03-5.69)	<0.001	4.63 (3.97-5.38)	<0.001	4.85 (3.39-6.71)	<0.001
Stomach	0.86 (0.44-1.51)	0.22	1.01 (0.75-1.31)	0.17	1.47 (0.94-2.21)	0.28
Small intestine	0.99 (0.32-2.32)	0.16	0.87 (0.43-1.56)	0.15	1.89 (0.61-4.41)	0.27
Colon excluding rectum	0.91 (0.72-1.14)	0.14	1.03 (0.91-1.18)	0.38	1.11 (0.87-1.37)	0.17
Rectum	0.89 (0.55-1.36)	0.11	0.89 (0.67-1.17)	0.29	0.92 (0.49-1.58)	0.15
Liver	1.38 (0.87-2.08)	0.17	1.57 (1.21-2.02)	<0.001	1.63 (0.81-2.92)	0.21
Pancreas	0.76 (0.44-1.23)	0.15	0.99 (0.78-1.23)	0.08	0.57 (0.31-0.98)	<0.001
Larynx	4.64 (3.31-6.32)	<0.001	3.37 (2.74-4.09)	<0.001	2.28 (1.09-4.19)	<0.001
Lung and bronchus	2.02 (1.76-2.31)	<0.001	2.76 (2.61-2.92)	<0.001	2.42 (2.12-2.75)	<0.001
Breast	1.09 (0.96-1.25)	0.13	0.96 (0.84-1.09)	NA	0.88 (0.62-1.21)	0.20
Corpus and uterus, NOS	1.11 (0.81-1.46)	0.18	0.66 (0.46-0.92)	<0.001	1.02 (0.44-2.01)	0.21
Ovary	0.98 (0.58-1.55)	0.28	0.83 (0.51-1.29)	0.25	0.73 (0.21-1.88)	0.15
Vagina	0 (0-4.49)	0.11	0 (0-2.68)	0.13	2.35 (0.05-13.13)	0.23
Testis	0.59 (0.07-2.16)	0.15	0.71 (0.01-3.99)	0.41	0 (0-27.55)	0.21
Penis	1.48 (0.03-8.26)	0.38	0 (0-1.18)	0.29	1.13 (0.02-6.32)	0.19
Urinary bladder	1.01 (0.71-1.41)	0.29	1.08 (0.94-1.25)	0.15	1.05 (0.79-1.38)	0.14
Kidney and renal pelvis	1.44 (1.07-1.91)	<0.001	1.22 (1-1.48)	<0.001	0.69 (0.34-1.24)	0.37
Ureter	0 (0-4.67)	0.33	0.81 (0.22-2.09)	0.17	0 (0-2.59)	0.19
Eye and orbit	1.54 (0.31-4.51)	0.34	1.82 (0.78-3.59)	0.27	0 (0-4.21)	0.44

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among head and neck cancer survivors to the expected number of cases in the US general population and was stratified by age at head and neck cancer diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S23 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by year of head and neck cancer diagnosis

SPM site	Year of head and neck primary cancer diagnosis							
	1975–1984		1985–1994		1995–2004		2005–2015	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	10.54 (8.05-13.53)	<0.001	10.35 (8.42-12.59)	<0.001	11.66 (9.78-13.78)	<0.001	13.55 (10.15-17.73)	<0.001
Floor of mouth	7.24 (4.29-11.44)	<0.001	8.89 (5.63-13.35)	<0.001	13.73 (9.12-19.84)	<0.001	9.74 (3.16-22.75)	<0.001
Nasopharynx	5.29 (1.94-11.53)	<0.001	5.83 (2.79-10.73)	<0.001	6.19 (3.09-11.91)	<0.001	6.69 (1.38-19.58)	<0.001
Oropharynx	12.21 (5.85-22.47)	<0.001	14.72 (8.72-23.26)	<0.001	12.47 (7.39-19.72)	<0.001	6.39 (1.31-18.69)	<0.001
Hypopharynx	11.97 (8.33-16.65)	<0.001	14.16 (10.24-19.07)	<0.001	17.89 (12.94-24.09)	<0.001	26.66 (15.24-43.29)	<0.001
Esophagus	6.85 (5.53-8.39)	<0.001	4.33 (3.45-5.38)	<0.001	3.44 (2.63-4.42)	<0.001	3.33 (1.86-5.49)	<0.001
Stomach	0.92 (0.58-1.39)	0.09	1.11 (0.77-1.57)	0.23	1.09 (0.71-1.58)	0.13	1.36 (0.59-2.69)	0.17
Small intestine	0.79 (0.16-2.33)	0.19	1.34 (0.61-2.56)	0.21	0.92 (0.37-1.91)	0.29	0.88 (0.11-3.21)	0.15
Colon excluding rectum	1.02 (0.84-1.24)	0.18	1.05 (0.88-1.26)	0.19	1.05 (0.86-1.27)	0.11	0.91 (0.56-1.39)	0.38
Rectum	0.81 (0.49-1.23)	0.21	1.11 (0.77-1.52)	0.14	0.71 (0.43-1.07)	0.23	1.11 (0.51-2.12)	0.29
Liver	1.79 (1.06-2.83)	<0.001	1.88 (1.32-2.61)	<0.001	1.23 (0.84-1.75)	0.27	1.21 (0.55-2.29)	0.19
Pancreas	0.82 (0.52-1.22)	0.08	0.99 (0.72-1.35)	0.10	0.76 (0.52-1.07)	0.12	1.01 (0.52-1.77)	0.14
Larynx	3.23 (2.33-4.35)	<0.001	3.26 (2.41-4.33)	<0.001	4.23 (3.15-5.56)	<0.001	3.08 (1.41-5.86)	<0.001
Lung and bronchus	2.92 (2.68-3.18)	<0.001	2.61 (2.41-2.83)	<0.001	2.48 (2.27-2.71)	<0.001	1.78 (1.43-2.19)	<0.001
Breast	0.89 (0.68-1.14)	0.13	0.98 (0.83-1.15)	0.19	1.01 (0.87-1.16)	0.21	1.19 (0.95-1.49)	0.20
Corpus and uterus, NOS	0.75 (0.37-1.35)	0.11	0.99 (0.68-1.39)	0.15	0.81 (0.55-1.12)	0.19	0.91 (0.49-1.53)	0.13
Ovary	1.01 (0.43-1.99)	0.18	0.67 (0.33-1.21)	0.11	0.83 (0.46-1.37)	0.26	1.41 (0.61-2.79)	0.15
Vagina	0 (0-8.18)	0.51	1.14 (0.02-6.41)	0.18	0 (0-3.73)	0.11	0 (0-11.88)	0.81
Testis	1.48 (0.03-8.25)	0.48	0 (0-2.43)	0.15	1.01 (0.12-3.65)	0.22	0 (0-5.26)	0.32
Penis	0 (0-2.83)	0.17	0.62 (0.01-3.49)	0.28	0.69 (0.01-3.86)	0.31	0 (0-11.05)	0.12
Urinary bladder	1.13 (0.91-1.42)	0.46	0.97 (0.78-1.19)	0.11	1.11 (0.88-1.35)	0.17	1.18 (0.75-1.78)	0.37
Kidney and renal pelvis	0.59 (0.34-0.97)	<0.001	1.36 (1.04-1.75)	<0.001	1.34 (1.04-1.71)	<0.001	1.51 (0.94-2.29)	0.33
Ureter	0.51 (0.01-2.83)	0.09	0.41 (0.01-2.26)	0.13	0.92 (0.11-3.32)	0.11	0 (0-7.36)	0.24
Eye and orbit	0.65 (0.01-3.62)	0.22	1.25 (0.25-3.67)	0.26	1.99 (0.64-4.64)	0.17	2.61 (0.31-9.42)	0.52

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among head and neck cancer survivors to the expected number of cases in the US general population and was stratified by year of head and neck cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S24 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by latency of thoracic cancer diagnosis

SPM site	Latency between thoracic primary cancer and RI-SPMs							
	All		60–119 months		120–239 months		240–360 months	
	SIR (95%CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	1.15 (0.91-1.42)	0.14	1.08 (0.75-1.50)	0.08	1.21 (0.85-1.64)	0.11	1.26 (0.54-2.48)	0.19
Floor of mouth	0.95 (0.54-1.55)	0.16	1.44 (0.74-2.52)	0.19	0.43 (0.09-1.26)	0.12	0.79 (0.02-4.42)	0.21
Nasopharynx	0.63 (0.23-1.37)	0.13	0.82 (0.22-2.10)	0.22	0.51 (0.06-1.84)	0.11	0 (0-5.76)	0.32
Oropharynx	1.07 (0.46-2.12)	0.19	1.73 (0.63-3.77)	0.27	0.62 (0.07-2.23)	0.25	0 (0-5.76)	0.27
Hypopharynx	1.97 (1.28-2.92)	<0.001	2.21 (1.21-3.71)	<0.001	1.71 (0.78-3.25)	0.22	2.09 (0.25-7.56)	0.51
Esophagus	1.98 (1.71-2.28)	<0.001	1.92 (1.53-2.38)	<0.001	2.02 (1.62-2.51)	<0.001	1.73 (0.97-2.85)	0.14
Stomach	0.97 (0.84-1.11)	0.16	1.07 (0.87-1.30)	0.14	0.89 (0.72-1.11)	0.11	0.86 (0.51-1.38)	0.13
Small intestine	0.84 (0.64-1.07)	0.12	0.95 (0.65-1.35)	0.18	0.77 (0.51-1.14)	0.15	0.71 (0.23-1.64)	0.20
Colon excluding rectum	0.89 (0.84-0.95)	<0.001	1.01 (0.93-1.10)	0.10	0.82 (0.75-0.91)	<0.001	0.72 (0.58-0.88)	<0.001
Rectum	0.78 (0.68-0.89)	<0.001	0.81 (0.66-0.98)	<0.001	0.73 (0.58-0.89)	<0.001	0.96 (0.61-1.46)	0.11
Liver	0.75 (0.61-0.91)	<0.001	0.81 (0.59-1.08)	0.13	0.68 (0.49-0.93)	<0.001	0.88 (0.44-1.57)	0.21
Pancreas	1.08 (0.99-1.17)	0.19	1.05 (0.92-1.19)	0.16	1.14 (1.01-1.28)	<0.001	0.97 (0.73-1.27)	0.17
Larynx	1.12 (0.86-1.45)	0.13	1.33 (0.93-1.85)	0.26	0.91 (0.55-1.39)	0.18	1.03 (0.28-2.64)	0.25
Lung and bronchus	1.31 (1.26-1.35)	<0.001	1.41 (1.34-1.49)	<0.001	1.21 (1.15-1.28)	<0.001	1.25 (1.11-1.41)	<0.001
Breast	2.04 (2.01-2.08)	<0.001	1.81 (1.74-1.86)	<0.001	2.25 (2.19-2.32)	<0.001	2.35 (2.19-2.51)	<0.001
Corpus and uterus, NOS	1.27 (1.21-1.34)	<0.001	1.35 (1.25-1.47)	<0.001	1.28 (1.17-1.39)	<0.001	0.81 (0.62-1.03)	0.16
Ovary	1.12 (1.03-1.22)	<0.001	1.14 (1.01-1.30)	<0.001	1.14 (0.99-1.29)	0.15	0.98 (0.69-1.34)	0.17
Vagina	0.79 (0.51-1.21)	0.11	0.56 (0.22-1.16)	0.21	1.06 (0.56-1.81)	0.19	0.77 (0.09-2.79)	0.28
Testis	0 (0-8.13)	0.54	0 (0-12.16)	0.75	0 (0-26.33)	0.83	0 (0-388.53)	0.96
Penis	1.35 (0.03-7.52)	0.43	2.15 (0.05-12.02)	0.61	0 (0-14.59)	0.42	0 (0-157.78)	0.92
Urinary bladder	1.06 (0.97-1.16)	0.17	1.12 (0.98-1.28)	0.14	1.02 (0.89-1.17)	0.11	0.98 (0.72-1.32)	0.21
Kidney and renal pelvis	0.88 (0.79-0.98)	<0.001	0.95 (0.81-1.11)	0.19	0.87 (0.74-1.02)	0.14	0.62 (0.39-0.94)	<0.001
Ureter	0.84 (0.48-1.34)	0.15	0.79 (0.32-1.64)	0.18	0.98 (0.45-1.87)	0.16	0.49 (0.01-2.71)	0.27
Eye and orbit	1.18 (0.79-1.69)	0.19	0.97 (0.48-1.74)	0.14	1.02 (0.51-1.82)	0.19	2.73 (1-5.93)	<0.001

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among thoracic cancer survivors to the expected number of cases in the US general population and was stratified by latency of thoracic cancer diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% confidence intervals were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S25 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by age at thoracic cancer diagnosis

SPM site	Age at thoracic primary cancer diagnosis					
	20–49 years		50–69 years		70–84 years	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	1.86 (1.25-2.68)	<0.001	1.01 (0.73-1.36)	0.15	0.76 (0.36-1.45)	0.19
Floor of mouth	1.19 (0.32-3.05)	0.23	0.67 (0.27-1.39)	0.16	1.66 (0.54-3.89)	0.28
Nasopharynx	0.38 (0-2.15)	0.19	0.54 (0.11-1.59)	0.19	1.44 (0.17-5.28)	0.31
Oropharynx	3.16 (1.02-7.39)	<0.001	0.21 (0-1.21)	0.11	1.62 (0.19-5.87)	0.32
Hypopharynx	0 (0-1.58)	0.13	2.56 (1.58-3.92)	<0.001	1.91 (0.51-4.86)	0.26
Esophagus	2.58 (1.77-3.62)	<0.001	2.07 (1.72-2.48)	<0.001	1.44 (1.01-2.01)	<0.001
Stomach	1.09 (0.74-1.55)	0.16	0.93 (0.77-1.12)	0.11	0.99 (0.76-1.26)	0.14
Small intestine	0.92 (0.49-1.58)	0.17	0.77 (0.53-1.07)	0.08	0.97 (0.54-1.66)	0.19
Colon excluding rectum	0.68 (0.56-0.83)	<0.001	0.83 (0.76-0.89)	<0.001	1.11 (1.01-1.21)	<0.001
Rectum	0.62 (0.47-0.81)	<0.001	0.86 (0.75-0.98)	<0.001	0.84 (0.67-1.04)	0.07
Liver	0.89 (0.54-1.38)	0.12	0.66 (0.51-0.87)	<0.001	0.87 (0.57-1.28)	0.14
Pancreas	1.08 (0.84-1.37)	0.16	1.07 (0.96-1.19)	0.14	1.09 (0.93-1.28)	0.16
Larynx	0.34 (0.09-0.88)	<0.001	1.33 (0.97-1.78)	0.18	1.41 (0.67-2.58)	0.22
Lung and bronchus	1.63 (1.51-1.78)	<0.001	1.27 (1.21-1.33)	<0.001	1.18 (1.08-1.28)	<0.001
Breast	3.01 (2.89-3.11)	<0.001	1.79 (1.74-1.85)	<0.001	1.48 (1.39-1.57)	<0.001
Corpus and uterus, NOS	1.04 (0.92-1.18)	0.17	1.24 (1.15-1.34)	<0.001	1.84 (1.61-2.09)	<0.001
Ovary	1.43 (1.21-1.69)	<0.001	1.01 (0.88-1.13)	0.12	1.14 (0.93-1.39)	0.14
Vagina	0.21 (0-1.16)	0.12	0.82 (0.44-1.42)	0.15	1.13 (0.48-2.22)	0.21
Testis	0 (0-18.68)	0.29	0 (0-16.61)	0.23	0 (0-109.03)	0.86
Penis	0 (0-75.49)	0.26	2.14 (0.05-11.94)	0.27	0 (0-16.44)	0.31
Urinary bladder	1.23 (0.95-1.56)	0.16	1.09 (0.97-1.22)	0.11	0.93 (0.77-1.11)	0.16
Kidney and renal pelvis	0.84 (0.65-1.08)	0.12	0.84 (0.73-0.97)	<0.001	1.04 (0.82-1.36)	0.11
Ureter	0.54 (0.01-3.05)	0.23	1.15 (0.63-1.94)	0.17	0.31 (0.03-1.14)	0.15
Eye and orbit	1.37 (0.55-2.83)	0.19	1.27 (0.77-1.99)	0.15	0.65 (0.13-1.94)	0.18

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among thoracic cancer survivors to the expected number of cases in the US general population and was stratified by age at thoracic cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S26 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by year of thoracic cancer diagnosis

SPM site	Year of thoracic primary cancer diagnosis							
	1975–1984		1985–1994		1995–2004		2005–2015	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	0.73 (0.23-1.72)	0.32	1.03 (0.65-1.57)	0.17	1.34 (0.98-1.79)	0.13	1.01 (0.48-1.85)	0.20
Floor of mouth	0.77 (0.09-2.81)	0.13	0.68 (0.18-1.76)	0.11	1.18 (0.51-2.32)	0.19	1.32 (0.16-4.78)	0.22
Nasopharynx	0 (0-3.34)	0.20	0.65 (0.07-2.36)	0.18	0.46 (0.05-1.68)	0.14	1.91 (0.23-6.92)	0.31
Oropharynx	0 (0-4.99)	0.34	0.92 (0.11-3.34)	0.31	1.15 (0.31-2.95)	0.28	1.91 (0.23-6.88)	0.45
Hypopharynx	2.17 (0.59-5.56)	0.34	2.98 (1.58-5.11)	0.39	1.15 (0.42-2.51)	0.15	1.59 (0.19-5.76)	0.23
Esophagus	2.82 (1.91-4.03)	<0.001	2.21 (1.72-2.79)	<0.001	1.55 (1.21-1.97)	<0.001	2.18 (1.38-3.28)	<0.001
Stomach	1.14 (0.77-1.63)	0.18	0.92 (0.71-1.17)	0.14	0.96 (0.77-1.18)	0.17	0.98 (0.62-1.47)	0.10
Small intestine	0.31 (0.03-1.14)	0.33	0.72 (0.41-1.17)	0.21	0.88 (0.61-1.25)	0.11	1.25 (0.66-2.15)	0.13
Colon excluding rectum	0.92 (0.79-1.08)	0.15	0.85 (0.77-0.94)	<0.001	0.94 (0.82-0.98)	<0.001	1.01 (0.84-1.21)	0.11
Rectum	0.69 (0.49-0.95)	<0.001	0.91 (0.75-1.07)	0.34	0.76 (0.64-0.89)	<0.001	0.85 (0.61-1.16)	0.09
Liver	0.21 (0.02-0.72)	<0.001	0.89 (0.61-1.25)	0.14	0.67 (0.49-0.91)	<0.001	1.01 (0.61-1.59)	0.24
Pancreas	1.02 (0.77-1.34)	0.19	0.91 (0.76-1.06)	0.12	1.18 (1.05-1.32)	<0.001	1.21 (0.95-1.51)	0.32
Larynx	0.58 (0.15-1.49)	0.22	1.17 (0.72-1.79)	0.31	1.09 (0.71-1.62)	0.27	1.76 (0.84-3.24)	0.19
Lung and bronchus	1.31 (1.17-1.47)	<0.001	1.17 (1.11-1.26)	<0.001	1.29 (1.22-1.36)	<0.001	1.71 (1.56-1.88)	<0.001
Breast	1.87 (1.75-2.01)	<0.001	2.19 (2.11-2.27)	<0.001	2.05 (1.98-2.11)	<0.001	1.79 (1.68-1.91)	<0.001
Corpus and uterus, NOS	0.87 (0.71-1.08)	0.14	1.43 (1.29-1.57)	<0.001	1.31 (1.21-1.41)	<0.001	1.11 (0.92-1.31)	0.12
Ovary	0.97 (0.73-1.28)	0.17	1.26 (1.09-1.46)	<0.001	1.08 (0.94-1.23)	0.11	1.02 (0.76-1.35)	0.21
Vagina	1.64 (0.53-3.83)	0.31	0.79 (0.31-1.64)	0.15	0.71 (0.32-1.34)	0.14	0.32 (0-1.82)	0.25
Testis	0 (0-256.06)	0.88	0 (0-26.26)	0.93	0 (0-16.25)	0.32	0 (0-51.67)	0.87
Penis	0 (0-119.95)	0.71	0 (0-15.85)	0.27	2.83 (0.07-15.82)	0.29	0 (0-29.62)	0.69
Urinary bladder	1.11 (0.83-1.45)	0.13	1.05 (0.89-1.23)	0.11	1 (0.87-1.14)	0.09	1.32 (1.03-1.68)	<0.001
Kidney and renal pelvis	0.67 (0.42-1.01)	0.09	0.82 (0.66-1.01)	0.12	0.99 (0.85-1.14)	0.11	0.76 (0.54-1.06)	0.18
Ureter	1.41 (0.29-4.12)	0.14	0.61 (0.16-1.55)	0.17	0.84 (0.36-1.67)	0.21	0.96 (0.11-3.48)	0.33
Eye and orbit	2.47 (0.91-5.38)	0.19	1.18 (0.54-2.25)	0.28	0.86 (0.41-1.59)	0.18	1.32 (0.35-3.38)	0.27

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among thoracic cancer survivors to the expected number of cases in the US general population and was stratified by year of thoracic cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S27 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by latency of abdominal and pelvic cancer diagnosis

SPM site	Latency between abdominal and pelvic primary cancer and RI-SPMs							
	All		60–119 months		120–239 months		240–360 months	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	0.86 (0.71-1.04)	0.09	0.85 (0.65-1.09)	0.11	0.93 (0.68-1.25)	0.13	0.41 (0.09-1.21)	0.18
Floor of mouth	1.13 (0.75-1.63)	0.17	1.19 (0.69-1.91)	0.25	1.13 (0.54-2.09)	0.22	0.71 (0.02-3.93)	0.19
Nasopharynx	0.77 (0.41-1.32)	0.14	0.82 (0.35-1.63)	0.20	0.82 (0.27-1.91)	0.19	0 (0-4.29)	0.14
Oropharynx	1.28 (0.81-1.94)	0.16	1.21 (0.62-2.10)	0.22	1.48 (0.67-2.81)	0.16	1.22 (0.03-6.79)	0.28
Hypopharynx	0.65 (0.41-0.98)	<0.001	0.52 (0.26-0.94)	<0.001	0.82 (0.39-1.51)	0.12	0.73 (0.02-4.04)	0.35
Esophagus	0.98 (0.86-1.11)	0.12	1.07 (0.91-1.25)	0.13	0.85 (0.68-1.04)	0.27	0.97 (0.48-1.73)	0.22
Stomach	1.08 (0.99-1.19)	0.09	1.01 (0.88-1.16)	0.19	1.14 (0.98-1.32)	0.15	1.31 (0.84-1.92)	0.24
Small intestine	1.39 (1.17-1.64)	<0.001	1.24 (0.96-1.58)	0.24	1.42 (1.08-1.84)	<0.001	2.61 (1.42-4.37)	<0.001
Colon excluding rectum	1.04 (0.99-1.11)	0.13	1.01 (0.93-1.08)	0.11	1.05 (0.97-1.13)	0.13	1.35 (1.14-1.59)	<0.001
Rectum	1.39 (1.28-1.52)	<0.001	1.08 (0.95-1.24)	0.12	1.75 (1.55-1.98)	<0.001	1.99 (1.44-2.67)	<0.001
Liver	0.77 (0.68-0.88)	<0.001	0.74 (0.62-0.89)	<0.001	0.81 (0.65-0.99)	<0.001	0.68 (0.33-1.25)	0.11
Pancreas	1.11 (1.02-1.18)	<0.001	1.02 (0.92-1.14)	0.19	1.15 (1.02-1.28)	<0.001	1.32 (0.99-1.73)	0.31
Larynx	0.99 (0.85-1.15)	0.12	1.16 (0.96-1.39)	0.14	0.77 (0.57-1.02)	0.21	0.62 (0.17-1.58)	0.26
Lung and bronchus	0.97 (0.93-1.01)	0.08	1.01 (0.96-1.06)	0.28	0.95 (0.89-1.01)	0.11	0.85 (0.71-1.01)	0.10
Breast	0.84 (0.79-0.89)	<0.001	0.99 (0.91-1.08)	0.15	0.76 (0.69-0.83)	<0.001	0.68 (0.56-0.81)	<0.001
Corpus and uterus, NOS	0.66 (0.57-0.76)	<0.001	0.81 (0.65-0.99)	<0.001	0.63 (0.51-0.79)	<0.001	0.36 (0.19-0.62)	<0.001
Ovary	0.59 (0.47-0.73)	<0.001	0.37 (0.23-0.58)	<0.001	0.67 (0.49-0.91)	<0.001	0.81 (0.46-1.31)	0.14
Vagina	7.44 (5.76-9.47)	<0.001	4.84 (2.77-7.87)	<0.001	7.91 (5.37-11.23)	<0.001	13.04 (7.73-20.62)	<0.001
Testis	6.49 (5.28-7.91)	<0.001	6.96 (5.31-8.99)	<0.001	5.27 (3.58-7.49)	<0.001	8.69 (3.75-17.12)	<0.001
Penis	1.14 (0.79-1.61)	0.24	0.81 (0.42-1.37)	0.19	1.54 (0.91-2.43)	0.32	0 (0-5.38)	0.45
Urinary bladder	1.43 (1.37-1.49)	<0.001	1.25 (1.18-1.33)	<0.001	1.57 (1.48-1.68)	<0.001	2.29 (1.91-2.72)	<0.001
Kidney and renal pelvis	0.88 (0.81-0.96)	<0.001	0.91 (0.82-1.02)	0.11	0.85 (0.74-0.97)	<0.001	0.89 (0.59-1.28)	0.19
Ureter	1.22 (0.91-1.62)	0.21	0.96 (0.59-1.48)	0.19	1.07 (0.62-1.71)	0.17	5.53 (2.65-10.16)	<0.001
Eye and orbit	0.91 (0.61-1.31)	0.24	1.02 (0.59-1.64)	0.27	0.75 (0.34-1.42)	0.15	1.13 (0.14-4.08)	0.22

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among abdominal and pelvic cancer survivors to the expected number of cases in the US general population and was stratified by latency of abdominal and pelvic cancer Diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S28 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by age at abdominal and pelvic cancer diagnosis

SPM site	Age at abdominal and pelvic primary cancer diagnosis					
	20–49 years		50–69 years		70–84 years	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	0.87 (0.47-1.47)	0.20	0.86 (0.67-1.09)	0.11	0.87 (0.59-1.25)	0.19
Floor of mouth	1.21 (0.33-3.12)	0.27	1.23 (0.74-1.93)	0.19	0.82 (0.26-1.92)	0.14
Nasopharynx	0.39 (0.01-2.23)	0.18	0.79 (0.34-1.56)	0.22	0.94 (0.25-2.42)	0.28
Oropharynx	1.55 (0.32-4.55)	0.24	1.18 (0.62-2.02)	0.24	1.43 (0.52-3.12)	0.15
Hypopharynx	0.97 (0.21-2.85)	0.27	0.59 (0.31-1.02)	0.10	0.68 (0.27-1.42)	0.12
Esophagus	0.81 (0.43-1.35)	0.16	0.89 (0.75-1.06)	0.09	1.13 (0.94-1.35)	0.17
Stomach	1.79 (1.28-2.45)	<0.001	1.13 (0.99-1.28)	0.14	0.95 (0.81-1.11)	0.24
Small intestine	2.58 (1.61-3.95)	<0.001	1.36 (1.08-1.71)	<0.001	1.16 (0.84-1.57)	0.39
Colon excluding rectum	1.82 (1.56-2.12)	<0.001	0.98 (0.92-1.06)	0.11	1.01 (0.93-1.09)	0.11
Rectum	1.86 (1.52-2.27)	<0.001	1.24 (1.12-1.37)	<0.001	0.78 (0.61-0.97)	<0.001
Liver	0.93 (0.61-1.36)	0.12	0.75 (0.63-0.89)	<0.001	1.02 (0.91-1.15)	0.17
Pancreas	2.21 (1.76-2.73)	<0.001	1.04 (0.93-1.15)	0.12	1.28 (1.01-1.61)	<0.001
Larynx	0.54 (0.23-1.07)	0.21	0.91 (0.73-1.11)	0.17	0.91 (0.85-0.96)	<0.001
Lung and bronchus	1.29 (1.14-1.47)	<0.001	0.97 (0.93-1.03)	0.10	0.92 (0.81-1.05)	0.12
Breast	0.65 (0.55-0.76)	<0.001	0.87 (0.81-0.94)	<0.001	0.74 (0.49-1.07)	0.19
Corpus and uterus, NOS	0.61 (0.41-0.84)	<0.001	0.66 (0.55-0.79)	<0.001	0.51 (0.27-0.85)	<0.001
Ovary	1.35 (0.93-1.89)	0.23	0.41 (0.29-0.57)	<0.001	3.21 (1.28-6.61)	<0.001
Vagina	21.28 (13.77-31.41)	<0.001	6.17 (4.27-8.63)	<0.001	2.67 (0.86-6.24)	0.47
Testis	10.29 (8.28-12.64)	<0.001	0.85 (0.23-2.19)	0.23	1.22 (0.71-1.96)	0.15
Penis	2.46 (0.59-7.22)	0.43	0.94 (0.51-1.62)	0.18	1.27 (1.19-1.36)	<0.001
Urinary bladder	2.09 (1.75-2.49)	<0.001	1.53 (1.45-1.63)	<0.001	0.84 (0.72-0.97)	<0.001
Kidney and renal pelvis	0.91 (0.67-1.19)	0.13	0.91 (0.81-1.01)	0.09	0.77 (0.56-1.02)	0.11
Ureter	7.18 (3.44-13.22)	<0.001	0.94 (0.56-1.48)	0.16	1.08 (0.66-1.67)	0.14
Eye and orbit	0.32 (0-1.79)	0.15	1.06 (0.62-1.68)	0.19	0.84 (0.38-1.61)	0.17

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among abdominal and pelvic cancer survivors to the expected number of cases in the US general population and was stratified by age at abdominal and pelvic cancer diagnosis. The statistical significance of SIRs was based on a $P < 0.05$ (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S29 Standardized incidence ratio of site-specific observed second primary malignancy in RI-SPMs receiving radiotherapy by year of abdominal and pelvic cancer diagnosis

SPM site	Year of abdominal and pelvic primary cancer diagnosis							
	1975–1984		1985–1994		1995–2004		2005–2015	
	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value	SIR (95% CI)	P value
Tongue	1.12 (0.59-1.92)	0.17	0.58 (0.25-1.16)	0.12	0.82 (0.63-1.05)	0.08	1.02 (0.67-1.48)	0.15
Floor of mouth	1.23 (0.41-2.89)	0.26	1.16 (0.31-2.98)	0.22	0.95 (0.51-1.63)	0.12	1.61 (0.59-3.52)	0.27
Nasopharynx	0.54 (0.01-3.01)	0.29	0.97 (0.11-3.52)	0.26	0.72 (0.29-1.49)	0.14	0.91 (0.18-2.68)	0.25
Oropharynx	1.51 (0.18-5.43)	0.33	0.64 (0.01-3.62)	0.29	1.33 (0.72-2.23)	0.21	1.32 (0.43-3.11)	0.24
Hypopharynx	0.89 (0.18-2.62)	0.22	0.31 (0.01-1.71)	0.15	0.67 (0.37-1.11)	0.15	0.64 (0.17-1.65)	0.16
Esophagus	0.66 (0.35-1.13)	0.14	0.87 (0.53-1.36)	0.13	0.99 (0.85-1.14)	0.11	1.09 (0.82-1.42)	0.12
Stomach	1.29 (0.97-1.69)	0.11	1.52 (1.17-1.95)	<0.001	1.01 (0.89-1.14)	0.09	1.01 (0.77-1.28)	0.11
Small intestine	1.47 (0.78-2.53)	0.21	2.27 (1.45-3.39)	<0.001	1.21 (0.95-1.51)	0.13	1.48 (0.99-2.14)	0.24
Colon excluding rectum	1.33 (1.21-1.47)	<0.001	1.28 (1.15-1.42)	<0.001	0.94 (0.88-1.01)	0.11	0.94 (0.81-1.09)	0.12
Rectum	1.41 (1.17-1.69)	<0.001	1.28 (1.04-1.56)	<0.001	1.25 (1.13-1.37)	<0.001	1.12 (0.91-1.37)	0.16
Liver	0.75 (0.41-1.27)	0.14	0.79 (0.49-1.22)	0.12	0.78 (0.66-0.91)	<0.001	0.75 (0.56-0.99)	<0.001
Pancreas	1.06 (0.84-1.33)	0.12	1.41 (1.14-1.69)	<0.001	1.04 (0.94-1.14)	0.13	1.11 (0.93-1.33)	0.16
Larynx	1.16 (0.66-1.89)	0.19	0.81 (0.41-1.42)	0.15	0.94 (0.78-1.14)	0.09	1.18 (0.84-1.62)	0.18
Lung and bronchus	1.07 (0.96-1.19)	0.11	1.23 (1.11-1.35)	<0.001	0.91 (0.86-0.95)	<0.001	0.97 (0.89-1.07)	0.08
Breast	0.74 (0.67-0.83)	<0.001	0.87 (0.78-0.97)	<0.001	0.87 (0.77-0.97)	<0.001	1.01 (0.81-1.22)	0.11
Corpus and uterus, NOS	0.39 (0.28-0.54)	<0.001	0.69 (0.53-0.89)	<0.001	0.84 (0.64-1.08)	0.11	1.23 (0.81-1.81)	0.17
Ovary	0.53 (0.36-0.76)	<0.001	0.74 (0.51-1.03)	0.09	0.58 (0.35-0.91)	<0.001	0.12 (0.01-0.69)	<0.001
Vagina	6.66 (4.22-10.01)	<0.001	7.92 (5.02-11.89)	<0.001	7.24 (4.05-11.91)	<0.001	9.81 (3.18-22.91)	<0.001
Testis	9.08 (5.46-14.19)	<0.001	10.11 (7.03-14.19)	<0.001	5.28 (3.77-7.21)	<0.001	2.91 (1.17-6.01)	<0.001
Penis	5.15 (1.41-13.19)	<0.001	0 (0-2.92)	0.24	1.19 (0.77-1.76)	0.19	0.67 (0.18-1.73)	0.15
Urinary bladder	2.31 (2.01-2.64)	<0.001	1.65 (1.42-1.91)	<0.001	1.38 (1.31-1.45)	<0.001	1.26 (1.13-1.41)	<0.001
Kidney and renal pelvis	0.83 (0.61-1.12)	0.11	0.65 (0.47-0.88)	<0.001	0.91 (0.82-1.01)	0.07	0.92 (0.76-1.11)	0.09
Ureter	3.57 (1.84-6.24)	<0.001	2.24 (0.96-4.42)	0.35	0.99 (0.64-1.45)	0.17	0.43 (0.08-1.27)	0.12
Eye and orbit	0.58 (0.07-2.09)	0.23	0.54 (0.06-1.96)	0.18	1.13 (0.71-1.74)	0.18	0.56 (0.11-1.66)	0.15

SIR was defined as the ratio of the observed cases of site-specific observed SPM in RI-SPMs among abdominal and pelvic cancer survivors to the expected number of cases in the US general population and was stratified by year at abdominal and pelvic cancer diagnosis. The statistical significance of SIRs was based on a P<0.05 (2-sided); 95% CIs were calculated by Poisson exact methods. The background incidence of site-specific observed SPM in RI-SPMs was derived from data provided by the SEER database. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; US, United States.

Table S30 Comparisons of baseline characteristics of patients with RI-SPMs in all site cancer by treatment modality

Characteristic	Before PSM			After PSM		
	NRT for FPM (n=44760)	RT for FPM (n=34474)	P value	NRT for FPM (n=26785)	RT for FPM (n=26785)	P value
Age at RI-SPMs diagnosis, n (%)			<0.001			0.79
20–49 years	1575 (3.5)	1371 (4.0)		909 (3.4)	882 (3.3)	
50–69 years	14756 (33.0)	12597 (36.5)		8814 (32.9)	8850 (33.0)	
70–84 years	28429 (63.5)	20506 (59.5)		17062 (63.7)	17053 (63.7)	
Gender, n (%)			<0.001			0.46
Female	31897 (71.2)	22762 (66.0)		16990 (63.4)	17074 (63.4)	
Male	12863 (28.7)	11712 (34.0)		9795 (36.6)	9711 (36.3)	
Year at RI-SPMs diagnosis, n (%)			<0.001			0.42
1975–1984	889 (2.0)	328 (1.0)		256 (1.0)	230 (0.9)	
1985–1994	6765 (15.1)	2951 (8.6)		2385 (8.9)	2313 (8.6)	
1995–2004	12976 (29.0)	7740 (22.5)		6497 (24.3)	6488 (24.2)	
2005+	24130 (53.9)	23455 (68.0)		17647 (65.9)	17754 (66.3)	
Race, n (%)			<0.001			0.13
White	37947 (84.8)	28741 (83.4)		22717 (84.8)	22708 (84.8)	
Black	3822 (8.5)	3272 (9.5)		2287 (8.6)	2400 (9.0)	
Other	2991 (6.7)	2461 (7.1)		1781 (6.6)	1677 (6.3)	
Grade of RI-SPMs, n (%)			<0.001			0.28
Grade I/II	18869 (42.2)	14683 (42.6)		11335 (42.3)	11171 (41.7)	
Grade III/IV	12246 (27.4)	10102 (29.3)		7663 (28.6)	7808 (29.2)	
Unknown	13645 (30.5)	9689 (28.1)		7787 (29.1)	7806 (29.1)	
Stage of RI-SPMs, n (%)			<0.001			0.43
Localized	20208 (45.1)	15784 (45.8)		12099 (45.2)	12140 (45.3)	
Regional	10581 (23.6)	7336 (21.3)		6022 (22.5)	5875 (21.9)	
Distant	8813 (19.7)	6866 (19.9)		5358 (20.0)	5455 (20.4)	
Unknown	5158 (11.5)	4488 (13.0)		3306 (12.3)	3315 (12.4)	
Surgery for RI-SPMs, n (%)			0.03			0.37
No	14934 (33.4)	11750 (34.1)		9172 (34.2)	9272 (34.6)	
Yes	29826 (66.6)	22724 (65.9)		17613 (65.8)	17513 (65.4)	
Chemotherapy for RI-SPMs, n (%)			<0.001			0.47
No	33522 (74.9)	24711 (71.7)		19533 (72.9)	19458 (72.6)	
Yes	11238 (25.1)	9763 (28.3)		7252 (27.1)	7327 (27.4)	
Radiotherapy for RI-SPMs, n (%)			<0.001			0.32
No	33785 (75.5)	25278 (73.3)		20489 (76.5)	20390 (76.1)	
Yes	10975 (24.5)	9196 (26.7)		6296 (23.5)	6395 (23.9)	

Patients developed RI-SPMs who received RT for FPM in all sites were matched with patients who didn't receive RT for FPM in all sites at a PSM ratio of 1:1. The matched variables for PSM included age at RI-SPMs diagnosis, year at RI-SPMs diagnosis, gender, grade of RI-SPMs, stage of RI-SPMs, surgery for RI-SPMs, chemotherapy for RI-SPMs, and radiotherapy for RI-SPMs. RT, radiation therapy; NRT, no radiation therapy; PSM, propensity score matching; RI-SPMs, risk increased-SPMs; NOS, not otherwise specified; FPM, first primary malignancies; SPM, second primary malignancy.

Table S31 Comparisons of baseline characteristics of patients with RI-SPMs in head and neck cancer by treatment modality

Characteristic	Before PSM			After PSM		
	NRT for FPM (n=4126)	RT for FPM (n=4533)	P value	NRT for FPM (n=2919)	RT for FPM (n=2919)	P value
Age at RI-SPMs diagnosis, n (%)			<0.001			0.34
20–49 years	266 (6.4)	198 (4.4)		162 (5.5)	144 (4.9)	
50–69 years	1883 (45.6)	2069 (45.6)		1312 (44.9)	1359 (46.6)	
70–84 years	1977 (47.9)	2266 (50.0)		1445 (49.5)	1416 (48.5)	
Gender, n (%)			<0.001			0.58
Female	2275 (55.1)	1668 (36.8)		1366 (46.8)	1388 (47.6)	
Male	1851 (44.9)	2865 (63.2)		1553 (53.2)	1531 (52.4)	
Year at RI-SPMs diagnosis, n (%)			0.56			0.55
1975–1984	123 (3.0)	119 (2.6)		82 (2.8)	78 (2.7)	
1985–1994	837 (20.3)	883 (19.5)		570 (19.5)	568 (19.5)	
1995–2004	1188 (28.8)	1334 (29.4)		800 (27.4)	757 (25.9)	
2005+	1978 (47.9)	2197 (48.5)		1467 (50.3)	1516 (51.9)	
Race, n (%)			<0.001			0.052
White	3537 (85.7)	3722 (82.1)		2497 (85.5)	2471 (84.7)	
Black	316 (7.7)	440 (9.7)		241 (8.3)	255 (8.7)	
Other	273 (6.6)	371 (8.2)		181 (6.2)	193 (6.6)	
Grade of RI-SPMs, n (%)			<0.001			0.72
Grade I/II	1825 (44.2)	1752 (38.6)		1248 (42.8)	1221 (41.8)	
Grade III/IV	1112 (27.0)	1277 (28.2)		793 (27.2)	817 (28.0)	
Unknown	1189 (28.8)	1504 (33.2)		878 (30.1)	881 (30.2)	
Stage of RI-SPMs, n (%)			<0.001			0.32
Localized	1665 (40.4)	1553 (34.3)		1065 (36.5)	1117 (38.3)	
Regional	1063 (25.8)	1094 (24.1)		729 (25.0)	691 (23.7)	
Distant	852 (20.6)	1114 (24.6)		672 (23.0)	639 (21.9)	
Unknown	546 (13.2)	772 (17.0)		453 (15.5)	472 (16.2)	
Surgery for RI-SPMs, n (%)			<0.001			0.90
No	1541 (37.3)	2133 (47.1)		1256 (43.0)	1250 (42.8)	
Yes	2585 (62.7)	2400 (52.9)		1663 (57.0)	1669 (57.2)	
Chemotherapy for RI-SPMs, n (%)			0.38			0.77
No	2962 (71.8)	3294 (72.7)		2099 (71.9)	2088 (71.5)	
Yes	1164 (28.2)	1239 (27.3)		820 (28.1)	831 (28.5)	
Radiotherapy for RI-SPMs, n (%)			0.24			0.91
No	2744 (66.5)	3070 (67.7)		1937 (66.4)	1932 (66.2)	
Yes	1382 (33.5)	1463 (32.3)		982 (33.6)	987 (33.8)	

Patients developed RI-SPMs who received RT for FPM in head and neck were matched with patients who didn't receive RT for FPM in head and neck at a PSM ratio of 1:1. The matched variables for PSM included age at RI-SPMs diagnosis, year at RI-SPMs diagnosis, gender, grade of RI-SPMs, stage of RI-SPMs, surgery for RI-SPMs, chemotherapy for RI-SPMs, and radiotherapy for RI-SPMs. RT, radiation therapy; NRT, no radiation therapy; PSM, propensity score matching; RI-SPMs, risk increased-SPMs; FPM, first primary malignancies; SPM, second primary malignancy.

Table S32 Comparisons of baseline characteristics of patients with RI-SPMs in thoracic cancer by treatment modality

Characteristic	Before PSM			After PSM		
	NRT for FPM (n=23646)	RT for FPM (n=17728)	P value	NRT for FPM (n=12226)	RT for FPM (n=12226)	P value
Age at RI-SPMs diagnosis, n (%)			<0.001			0.98
20–49 years	898 (3.8)	934 (5.3)		509 (4.2)	512 (4.2)	
50–69 years	8145 (34.4)	7618 (43.0)		4715 (38.6)	4701 (38.5)	
70–84 years	14603 (61.8)	9176 (51.8)		7002 (57.3)	7013 (57.4)	
Gender, n (%)			<0.001			0.34
Female	22032 (93.2)	17073 (96.3)		11798 (96.5)	11769 (96.3)	
Male	1614 (6.8)	655 (3.7)		428 (3.5)	457 (3.7)	
Year at RI-SPMs diagnosis, n (%)			<0.001			0.31
1975–1984	488 (2.1)	110 (0.6)		74 (0.6)	58 (0.5)	
1985–1994	4031 (17.0)	1116 (6.3)		880 (7.2)	830 (6.8)	
1995–2004	7937 (33.6)	4154 (23.4)		3518 (28.8)	3550 (29.0)	
2005+	11190 (47.3)	12348 (69.7)		7754 (63.4)	7788 (63.7)	
Race, n (%)			0.01			0.42
White	20259 (85.7)	14990 (84.6)		10681 (87.4)	10693 (87.5)	
Black	1858 (7.9)	1473 (8.3)		769 (6.3)	799 (6.5)	
Other	1529 (6.5)	1265 (7.1)		776 (6.3)	734 (6.0)	
Grade of RI-SPMs, n (%)			<0.001			0.72
Grade I/II	10268 (43.4)	8445 (47.6)		5738 (46.9)	5675 (46.4)	
Grade III/IV	6535 (27.6)	5242 (29.6)		3623 (29.6)	3651 (29.9)	
Unknown	6843 (28.9)	4041 (22.8)		2865 (23.4)	2900 (23.7)	
Stage of RI-SPMs, n (%)			<0.001			0.56
Localized	11674 (49.4)	9404 (53.0)		6513 (53.3)	6469 (52.9)	
Regional	5426 (22.9)	3497 (19.7)		2628 (21.5)	2579 (21.1)	
Distant	4311 (18.2)	2874 (16.2)		1982 (16.2)	2033 (16.6)	
Unknown	2235 (9.5)	1953 (11.0)		1103 (9.0)	1145 (9.4)	
Surgery for RI-SPMs, n (%)			<0.001			0.22
No	6827 (28.9)	4515 (25.5)		3008 (24.6)	3095 (25.3)	
Yes	16819 (71.1)	13213 (74.5)		9216 (75.4)	9131 (74.7)	
Chemotherapy for RI-SPMs, n (%)			<0.001			0.63
No	18120 (76.6)	12514 (70.6)		8986 (73.5)	8952 (73.2)	
Yes	5526 (23.4)	5214 (29.4)		3240 (26.5)	3274 (26.8)	
Radiotherapy for RI-SPMs, n (%)			<0.001			0.52
No	18387 (77.8)	12732 (71.8)		9508 (77.8)	9465 (77.4)	
Yes	5259 (22.2)	4996 (28.2)		2718 (22.2)	2761 (22.6)	

Patients developed RI-SPMs who received RT for FPM in thoracic were matched with patients who didn't receive RT for FPM in thoracic at a PSM ratio of 1:1. The matched variables for PSM included age at RI-SPMs diagnosis, year at RI-SPMs diagnosis, gender, grade of RI-SPMs, stage of RI-SPMs, surgery for RI-SPMs, chemotherapy for RI-SPMs, and radiotherapy for RI-SPMs. RT, radiation therapy; NRT, no radiation therapy; PSM, propensity score matching; RI-SPMs, risk increased-SPMs; FPM, first primary malignancies.

Table S33 Comparisons of baseline characteristics of patients with RI-SPMs in abdominal and pelvic cancer by treatment modality

Characteristic	Before PSM			After PSM		
	NRT for FPM (n=16805)	RT for FPM (n=12021)	P value	NRT for FPM (n=11640)	RT for FPM (n=11640)	P value
Age at RI-SPMs diagnosis, n (%)			<0.001			0.85
20–49 years	400 (2.4)	232 (1.9)		238 (2.0)	226 (1.9)	
50–69 years	4660 (27.7)	2833 (23.6)		2787 (23.9)	2790 (24.0)	
70–84 years	11745 (69.9)	8956 (74.5)		8615 (74.0)	8624 (74.1)	
Gender, n (%)			<0.001			0.21
Female	7476 (44.5)	3924 (32.6)		3826 (32.9)	3917 (33.7)	
Male	9329 (55.5)	8097 (67.4)		7814 (67.1)	7723 (66.3)	
Year at RI-SPMs diagnosis, n (%)			<0.001			0.93
1975–1984	270 (1.6)	95 (0.8)		100 (0.9)	94 (0.8)	
1985–1994	1865 (11.1)	928 (7.7)		935 (8.0)	915 (7.9)	
1995–2004	3795 (22.6)	2199 (18.3)		2179 (18.7)	2181 (18.7)	
2005+	10875 (64.7)	8799 (73.2)		8426 (72.4)	8450 (72.6)	
Race, n (%)			<0.001			0.13
White	13995 (83.3)	9867 (82.1)		9539 (82.0)	9584 (82.3)	
Black	1630 (9.7)	1342 (11.2)		1275 (11.0)	1306 (11.2)	
Other	1180 (7.0)	812 (6.8)		826 (7.1)	750 (6.4)	
Grade of RI-SPMs, n (%)			<0.001			0.37
Grade I/II	6701 (39.9)	4410 (36.7)		4349 (37.4)	4275 (36.7)	
Grade III/IV	4555 (27.1)	3514 (29.2)		3247 (27.9)	3340 (28.7)	
Unknown	5549 (33.0)	4097 (34.1)		4044 (34.7)	4025 (34.6)	
Stage of RI-SPMs, n (%)			<0.001			0.44
Localized	6792 (40.4)	4756 (39.6)		4521 (38.8)	4554 (39.1)	
Regional	4050 (24.1)	2688 (22.4)		2665 (22.9)	2605 (22.4)	
Distant	3602 (21.4)	2832 (23.6)		2704 (23.2)	2783 (23.9)	
Unknown	2361 (14.0)	1745 (14.5)		1750 (15.0)	1698 (14.6)	
Surgery for RI-SPMs, n (%)			<0.001			0.79
No	6506 (38.7)	5020 (41.8)		4906 (42.1)	4927 (42.3)	
Yes	10299 (61.3)	7001 (58.2)		6734 (57.9)	6713 (57.7)	
Chemotherapy for RI-SPMs, n (%)			0.48			0.67
No	12311 (73.3)	8760 (72.9)		8448 (72.6)	8418 (72.3)	
Yes	4494 (26.7)	3261 (27.1)		3192 (27.4)	3222 (27.7)	
Radiotherapy for RI-SPMs, n (%)			<0.001			0.43
No	12528 (74.5)	9346 (77.7)		9044 (77.7)	8993 (77.3)	
Yes	4277 (25.5)	2676 (22.3)		2596 (22.3)	2647 (22.7)	

Patients developed RI-SPMs who received RT for FPM in abdominal and pelvic were matched with patients who did not receive RT for FPM in abdominal and pelvic at a PSM ratio of 1:1. The matched variables for PSM included age at RI-SPMs diagnosis, year at RI-SPMs diagnosis, gender, grade of RI-SPMs, stage of RI-SPMs, surgery for RI-SPMs, chemotherapy for RI-SPMs, and radiotherapy for RI-SPMs. RT, radiation therapy; NRT, no radiation therapy; PSM, propensity score matching; RI-SPMs, risk increased-SPMs; FPM, first primary malignancies.