

## SUPPLEMENTAL DATA

# Risk and prognosis of second cutaneous melanoma after radiotherapy for breast cancer: A population-based analysis

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**Table S1. Comparison of clinicopathologic baseline characteristics of patients with BC and SCM by treatment modality.**

Characteristics	All BC patients NO. (%)		<i>P</i>	All SCM patients NO. (%)		<i>P</i>
	NRT (n=277301)	RT (n=243676)		NRT (n=932)	RT (n=944)	
TNM Stage						
I	84303 (30.4)	104709 (43.0)	<b>&lt;0.001<sup>b</sup></b>	324 (34.8)	477 (50.5)	<b>&lt;0.001<sup>b</sup></b>
II	67125 (24.2)	59850 (24.6)		219 (23.5)	229 (24.3)	
III	18505 (6.7)	26324 (10.8)		57 (6.1)	85 (9.0)	
Unknown	107368 (38.7)	52793 (21.7)		332 (35.6)	153 (16.2)	
Tumor stage						
T1	105273 (38.0)	128443 (52.7)	<b>&lt;0.001<sup>b</sup></b>	406 (43.6)	578 (61.2)	<b>&lt;0.001<sup>b</sup></b>
T2	53886 (19.4)	47817 (19.6)		166 (17.8)	172 (18.2)	
T3	6768 (2.4)	9399 (3.9)		17 (1.8)	28 (3.0)	
T4	3275 (1.2)	4679 (1.9)		8 (0.9)	13 (1.4)	
Unknown	108099 (39.0)	53338 (21.9)		335 (35.9)	153 (16.2)	
Nodal stage						
N0	119543 (43.1)	131335 (53.9)	<b>&lt;0.001<sup>b</sup></b>	434 (46.6)	572 (60.6)	<b>&lt;0.001<sup>b</sup></b>
N1	36532 (13.2)	39612 (16.3)		123 (13.2)	160 (16.9)	
N2	9500 (3.4)	13329 (5.5)		34 (3.6)	50 (5.3)	
N3	4804 (1.7)	6916 (2.8)		13 (1.4)	13 (1.4)	
Unknown	106922 (38.6)	52484 (21.5)		328 (35.2)	149 (15.8)	
ER Status						
Negative	32980 (11.9)	37607 (15.4)	<b>&lt;0.001<sup>b</sup></b>	92 (9.9)	113 (12.0)	<b>&lt;0.001<sup>b</sup></b>
Positive	127405 (45.9)	169145 (69.4)		437 (46.9)	664 (70.3)	
Unknown	116916 (42.2)	36924 (15.2)		403 (43.2)	167 (17.7)	
PR Status						
Negative	49748 (17.9)	57912 (23.8)	<b>&lt;0.001<sup>b</sup></b>	146 (15.7)	206 (21.8)	<b>&lt;0.001<sup>b</sup></b>
Positive	108533 (39.1)	146947 (60.3)		369 (39.6)	565 (59.9)	
Unknown	119020 (42.9)	38817 (15.9)		417 (44.7)	173 (18.3)	
HER2 status						
Negative	39212 (14.1)	71196 (29.2)	<b>&lt;0.001<sup>b</sup></b>	73 (7.8)	146 (15.5)	<b>&lt;0.001<sup>b</sup></b>
Positive	7528 (2.7)	11075 (4.5)		11 (1.2)	28 (3.0)	
Unknown	230561 (83.1)	161405 (66.2)		848 (91.0)	770 (81.6)	

Molecular subtype (2010+)				
HR-/HER2- (Triple negative)	4987 (1.8)	8444 (3.5)	4 (0.4)	10 (1.1)
HR-/HER2+ (HER2 enriched)	2289 (0.8)	3025 (1.2)	2 (0.2)	7 (0.7)
			<b>&lt;0.001<sup>b</sup></b>	<b>&lt;0.001<sup>b</sup></b>
HR+/HER2- (Luminal A)	34153 (12.3)	62675 (25.7)	69 (7.4)	136 (14.4)
HR+/HER2+ (Luminal B)	5215 (1.9)	8032 (3.3)	9 (1.0)	21 (2.2)
Unknown	230657 (83.2)	161500 (66.3)	848 (91.0)	770 (81.6)

<sup>b</sup>*P* value was calculated using  $X^2$  test for categorical variables; Significant *P* values are in [bold]. BC: Breast cancer; SCM: Second cutaneous melanoma.

**Table S2. Univariable and multivariable competing risk regression analysis if there is risk of developing SCM in BC patients.**

Characteristics	Univariable competing risk regression		Multivariable competing risk regression	
	sHR (95CI)	<i>P</i>	sHR (95CI)	<i>P</i>
Age, per year	0.99 (0.99-0.10)	<b>&lt;0.001</b>	0.99 (0.99-0.99)	<b>&lt;0.001</b>
Diagnosis, per year	1.02 (1.01-1.52)	<b>&lt;0.001</b>	1.02 (1.01-1.02)	<b>&lt;0.001</b>
Race				
White	1			
Black	0.08 (0.05-0.13)	<b>&lt;0.001</b>	0.08 (0.05-0.12)	<b>&lt;0.001</b>
Other	0.16 (0.11-0.22)	<b>&lt;0.001</b>	0.14 (0.10-0.20)	<b>&lt;0.001</b>
Tumor grade				
Grade I/II	1			
Grade III/IV	0.76 (0.69-0.84)	<b>&lt;0.001</b>	0.89 (0.80-0.98)	0.053
Unknown	0.71 (0.65-0.78)	<b>&lt;0.001</b>	0.96 (0.86-1.08)	0.600
Tumor stage				
Localized	1			
Regional	0.88 (0.81-0.96)	<b>0.010</b>	0.97 (0.86-1.11)	0.650
Tumor site				
UI	1			
LI	0.99 (0.81-1.21)	0.940	1.00 (0.82-1.22)	
UO	0.94 (0.83-1.08)	0.470	0.95 (0.84-1.09)	
LO	0.95 (0.79-1.15)	0.680	0.97 (0.81-1.17)	
CEN	0.88 (0.73-1.06)	0.260	0.94 (0.77-1.13)	
Other	0.93 (0.81-1.06)	0.340	0.96 (0.84-1.10)	
laterality				
Left	1			
Right	0.98 (0.91-1.06)	0.650		
Tumor histology				
Ductal	1			
Ductal and lobular	1.29 (1.11-1.51)	<b>0.007</b>	1.14 (0.97-1.34)	0.180

Lobular	1.25 (1.10-1.43)	<b>0.005</b>	1.19 (1.04-1.37)	<b>0.036</b>
Other	0.90 (0.80-1.02)	0.160	1.01 (0.89-1.14)	0.930
Chemotherapy				
No/unknown	1			
Yes	1.08 (0.99-1.17)	0.130		
Radiotherapy				
No	1			
Yes	1.40 (1.30-1.51)	<b>&lt;0.001</b>	1.24 (1.14-1.34)	<b>&lt;0.001</b>
TNM stage				
I	1			
II	0.85 (0.77-0.93)	<b>0.004</b>	0.99 (0.79-1.23)	0.920
III	0.72 (0.62-0.84)	<b>&lt;0.001</b>	1.30 (0.78-2.14)	0.400
Unknown	0.67 (0.61-0.74)	<b>&lt;0.001</b>	2.86 (0.96-8.53)	0.110
Tumor stage				
T1	1			
T2	0.80 (0.72-0.89)	<b>&lt;0.001</b>	0.89 (0.75-1.07)	0.300
T3	0.70 (0.54-0.90)	<b>0.018</b>	0.70 (0.49-0.98)	0.082
T4	0.61 (0.42-0.88)	<b>0.024</b>	0.64 (0.39-1.04)	0.130
Unknown	0.68 (0.62-0.74)	<b>&lt;0.001</b>	0.61 (0.23-1.61)	0.400
Nodal stage				
N0	1			
N1	0.94 (0.85-1.06)	0.390	1.00 (0.82-1.24)	0.970
N2	0.87 (0.72-1.05)	0.210	0.78 (0.48-1.24)	0.370
N3	0.52 (0.37-0.72)	<b>&lt;0.001</b>	0.47 (0.27-0.82)	<b>0.024</b>
Unknown	0.70 (0.64-0.77)	<b>&lt;0.001</b>	0.52 (0.31-0.86)	<b>0.032</b>
ER status				
Negative	1			
Positive	1.39 (1.23-1.58)	<b>&lt;0.001</b>	1.20 (1.02-1.41)	0.073
Unknown	0.93 (0.81-1.06)	0.370	1.05 (0.75-1.47)	0.810
PR status				
Negative	1			
Positive	1.20 (1.08-1.33)	<b>0.004</b>	0.94 (0.82-1.07)	0.410
Unknown	0.82 (0.73-0.91)	<b>0.002</b>	0.98 (0.72-1.35)	0.930
HER2 status				
Negative	1			
Positive	1.13 (0.85-1.50)	0.500		
Unknown	0.80 (0.71-0.90)	<b>0.002</b>		
Molecular subtype				
HR-/HER2- (Triple negative)	1			
HR-/HER2+ (HER2 enriched)	1.89 (0.94-3.82)	0.140	1.86 (0.92-3.76)	0.150
HR+/HER2- (Luminal A)	2.36 (1.50-3.72)	<b>0.002</b>	1.72 (1.07-2.77)	0.059
HR+/HER2+ (Luminal B)	2.68 (1.57-4.57)	<b>0.002</b>	2.11 (1.21-3.68)	<b>0.026</b>
Unknown	1.72 (1.11-2.68)	<b>0.042</b>	1.68 (1.06-2.67)	0.066

Fine-Gray competing risk regression analyses are used to calculate the HR and 95 CI for SCM in BC patients treated with RT versus patients not treated with RT. Covariables that are significant in univariable competing risk regression analysis ( $P < 0.05$ ) are included in the multivariable analysis. The other sites of BC include axillary tail of breast, overlapping lesion of breast. Significant  $P$  values are in [bold]. sHR: subdistribution hazard ratio; CI: Confidence interval; BC: Breast cancer; SCM: Second cutaneous melanoma; RT: Radiation therapy; UO: Upper outer quadrant of breast; UI: Upper inner quadrant of breast; LI: Lower inner quadrant of breast; LO: Lower outer quadrant of breast; CEN: Central portion quadrant of breast; HR: Hazard ratio. CI: Confidence interval.

**Table S3. Radiation-attributed risk of SCM subgroup.**

Characteristics	RR (95CI)	<i>P</i>	Adjusted RR (95CI)	<i>P</i>
Age at BC diagnosis, per year				
20-49	1.01(0.87-1.17)	0.897	1.19(1.02-1.39)	0.060
50-69	1.06(0.95-1.18)	0.366	1.27(1.14-1.43)	<b>&lt;0.001</b>
≥70	1.47(1.25-1.73)	<b>&lt;0.001</b>	1.41(1.19-1.68)	<b>&lt;0.001</b>
Year of BC diagnosis, per year				
1975-1984	1.28 (1.00-1.63)	0.095	1.20 (0.93-1.53)	0.218
1985-1994	1.22 (1.04-1.42)	<b>0.037</b>	1.14 (0.97-1.34)	0.173
1995-2004	1.40 (1.22-1.60)	<b>&lt;0.001</b>	1.40 (1.23-1.61)	<b>&lt;0.001</b>
≥2005	1.10 (0.95-1.29)	0.280	1.19 (1.02-1.39)	0.060
Latency				
12-120	1.00 (0.91-1.1)	1.000	1.00 (0.9-1.11)	1.000
121-240	1.00 (0.87-1.15)	1.000	1.00 (0.86-1.16)	1.000
≥240	1.00 (0.74-1.33)	1.000	1.00 (0.74-1.33)	1.000

Poisson regression analyses were used to calculate the RR and 95 CIs of SCM for patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at BC diagnosis and calendar year of BC diagnosis. A determination of statistical significance of RRs was based on  $P < 0.05$  (two sided). Significant  $P$  values are in [bold]. RR: Radiation-attributed risk; BC: Breast cancer; SCM: Second cutaneous melanoma; RR: Radiation-attributed risk; CI: Confidence interval.

**Table S4. Radiation-attributed risk of second SSM subgroup.**

Characteristic	RR (95CI)	<i>P</i>	Adjusted RR (95CI)	<i>P</i>
<b>Age, per year</b>				
20-49	1.07 (0.85-1.35)	0.614	1.26 (0.99-1.60)	0.113
50-69	1.14 (0.95-1.37)	0.249	1.27 (1.04-1.55)	<b>0.047</b>
≥70	1.67 (1.24-2.25)	0.005	1.49 (1.08-2.06)	<b>0.042</b>
<b>Diagnosis, per year</b>				
1975-1984	1.40 (0.91-2.08)	0.184	1.25 (0.81-1.87)	0.381
1985-1994	1.17 (0.88-1.53)	0.359	1.06 (0.80-1.40)	0.729
1995-2004	1.53 (1.19-1.96)	0.005	1.48 (1.16-1.91)	<b>0.010</b>
≥2005	1.23 (0.97-1.57)	0.148	1.30 (1.03-1.66)	0.072
<b>Latency</b>				
12-120	1.05 (0.89-1.24)	0.605	0.98 (0.83-1.16)	0.831
121-240	1.15 (0.90-1.47)	0.347	1.16 (0.90-1.51)	0.338
≥240	0.97 (0.57-1.59)	0.924	0.93 (0.54-1.55)	0.823

Poisson regression analyses were used to calculate the RR and 95 CIs of SSM for patients with radiation therapy versus patients without radiation therapy. Adjusted RRs were stratified by age at BC diagnosis and calendar year of BC diagnosis. A determination of statistical significance of RRs was based on  $P < 0.05$  (two sided). Significant  $P$  values are in [bold]. RR: Radiation-attributed risk; BC: Breast cancer; SSM: Superficial spreading melanoma; CI: Confidence interval.

**Table S5. Standardized incidence ratio of SCM.**

Characteristics	RT			NRT		
	Observed	Expected	SIR (95CI)	Observed	Expected	SIR (95CI)
All patients	985	882.52	<b>1.12(1.05-1.19)#</b>	1002	1075.29	<b>0.93(0.88-0.99)#</b>
Age at diagnosis, year						
20-49	78	55.6	<b>1.40(1.11-1.75)#</b>	73	60.76	1.20(0.94-1.51)
50-69	451	401.35	<b>1.12(1.02-1.23)#</b>	404	400.16	1.01(0.91-1.11)
$\geq 70$	456	425.56	1.07(0.98-1.17)	525	614.37	<b>0.85(0.78-0.93)#</b>
Year of BC diagnosis						
1975-1984	12	6.94	1.73(0.89-3.02)	29	34.23	0.85(0.57-1.22)
1985-1994	48	37.33	1.23(0.90-1.64)	153	143.71	1.06(0.90-1.25)
1995-2004	205	166.90	<b>1.23(1.07-1.41)#</b>	282	289.30	0.97(0.86-1.10)
$\geq 2005$	722	671.35	1.08(1.00-1.16)	538	608.04	<b>0.88(0.81-0.96)#</b>
Latency between BC and SCM, months						
12-59	351	275.11	<b>1.28(1.15-1.42)#</b>	297	274.26	1.08(0.96-1.21)
60-119	281	257.97	1.09(0.97-1.22)	258	266.97	0.97(0.85-1.09)
120-239	299	277.60	1.08(0.96-1.21)	299	339.11	<b>0.88(0.78-0.99)#</b>
$\geq 240$	54	71.84	<b>0.75(0.56-0.98)#</b>	148	194.95	<b>0.76(0.64-0.89)#</b>

SIR was defined as the ratio of the number of observed SCM cases among BC survivors to the expected number of cases in the US general population and was stratified by age at BC diagnosis, calendar year of BC diagnosis and latency period calendar. A determination of the statistical significance of SIRs was based on a  $P < 0.05$  (two sided). 95 confidence intervals were calculated by Poisson exact methods. The background incidence of SCM was derived from data provided by the SEER database. # indicates  $P < 0.05$ . Significant  $P$  values are in [bold]. BC: Breast cancer; RT: Radiation therapy; NRT: No radiation therapy; SIR: Standardized incidence ratio; SCM: Second cutaneous melanoma.

**Table S6. Subgroup analyses of sHR of developing SCM in BC patients who received RT versus those who did not.**

Subgroup	RT (No. of events/total no.)	NRT (No. of events/total no.)	sHR (95CI)	$P$
TNM Stage				
I	477 /104709	324 /84303	1.30(1.15-1.46)	<b>&lt;0.001</b>
II	229 /59850	219 /67125	1.32(1.13-1.55)	<b>0.003</b>
III	85 /26324	57 /18505	1.17(0.88-1.55)	0.360
Unknown	153 /52793	332 /107368	1.39(1.19-1.64)	<b>&lt;0.001</b>
Tumor stage				

T1	578 /128443	406 /105273	1.29(1.16-1.43)	<b>&lt;0.001</b>
T2	172 /47817	166 /53886	1.31(1.09-1.56)	<b>0.014</b>
T3	28 /9399	17 /6768	1.41(0.84-2.35)	0.270
T4	13 /4679	8 /3275	1.19(0.57-2.49)	0.690
Unknown	153 /53338	335 /108099	1.37(1.17-1.61)	0.001
Nodal stage				
N0	572 /131335	434 /119543	1.31(1.18-1.46)	<b>&lt;0.001</b>
N1	160 /39612	123 /36532	1.39(1.14-1.69)	<b>0.007</b>
N2	50 /13329	34 /9500	1.17(0.81-1.69)	0.480
N3	13 /6916	13 /4804	0.76(0.40-1.46)	0.490
Unknown	149 /52484	328 /106922	1.38(1.18-1.62)	<b>0.001</b>
ER Status				
Negative	113 /37607	92 /32980	1.17(0.93-1.47)	0.270
Positive	664 /169145	437 /127405	1.28(1.16-1.42)	<b>&lt;0.001</b>
Unknown	167 /36924	403 /116916	1.35(1.16-1.57)	<b>0.001</b>
PR Status				
Negative	206 /57912	146 /49748	1.31(1.10-1.57)	<b>0.011</b>
Positive	565 /146947	369 /108533	1.27(1.14-1.42)	<b>&lt;0.001</b>
Unknown	173 /38817	417 /119020	1.31(1.13-1.52)	<b>0.003</b>
HER2 status				
Negative	146 /71196	73 /39212	1.15(0.91-1.45)	0.330
Positive	28 /11075	11 /7528	1.79(1.00-3.20)	0.100
Unknown	770 /161405	848 /230561	1.41(1.30-1.53)	<b>&lt;0.001</b>
Molecular subtype				
HR-/HER2- (Triple negative)	10 /8444	4 /4987	1.45(0.55-3.83)	0.530
HR-/HER2+ (HER2 enriched)	7 /3025	2 /2289	2.60(0.67-10.10)	0.240
HR+/HER2- (Luminal A)	136 /62675	69 /34153	1.13(0.89-1.44)	0.410
HR+/HER2+ (Luminal B)	21 /8032	9 /5215	1.58(0.83-3.02)	0.240
Unknown	770 /161500	848 /230657	1.41(1.30-1.53)	<b>&lt;0.001</b>

BC: Breast cancer; RT: Radiation therapy; NRT: Non-radiation therapy; sHR: Subdistribution hazard ratio.

**Table S7. Comparisons of baseline characteristics of SCM between RT group and NRT group.**

Characteristics	NRT		P	Characteristics	RT		P
	(N=932)	(N=944)			(N=932)	(N=944)	
<b>Age</b>				<b>M</b>			
20-49	69 (7.4)	79 (8.4)	<b>0.040</b>	M0	388 (41.6)	495(52.4)	
50-69	383 (41.1)	434 (46.0)		M1	10 (1.1)	9 (1.0)	<b>&lt;0.001</b>
70+	480 (51.5)	431 (45.7)		Unknown	534 (57.3)	440 (46.6)	
<b>Diagnosis</b>				<b>Thickness</b>			
1975-1984	27 (2.9)	13 (1.4)	<b>&lt;0.001</b>	≤1.00	207 (22.2)	342 (36.2)	
1985-1994	145 (15.6)	44 (4.7)		1.01-2.00	40 (4.3)	76 (8.1)	<b>&lt;0.001</b>
1995-2004	267 (28.6)	195 (20.7)		2.01-4.00	30 (3.2)	31 (3.3)	
2005+	493 (52.9)	692 (73.3)		≥4.01	19 (2.0)	23 (2.4)	
<b>Sex</b>				Unknown	636 (68.2)	472 (50.0)	

Female	916 (98.3)	937 (99.3)	0.087	<b>Ulceration</b>			
				Not present	268 (28.8)	440 (46.6)	
<b>Race</b>				Present	31 (3.3)	43 (4.6)	<b>&lt;0.001</b>
White	912 (97.9)	927 (98.2)		Unknown	633 (67.9)	461 (48.8)	
Black	10 (1.1)	4 (0.4)	0.222	<b>History</b>			
Other	10 (1.1)	13 (1.4)		SSM	308 (33.0)	337 (35.7)	
<b>Stage</b>				ALM	17 (1.8)	19 (2.0)	<b>0.005</b>
Localized	782 (83.9)	839 (88.9)	<b>0.011</b>	LMM	112 (12.0)	74 (7.8)	
Regional	82 (8.8)	63 (6.7)		NM	90 (9.7)	66 (7.0)	
Distant	30 (3.2)	22 (2.3)		Other	405 (43.5)	448 (47.5)	
Unstaged	38 (4.1)	20 (2.1)		<b>Site</b>			
<b>T stage</b>				Head and neck	174 (18.7)	132 (14.0)	
T0	10 (1.1)	9 (1.0)		Trunk	188 (20.2)	207 (21.9)	0.050
T1	266 (28.5)	362 (38.3)	<b>&lt;0.001</b>	Upper limb and shoulder	284 (30.5)	302 (32.0)	
T2	57 (6.1)	62 (6.6)		Lower limb and hip	255 (27.4)	280 (29.7)	
T3	39 (4.2)	38 (4.0)		Unknown	31 (3.3)	23 (2.4)	
T4	22 (2.4)	27 (2.9)		<b>Surgery</b>			
TX	25 (2.7)	24 (2.5)		Performed	863 (92.6)	902 (95.6)	
Unknown	513 (55.0)	422 (44.7)		Not performed	19 (2.0)	10 (1.1)	<b>0.023</b>
<b>N stage</b>				Unknown	50 (5.4)	32 (3.4)	
N0	362 (38.8)	470 (49.8)		<b>Radiation</b>			
N1	18 (1.9)	15 (1.6)	<b>&lt;0.001</b>	Beam radiation	13 (1.4)	12 (1.3)	
N2	6 (0.6)	8 (0.8)		None/Unknown	919 (98.6)	932 (98.7)	0.974
N3	3 (0.3)	2 (0.2)		<b>Chemotherapy</b>			
NX	30 (3.2)	27 (2.9)		Yes	13 (1.4)	6 (0.6)	
Unknown	513 (55.0)	422 (44.7)		No/Unknown	919 (98.6)	938 (99.4)	0.158



**Table S8. Propensity score-matched patients who developed SCM after RT and after no RT.**

Characteristics	NRT 681	RT 681	<i>P</i>	Characteristics	NRT 681	RT 681	<i>P</i>
Age ()			0.31 4	Breslow ()			0.84
≥70	344 (50.5)	316 (46.4)		≤1.00	199 (29.2)	199 (29.2)	
20-49	48 (7.0)	51 (7.5)		≥4.00	15 (2.2)	19 (2.8)	
50-69	289 (42.4)	314 (46.1)		1.01-2.00	38 (5.6)	40 (5.9)	
Year ()			0.87 6	2.01-4.00	22 (3.2)	28 (4.1)	
≥2005	443 (65.1)	455 (66.8)		Unknown	407 (59.8)	395 (58.0)	
1975-1984	12 (1.8)	10 (1.5)		Ulceration ()			0.434
1985-1994	40 (5.9)	41 (6.0)		Not present	254 (37.3)	259 (38.0)	
1995-2004	186 (27.3)	175 (25.7)		Present	25 (3.7)	34 (5.0)	
Race ()			0.93 1	Unknown	402 (59.0)	388 (57.0)	
Black	3 (0.4)	4 (0.6)		Hist ()			0.059
other	9 (1.3)	9 (1.3)		ALM	14 (2.1)	10 (1.5)	
White	669 (98.2)	668 (98.1)		LMM	68 (10.0)	70 (10.3)	
Sex = Male ()	7 (1.0)	6 (0.9)	1	NM	51 (7.5)	63 (9.3)	
Stage ()			0.56 4	Other	319 (46.8)	270 (39.6)	
Distant	15 (2.2)	14 (2.1)		SSM	229 (33.6)	268 (39.4)	
Localize	601 (88.3)	601 (88.3)		Site ()			0.537
Region	43 (6.3)	51 (7.5)		Head neck and	101 (14.8)	109 (16.0)	
Unstage	22 (3.2)	15 (2.2)		Lower limb and hip	189 (27.8)	210 (30.8)	
Tumorsize ()			0.31 2	Other/unkno wn	20 (2.9)	16 (2.3)	
≤2cm	8 (1.2)	11 (1.6)		Trunk	149 (21.9)	147 (21.6)	

>2cm	305 (44.8)	279 (41.0)		Upper limb and shoulder	222 (32.6)	199 (29.2)	
Unknown	368 (54.0)	391 (57.4)		Surgery surgery ()	= 647 (95.0)	646 (94.9)	1
Chemotherapy = Yes ( )	6 (0.9)	6 (0.9)	1	Radio = Yes ( )	9 (1.3)	7 (1.0)	0.801

Survival comparison between BC patients who developed SCM after Radiation therapy (RT) and BC patients who developed SCM after no RT at a PSM ratio of 1:1. PSM: Propensity score matching; BC: Breast cancer; SCM: Second cutaneous melanoma.

**Table S9. Patients' characteristics of SCM and matched OPCM.**

Characteristics	SCM(RT)	OPCM matched with SCM (RT)	<i>P</i>	SCM(NRT)	OPCM matched with SCM (NRT)	<i>P</i>
	N=942	N=4,704		N=932	N=4,648	
Age ( )			0.939			0.982
≥70	458 (48.6)	2316 (49.2)		458 (49.1)	2289 (49.2)	
20-49	71 (7.5)	354 (7.5)		67 (7.2)	326 (7.0)	
50-69	413 (43.8)	2034 (43.2)		407 (43.7)	2033 (43.7)	
Year ( )			0.951			0.988
≥2005	690 (73.2)	3404 (72.4)		680 (73.0)	3368 (72.5)	
1975-1984	13 (1.4)	67 (1.4)		13 (1.4)	64 (1.4)	
1985-1994	44 (4.7)	234 (5.0)		44 (4.7)	229 (4.9)	
1995-2004	195 (20.7)	999 (21.2)		195 (20.9)	987 (21.2)	
Race ( )			0.169			0.103
Black	4 (0.4)	14 (0.3)		4 (0.4)	17 (0.4)	
other	13 (1.4)	37 (0.8)		13 (1.4)	33 (0.7)	
White	925 (98.2)	4653 (98.9)		915 (98.2)	4598 (98.9)	
Sex = Male ( )	7 (0.7)	35 (0.7)	1	6 (0.6)	34 (0.7)	0.939
stage ( )			0.974			0.929
Distant	21 (2.2)	97 (2.1)		21 (2.3)	108 (2.3)	
Localize	840 (89.2)	4203 (89.3)		831 (89.2)	4169 (89.7)	
Region	61 (6.5)	297 (6.3)		61 (6.5)	278 (6.0)	
Unstage	20 (2.1)	107 (2.3)		19 (2.0)	93 (2.0)	
Tumorsize ( )			0.96			0.996
≤2cm	10 (1.1)	55 (1.2)		11 (1.2)	56 (1.2)	
>2cm	382 (40.6)	1903 (40.5)		381 (40.9)	1895 (40.8)	
Unknown	550 (58.4)	2746 (58.4)		540 (57.9)	2697 (58.0)	
Breslow ( )			0.905			0.936
≤1.00	341 (36.2)	1716 (36.5)		333 (35.7)	1670 (35.9)	
≥4.00	23 (2.4)	91 (1.9)		23 (2.5)	109 (2.3)	
1.01-2.00	76 (8.1)	377 (8.0)		75 (8.0)	362 (7.8)	
2.01-4.00	31 (3.3)	154 (3.3)		31 (3.3)	132 (2.8)	
Unknown	471 (50.0)	2366 (50.3)		470 (50.4)	2375 (51.1)	
Ulceration ( )			0.827			0.833
Not present	438 (46.5)	2147 (45.6)		429 (46.0)	2106 (45.3)	
Present	43 (4.6)	232 (4.9)		43 (4.6)	202 (4.3)	
Unknown	461 (48.9)	2325 (49.4)		460 (49.4)	2340 (50.3)	
Hist ( )			0.996			0.969

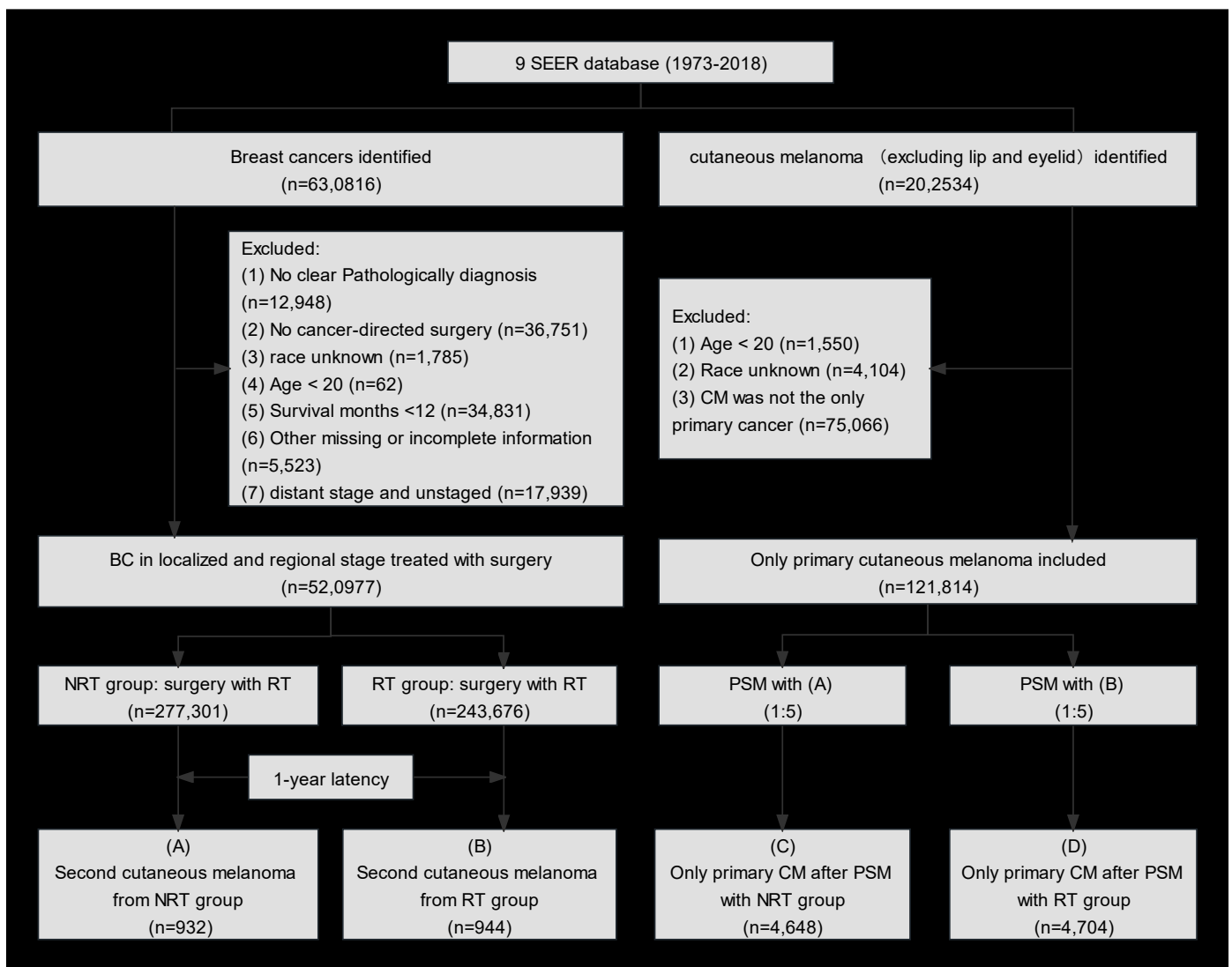
ALM	19 (2.0)	87 (1.8)		18 (1.9)	81 (1.7)	
LMM	74 (7.9)	367 (7.8)		72 (7.7)	356 (7.7)	
NM	66 (7.0)	326 (6.9)		66 (7.1)	333 (7.2)	
Other	448 (47.6)	2260 (48.0)		444 (47.6)	2265 (48.7)	
SSM	335 (35.6)	1664 (35.4)		332 (35.6)	1613 (34.7)	
Site ()			0.946			0.991
Head and neck	132 (14.0)	611 (13.0)		132 (14.2)	631 (13.6)	
Lower limb and hip	280 (29.7)	1423 (30.3)		277 (29.7)	1400 (30.1)	
Other/unknown	23 (2.4)	117 (2.5)		23 (2.5)	120 (2.6)	
Trunk	207 (22.0)	1047 (22.3)		201 (21.6)	1001 (21.5)	
Upper limb and shoulder	300 (31.8)	1506 (32.0)		299 (32.1)	1496 (32.2)	
Surgery = surgery ()	900 (95.5)	4508 (95.8)	0.75	891 (95.6)	4433 (95.4)	0.829
Radio = yes ()	12 (1.3)	49 (1.0)	0.648	12 (1.3)	50 (1.1)	0.695
Chemotherapy = Yes ()	6 (0.6)	25 (0.5)	0.874	6 (0.6)	34 (0.7)	0.939

BC patients who developed second SCM were matched with patients with OPCM at a PSM ratio of 1:5 for other SCM versus OPCM. BC: Breast cancer; RT: Radiation therapy; NRT: No radiation therapy; SCM: Second cutaneous melanoma; OPCM: Only primary cutaneous melanoma; PSM: Propensity score matching.

**Table S10. Studies of the risk of developing SCM after radiation therapy among BC patients.**

Author, study(year)	Study period	Registry	Latency period, year	Total no. of BCs	Total no. of SNBCs	Total no. of SCMs	Median follow-up time	Statistical method	Risk of SCMs
Rubino, 2000	1973-1992	IGR	1	4,416	193 (4.4)	10	9.5	SIR	Increased risk from RT
Galper, 2002	1970-1987	SEER	—	1,884	147 (8)	14	8	SIR	Increased risk from RT
Roychoudhuri, 2004	1961-2000	TCR	1	64,782	5,217 (8.1)	79	—	SIR	No increased risk from RT
Goggins, 2004	1973-1999	SEER	—	—	—	668	—	SIR	Increased risk from RT
Kirova, 2007	1981-1997	IC	—	16,705	709 (4.3)	37	10.5	Kaplan-Meier, Log-rank, SIR	No increased risk from RT
Schaapveld, 2008	1989-2003	CCCN CCCA CCCS	—	58,068	2,578 (4.4)	164	5.4	SIR, Cox regression analysis (adjusted for competing risks)	No increased risk from RT (increased risk with chemotherapy)
<b>The present study</b>	<b>1973-2018</b>	<b>SEER</b>	<b>1</b>	<b>520,977</b>	<b>—</b>	<b>1, 876</b>	<b>10</b>	<b>Fine–Gray competing risk regression, Poisson regression, SIR, Kaplan-Meier</b>	<b>Minimal risk from RT</b>

IGR: Institut gustave roussy; SEER: Surveillance, Epidemiology and End Results program; TCR: Thames cancer registry; IC: Institut curie; CCCN: Comprehensive cancer center-north netherlands; CCCA: Comprehensive cancer center amsterdam; CCCS: Comprehensive cancer center south.



**Figure S1. Flow diagram.** SEER: Surveillance, Epidemiology and End Results; PSM: Propensity score matching; RT: Radiation therapy; BC: Breast cancer; CM: Cutaneous melanoma.