The prevalence and risk of second primary malignancies after different stages of breast cancer women

Cheng-Yao Lin, MD, MS^{1,2,3}, Sheng-Yen Hsiao, MD¹, Chao-Jung Tsao, MD, PhD¹, Chung-Han Ho, PHD^{4,5},
Shih-Bin Su, MD, PhD^{6,7}, How-Ran Guo, MD, PhD⁸

¹Division of Hematology-Oncology, Department of Internal Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan

²Bachelor Program of Senior Services, Southern Taiwan University of Science and Technology, Tainan, Taiwan

³Department of Environmental and Occupational Health, National Cheng Kung University, Tainan, Taiwan

⁴Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan

⁵Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

⁶Department of Medical Research, Chi Mei Medical Center, Liouying, Tainan, Taiwan

⁷Department of Occupational Medicine, Chi-Mei Medical Center, Tainan, Taiwan

⁸Department of Environmental and Occupational Health, National Cheng Kung University, Tainan, Taiwan

Background & Aim

The incidence of breast cancer (BC) has increased gradually, it has been the most common cancer in women worldwide. Meanwhile, the survival of BC patients has been greatly improved in recent decades due to advances in medical care. Therefore, the incidence and risk factors for second primary malignancies (SPM) after BC was an important issue. For the BC treatment, the administration of chemotherapy and radiotherapy depend on the characteristics of the cancer and different stages, the risk of SPM in different stages of BC might be different. Our study was to evaluate the risk of SPM in different BC stage women.

Methods

We extracted BC women from Breast Cancer Health Database, which includes 4 different cancer registry datasets between 2002 and 2014 in Taiwan. We compared the incidence of SPM in BC patients with or without chemotherapy and radiotherapy in different American Joint Committee on Cancer (AJCC) stages. The baseline information between different stages was compared using Pearson's chi-square test. The risk of SPM was estimated using Cox regression model adjusted with potential risk factors.

Results

Total 85,947 eligible BC patients were enrolled. The median diagnosed age was 52 years. The median follow-up was 4.25 (1.96-6.13) years. 2,571 (2.99%) SPM cases were identified. The median duration of SPM occurrence was 2.70 (1.14-5.14) years after BC. Radiotherapy and chemotherapy were administrated in 40,946 (47.64%) and 52,120 (60.64%) BC patients respectively (table 1).

The most common SPM was digestive tract cancers (876, 31.89%) and followed by respiratory tract cancers (413, 15.03%) (table 2).

The SPM risk was significant diversities in stages, therapeutic strategies, ages and underlying co-morbidities (all $p < .0001$) (table 3).

Chemotherapy and radiotherapy didn't increase SPM risk in any stages. In contrast, patients who received both therapies has lower SPM risk in stage I, II and III/IV. After adjusted with ages and comorbidities, the reduced risk trend was still significant in stage III/IV BC patients ($p = 0.047$) (table 4).

Table 1. Baseline characteristics of breast cancer patients

Characteristic	Total	0	Stage I	II	III-IV
Number (%)	85947	11149	26982	35458	12358
No second cancer	83289(96.91)	10869(97.49)	26091(96.7)	34254(96.6)	12075(97.71)
Second cancer	2571(2.99)	274(2.46)	859(3.18)	1163(3.28)	275(2.23)
Time to second cancer					
Median follow-up, year (IQR)	2.70(1.14-5.14)	2.16(0.80-4.05)	2.75(1.19-5.10)	3.11(1.35-5.64)	1.73(0.39-3.75)
AJCC stage edit (Missing=1255)					
6th	29691(35.06)	2741(24.72)	9318(35.11)	13396(38.42)	4236(34.72)
7th	55001(64.94)	8345(75.28)	17222(64.89)	21468(61.58)	7966(65.28)
Follow person-years	380339.68	44853.70	128811.17	167366.21	39308.60
Median follow-up, years (IQR)	4.25(1.96-6.13)	3.49(1.60-5.77)	4.24(1.96-7.13)	4.14(1.93-7.03)	2.41(1.07-4.58)
Median diagnosed age, years	52 y.o.	51 y.o.	52 y.o.	52 y.o.	54 y.o.
Age (years)					
18-39	8879(10.33)	1000(8.97)	2699(10)	4054(11.43)	1126(9.11)
40-49	26502(30.84)	3822(34.28)	8786(32.56)	10733(30.27)	3161(25.58)
50-59	26806(31.19)	3737(33.52)	8518(31.57)	10606(29.91)	3945(31.92)
≥60	23760(27.64)	2590(23.23)	6979(25.87)	10065(28.39)	4126(33.39)
Comorbidities					
DM	8817(10.26)	955(8.57)	2487(9.22)	3967(11.19)	1408(11.39)
COPD	2841(3.31)	370(3.32)	890(3.3)	1186(3.34)	395(3.2)
Liver	2159(2.51)	292(2.62)	795(2.95)	864(2.44)	208(1.68)
CKD	1336(1.55)	174(1.56)	408(1.51)	554(1.56)	200(1.62)
Radiotherapy (yes/no)	40946(47.64)	4179(37.48)	14213(52.68)	16484(46.49)	6070(49.12)
Chemotherapy (yes/no)	52120(60.64)	925(8.3)	14200(52.63)	26817(75.63)	10178(82.36)

AJCC: American Joint Committee on Cancer; CKD: chronic kidney disease; COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes mellitus

Table 2. The second cancer types in breast cancer patients with different stages

Cancer type (ICD-9 code) & (ICD-O-3 code)	Total	stage			
		0	I	II	III-IV
Head and neck (140–149) & (C00–C14)	64(0.07)	5(0.04)	16(0.06)	37(0.10)	6(0.05)
Digestive (150–159) & (C15–C26 & C48)	876(1.02)	71(0.64)	291(1.08)	423(1.19)	91(0.74)
Respiratory (160–165) & (C30–C39)	413(0.48)	57(0.51)	153(0.57)	160(0.45)	43(0.35)
Bone, skin and soft tissues (170-173) & (C40–C41, C44, C47, C49)	124(0.14)	11(0.10)	36(0.13)	68(0.19)	9(0.07)
Urinary (188-189) & (C64–C68)	186(0.22)	19(0.17)	76(0.28)	73(0.21)	18(0.15)
F_Uterus (182) & (C54)	258(0.30)	32(0.29)	85(0.31)	121(0.34)	20(0.16)
F_Ovarian (183) & (C56, C570–C574)	90(0.10)	9(0.08)	30(0.11)	43(0.12)	8(0.06)
F_Cervical (180) & (C53)	272(0.32)	22(0.20)	92(0.34)	123(0.35)	35(0.28)
Hematological (200-208) & (C81–C96)	156(0.18)	16(0.14)	45(0.17)	74(0.21)	21(0.17)
Others (190–195, 199)& (C69–C76, C80)	308(0.36)	44(0.39)	100(0.37)	124(0.35)	40(0.32)

ICD-9: International Classification of Diseases, 9th Revision; ICD-O-3: International Classification of Diseases for Oncology, 3rd Edition

Table3. Overall risks for second primary malignancies.

	Second cancer		*P-value
	No N(%)=83291(96.91)	Yes N(%)=2656(3.09)	
Stage			
0	10869(13.05)	280(10.54)	<.0001
I	26092(31.33)	890(33.51)	
II	34255(41.13)	1203(45.29)	
III/IV	12075(14.50)	283(10.66)	
Therapy			<.0001
No	20549(24.67)	781(29.52)	
RT only	12156(14.59)	341(12.89)	
CH only	22892(27.48)	779(29.44)	
Both	27694(33.25)	745(28.16)	
Age (years)			<.0001
18-39	8748(10.50)	131(4.93)	
40-49	25899(31.09)	603(22.70)	
50-59	25972(31.18)	834(31.40)	
≥60	22672(27.22)	1088(40.96)	
Comorbidities			
DM	8422(10.11)	395(14.87)	<.0001
COPD	2720(3.27)	121(4.56)	0.0003
Liver	2019(2.42)	140(5.27)	<.0001
CKD	1364(1.64)	72(2.71)	<.0001

CKD: chronic kidney disease; COPD: Chronic Obstructive Pulmonary Disease; CH: Chemotherapy; DM: Diabetes mellitus; RT: radiotherapy
*P-value was derived from Pearson's Chi-square test.

Table 4. Crude and adjusted hazard ratio of radiotherapy and chemotherapy for second primary malignancies in different stages

	Crude HR (95% C.I.)	P-value	*Adjusted HR (95% C.I.)	P-value
Stage 0				
No	Ref.	-	Ref.	-
RT only	1.02(0.79-1.32)	0.8880	1.10(0.84-1.43)	0.4874
CH only	0.97(0.55-1.70)	0.9049	1.06(0.60-1.88)	0.8310
Both	1.28(0.71-2.29)	0.4134	1.46(0.81-2.63)	0.2098
Stage I				
No	Ref.	-	Ref.	-
RT only	0.76(0.63-0.92)	0.0041	0.90(0.74-1.09)	0.2844
CH only	0.73(0.61-0.87)	0.0004	0.90(0.75-1.09)	0.2743
Both	0.64(0.54-0.76)	<0.0001	0.88(0.73-1.07)	0.1962
Stage II				
No	Ref.	-	Ref.	-
RT only	0.94(0.73-1.22)	0.6371	1.07(0.83-1.39)	0.6093
CH only	0.73(0.63-0.85)	<0.0001	0.85(0.81-1.11)	0.4978
Both	0.66(0.57-0.77)	<0.0001	0.95(0.81-1.12)	0.5393
Stage III/IV				
No	Ref.	-	Ref.	-
RT only	0.84(0.43-1.63)	0.6122	0.82(0.42-1.59)	0.5504
CH only	0.63(0.44-0.91)	0.0128	0.71(0.49-1.02)	0.0629
Both	0.61(0.43-0.86)	0.0045	0.69(0.48-1.00)	0.0470

CH: Chemotherapy; HR: Hazard Ratio; RT: radiotherapy *The HRs were adjusted by the age, comorbidities

Conclusion

We concluded that the SPM was different in BC stages. Chemotherapy and radiotherapy would not increase the risk in BC women.