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Radiotherapy- and Chemotherapy-Induced Myelodysplasia Syndrome

A Nationwide Population-Based Nested Case–Control Study

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Abstract: This study explored which kinds of cancer are related to a higher incidence of subsequent myelodysplastic syndrome (MDS) after radiotherapy (RT) and chemotherapy (CT).

We performed a nested case–control study by using data from the Taiwanese National Health Insurance (NHI) system. The case group included cancer patients who developed MDS. For the control group, 4 cancer patients without MDS were frequency-matched with each MDS case by age, sex, year of cancer diagnosis, and MDS index year. A multivariable logistic regression analysis was conducted, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

Overall, cancer patients who received RT or CT exhibited secondary MDS more frequently than did those who did not (RT: OR = 1.53; 95% CI = 1.33–1.77; CT: OR = 1.51; 95% CI = 1.25–1.82). Analysis by cancer site showed that RT increased the risk of MDS for patients with stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers. By contrast, CT was more likely to increase the risk of MDS for patients with lung, endometrial, and cervical cancers. Further analysis revealed that RT and CT seemed to have a positive interaction. The major limitation of this study was the lack of certain essential data in the NHI Research Database, such as data regarding cancer stage and treatment dose details.

This population-based nested case–control study determined that RT and CT predisposed patients in Taiwan to the development of MDS. This effect was more prominent when both modalities were used.

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Abbreviations: AML = acute myeloid leukemia, CI = confidence interval, CT = chemotherapy, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, MDS = myelodysplastic syndrome, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute (NHRI), OR = odds ratio, RT = radiotherapy.

INTRODUCTION

In Taiwan, cancer has been the leading cause of death among the general population since 1982. The age-adjusted incidence rate has increased steadily since then; and it reached 320.65 new cases per 100,000 people in 2011.[1] The proportion of long-term cancer survivors is rising owing to successful cancer-screening programs, earlier detection, advanced diagnostic tools, timely and effective treatment, improved follow-up after treatment, and an aging population.[2] Consequently, the surveillance and monitoring of cancer survivors has become a crucial concern, regarding cancer control, as well as the emergence of cancer- and treatment-related health problems.[3]

Myelodysplastic syndrome (MDS) comprises a heterogeneous group of closely related clonal hematopoietic disorders that are characterized by hypocellular or hypercellular marrow with impaired morphology and maturation and peripheral blood cytopenias, followed by progressive impairment of the ability of myelodysplastic stem cells to differentiate and a tendency to evolve into acute myeloid leukemia (AML).[4–6] MDS has been identified to be associated with previous cancer treatment by using chemotherapy (CT) or radiotherapy (RT). Treatment-related MDS has been reported in various cancers, such as breast cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, endometrial cancer, ovarian cancer, prostate cancer, and brain

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Novelty & impact statements: Cancer patients who received RT or CT exhibited secondary MDS more frequently than those who did not (RT: OR = 1.53; 95% CI = 1.33–1.77; CT: OR = 1.51; 95% CI = 1.25–1.82). RT increased the risk of MDS for patients with stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers. CT was more likely to increase the risk of MDS for patients with lung, endometrial, and cervical cancers.
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tumors.[7–13] Although the absolute number of treatment-related MDS cases is small,[7] the poor prognosis of MDS warrants concern.

To the best of our knowledge, no nationwide population-based study has measured treatment-related MDS for cancer overall and for various individual cancers. We explored this topic in Taiwan. We designed this research to determine, among cancer survivors, which primary sites of cancer were more susceptible to the development of MDS after treatment, and whether CT and RT interact. We used a database from the National Health Insurance (NHI) system of Taiwan to conduct this study.

METHODS

Data Source

Taiwan has implemented the NHI program since 1995 and approximately 99% of the population (N = 23.74 million) is currently enrolled in the program.[14] This retrospective nested case–control study used the Longitudinal Health Insurance Database 2000 (LHID2000), a part of the National Health Insurance Research Database (NHIRD); the database was established and is maintained by the National Health Research Institutes (NHRI). The LHID2000 consists of claims data from 1,000,000 individuals randomly sampled (approximately 4.5% of Taiwan's population) from the registry of the NHIRD in 2000. There were no statistically significant differences in the distribution of sex, age, or health-care costs between the cohorts in the LHID2000 and insurance enrollees overall as reported by the NHRI in Taiwan. All personal information was confidential because patient identification numbers and other sensitive personal data were encrypted. This study was approved by the institutional review board of China Medical University in Central Taiwan (CMU-REC-101-012). The diagnoses were identified using diagnostic and procedural codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Sampled Participants

A nested case–control study based on the LHID2000 was conducted. We identified patients in the Registry for Catastrophic Illness Database who were 20 years of age and older and had been newly diagnosed with primary cancer with the ICD-9-CM codes 140–195 and 200–208, not including AML and chronic myeloid leukemia (ICD-9-CM codes 205.0 and 205.10, respectively) between January 1, 2000 and December 31, 2011; these patients comprised the exposure cohort. To register a case in the catastrophic illness registry, a diagnosis made by a physician with confirmatory pathological results or other supporting medical information is required; these documents are formally reviewed by the insurance authority. We excluded patients with a history of MDS before 2000 and patients with a history of MDS before the diagnosis of cancer. Each patient in the case group was followed until the diagnosis of MDS (ICD-9-CM codes 284.9, 285.0, 205.10, and 205.0); patients without MDS in the period 2000–2011 comprised the non-MDS group. The date of diagnosis for MDS was defined as the index date. To construct the comparison group, we randomly selected 4 people from the non-MDS group in the same period who were frequency-matched with the case group by age (at 5-year intervals), sex, year of cancer diagnosis, and MDS index year. We included 1265 patients in the MDS case group and 5057 non-MDS controls in this study.

Potential Comorbidities and Treatments Associated With MDS

The diseases considered comorbidities included diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM code 401-405), hyperlipidemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), ischemic heart disease (ICD-9-CM codes 410–414), chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), and alcoholic liver damage (ICD-9-CM codes 571.0, 571.1, and 571.3). We also considered anticancer drugs and included alkylating agents, topoisomerase II inhibitors, and antimetabolites which are suggested to have increased risks of MDS.[13]

Two kinds of treatment before the index date were examined for their possible association with MDS: RT and CT.

Statistical Analysis

The baseline distributions of demographic characteristics, comorbidities, and treatments between MDS group and non-MDS group were compared using the χ^2 test for categorical variables and the *t* test for continuous variables. Univariable and multivariable unconditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between MDS and RT and CT. The multivariable models were simultaneously adjusted for the comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, and anticancer drugs. Models were also used for estimating the risks of using RT and CT for MDS. All analyses were performed using SAS statistical software for Windows (version 9.3; SAS Institute, Inc., Cary, NC), and the significance level was set at 0.05.

RESULTS

Table 1 shows a comparison of distributions of demographic characteristics, baseline comorbidities, and treatments between the MDS and the non-MDS groups. Among the 1265 patients with MDS, 50.8% of them were women and most were older than 65 years of age (56.1%). The mean ages of the MDS and non-MDS groups were 65.2 (SD = 14.8) and 65.2 (SD = 14.8) years, respectively. Compared with the non-MDS group, the MDS group patients were more likely to have diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, alkylating agents use, topoisomerase II inhibitors use, and antimetabolites use (all $P < 0.05$). The proportions of those treated with RT and CT were significantly higher in the MDS group than in the non-MDS group. The results of the multivariable logistic regression models for the association of RT and CT with MDS risk among patients with cancer are shown in Table 2. Overall, compared with patients who did not receive RT treatment, we observed a significant, 1.53-fold increase of MDS in cancer patients who received RT treatment (95% CI = 1.33–1.77) after adjusting for the comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, and anticancer drugs. Compared with non-CT patients, the adjusted OR for MDS risk was 1.51-fold (95% CI = 1.25–1.82) higher than that for CT. Patients with diabetes, stroke, ischemic heart disease, alkylating agents use, and topoisomerase II inhibitors use also demonstrated a significant association with increased MDS risk.

Furthermore, we estimated the risk of MDS following treatment with RT and CT for patients with various types of cancer (Table 3). A statistically significantly higher risk of MDS

TABLE 1. Baseline Characteristics Between Myelodysplastic Syndrome Group and Non-Myelodysplastic Syndrome Group

	Myelodysplastic syndrome				
	No N = 5057		Yes N = 1265		
	N	%	n	%	*P* value*
Gender					0.99
Women	2572	(50.9)	643	(50.8)	
Men	2485	(49.1)	622	(49.2)	
Age group (y)					0.99
20–49	880	(17.4)	220	(17.4)	
50–64	1344	(26.6)	336	(26.6)	
65–74	1284	(25.4)	321	(25.4)	
≥75	1549	(30.6)	388	(30.7)	
Mean (SD) (y) *	65.2	(14.8)	65.2	(14.8)	0.87
Baseline comorbidities					
Diabetes	850	(16.8)	254	(20.1)	0.006
Hypertension	2516	(49.8)	652	(51.5)	0.26
Hyperlipidemia	1281	(25.3)	290	(22.9)	0.08
Stroke	393	(7.77)	131	(10.4)	0.003
Ischemic heart disease	1283	(25.4)	392	(31.0)	< 0.001
Chronic obstructive pulmonary disease	1977	(39.1)	550	(43.5)	0.004
Alcoholism	75	(1.48)	31	(2.45)	0.02
Alcoholic liver damage	105	(2.08)	33	(2.61)	0.25
Treatment					
Radiotherapy	1205	(23.8)	443	(35.0)	<0.001
Chemotherapy	1507	(29.8)	542	(42.9)	<0.001
Anti-cancer drugs					
Alkylating agents	571	(11.3)	233	(18.4)	<0.001
Topoisomerase II inhibitors	582	(11.5)	235	(18.6)	<0.001
Antimetabolites	1300	(25.7)	393	(31.1)	<0.001

χ^2 test and *t test comparing subjects with and without myelodysplastic syndrome. Data are presented as the number of subjects in each group, with percentages given in parentheses.

was observed for endometrial cancer patients who received RT and CT compared with those who did not receive RT and CT (adjusted OR = 3.16, 95% CI = 1.05–9.49 and adjusted OR = 7.59, 95% CI = 1.07–53.6, respectively). Compared with stomach cancer patients who did not receive RT, stomach cancer patients who received RT were at a much higher risk of MDS. Similar results were observed for patients with colorectal, liver, female breast, prostate, and kidney cancers; for all of these, receiving RT increased the risk of MDS. Compared with lung cancer patients who did not receive CT, lung cancer patients who received CT had a 2.67-fold risk of MDS. Similar results were observed for cervical cancer patients; for all of these, CT increased the risk of MDS.

Colorectal cancer patients who received alkylating agents treatment and topoisomerase II inhibitors treatment had higher risks of MDS compared with those who did not receive alkylating agents treatment and topoisomerase II inhibitors treatment (adjusted OR = 4.49, 95% CI = 1.29–15.6 and adjusted OR = 24.2, 95% CI = 2.63–222.9, respectively) (Table 4).

Compared with head and neck cancer patients who did not receive alkylating agent treatment, head and neck cancer patients who received alkylating agent treatment were at a much higher risk of MDS. Compared with cervix cancer patients who did not receive topoisomerase II inhibitor treatment, cervical cancer patients who received topoisomerase II inhibitor treatment had a higher risk of MDS. Bladder patients and non-Hodgkin lymphoma with antimetabolite use also demonstrated a significant association with increased MDS risk compared with their counterparts who did not receive antimetabolite treatment.

Table 5 illustrates the joint effect of RT and CT on MDS risk. Compared with endometrial cancer patients who did not receive RT and CT, endometrial cancer patients who received both RT and CT had a higher risk of MDS (adjusted OR = 37.0, 95% CI = 2.96–462.4). Compared with lung cancer patients who did not receive RT and CT, lung cancer patients who received both RT and CT demonstrated a higher risk of MDS (adjusted OR = 3.62, 95% CI = 1.33–9.85). Similar results were observed for colorectal cancer, female breast cancer, and cervical cancer patients; receiving both RT and CT had a higher risk of MDS. Relative to the female breast cancer patients only receiving CT, female breast cancer patients who received both RT and CT had higher risk of MDS (adjusted OR = 1.93, 95% CI = 1.13–3.29). Compared with cervical cancer patients only receiving RT, cervical cancer patients who received both RT and CT had higher risk of MDS (adjusted OR = 2.43, 95% CI = 1.09–5.44).

DISCUSSION

The results from this population-based nested case–control study highlighted the fact that overall cancer treatment

TABLE 2. ORs and 95% CIs of Myelodysplastic Syndrome Associated With RT, CT, and Covariates

	Crude		Adjusted†	
Variable	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Gender (women vs. men)	1.00	(0.89, 1.13)	—	—
Age, y	1.00	(1.00, 1.01)	—	—
Baseline comorbidities				
Diabetes	1.24	(1.06, 1.45)**	1.21	(1.03, 1.42)*
Hypertension	1.07	(0.95, 1.22)	—	—
Hyperlipidemia	0.88	(0.76, 1.01)	—	—
Stroke	1.37	(1.11, 1.69)**	1.30	(1.05, 1.62)*
Ischemic heart disease	1.32	(1.15, 1.51)****	1.34	(1.15, 1.56)***
Chronic obstructive pulmonary disease	1.20	(1.06, 1.36)**	1.13	(0.99, 1.30)
Alcoholism	1.67	(1.09, 2.55)*	1.54	(1.00, 2.38)
Alcoholic liver damage	1.26	(0.85, 1.88)	-	-
Treatment				
RT	1.72	(1.51, 1.97)***	1.53	(1.33, 1.77)***
CT	1.77	(1.56, 2.00)***	1.51	(1.25, 1.82)***
Anticancer drugs				
Alkylating agents	1.77	(1.50, 2.10)****	1.27	(1.02, 1.57)*
Topoisomerase II inhibitors	1.75	(1.49, 2.07)***	1.27	(1.03, 1.55)*
Antimetabolites	1.30	(1.14, 1.49)***	0.91	(0.77, 1.08)

CI = confidence interval, CT = chemotherapy, OR = odds ratio, RT = radiotherapy.
† Adjusted for comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, and alcoholism, and anticancer drugs; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

TABLE 3. ORs and 95% CIs of Myelodysplastic Syndrome Associated With RT, CT, and Covariates in Subdivision Cancer

			RT		CT	
			No	**Yes**	**No**	**Yes**
Cancer (ICD-9-CM)	**No. of myelodysplastic syndrome/ No. of RT**	**No. of myelodysplastic syndrome/ No. of CT**	**Adjusted† OR(95% CI)**		**Adjusted† OR(95% CI)**	
Head and neck (140–149, 161)	50/243	68/355	1.00 (Reference)	1.41 (0.80, 2.48)	1.00 (Reference)	1.11 (0.50, 2.49)
Esophagus (150)	11/47	11/38	1.00 (Reference)	0.84 (0.21, 3.33)	1.00 (Reference)	1.53 (0.18, 12.7)
Stomach (151)	12/22	34/92	1.00 (Reference)	2.76 (1.06, 7.19)***	1.00 (Reference)	1.72 (0.80, 3.71)
Colorectum (153–154)	30/131	60/335	1.00 (Reference)	1.94 (1.16, 3.23)***	1.00 (Reference)	1.63 (0.94, 2.83)
Liver (155)	14/43	15/86	1.00 (Reference)	2.57 (1.22, 5.38)***	1.00 (Reference)	0.92 (0.43, 1.97)
Lung (162)	25/130	38/177	1.00 (Reference)	1.32 (0.69, 2.52)	1.00 (Reference)	2.67 (1.07, 6.67)*
Female breast (174)	54/257	75/452	1.00 (Reference)	1.86 (1.20, 2.89)***	1.00 (Reference)	1.87 (0.71, 4.95)
Uterus/endometrium (179, 182)	13/45	7/16	1.00 (Reference)	3.16 (1.05, 9.49)*	1.00 (Reference)	7.59 (1.07, 53.6)*
Cervix (180)	50/179	38/99	1.00 (Reference)	1.44 (0.77, 2.69)	1.00 (Reference)	2.41 (1.16, 5.00)*
Prostate (185)	39/129	13/31	1.00 (Reference)	2.12 (1.22, 3.67)**	1.00 (Reference)	1.61 (0.63, 4.12)
Bladder (188)	8/24	18/55	1.00 (Reference)	0.98 (0.28, 3.41)	1.00 (Reference)	1.26 (0.48, 3.34)
Brain tumor (191)	7/38	3/8	1.00 (Reference)	0.18 (0.02, 2.18)	1.00 (Reference)	12.3 (0.38, 403.4)
Kidney (189)	8/12	13/28	1.00 (Reference)	5.59 (1.36, 23.1)*	1.00 (Reference)	1.31 (0.20, 8.44)
Non-Hodgkin lymphoma (202)	14/42	23/86	1.00 (Reference)	0.91 (0.33, 2.53)	1.00 (Reference)	0.27 (0.04, 1.65)
Lymphoblastic l eukemia (204)	3/7	4/8	1.00 (Reference)	2.88 (0.02, 339.9)	1.00 (Reference)	0.08 (0.02, 3.37)
Myeloid leukemia (205)	23/28	33/44	1.00 (Reference)	3.12 (0.75, 12.9)	1.00 (Reference)	2.04 (0.19, 22.4)

CI = confidence interval, CT = chemotherapy, ICD-9-CM = International Classification of Diseases, OR = odds ratio, RT = radiotherapy.
† Adjusted for comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, and alcoholism, and anticancer drugs; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

TABLE 4. ORs and 95% CIs of myelodysplastic syndrome associated with anticancer drugs and covariates in subdivision cancer

	Alkylating agents		Topoisomerase II inhibitors		Antimetabolites	
Cancer (ICD-9-CM)	No	Yes	No	Yes	No	Yes
	Adjusted† OR (95 % CI)		Adjusted† OR (95% CI)		Adjusted† OR (95% CI)	
Head and neck (140–149, 161)	1.00 (Reference)	7.08 (2.35,21.3)***	1.00 (Reference)	0.43 (0.09,2.05)	1.00 (Reference)	1.61 (0.76, 3.41)
Esophagus (150)	1.00 (Reference)	2.15 (0.19, 24.2)	1.00 (Reference)	1.42 (0.12, 16.6)	1.00 (Reference)	1.01 (0.14, 7.45)
Stomach (151)	1.00 (Reference)	0.66 (0.16, 2.71)	1.00 (Reference)	1.18 (0.42, 3.33)	1.00 (Reference)	0.95 (0.50, 1.81)
Colorectum (153–154)	1.00 (Reference)	4.49 (1.29, 15.6)*	1.00 (Reference)	24.2 (2.63, 222.9)**	1.00 (Reference)	0.94 (0.56, 1.57)
Liver (155)	1.00 (Reference)	10.8 (0.46, 253.3)	1.00 (Reference)	0.90 (0.48, 1.69)	1.00 (Reference)	1.38 (0.55, 3.48)
Lung (162)	1.00 (Reference)	0.44 (0.05, 3.88)	1.00 (Reference)	0.92 (0.34, 2.47)	1.00 (Reference)	1.35 (0.60, 3.02)
Female breast (174)	1.00 (Reference)	0.83 (0.31, 2.23)	1.00 (Reference)	1.14 (0.66, 1.99)	1.00 (Reference)	0.70 (0.39, 1.26)
Uterus/ endometrium (179, 182)	1.00 (Reference)	2.08 (0.15, 29.3)	1.00 (Reference)	0.06 (0.00, 1.000	1.00 (Reference)	0.85 (0.34, 23.6)
Cervix (180)	1.00 (Reference)	2.79 (0.89, 8.78)	1.00 (Reference)	10.5 (1.05, 105.1)*	1.00 (Reference)	1.05 (0.41, 2.71)
Prostate (185)	1.00 (Reference)	-	1.00 (Reference)	2.93 (0.13, 68.4)	1.00 (Reference)	3.98 (0.93, 17.1)
Bladder (188)	1.00 (Reference)	9.94 (0.63, 157.5)	1.00 (Reference)	1.80 (0.82, 3.95)	1.00 (Reference)	12.0 (2.81, 51.5)***
Brain tumor (191)	1.00 (Reference)	10.9 (0.67, 179.1)	1.00 (Reference)	-	1.00 (Reference)	0.22 (0.00, 23.7)
Kidney (189)	1.00 (Reference)	0.55 (0.02, 16.8)	1.00 (Reference)	4.25 (0.62, 29.2)	1.00 (Reference)	0.83 (0.14, 4.81)
Non-Hodgkin lymphoma (202)	1.00 (Reference)	1.21 (0.24, 5.98)	1.00 (Reference)	1.40 (0.36, 5.55)	1.00 (Reference)	7.49 (2.21, 25.3)**
Lymphoblastic leukemia (204)	1.00 (Reference)	5.94 (0.55, 64.3)	1.00 (Reference)	1.92 (0.03, 143.4)	1.00 (Reference)	—
Myeloid leukemia (205)	1.00 (Reference)	0.73 (0.17, 3.11)	1.00 (Reference)	0.81 (0.14, 4.52)	1.00 (Reference)	0.66 (0.05, 8.98)

CI = confidence interval, ICD-9-CM = International Classification of Diseases, OR = odds ratio.

† Adjusted for comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, and alcoholism, radiotherapy, and chemotherapy; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

with either RT or CT can significantly increase the risk of subsequently developing MDS. Analysis by cancer site indicated that patients with stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers after RT had a significantly high risk of developing MDS. By contrast, CT was more likely to increase MDS incidence among patients with lung, endometrial, and cervical cancers. Different patterns of MDS risk among various cancers in 3 kinds of anticancer drugs were also found. Further analysis revealed that RT and CT tended to have a positive joint effect on MDS occurrence.

MDS is not uncommon. Approximately 20,000 cases of MDS were diagnosed in the United States in 2008, of which approximately 10% were therapy related.[15] From our NHI database, 454 cases of MDS were diagnosed in Taiwan in 2008. The French–American–British Cooperative Group proposed a classification based on easily obtainable laboratory information.[16] The 5 classes are refractory anemia (RA), RA with ringed sideroblasts, RA with excess blasts (RAEBs), RAEB in transformation, and chronic myelomonocytic leukemia. The prognosis of MDS is relatively poor, and the majority of patients progress to refractory AML within a few months. The median survival time varies from months to years, depending on its subtypes.[17] Therapy-related MDS is a serious long-term consequence of cytotoxic treatments for an antecedent disease. Traditional cancer therapy operates by producing extensive DNA damage that in turn inhibits proliferation and activates cell-death pathways. RT and CT do not target cancer cells exclusively; therefore, mutations may also be induced among normal cells. When they persist and affect genes controlling the growth and differentiation of hematopoietic stem and precursor cells, a neoplastic myeloid clone may be generated.[13]

People accidentally exposed to ionizing radiation, as well as cancer patients receiving RT, have been extensively linked to hematological malignancies.[18–20] By contrast, alkylating agents, topoisomerase II inhibitors, and antimetabolites are frequently cited perpetrators of CT-induced MDS.[13,15] Alkylating agents comprise a large group of anticancer drugs with clinical applications across almost all types of cancer.[13] Alkylating agents are the principal cause of therapy-related MDS. The syndrome was first recognized in the treatment of Hodgkin disease.[15] MDS from exposure to topoisomerase II inhibitors usually has an early onset (within 1–3 years) and causes balanced genetic alterations typically involving 11q23.[21,22] However, exposure to alkylating agents results in a later onset (within 5–10 years) and yields unbalanced chromosomal alterations often involving chromosomes 5 and 7.[23,24] Researchers have found that the specific effects and chromosomal abnormalities caused by radiation seem to be similar to those seen from exposure to alkylating agents.[25] Antimetabolites are yet another group of cytostatic drugs causally involved in the development of therapy-related myeloid neoplasms.[13,26] For cancer overall,

TABLE 5. ORs and 95% CIs of myelodysplastic syndrome associated radiotherapy with joint effect of chemotherapy

Variables		No. of myelodysplastic syndrome		Adjusted OR†	Adjusted OR†	Adjusted OR†
		No	Yes	(95% CI)	(95% CI)	(95% CI)
Colorectal cancer						
Radiotherapy	Chemotherapy					
No	No	610	69	1 (Reference)		
No	Yes	204	39	1.87 (1.04, 3.38)*	1 (Reference)	
Yes	No	30	9	2.93 (1.30, 6.60)**	—	1 (Reference)
Yes	Yes	71	21	2.89 (1.39, 6.00)**	1.79 (0.93, 3.48)	1.62 (0.44, 6.00)
Liver cancer						
Radiotherapy	Chemotherapy					
No	No	325	53	1 (Reference)		
No	Yes	59	11	1.14 (0.51, 2.55)	1 (Reference)	
Yes	No	17	10	3.48 (1.47, 8.24)**	—	1 (Reference)
Yes	Yes	12	4	1.39 (0.36, 5.35)	1.48 (0.24, 9.17)	0.17 (0.02, 2.01)
Lung cancer						
Radiotherapy	Chemotherapy					
No	No	122	10	1 (Reference)		
No	Yes	68	17	2.90 (1.00, 8.39)	1 (Reference)	
Yes	No	34	4	1.55 (0.45, 5.34)	—	1 (Reference)
Yes	Yes	71	21	3.62 (1.33, 9.85)*	1.24 (0.58, 2.64)	1.60 (0.40, 6.44)
Female breast cancer						
No	No	257	31	1 (Reference)		
No	Yes	217	30	1.75 (0.63, 4.87)	1 (Reference)	
Yes	No	43	9	1.61 (0.70, 3.68)	—	1 (Reference)
Yes	Yes	160	45	3.46 (1.28, 9.33)*	1.93 (1.13, 3.29)*	3.60 (0.92, 14.1)
Uterine/endometrial cancer						
Radiotherapy	Chemotherapy					
No	No	55	8	1 (Reference)		
No	Yes	4	2	3.15 (0.21, 47.6)	1 (Reference)	
Yes	No	27	8	2.63 (0.81, 8.49)	—	1 (Reference)
Yes	Yes	5	5	37.0 (2.96, 462.4)**	1.70 (0.13, 21.6)	3.21 (0.72, 14.3)
Cervical cancer						
Radiotherapy	Chemotherapy					
No	No	209	31	1 (Reference)		
No	Yes	6	4	1.45 (0.26, 8.19)	1(Reference)	
Yes	No	74	16	1.32 (0.67, 2.62)	—	1 (Reference)
Yes	Yes	55	34	3.46 (1.79, 6.65)***	2.45 (0.43, 14.2)	2.43 (1.09, 5.44)*

CI = confidence interval, OR = odds ratio.

† Adjusted for comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, and anticancer drugs; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

our data revealed that both RT and CT are associated with a higher risk of subsequent MDS. Regarding individual cancers, several studies have found that RT and/or CT for breast cancer can induce MDS.[7,8,27,28] Our results showed that breast cancer survivors who received RT are more vulnerable to developing MDS compared with their counterparts, but not breast cancer survivors who received CT (Table 3). When we used breast cancer patients without RT and CT as the reference, neither the RT nor the CT group showed a significantly higher risk of MDS, but the group treated with both RT and CT did manifest a significantly higher risk of MDS (Table 5, OR = 3.46; 95% CI = 1.28–9.33). This was partially consistent with Kaplan et al, who performed a registry cohort analysis and found that an elevated rate of MDS and AML was observed among breast cancer patients treated with RT and those treated with RT and CT compared with available population incidence data.[7] The authors used records from the 2001–2009 Surveillance, Epidemiology, and End Results database to identify a cohort of women with first primary Stage 0 breast cancer who were treated with RT, a group that is not treated with CT. They suggested that using RT to treat breast cancer is associated with an increased risk of MDS/AML and affects an extremely small number of patients.[27] It is reasonable that there have been more reports of MDS development among breast cancer survivors compared with other cancer survivors. Because of the relative success of cancer-screening programs, early detection and timely and appropriate treatment have yielded more favorable prognoses for patients with breast cancer compared with patients with most other types of cancer.

Another primary cancer site that has been gaining interest among researchers is the prostate gland. In general, prostate cancer is characterized by its relatively older average age at diagnosis and slower progression compared with most other types of cancer. More survivors of prostate cancer can be expected compared with other cancers. RT is one of the major therapies for prostate cancer, but CT does not play a crucial role in the treatment of prostate cancer. Prostate cancer patients treated with radical RT with curative intent typically receive higher doses (up to >70 Gy) than those involved in adjuvant RT. Mukherjee et al evaluated the risk of developing MDS among prostate cancer patients definitively treated with RT and found that RT did not appear to induce a statistically increased risk of subsequent MDS.[11] However, our data showed that after RT, prostate cancer patients have a significantly higher risk of developing MDS. Our population-based nested case–control study had more MDS patients and, thus, our study was more likely to detect a significant difference, which may account for this observation. The association between CT and MDS in prostate cancer was not that obvious because of the relatively small number of patients receiving CT (Table 3). Hematological malignancies were also studied to determine the association between cancer treatment and subsequent MDS.[13,29,30] The present study failed to find any significant relationship between cancer treatment and MDS in these malignancies except for antimetabolites users among non-Hodgkin lymphoma with a higher MDS risk (Table 4). Previous case reports have highlighted MDS cases after abdominopelvic RT for endometrial cancer, as well as after CT and RT for brain tumors.[10,12] Our study revealed a positive relationship between MDS cases after RT or CT for endometrial cancer and our results yielded no significant association was found between brain tumor treatment and MDS. In addition, treatment-related MDS in testicular cancer, ovarian cancer, and sarcoma has been reported,[31,32] however, we did not have enough cases of these cancers and no significant findings were observed (data not shown). We found that treatment for certain cancer sites was linked to MDS, although such sites have been seldom mentioned in previous studies. These sites included stomach, colorectal, liver, and kidney cancers in the RT group and lung and cervical cancers in the CT group. Nevertheless, our finings need to be supported by further investigation of these cancers.

We subclassified CT into alkylating agent, topoisomerase II inhibitors, and antimetabolites to analyze because they are suggested to have increased risks of MDS.[13] Because of the dilute effect of case classification, less cancer sites were identified to have the statistically significant level for an increased risk of MDS. Our data revealed that head and neck cancer and colorectal cancer patients with alkylating use had significantly higher risks for MDS. Alkylating agents are commonly used in head and neck cancer and colorectal cancer patients,[33,34] and it may enhance the ability to detect a statistically significant difference. Tebbi et al found a novel association between topoisomerase inhibition and risk of secondary myeloid neoplasms in pediatric Hodgkin disease..[35] Le Deley et al found that the risk of MDS is much higher with mitoxantrone-based CT than with anthracycline-based CT in breast cancer patients.[20] Users of topoisomerase II inhibitors were found to have significantly higher risks for MDS among colorectal cancer and cervical cancer patients in our study. Antimetabolites, and in particular the immunosuppressive agents azathioprine and fludarabine, have also been associated with MDS.[9] Our data revealed that antimetabolite users had significantly higher risks of MDS among bladder cancer and non-Hodgkin lymphoma patients.

A tendency of a positive joint effect of RT and CT was observed in our study. As shown in Table 5, a reference group of patients who did not receive RT or CT exhibited the joint effect of both treatments in lung, breast, endometrial, and cervical cancers. In these cancer sites, double-treatment groups, but not single-treatment groups, had significantly higher risks of MDS. When used single-treatment group as the reference, Table 5 also revealed consistent higher adjusted ORs of double-treatment group compared with single-treatment group (except for liver cancer), although *P* values seldom reached the significant level due to small case number. The positive interaction between RT and CT was observed in an early study conducted by Smith et al, who indicated that among patients receiving adjuvant CT for breast cancer, the risk of MDS increases with age, with the intensity of therapy, and with the use of breast RT.[28] This implied that a synergistic effect of MDS may exist between RT and CT. Combining RT and CT (either concurrent or sequential) in cancer treatment has been proven to increase therapeutic results in several cancers.[36–40] Treatment-related toxicity may be also additive.[41–43] Therefore, combination therapy may confer a higher risk of MDS.

This study demonstrated the strengths of its population-based nationwide source and subsequent follow-up period. Unlike most studies using population-based registries of the general population as the comparison group,[7,11,27] our control group comprised cancer patients without MDS. This was logical; this design eliminated the concern that possible malignancies may themselves be related to MDS.[44] However, some limitations of this study must be addressed. First, information regarding RT and CT dosages was unavailable in the NHI database. Therefore, comprehensive analyses to determine whether the relationship between RT/CT and MDS is dose-responsive were not possible. Smith et al evaluated MDS after doxorubicin–cyclophosphamide adjuvant therapy for operable breast cancer and found that the incidence of MDS was sharply elevated in the more intense regimens;[28] however, we cannot conduct the similar analysis. Second, the NHI database also lacks cancer clinical stage and pathological types, and we cannot adjust these factors to minimize the possible confounding. In additional, it also hampers us using current data to demonstrate the treatment benefit regarding survival rate due to uncontrolled biases.

In conclusion, this population-based nested case–control study found that both RT and CT are related to the subsequent development of MDS. Some cancer sites are more susceptible to developing MDS after cancer treatment. A possible positive interaction between RT and CT may exist. Further research is warranted to validate our findings. The study highlights that physicians must keep in mind the long-term risks of CT and RT, including the development of MDS. Nevertheless, these results do not dispute the proven benefits of RT and CT in cancer control, which far outweigh the potential risk of MDS.

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