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Leukemia Risk After Cardiac Fluoroscopic Interventions Stratified by Procedure Number, Exposure Latent Time, and Sex

A Nationwide Population-Based Case-Control Study

Kai-Che Wei, MD, Hon-Yi Lin, MD, PhD, Shih-Kai Hung, MD, PhD, Yu-Tung Huang, PhD, Moon-Sing Lee, MD, Wen-Hua Wang, MD, Chieh-Shan Wu, MD, Yu-Chieh Su, MD, Bing-Jie Shen, MD, Shiang-Jiun Tsai, MS, Wei-Ta Tsai, MS, Liang-Cheng Chen, MD, Chung-Yi Li, PhD, and Wen-Yen Chiou, MD

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From the Department of Dermatology (K-CW, C-SW), Kaohsiung Veterans General Hospital, Kaohsiung; Institute of Clinical Medicine (K-CW), College of Medicine, National Cheng Kung University, Tainan; Faculty of Yuhing Junior College of Health Care and Management (K-CW), Kaohsiung; Department of Radiation Oncology (H-YL, S-KH, M-SL, BJS, S-JT, W-TT, L-CC, W-YC), Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi; School of Medicine (H-YL, S-KH, M-SL, B-JS, Y-CS, W-YC), Tzu Chi University, Hualien; Master Degree Program in Aging and Long-Term Care (Y-TH), College of Nursing, Kaohsiung Medical University; Department of Cardiology (W-HW), Kaohsiung Veterans General Hospital, Kaohsiung; Division of Hematology Oncology (Y-CS), Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi; Department of Biomedical Imaging and Radiological Sciences (W-TT), National Yang-Ming University, Taipei; Department of Public Health (C-YL, W-YC), College of Medicine, National Cheng Kung University, Tainan; and Department of Public Health (C-YL), China Medical University, Taichung, Taiwan.

Correspondence: Chung-Yi Li, Department of Public Health, College of Medicine, National Cheng Kung University, No. 1, University Road, Tainan City; and Department of Public Health, China Medical University, No. 91, Hsueh-Shih Road, Taichung City, Taiwan (e-mail: c yli99@mail.ncku.edu.tw).

Wen-Yen Chiou, Department of Radiation Oncology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 2, Min-Sheng Road, Dalin Town, Chiayi, Taiwan

(e-mail: armstrong_washington@yahoo.com.tw).

What has been known in this topic?

Iatrogenic radiation exposure can increase the risk of malignancies.

The frequency of percutaneous cardiac fluoroscopic interventions is increasing, as well as cumulative radiation exposure over the past 10 years.

What does this paper add?

The risk of leukemia in patients who underwent cardiac angiographic catheterization increased by 1.566-fold and occurred as early as 3 years following the procedure.

Leukemia risk is more significant in patients who received multiple procedures, indicative of a possible dose-dependent relationship.

This study is partly based on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health in Taiwan and managed by National Health Research Institutes (registry number 100266). However, the interpretation and conclusions contained herein are not those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

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Abstract: A number of cardiac fluoroscopic interventions have increased rapidly worldwide over the past decade. Percutaneous transluminal coronary angioplasty (PTCA) and stent implantation have become increasingly popular, and these advancements have allowed patients to receive repetitive treatments for restenosis. However, these advancements also significantly increase radiation exposure that may lead to higher cumulative doses of radiation. In the present study, a nationwide population-based case-controlled study was used to explore the risk of leukemia after cardiac angiographic fluoroscopic intervention.

A total of 5026 patients with leukemia and 100,520 control patients matched for age and sex (1:20) by a propensity score method without any cancer history were enrolled using the Registry Data for Catastrophic Illness and the National Health Insurance Research Database (NHIRD) of Taiwan between 2008 and 2010. All subjects were retrospectively surveyed (from year 2000) to determine receipt of cardiac fluoroscopic interventions. Data were analyzed using conditional logistic regression models, and estimated crude and adjusted odds ratios (95% confidence interval).

After adjusting for age, gender, and comorbidities, PTCA was found to be associated with an increased risk of leukemia with an adjusted OR of 1.566 (95% CI, 1.282–1.912), whereas coronary angiography alone without PTCA and cardiac electrophysiologic study were not. Our results also showed that an increased frequency of PTCA and coronary angiography was associated with a higher risk of leukemia (adjusted OR: 1.326 to 1.530 [all $P < 0.05$]). Gender subgroup analyses demonstrated that men were associated with a higher risk of leukemia compared with women.

These results provide additional data in the quantification of the long-term health effects of radiation exposure derived from the cardiac fluoroscopic diagnostic and therapeutic intervention. PTCA alone or PTCA with coronary angiography was associated with an elevated risk of leukemia. Continued follow-up of existing cohorts will be valuable to help assess lifetime risks of cancer.

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Abbreviations: CAD = coronary artery disease, CHF = chronic heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, EPS = electrophysiological study, Gy = gray (unit), ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, OR = odds ratio, PTCA = percutaneous transluminal coronary angioplasty.

INTRODUCTION

It has been well established that radiation increases the risk of cancer, based historically on survivors of atomic bombs and nuclear accidents.¹ Leukemia, thyroid cancer, and breast cancer are the types most associated with nuclear/radiation exposure. Malignancies arising from iatrogenic radiation sources have been documented following various types of exposure, including radiation therapy for cancer or benign disease. Squamous cell carcinoma, basal cell carcinoma, breast cancer, and sarcoma are the most common types.^{2,3} In addition to radiotherapy, it has been reported that 0.9% of cancers in the USA (2004) may be caused by diagnostic x-rays, including plain films and computerized tomography (CT) scans.⁴

Cardiac fluoroscopic interventions, including percutaneous transluminal coronary angioplasty (PTCA) and electrophysiologic studies (EPS), utilizing low-energy x-ray can exert higher doses of radiation than most other x-ray examinations. Therefore, a cardiac fluoroscopy intervention with its associated radiation exposure might pose a higher risk of radiation-induced malignancy. However, the risk of malignancy was considered to be low, because the radiation dose delivered during each single procedure of cardiac catheter intervention was typically low and the net benefits for current heart disease outweighed possible risks of malignancy in the future.

PTCA has increased rapidly worldwide in the past 10 years. According to the registry, PTCA has been performed >1 million times annually in the USA⁵ and an estimated 35,000 times in Taiwan. Furthermore, these advancements allow patients to receive repetitive treatments for restenosis; however, inevitably the radiation exposure increases significantly and may lead to higher life-long cumulative dose of radiation. An increasing number of cases have emerged with cardiac fluoroscopy-induced radiation skin ulcers, the more severe form of skin damage associated with high doses of radiation (>15 Gy).⁶ This type of patient is no longer rare in the daily practice. Taken together, patients today who received PTCA have been exposed to an increased radiation dose compared with those patients treated over a decade ago.

Since the use of cardiac angiographic fluoroscopic interventions in medicine is widespread and appears to be increasing, there is a compelling need for additional data to quantify the long-term health effects of the diagnostic and therapeutic uses of radiation. However, there is a paucity of research regarding the relationship between radiation exposure from cardiac fluoroscopic procedures and the risk of cancer. There is currently a lack of definitive data and regulations about safe radiation thresholds of cumulative radiation exposure over a lifetime.^{7,8} In the present study, a nationwide population-based case-control study was used to explore the risk of leukemia postcardiac angiographic fluoroscopic intervention.

MATERIALS AND METHODS

Ethics Statement

All study protocols and procedures were approved by the Buddhist Dailin Tzu Chi Hospital Institutional Review Boards (Approval number B10402021). The IRB exempted requirement for written informed consent as this was a deidentified and encrypted database.

Databases

Patients were drawn from the National Health Insurance Research Database (NHIRD), one of the largest and most

comprehensive databases in the world, which was released for research purposes by the National Health Research Institutes (NHRI), Taiwan.^{9,10} The NHIRD provides all medical claims for ~99% of Taiwanese people.¹¹ In order to ensure accuracy of the claims, NHIRD performs quarterly expert reviews on a sample taken from every 50 to 100 ambulatory and inpatient claims.¹² False diagnostic reports yield severe penalties from NHIRD.¹³ Several studies have proved data accuracy of NHIRD.¹⁴

Study Groups

This was a population-based case-control study. First, leukemia patients were identified using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code (Code 202.4, 203.1, 204.0, 204.1, 204.2, 204.8, 204.9, 205.0, 205.1, 205.2, 205.8, 205.9, 206.0, 206.1, 206.2, 206.8, 206.9, 207.0, 207.2, 207.8, 208.0, 208.1, 208.2, 208.8, 208.9) from Registry Data for Catastrophic Illness. Catastrophic illness certificate, a peer-confirmed data subset, which could further ensure the accuracy of a cancer diagnosis was used for validation of a leukemia diagnosis.^{9,10} Patients with previously diagnosed leukemia and any other cancer history were excluded. Between January 2008 and December 2010, 5026 newly diagnosed leukemia patients were recruited. Second, 884,023 persons without any cancer history based on results from the Longitudinal Health Insurance Database served as controls. One million beneficiaries were randomly selected using the NHIRD by the NHRI and were included in the Longitudinal Health Insurance Database, which contained all claim data of the cohort from 1996 to 2010.

According to Facts 2014–2015 From the Leukemia and Lymphoma Society, age and sex are significantly associated with the incidence of leukemia and the incidence rates for all types of leukemia are higher among men than women.¹⁵ We used a propensity score to balance groups before all analyses because of an initial significant between-group difference in age and gender. With a match ratio of 1:20, 5026 leukemia patients and 100,520 controls were eligible for study inclusion.

Measurements of Endpoints and Covariates

To evaluate the association between the cardiac angiographic fluoroscopic intervention and leukemia, the data, including PTCA (ICD-9-CM procedure code 36.0, 36.01, 36.02, 36.05, 36.06, 36.09, 36.2), coronary angiography only without PTCA (ICD-9-CM procedure code 37.21, 37.22, 37.23, 37.29, 88.53, 88.54, 88.55, 88.56), and cardiac electrophysiological study (EPS) (ICD-9-CM procedure code 37.26, 37.27, 37.34), were collected. The number of PTCA, coronary angiography only without PTCA, and cardiac EPS were recorded, and the time between 1st PTCA/1st coronary angiography/1st cardiac EPS to the last day of observation were calculated.

The observation period for both groups was determined to begin January 1, 2000. The end of observation was defined as the last day before a leukemia diagnosis was made. The observation period of persons in the control group was the same as their corresponding leukemia patient after matching.

The potential risk factors of leukemia included gender, age, previous cancer treatment, exposure to certain chemicals, and life style such as smoking. People who had any cancer history other than leukemia were excluded from our study. Adjusted independent variables included age, gender, and comorbidities. Persons who had previous certain chemicals exposure history were very few in general population and could be omitted in this large-scale population-based study. Adjusted

comorbidities included a number of major life-style-related illnesses, such as hyperlipidemia, diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and congestive heart failure (CHF). Though our study database has no information about smoking status, COPD, a surrogate variable of chronic smoking behavior, has been adjusted in this study.

Statistical Analysis

For patient characteristics and comorbidities in each group, chi-square and *t* tests were used to evaluate differences between category and continuous variables. Conditional logistic regression models and estimated odds ratios and their 95% confidence intervals were then used. Crude odds ratios were estimated from simple conditional logistic regression that takes into account the matching variables including age and gender in the analysis. We then adjusted for all the risk factors investigated in the conditional logistic regression model. In this study, we used 2 statistical packages (SAS [version 9.2; SAS Institute, Inc, Cary, NC] and SPSS [version 12, SPSS Inc, Chicago, IL]) to analyze data. A *P* value <0.05 was indicative of a statistically significant difference.

RESULTS

Patient characteristics and comorbidities for each group are shown in Table 1. Mean patient age was 52.7 years for both groups. In the leukemia group, men accounted for 57% of the newly diagnosed leukemia patients, which was the same proportion reported by the Facts 2014–2015 From the Leukemia and Lymphoma Society.¹⁵ No significant differences between proportions of gender were observed between study groups after matching.

Conditional logistic regression analysis showed an association between percutaneous cardiac fluoroscopic procedures and leukemia (Table 2). Taken together, PTCA and coronary angiography were significantly associated with leukemia. If analyzed separately, PTCA was significantly associated with leukemia but coronary angiography alone without any PTCA was not significant after adjustment. The association between cardiac EPS and leukemia was not statistically significant.

An elevated risk of leukemia was observed for time from the first time PTCA or first time PTCA/coronary angiography to the last day of observation time in 2 time periods, ≤3 years and ≥7 years post 1st procedure (Table 3). Our results also showed that PTCA and coronary angiography were associated with a higher risk of leukemia.

Gender subgroup analyses (Table 4) showed that men had a higher risk of leukemia than women. The greater number of PTCA and coronary angiography in both men and women, the higher the adjusted odds ratio (OR) of leukemia was observed. Men also showed an elevated risk of leukemia during these 2 latent periods, ≤3 years and ≥7 years, whereas women had elevated risk during the period of ≤3 years.

DISCUSSION

In this study, we have used a national health insurance database to examine the effects of cardiac fluoroscopic intervention on the incidence of leukemia. We demonstrate that cardiac fluoroscopic intervention increases the risk (OR: 1.566) of leukemia. The risk becomes significant within 3 years after receiving the initial cardiac fluoroscopic catheterization procedure. Compatible with the carcinogenic effect of radiation, a stochastic effect (i.e., the higher cumulative radiation exposure) leads to a higher risk of radiation malignancy. Furthermore, the

TABLE 1. Patient Demographic and Clinical Characteristics Stratified by the Disease Group

	Leukemia n (%)	Control n (%)	Chi-Squared <i>P</i> Value [#]
Total	5026	100520	
Age*	52.7	52.7	0.984
Gender*			0.773
Male	2865 (57.0)	57092 (56.8)	
Female	2161 (43.0)	43428 (43.2)	
Hyperlipidemia			0.656
No	3313 (65.9)	65953 (65.6)	
Yes	1713 (34.1)	34567 (34.4)	
Diabetes			<0.001
No	3483 (69.3)	74623 (74.2)	
Yes	1543 (30.7)	25897 (25.8)	
Hypertension			0.466
No	2710 (53.9)	54728 (54.4)	
Yes	2316 (46.1)	45792 (45.6)	
COPD			<0.001
No	3435 (68.3)	73076 (72.7)	
Yes	1591 (31.7)	27444 (27.3)	
CAD			0.114
No	3599 (71.6)	73005 (72.6)	
Yes	1427 (28.4)	27515 (27.4)	
Time between CAD to the last day of observation period**			0.138
No	3599 (71.6)	73005 (72.6)	
≤3 years	343 (24.0)	6221 (22.6)	
4–6 years	283 (19.8)	5803 (21.1)	
7–9 years	422 (29.6)	8759 (31.8)	
10–12 years	334 (23.4)	5969 (21.7)	
13–15 years	45 (3.2)	763 (2.8)	
CHF			<0.001
No	4482 (89.2)	93328 (92.8)	
Yes	544 (10.8)	7192 (7.2)	

CAD = coronary artery disease, CHF = chronic heart failure, COPD = chronic obstructive pulmonary disease.

* Factors were used for propensity-score match to balance study groups.

** The end of observation period was defined as the last day of the year before a diagnosis of leukemia. The observation period of persons in the control group was the same date as their matched leukemia patient.

All *P* values were calculated using a *t* test or chi-square test.

odds ratio of leukemia was increased with an increased number of interventions received in our study. This data reinforces the importance of reducing radiation exposure during procedures and for the arrangement of proper postprocedure follow-up.

Radiation exposure is inevitable when patients receive cardiac catheterization; however, the benefits are believed to outweigh the possible risks of radiation damage. However, the dose of radiation exposure can be reduced without adversely affecting the treatment outcome through the better technique and strict adherence to established safety guidelines. There have been many comprehensive reviews and practicable recommendations regarding how to reduce radiation dose that demonstrate practicality and feasibility.¹⁶

The possibility of cancer risk derived from cardiac fluoroscopic catheterization has been reviewed in the literature.

TABLE 2. Association Between Cardiac Fluoroscopic Intervention Procedures and Leukemia

	Leukemia n (%)	Control n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
PTCA [‡]				
No	4910 (97.7)	99152 (98.6)	1	1
Yes	116 (2.3)	1368 (1.4)	1.718 (1.417, 2.082)*	1.566 (1.282–1.912)*
Coronary angiography alone without PTCA [§]				
No	4906 (97.6)	98781 (98.3)	1	1
Yes	120 (2.4)	1739 (1.7)	1.391 (1.153–1.678)*	1.206 (0.993–1.466)
PTCA or coronary angiography				
No	4790 (95.3)	97413 (96.9)	1	1
Yes	236 (4.7)	3107 (3.1)	1.552 (1.354–1.778)*	1.402 (1.211–1.624)*
Cardiac electrophysiologic study				
No	5008 (99.6)	100232 (99.7)	1	1
Yes	18 (0.4)	288 (0.3)	1.251 (0.776, 2.016)	1.157 (0.716–1.868)

CI = confidence interval, OR = odds ratio, PTCA = percutaneous transluminal coronary angioplasty.

* *P* value < 0.05.

† Adjusting for age, gender, hyperlipidemia, diabetes, hypertension, COPD, CAD, and CHF.

‡ Persons who have ever received PTCA before a diagnosis of leukemia.

§ Persons who have ever received a coronary angiography but never PTCA.

|| Persons who have ever received PTCA and persons who have ever received coronary angiography but never PTCA.

TABLE 3. Association Between Cardiac Fluoroscopic Intervention Procedures and Leukemia by Time to Disease and Number of Procedure

	Leukemia n (%)	Control n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Time from 1st PTCA to the last day of observation period [‡]				
No	4910 (97.7)	99152 (98.6)	1	1
≤3 years	64 (1.3)	655 (0.7)	1.979 (1.528–2.563)*	1.776 (1.362–2.315)*
4–6 years	20 (0.4)	371 (0.4)	1.092 (0.695–1.714)	1.007 (0.639–1.587)
≥7 years	32 (0.6)	342 (0.3)	1.898 (1.318–2.733)*	1.764 (1.219–2.553)*
Number of PTCA				
0	4910 (97.7)	99152 (98.6)	1	1
1	63 (1.3)	782 (0.8)	1.633 (1.260–2.116)*	1.523 (1.169–1.984)*
2	35 (0.7)	369 (0.4)	1.920 (1.356–2.720)*	1.734 (1.218–2.468)*
≥3	18 (0.4)	217 (0.2)	1.679 (1.037–2.717)*	1.435 (0.883–2.334)
Time from 1st PTCA/coronary angiography to the last day of observation period [‡]				
No	4790 (95.3)	97413 (96.9)	1	1
≤3 years	103 (2.0)	1354 (1.3)	1.553 (1.268–1.902)*	1.391 (1.127–1.717)*
4–6 years	55 (1.1)	853 (0.8)	1.318 (1.001–1.735)*	1.190 (0.899–1.576)
≥7 years	78 (1.6)	900 (0.9)	1.771 (1.402–2.237)*	1.622 (1.275–2.062)*
Sum number of PTCA and coronary angiography				
0	4790 (95.3)	97413 (96.9)	1	1
1	137 (2.7)	1923 (1.9)	1.455 (1.220–1.735)*	1.326 (1.103–1.594)*
2	60 (1.2)	726 (0.7)	1.689 (1.295–2.201)*	1.523 (1.161–1.998)*
≥3	39 (0.8)	458 (0.5)	1.744 (1.255–2.424)*	1.530 (1.095–2.140)*
Time from 1st cardiac electrophysiologic study to the last day of observation period [‡]				
No	5008 (99.6)	100232 (99.7)	1	1
≤3 years	0.9 (0.2)	99 (0.1)	1.821 (0.919–3.606)	1.616 (0.813–3.210)
4–6 years	3 (0.1)	74 (0.1)	0.812 (0.256–2.576)	0.736 (0.231–2.342)
≥7 years	6 (0.1)	115 (0.1)	1.045 (0.459–2.375)	1.017 (0.446–2.316)
Number of cardiac electrophysiologic study				
0	5008 (99.6)	100232 (99.7)	1	1
1	16 (0.3)	235 (0.2)	1.363 (0.820–2.263)	1.261 (0.758–2.099)
2	1 (0.0)	50 (0.0)	0.400 (0.055–2.899)	0.374 (0.052–2.715)
≥3	1 (0.0)	3 (0.0)	6.667 (0.693–64.090)	5.166 (0.529–50.414)

CI = confidence interval, OR = odds ratio, PTCA = percutaneous transluminal coronary angioplasty.

* *P* value < 0.05.

† Adjusting for age, gender, hyperlipidemia, diabetes, hypertension, COPD, CAD, and CHF.

‡ The end of the observation period was defined as the last day of the year before a diagnosis of leukemia. The observation period of persons in the control group was the same as their matched leukemia patient.

TABLE 4. Association Between Cardiac Fluoroscopic Intervention Procedures and Leukemia by Gender

	Total			Male		Female	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	
Time from 1st PTCA to the last day of the observation period [†]							
No	1	1	1	1	1	1	
≤3 years	1.979 (1.528–2.563)*	1.775 (1.362–2.313)*	1.996 (1.443–2.761)*	1.870 (1.340–2.611)*	2.235 (1.363–3.664)*	2.006 (1.211–3.323)*	
4–6 years	1.092 (0.695–1.714)	1.006 (0.638–1.586)	1.168 (0.696–1.959)	1.077 (0.637–1.820)	0.946 (0.337–2.655)	0.861 (0.305–2.432)	
≥7 years	1.898 (1.318–2.733)*	1.763 (1.219–2.550)*	1.916 (1.250–2.936)*	1.768 (1.144–2.730)*	2.341 (1.017–5.388)*	2.269 (0.979–5.263)	
Number of PTCA							
0	1	1	1	1	1	1	
1	1.633 (1.260–2.116)*	1.522 (1.168–1.983)*	1.597 (1.164–2.192)*	1.526 (1.102–2.113)*	1.721 (1.036–2.859)*	1.622 (0.968–2.719)	
2	1.920 (1.356–2.720)*	1.732 (1.217–2.466)*	1.833 (1.189–2.827)*	1.670 (1.074–2.595)*	2.855 (1.442–5.649)*	2.612 (1.308–5.214)*	
≥3	1.679 (1.037–2.717)*	1.435 (0.882–2.332)	2.118 (1.238–3.622)*	1.849 (1.073–3.187)*	1.086 (0.251–4.707)	0.826 (0.189–3.605)	
Time from 1st PTCA/coronary angiography to the last day of observation period [‡]							
No	1	1	1	1	1	1	
≤3 years	1.553 (1.268–1.902)*	1.390 (1.126–1.716)*	1.466 (1.128–1.906)*	1.334 (1.015–1.754)*	1.818 (1.271–2.598)*	1.659 (1.146–2.400)*	
4–6 years	1.318 (1.001–1.735)*	1.190 (0.899–1.575)	1.440 (1.037–2.001)*	1.316 (0.938–1.845)	1.064 (0.610–1.858)	0.964 (0.547–1.697)	
≥7 years	1.771 (1.402–2.237)*	1.621 (1.275–2.060)*	1.819 (1.367–2.421)*	1.663 (1.237–2.235)*	1.609 (1.014–2.553)*	1.487 (0.927–2.383)	
Sum number of PTCA and coronary angiography							
0	1	1	1	1	1	1	
1	1.455 (1.220–1.735)*	1.325 (1.102–1.593)*	1.413 (1.130–1.767)*	1.302 (1.029–1.647)*	1.444 (1.054–1.978)*	1.349 (0.973–1.869)	
2	1.689 (1.295–2.201)*	1.523 (1.161–1.997)*	1.739 (1.248–2.423)*	1.594 (1.133–2.241)*	1.850 (1.122–3.048)*	1.622 (0.973–2.703)	
≥3	1.744 (1.255–2.424)*	1.529 (1.094–2.137)*	1.903 (1.298–2.789)*	1.673 (1.129–2.478)*	1.609 (0.759–3.411)	1.401 (0.654–2.999)	

CI = confidence interval, OR = odds ratio, PTCA = percutaneous transluminal coronary angioplasty.

* *P* value < 0.05.

[†] Adjusting for age, hyperlipidemia, diabetes, hypertension, COPD, CAD, and CHF.

[‡] The end of observation period was defined as the last day of the year before a diagnosis of leukemia. The observation period of persons in the control group was the same as their matched leukemia patient.

However, most studies used the methods of presumptive estimation dose-risk—that is LAR (lifetime attributable risk) to estimate the cancer risk.^{7,17} The cancer risk estimations were based on theoretical conjectures, which were mainly derived from observations of effects of radiation in survivors of the Hiroshima/Nagasaki atomic bomb.^{18–20} These estimates may not fit for patients who received cardiac fluoroscopic procedures who are exposed to pure x-rays with an energy spectrum between 40 kV (kilo-volt) and 120 kV. However, the survivors of an atomic bomb or nuclear plant accident are exposed simultaneously to multiple types of radiation sources (including alpha particles, beta particles, and gamma ray) and absorption of radio-isotopes and x-rays in a wide range of different energy levels (from energy levels from kilo-volts to million-volts) at the same time. Therefore, compared to previous studies, our study results are more applicable in clinical practice.

Based on the database of survivors of atomic bombs, radiation-related malignancies have a latency period before tumors develop.^{17,18} This latency period depends upon the cancer types. Hematologic malignancies are the earliest type of radiation malignancies, as early as 2 to 3 years, whereas an excess of solid tumors is observed after >10 years. The effects of age at exposure and sex and in the temporal pattern of risks are also significant. Our data is consistent with the prevalence of hematologic malignancies in atomic bomb survivors.

The difficulties in studying cardiac fluoroscopy-induced radiation carcinogenesis may be due to the fact that radiation-induced cancers are biologically indistinguishable from other extrinsic and intrinsic cancers. Further, the background radiation is omnipresent and is one of the leading causes of leukemia. As radiation-induced tumors cannot be distinguished from tumors in general, only the epidemiologic studies may be best suited to answer this question. However, the risk of radiation would be masqueraded, whereas there were only a small numbers of subjects with cancers related to low-dose radiation as reported in the literature.^{21,22} Our study was a nationwide population-based study which included all patients with leukemia and all hospitals in Taiwan; therefore, this study had a sufficient number of cases for epidemiologic analysis.

To the best of our knowledge, there have been only 2 large-scale studies investigating cancer risk associated with cardiac fluoroscopic intervention. In 2005, Lambe et al²³ reported there was no indication of increased risk of cancer except for a transient excess of lung cancers, following PTCA performed between 1989 and 1998. However, in 2005 the variables associated with these procedures may be much different, as the radiation exposure dose derived from PTCA 10 years ago was significantly less than that it is currently. Radiation dose in each procedure of PTCA in each patient has increased in the last 10 years.²⁴ Furthermore, repeated cardiac fluoroscopy procedures in a short time, as well as considering the procedure length increases the cumulative dose. Therefore, the risk of cancer could be increasing whereas the total radiation exposure is also increasing. In 2013, Hung and Hwang²⁵ used a population database to report elevated risk of breast cancer in female cardiovascular patients and lung cancer in both genders after cardiac radiation exposure, but the risk of leukemia was not elevated. However, leukemia is a relatively rare disease, with incidence ranges between 7.3 and 13.9 per 100,000 people for different races,¹⁵ and the absolute number of leukemia cases among the 1-million-population database is small even though the relative risk could be high. Our study design was case-controlled rather than cohort as previous studies and therefore could find the elevated relative risk of leukemia.

Common risk factors for leukemia and coronary vascular diseases (CVD) may cause statistic bias. Fortunately, none of the major risks of CVD, including diabetes mellitus, obesity, male gender, and hyperlipidemia, are also risk factors for leukemia. Smoking is well known to increase the risk of CVD and cancer, but it does not increase the risk of leukemia. By careful adjustment of basic characters of study and control group, such as age and gender, the bias has been minimized.¹⁵

There are several limitations in our study. First, the radiation exposed dose is not available for calculation in each cardiac fluoroscopic procedure; therefore, the recommendation for a safe limit of radiation exposure for cardiac fluoroscopy procedures cannot be provided. However, our data demonstrated that the risk of leukemia increases with an increasing number of PTCA procedures, suggesting a dose-dependent correlation of radiation dose and risk of leukemia. Second, our study design provided little information about exposure upon the radiation-vulnerable groups, such as children and pregnant women. Because PTCA, indicated for coronary artery disease, had been performed mostly in middle aged to elderly groups, it was unlikely to answer the radiation effect of PTCA upon these vulnerable groups. On the other hand, EPS was performed for patients with a wide age range; but the case numbers of EPS were too small to answer this question based on our data.

CONCLUSIONS

Since the use of cardiac angiographic fluoroscopic intervention in medicine is widespread and appears to be increasing, our study results provide additional data to quantify the long-term health effects of radiation exposure derived from the cardiac fluoroscopic diagnostic and therapeutic intervention. In our study, PTCA alone or PTCA with coronary angiography was associated with an elevated risk of leukemia. Continued follow-up and establishment of cohorts of patients exposed to new or modified diagnostic and treatment protocols may help resolve questions in these emerging areas.

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