RESEARCH ARTICLE

Cancer Risk from Medical Radiation Procedures for Coronary Artery Disease: A Nationwide Population-based Cohort Study

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Abstract

To assess the risk of cancer incidence after medical radiation exposure for coronary artery disease (CAD), a retrospective cohort study was conducted based on Taiwan's National Health Insurance Research Database (NHIRD). Patients with CAD were identified according to the International Classification of Diseases code, 9th Revision, Clinical Modification (ICD-9-CM), and their records of medical radiation procedures were collected from 1997 to 2010. A total of 18,697 subjects with radiation exposure from cardiac imaging or therapeutic procedures for CAD were enrolled, and 19,109 subjects receiving cardiac diagnostic procedures without radiation were adopted as the control group. The distributions of age and gender were similar between the two populations. Cancer risks were evaluated by age-adjusted incidence rate ratio (aIRR) and association with cumulative exposure were further evaluated with relative risks by Poisson regression analysis. A total of 954 and 885 subjects with various types of cancers in both cohorts after following up for over 10 years were found, with incidences of 409.8 and 388.0 per 100,000 person-years, respectively. The risk of breast cancer (aIRR=1.85, 95% confidence interval: 1.14-3.00) was significantly elevated in the exposed female subjects, but no significant cancer risk was found in the exposed males. In addition, cancer risks of the breast and lung were increased with the exposure level. The study suggests that radiation exposure from cardiac imaging or therapeutic procedures for CAD may be associated with the increased risk of breast and lung cancers in CAD patients.

Keywords: Coronary artery disease (CAD) - cardiac imaging - cancer risk - incidence rate ratio (IRR)

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Introduction

Incidence of malignancy has been reported to be correlated to acute radiation exposure. Significantly increased risks of cancers were found in Japanese A-bomb survivors, including esophagus, lung, breast, stomach, liver, colon, gallbladder, ovary and bladder cancers, etc. (Pierce et al., 2000; Preston et al., 2003; Ozasa et al., 2012). The risks of thyroid cancer were increased in Chernobyl residents exposed as children, as well as increased risk of leukemia in Chernobyl cleanup workers (Cardis et al., 2005a; Romanenko et al., 2008). However, the risk of cancer due to the prolonged low-dose radiation exposure has not been proven consistently. This may be contributed by several factors: individualization of radiation dose is difficult, the background radiation is omnipresent, the radiation-induced cancers are biologically indistinguishable from other extrinsic/intrinsic cancers, the risk of intrinsic cancer is high relative to low projected risk of radiation-induced cancer, and appropriate observational number of the subjects with cancers related to low-dose radiation is difficult (Brenner et al., 2003; Mullenders et al., 2009). Nevertheless, excess relative risks for cancers have been reported among workers in the nuclear power plants and residents in the radiocontaminated buildings. About 1-2% of deaths from cancer among the nuclear reactor workers may be attributable to radiation (Cardis et al., 2005b). In Taiwan, the risks of cancers in 7,271 persons received prolonged low dose-rate and low dose for about 10 years due to reside in the buildings containing ^{60}Co-contaminated steels have been estimated. The risks of leukemia and thyroid cancer were increased in the population under 30 years of age at exposure (Hwang et al., 2006).

CAD is diagnosed by electrocardiography (ECG), echocardiography, myocardial perfusion scintigraphy (MPS), coronary angiography (CA), cardiac ventriculography (CV), computed tomographic coronary angiography (CTCA), and treated via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) (Lucas et al., 2006). The effective doses of MPS, CA, CV, CTCA and PTCA are relatively higher than those of other radiological procedures, about 7-40 mSv (Einstein et al., 2007a; Mettler et al., 2008). The increasing utilization of the above procedures may result in the increment of projected cancer risks (Lucas et al., 2006; Einstein et al., 2007b). Justification between the effectiveness obtained from

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medical radiation procedure and the risk of radiation-induced cancer is becoming an important issue. However, little is known about the real correlation between the radiation exposure from these procedures and the risk of cancer incidence.

National Health Insurance (NHI) program in Taiwan has been launched since 1995. It is an unique mandatory health-care system with approximately 100% of the Taiwanese population are enrolled, and covers the vast majority of medical radiation procedures (Chen et al., 2011). A large amount of health-care data are completely collected in the National Health Insurance Research Database (NHIRD). The utilization of medical radiation procedures for diagnosing or treating CAD and their correlation with cancer risks were studied with NHIRD.

Materials and Methods

Study cohorts

A retrospective cohort study was conducted based on the Longitudinal Health Insurance Database 2000 (LHID2000) from NHIRD of Taiwan. One million individuals with random sampling were enrolled in LHID2000. Subjects with CAD were identified by ICD-9-CM code and their records of medical radiation procedures were collected from 1997 to 2010. Only subjects without cancers before medical radiation exposure were included to correlate the effect of radiation on carcinogenesis. According to the medical radiation procedures, subjects who ever received one of the following diagnosis or treatment for CAD: myocardial perfusion scintigraphy (MPS), coronary angiography (CA), cardiac ventriculography (CV), computed tomographic coronary angiography (CTCA) and percutaneous transluminal coronary angioplasty (PTCA) accompanied by any type of medical radiation exposure including medical and dental radiography, conventional and interventional fluoroscopy, and nuclear medicine procedures during the follow-up period were adopted as the exposed cohort. Subjects who ever underwent electrocardiography (ECG) or echocardiography for the diagnosis of CAD, accompanied by most of medical radiation procedures except MPS, CA, CV, CTCA and PTCA were adopted as the control cohort.

The follow-up period of each cohort was calculated from the first time they underwent the medical procedure for CAD in the database to December 31, 2010, the date of cancer identification, or the date of death, whichever came first. According to 1990 Recommendations of the International Commission on Radiological Protection (ICRP 60), the minimum latency period for radiation-induced cancers is ten years. Therefore, subjects with following up for more than ten years were extracted in each cohort, and the "person-years at risk" of these subjects were obtained from the duration of observation. The numbers of subjects in the exposure/control cohort are 18,697 and 19,109, respectively.

Statistical analysis

Descriptive statistics was adopted to analyze the distributions of age, medical radiation procedures and cancers. Analysis of variance (ANOVA) was employed to analyze the difference in the utilization of medical radiation procedures between the two cohorts. The cancer risk after medical radiation exposure for CAD was assessed by incidence rate ratio (IRR) adjusted for age in 10-year intervals, which was calculated from dividing the incidence rate of cancer in the exposed group by the incidence rate of cancer in the control group. The significance of IRR was judged by 95% confidence interval (95% CI). Specific cancer risks associated with cumulative exposure were analyzed by Poisson regression analysis. The numbers of cancer cases at the ith stratum are assumed to follow the independent Poisson distributions with the mean equal to μ_i. The mean at the ith stratum is influenced by three regression parameters in the model:

$$\mu_i = P_i \times \exp[\beta_0 + \beta_1 I(X_{1i}=M) + \Sigma^3_{j=1} \beta_{2j} I(X_{2i}=j) + \Sigma^3_{j=1} \beta_{3j} I(X_{3i}=j)$$

where P_i is the person-years at risk in the ith stratum; I(.) is an indicator function; X_{1i} is a gender variable; X_{2i}=1, 2 and 3 correspond to the average age at examination, i.e. <40, 40-65, and >65 years old, respectively; and X_{3i}=1, 2 and 3 correspond to the cumulative exposed numbers 0, 1-5 and >5, respectively. All statistics was performed by SPSS 18.0 (SPSS Taiwan Crop. Taipei, Taiwan).

Results

The characteristics of study population

The characteristics of study population are listed in Table 1. The total numbers were 10,367 versus (vs.) 8,310 in the male exposed vs. control subjects, while 8,330 vs. 10,799 in the female exposed vs. control subjects. The total person-years at risk were 125,325 and 100,763 in the male exposed/control cohorts; 101,869 and 132,194 in the female exposed/control cohorts, respectively. The total cases of cancer were 565 vs. 433 in the male exposed vs. control subjects; 389 vs. 452 in the female exposed vs. control subjects. Most subjects (93.5%) underwent the medical procedures for CAD over 40 years of age. The average age at examination was 61.5±15.7 and 59.7±15.6 years in the male exposed/control subjects; 63.8±11.6 and 60.6±14.1 years in the female exposed/control subjects, respectively.

Table 1. The Characteristics of Study Population

	Male		Female		Total	
	Exposed	Control	Exposed	Control	Exposed	Control
Number of population	10,367	8,310	8,330	10,799	18,697	19,109
Person-years at risk	125,325	100,763	101,869	132,194	227,194	232,957
Number of cancer case	565	433	389	452	954	885
Average age at examination	61.5±15.7	59.7±15.6	63.8±11.6	60.6±14.1	62.5±13.9	60.2±14.8

The distribution of medical radiation procedures

The medical radiation procedures performed during the follow-up duration are summarized in Table 2. Medical radiography, dental radiography and CT scan were performed most frequently and accounted for more than 80% of total procedures for both cohorts and genders. The average numbers of all medical radiation procedures were 36.9 and 33.5 in the male exposed/ control subjects, and 41.9 and 36.6 in the female exposed/ control subjects. Except cardiac imaging and PTCA, no significant difference in the utilization of medical radiation procedures between the two cohorts was found.

The risks of cancers

The age-adjusted incidence rate ratios (aIRRs) are shown in Table 3. No significant increase of cancer risks

Table 2. The Average Number of Commonly Performed Medical Radiation Procedures

Procedure	Male	Female	Total
Medical radiography	28.4/26.6[a]	34.2/31.2	31.0/29.2
Dental radiography	1.8/1.5	1.5/1.4	1.7/1.4
CT scan	1.5[b]/1.6	1.4[b]/1.3	1.5[b]/1.4
MPS	0.9/-	0.9/-	0.9/-
CA	0.6/-	0.4/-	0.5/-
PTCA	0.5/-	0.3/-	0.4/-
CV	0.5/-	0.4/-	0.5/-
IVU	0.3/0.4	0.2/0.2	0.3/0.3
Lower GI	0.1/0.1	0.1/0.1	0.1/0.1
Upper GI	0.1/0.1	0.1/0.1	0.1/0.1
All procedures	36.9/ 33.5	41.9/ 36.6	39.1/35.3

[a]exposed cohort/control cohort; [b]excluding CT scan for CAD; MPS, myocardial perfusion scan; CA, coronary angiography; PTCA, percutaneous transluminal coronary angioplasty; CV, cardiac ventriculography; IVU, intravenous urography

Table 3. Age-adjusted Incidence Rate Ratio (aIRR) of Cancers

Cancer site	Male				Female				Total			
	aIR*		aIRR	95% CI	aIR		aIRR	95% CI	aIR		aIRR	95% CI
	Exposed	Control			Exposed	Control			Exposed	Control		
Lung	87.7	84.3	1.04	(0.78, 1.38)	56.8	41.4	1.37	(0.95, 1.99)	73.2	60.0	1.22	(0.97, 1.53)
Colon	57.0	53.3	1.07	(0.75, 1.52)	54.6	51.7	1.06	(0.74, 1.50)	56.3	52.4	1.07	(0.84, 1.37)
Liver	54.8	61.9	0.89	(0.63, 1.25)	49.9	53.4	0.93	(0.65, 1.34)	51.8	56.4	0.92	(0.72, 1.18)
Stomach	20.8	20.2	1.03	(0.58, 1.82)	20.2	15.6	1.29	(0.71, 2.37)	20.6	17.8	1.16	(0.77, 1.76)
Bladder	16.4	22.7	0.72	(0.40, 1.31)	4.4	9.4	0.47	(0.16, 1.32)	11.0	15.2	0.72	(0.43, 1.21)
Rectum	15.7	18.8	0.83	(0.44, 1.56)	12.5	14.9	0.84	(0.42, 1.67)	14.3	16.5	0.87	(0.55, 1.37)
Kidney	14.4	19.9	0.73	(0.38, 1.37)	19.8	16.8	1.18	(0.65, 2.15)	16.8	18.0	0.93	(0.60, 1.44)
Skin	13.3	9.4	1.42	(0.65, 3.11)	6.3	11.1	0.56	(0.23, 1.39)	10.2	10.4	0.98	(0.56, 1.72)
Esophagus	12.1	9.6	1.27	(0.56, 2.87)	1.9	2.8	0.67	(0.12, 3.67)	7.6	5.7	1.34	(0.66, 2.74)
Nasopharynx	11.2	5.8	1.92	(0.73, 5.05)	16.2	10.1	1.61	(0.75, 3.42)	12.9	8.4	1.54	(0.86, 2.76)
Oral	10.0	11.9	0.84	(0.39, 1.80)	2.7	1.5	1.84	(0.31, 11.00)	6.9	6.0	1.14	(0.56, 2.31)
Pancreas	7.8	8.3	0.93	(0.37, 2.36)	10.0	9.2	1.09	(0.48, 2.46)	8.9	8.9	0.99	(0.54, 1.83)
Lymphoid	7.7	4.0	1.92	(0.60, 6.12)	6.4	4.9	1.30	(0.44, 3.86)	7.2	4.5	1.58	(0.73, 3.46)
Brain	7.6	12.7	0.60	(0.26, 1.36)	15.0	20.1	0.75	(0.39, 1.43)	10.5	16.8	0.63	(0.38, 1.04)
Bone	3.8	6.4	0.59	(0.18, 1.94)	3.0	4.4	0.70	(0.17, 2.79)	3.3	5.3	0.64	(0.26, 1.56)
Leukemia	3.7	4.4	0.84	(0.19, 3.73)	8.0	6.5	1.22	(0.46, 3.25)	5.8	5.5	1.05	(0.46, 2.38)
Thyroid	0.8	2.1	0.39	(0.04, 4.26)	3.2	5.8	0.54	(0.14, 2.04)	1.8	4.3	0.43	(0.13, 1.36)
Intestine	0.8	1.0	0.78	(0.05, 12.50)	1.9	0.8	2.25	(0.20, 24.79)	1.2	0.9	1.33	(0.22, 7.95)
Prostate	71.3	61.9	1.15	(0.83, 1.59)	-	-	-	-	71.3	61.9	1.15	(0.83, 1.59)
Breast	-	-	-	-	39.7	21.5	1.85[a]	(1.14, 3.00)	39.7	21.5	1.85[a]	(1.14, 3.00)
Cervix Uteri	-	-	-	-	5.5	6.2	0.88	(0.31, 2.55)	5.5	6.2	0.88	(0.31, 2.55)
Corpus Uteri	-	-	-	-	6.4	8.1	0.79	(0.31, 2.03)	6.4	8.1	0.79	(0.31, 2.03)
Ovary	-	-	-	-	22.8	17.1	1.33	(0.73, 2.44)	22.8	17.1	1.33	(0.73, 2.44)
Others	23.5	21.0	1.12	0.63 1.98	12.8	15.6	0.82	(0.41, 1.63)	12.8	15.6	0.82	(0.41, 1.63)
All cancers	440.3	439.7	1.00	(0.88, 1.14)	379.7	348.8	1.09	(0.95, 1.25)	409.8	388.0	1.06	(0.96, 1.16)

*age-adjusted incidence rate; unit: per 100,000 person-years; [a]$p<0.05$

Table 4. Relative Risks (RR) of Specific Cancer by Gender, Average Age at Examination and Exposure Level

	Subjects	Lung cancer			Breast cancer			All cancer		
		N	RR	(95%CI)	N	RR	(95%CI)	N	RR	(95%CI)
Gender										
Male	18,677	193		1	-		-	998		1
Female	19,129	112	0.8	(0.5, 1.1)	67		1	841	0.9	(0.8, 1.1)
Age										
<40	2,458	7		1	3		1	56		1
40~65	18,891	95	1.1	(0.3, 3.6)	37	0.9	(0.1, 6.9)	790	2.9	(0.8, 5.7)
>65	16,457	203	2.5	(0.7, 7.8)	27	0.7	(0.1, 5.5)	993	4.5	(0.5, 9.4)
Number										
0	19,109	134		1	29		1	885		1
1~5	13,294	106	1.9[a]	(1.1, 3.3)	22	1.8[b]	(1.0, 4.1)	657	1.2	(0.9, 1.4)
>5	5,403	65	2.2[a]	(1.2, 3.9)	16	3.3[a]	(1.1, 10.4)	297	1.1	(0.9, 1.4)

[a]$p<0.05$; [b]$0.05<p<0.1$

was found in the male subjects undergoing radiation cardiac imaging or PTCA. Though the aIRRs of cancers of lung, prostate, colon, stomach, skin, esophagus, nasopharynx and lymphoid are higher than one, all 95% CI of aIRRs encompass the unity. Notably, the risk of breast cancer (aIRR=1.85, 95% CI: 1.14-3.00) in women exposed to cardiac radiation procedures are significantly increased. In addition, the aIRRs of cancers of lung, colon, stomach, kidney, ovary, nasopharynx, pancreas, leukemia, lymphoid, oral and intestine are more than the unity, but no significant risk of cancer is found.

The exposure-dependent cancer risks were further evaluated by Poisson regression analysis as shown in Table 4. The relative risk (RR) of lung cancer is significantly increased for those cumulated more than 5 cardiac diagnostic/therapeutic procedures and those with 1-5 procedures as compared with those never received cardiac exposure (RR=2.2 and 1.9, 95% CI: 1.2-3.9 and 1.1-3.3, respectively). Additionally, exposure-dependent risk was found in breast cancer among those cumulated more than 5 procedures and 1-5 procedures as compared with those with no cardiac exposure (RR=3.3 and 1.8, 95% CI: 1.1-10.4 and 1.0-4.1, respectively). However, no significant exposure-dependent risks were found for other cancers and all cancers combined.

Discussion

The collection of nationwide data, NHIRD, is free from the potential bias resulting from the small sample sizes and the limited demographic scope. In addition, applying the database can avoid missing the radiological records or recall bias over the follow-up duration. Thus, this study can be considered as an accurate assessment for medical radiation-related cancer risks.

The exposed cohort received prolonged medical radiation exposure in this study is similar to the population exposed to the low dose-rate γ-radiation in radiocontaminated buildings in Taiwan, but differs from the A-bomb survivors who received the acute radiation exposure. Different from the residents in the radiocontaminated buildings, the cohorts studied here consist primarily of the senior population. Nevertheless, our results demonstrate that multiple medical radiation exposures for CAD may increase the risk of specific cancers.

In this study, we evaluated the cancer risks after radiation diagnostic or therapeutic procedures for CAD. Such analysis could limit the probability of work-up bias, because these medical radiation procedures are seldom indicated for the work-up of cancer. Also, except cardiac procedures, radiation from noncardiac procedures were similar between the exposed and control cohorts. Thus, the result should be able to reflect the effects of cardiac radiation exposure on carcinogenesis specifically. In addition, since the latent period for the most radiation-related cancers is 10 or more years, the follow-up for the incident cancers is more than ten years after undertaking the first medical radiation procedure in the database. This time lag could minimize the spurious association between irradiation and cancer occurrence soon thereafter.

Other common risk factors for CAD are physical inactivity, obesity, hypertension, high blood cholesterol, diabetes, smoking, age and gender, in which the last three factors could also contribute to the risk for developing cancers. Therefore, the CAD subjects received cardiac diagnostic procedures without radiation are adopted as the positive control cohort to compare with the exposed CAD subjects with the similar distributions of risk factors for the cancer-risk assessment.

Significantly elevated risk of the breast cancer was found in the female CAD patients after cardiac radiation exposure in this study. This could be due to the high radiosensitivity of breast whose tissue weighting factor is 0.12 (ICRP 2007) and breast is within the high-exposed area from cardiac radiation procedures. Similarly, the increased breast cancer risk among women who had undergone multiple chest radiography or mammography was found (odds ratio [OR] = 1.80, 95% CI: 0.95-3.42) in 1,742 population-based case patients aged 20-49 years and 441 control subjects identified from neighborhoods of case patients in Los Angeles County (Ma et al., 2008). The possible mechanism has been suggested to be an interaction between the rs5277 variant in PTGS2 gene and the radiation-related breast cancer risk among 859 breast cancer cases and 1,083 controls nested within the US radiological technologists cohort (Schonfeld et al., 2010). The mechanism of radiation-related breast cancer in this study, however, is needed to be further investigated.

Several limitations in this study should be noted. Firstly, lack of individual radiation doses for the CAD patients, so we adopted exposure number instead of exposure dose to analyze the cancer risks. Secondly, lack of information on other confounding risk factors related to the lifestyle, particularly smoking, might lead to the random measurement bias. In this study, we chose the CAD subjects received non-radiation cardiac diagnostic procedures as the control cohort, and assumed the distribution of smoking subjects were similar in both cohorts to limit this bias. Thirdly, lack of detailed records of medical radiation procedures before 1997 may result in information or misclassification bias. Nevertheless, the tendency of using medical radiation procedures in both cohorts before and after 1997 would not be changed significantly since the accessibility was promoted for everyone after the initiation of the NHI program. Fourthly, because the latent period for most radiation-related cancers is 10 or more years, the average follow-up period of 12 years was not long enough to observe the development of the whole spectrum of cancers in this study. Therefore, continuous follow-up to verify our findings and identify other types of cancers related to the cardiac radiation exposure is needed.

In conclusion, exposure to ionizing radiation from cardiac imaging or therapeutic procedures for CAD may be associated with the increased risks of breast and lung cancers in the CAD patients, especially in those with high exposure levels. Thus, these medical radiation procedures for the patients should be taken with more consideration, at least prospectively documenting the cardiac imaging and therapeutic procedures that each patient has undergone and estimating the cumulative exposure to ionizing radiation.

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