RESEARCH ARTICLE

Nested Case-control Study of Occupational Radiation Exposure and Breast and Esophagus Cancer Risk among Medical Diagnostic X Ray Workers in Jiangsu of China

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Abstract

Medical diagnostic X-ray workers are one occupational group that expose to the long-term low-dose external radiation over their working lifetime, and they may under risk of different cancers. This study aims to determine the relationship between the occupational X-ray radiation exposure and cancer risk among these workers in Jiangsu, China. We conducted Nested case-control study to investigate the occupational X-ray radiation exposure and cancer risk. Data were collected through self-administered questionnaire, which includes but not limits to demographic data, personal behaviors and family history of cancer. Retrospective dose reconstruction was conducted to estimate the cumulative doses of the x-ray workers. Inferential statistics, t-test and 2 tests were used to compare the differences between each group. We used the logistic regression model to calculate the odds ratio (OR) and 95% confidence interval (CI) of cancer by adjusting the age, gender. All 34 breast cancer cases and 45 esophageal cancer cases that detected in a cohort conducted among health workers between 1950~2011 were included in this presented study, and 158 cancer-free controls were selected by frequency-matched (1:2). Our study found that the occupational radiation exposure was associated with a significantly increased cancer risk compared with the control, especially in breast cancer and esophageal cancer (adjusted OR=2.90, 95% CI: 1.19-7.04 for breast cancer; OR=4.19, 95% CI: 1.87-9.38 for esophageal cancer, and OR=3.43, 95% CI: 1.92-6.12 for total cancer, respectively). The occupational X-ray radiation exposure was associated with increasing cancer risk, which indicates that proper intervention and prevention strategies may be needed in order to bring down the occupational cancer risk.

Keywords: Nested case-control study - occupational radiation - medical diagnostic X ray workers - cancer risk

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Introduction

The only confirmed fatal health hazards of human induced by low dose radiation is the ionizing radiation carcinogenesis (Charles, 2001). Although the radiation does not play so prominent role as chemical carcinogen in all human cancer causes, due to the application of nuclear technology in human production and life, especially in medical diagnosis and treatment field occupies a more and more special position, the potential hazards of radiation on humans are increasing. Therefore, research on the relationship between radiation and cancer has been the oncology, radiation biology, radiation protection and epidemiological research focus (Thompson et al., 1994; Sun et al., 1996; Yu et al., 2001; Wang et al., 2002). Number of animal studies confirmed that long-term low dose radiation exposure may induce tumorigenesis (Hattori et al., 1988; Yoshida et al., 1997; Nishimura et al., 1999; Saito et al., 2001). However, due to the presence of species, individual and organization-specific genetic differences, it is not yet established *in vitro* study using the theoretical model to evaluate its relationship with human tumors. Epidemiological studies of radiation carciongenesis are important in order that people exposed to man-made sources radiation should be protected from its harmful effects, and human carcinogenic risk of radiation research mainly based on it.

Early studies, staring with the ongoing cohort study on the Japanese bomb survivors, focused on acute exposures to high doses of radiation and became the most important information on quantitative estimates of radiation-related cancer risk. Shimizu et al. (1990) conducted a follow-up study on Nagasaki, Hiroshima atomic bomb survivors long-term effects from 1950 to 1985 found that the

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incidence of solid cancer began to dramatic rise, and the increased incidence of breast cancer among women is particularly prominent. However, it may not be possible to extrapolate directly from the effects of acute high doses to the long-term low-dose ionizing radiation exposure.

Medical diagnostic X-ray workers are one occupational group that expose to the long-term low-dose external radiation over their working lifetime, and they may under risk of different cancers. Word widely, there are over 2.3 million medical radiation workers, and about half of their work time is exposed to human-made sources of low-dose radiation (Yoshinaga et al., 2004). However, the lack of information on individual radiation doses of previous studies limited the findings. Therefore, there is a pressing need to conduct relevant studies among medical radiation workers to address this identified issue.

A cohort study was conducted on survival and cancer incidence among medical diagnostic X ray workers during 1950~2011 in Jiangsu, China. Based on this finished cohort study, a nested case control study was conducted, in order to investigate the occupational X-ray radiation exposure and cancer risk, particular for breast and esophageal cancers, two cancers which were considered to be sensitive to ionizing radiation (Thompson et al., 1994; Wang et al., 2002).

Materials and Methods

Study population

A cohort study involving healthcare workers was conducted in 13 cities of Jiangsu province, from 1950 to 2011. We selected the medical diagnostic X-ray workers working at the department of radiology in selected hospitals from 1950 to 1980 as the radiology group (3,961subjects until June 30, 2011). Control group were those medical workers who were selected from the department of internal medicine, ENT, pediatrics, who had not engaged in radiation work in the same hospital during the same period (3,742 subjects until June 30, 2011).

All 34 breast cancer cases (ICD-10 34) and 45 esophageal cancer cases (ICD-10 25) that detected in the designed cohort conducted between 1950 and 2011 were selected into this nest case control study. In order to be an eligible cancer case, a clear diagnosis hospital, date of diagnosis or the basis of diagnosis were needed. In total, there are 79 cancer patients in the case group. We randomly selected 158 cancer-free controls by using cumulative (case-non-case) sampling strategy at the end of the study (June 30, 2011), by frequency-matched (1:2), which was matched on gender, age (±5 years), age at participate in the work (±5 years) and residential area, while exposure status was not matched.

After informed consent was obtained, we interviewed the subject, or his relatives, or other insiders by trained interviewers using a pre-tested standard questionnaire to obtain information on demographic data, disease history, personal habits, environmental exposure history, and family history of cancer in first-degree relatives (parents, siblings and children). We used the following order to select respondents: respondents themselves, their spouses, their children, their colleagues and other insiders.

We tried to make the survey content comprehensive and concise and all investigators had been accepted the epidemiologists and psychologists training. We unified the investigation standards and selected investigator who had passed the qualified test.

Ethical consideration

This study was approved by the Survey and Behavioral Research Ethics Committee of the Jiangsu Provincial Center for Disease Prevention and Control. Respondents were assured of their information and confidentiality, and they were informed of their right to withdraw from the study at any time. Informed consent was obtained prior to data collection.

Retrospective dose reconstruction

Before 1985 there was no individual dose monitoring system for Chinese medical x-ray workers. In order to estimate the accumulative dose for the x-ray workers, the main characteristics of the occupational exposure were investigated. Exposure doses at x-ray machines and workplaces were measured by simulating the past working conditions. The x-ray workers were chosen by stratified random sampling method and interviewed concerning the details of their occupational histories. A mathematical model and computerizing system for dose reconstruction of occupational exposure were designed and developed (Zhang L, 1998). Using these data and methods, we estimated the reconstructed average annual dose and cumulative doses of the x-ray workers by calendar year of initial employment.

Statistical analysis

Data were entered by double-entry and passed the consistency test by Epidata 3.02. All data analyzes were performed by using SAS 9.1 SAS Institute, Cary, NC, USA and stata13.0. Descriptive statistics, which include means and standard deviations, were used to summarize the demographic data. Inferential statistics, t-test and 2 tests were used to compare the differences between each group. We used the logistic regression model to gain the odds ratio (OR) and 95% confidence interval (CI) by adjusting the age, gender, which were consider to be two important confounders between cancer and radiation.

In the original study, information regarding smoking and alcohol drinking, two important potential confounders were not completely collected. To solve this problem, we performed sensitivity analysis to further adjust for these two variables. The detailed assumption and SAS code for sensitivity analyses are presented in supplementary information A.

Results

Table 1 shown us the characteristics of the 79 cancer cases and 158 cancer-free controls, including 34 breast cancer cases and 68 controls, 45 esophageal cancer cases and 90 controls. The cases and controls appeared to be adequately matched on age and age at participate work in each group. As shown in Table 1, there were no significantly differences between the cases and controls

Table 1. Distributions of Select Variables in Cancer Cases and Controls

Variables	Case	Control	P[a]
Breast cancer	N=34	N=68	
Age, yr (Mean±SD)	70.41±8.72	69.28±7.81	0.508
Age at participate in the work, yr (Mean±SD)	24.32±5.08	23.93±4.54	0.69
Age at menarche, yr (Mean±SD)	15.06±1.65	15.5±1.75	0.432
Age at marriage, yr (Mean±SD)	26.38±3.34	25.00±2.75	0.412
Age at menopause, yr (Mean±SD)	50.33±4.50	52.86±5.19	0.138
Age at first live birth, yr (Mean±SD)	27.06±2.77	26.00±3.04	0.277
Abortion			
Negative	6	10	0.752
Positive	10	13	
Breastfeeding			
Negative	4	3	0.415
Positive	12	20	
Oral contraceptives			
Negative	12	20	0.415
Positive	4	3	
Family history of cancer			
Negative	3	6	0.717
Positive	13	18	
Esophageal cancer	N=45	N=90	
Age, yr (Mean±SD)	72.27±9.36	71.74±7.99	0.736
Age at participate in the work, yr (Mean±SD)	28.80±6.87	27.63±4.95	0.181
Smoking			
Negative	13	22	0.242
Positive	15	14	
Drinking			
Negative	12	20	0.383
Positive	15	16	
Family history of cancer			
Negative	20	27	0.933
Positive	7	9	
Total cancer	N=79	N=158	
Age, yr (Mean±SD)	71.49±9.02	70.58±7.99	0.477
Age at participate in the work, yr (Mean±SD)	26.9±6.53	26.08±5.12	0.259
Family history of cancer			
Negative	23	31	0.997
Positive	20	27	

[a]Two-sided *p* value from c2test or t test for difference in frequency distribution between cases and controls

Table 2. Logistic Regression Analyses on Associations between Radiation Exposure and Cancer Risk

Variables	Cases	Controls	P[a]	Crude OR (95%CI)	Adjusted OR (95%CI)[b]
Breast cancer					
non-radiology	18	52	0.018	1	
radiology	16	16		2.89(1.20-6.94)	2.90(1.19-7.04)
Esophageal cancer					
non-radiology	14	56	0.001	1	
radiology	31	34		3.65(1.70-7.81)	4.19(1.87-9.38)
Total cancer					
non-radiology	32	108	0.001	1	
radiology	47	50		3.17(1.81-5.56)	3.43(1.92-6.12)

[a]Two-sided c2 test for difference in frequency distribution between cases and controls; [b]Adjusted for age, gender

Table 3. Correlation between Health Work Environmental Radiation and Cancers after Sensitivity Analysis

Variables	Model 1[a]	Model 2[b]	Model 3[c]
Breast cancer	2.76 (1.20-9.84)	2.84 (1.20-10.11)	2.70 (0.97-12.14)
Esophageal cancer	4.00 (1.88-12.64)	4.10 (1.88-12.99)	3.92 (1.55-15.28)
Total cancer	3.27 (1.93-7.50)	3.36 (1.93-7.69)	3.12 (1.66-8.23)

[a] Model 1 was adjusted for smoking, [b]model 2 was adjusted for alcohol, and [c]model 3was adjusted for both smoking and alcohol

in the median age at menarche, median age at marriage, median age at menopause, median age at having first live birth, smoking, drinking and family history of cancer.

For the breast cancer group, the proportions of abortion history were 43.5% in case group and 37.5% in control group, while the average ages at first abortion were 30.0

and 26.6 years old respectively. The breastfeeding rates were 75.0% in case and 87.0% in control, while the oral contraceptive using rates were 25.0% and 13.0% respectively. For the esophageal cancer group, the proportions of smokers were 53.6% in case group and 38.9% in control group, while the average ages of smoking initiation were 21.8 and 23.8 years old respectively. About 55.6% were drinkers in case group, while about 44.4% were drinkers in control group, with the average ages of drinking initiation at 24.3 and 23.8 years respectively.

Results from logistic regression shown that the occupational radiation exposure was significantly associated with an increased cancer risk, compared with the control (adjusted OR=2.90, 95% CI: 1.19-7.04 for breast cancer; OR=4.19, 95%CI: 1.87-9.38 for esophageal cancer, and OR=3.43, 95%CI: 1.92-6.12 for total cancer, respectively).

After further adjusted for both smoking and alcohol (model 3 in Table 3), we found that health work environmental radiation was highly related to breast cancer, esophageal cancer and total cancers, even the 95% CI of breast cancer includes one.

To further analyze whether there is a dose-response relationship between occupational radiation dose and cancer, we conducted stratified analysis focused on the objects had occupational radiation exposure (radiology staff). Finally, we collected all 97 radiology staff, including 50 cancer cases and 47 controls with cumulative doses data. The distributions of cumulative dose in radiology group between cancer cases and controls were shown in Table 4 and Figure 1. From the Table 4 and Figure 1, we can found that both the P50% and Mean of cumulative doses in case group are higher than control in each cancer group. Multivariate logistic regression analyses results between variant levels of cumulative dose and cancer risk were shown in Table 5. We stratified the dose group by P25% and P75% of cumulative dose in each cancer group respectively. Although we failed to find any significant association between variant levels of cumulative dose and cancer risk, as the dose increasing, we found that the odds ratio (OR) were rising in each cancer group.

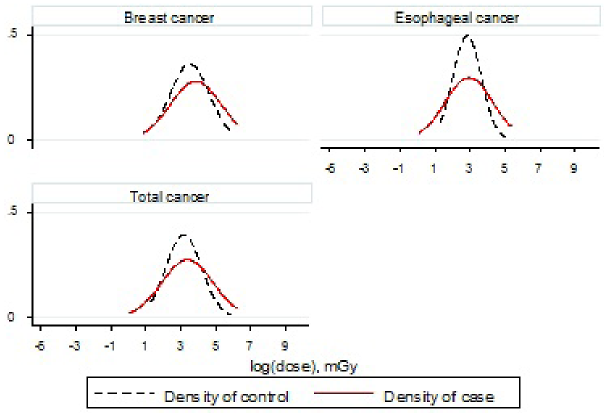

Figure 1. The Normal Distributions of Cumulative dose (log (dose)) in Radiology Group between Cancer Case and Controls

Table 4. Distributions of Cumulative dose in Radiology Group between Cancer Cases and Controls

Group		Cumulative dose (mGy) Case	Control
Breast cancer	P50%	31.23	18.11
	Mean	116.49	39.14
Esophageal cancer	P50%	24.29	16.92
	Mean	66.09	24.76
Total cancer	P50%	23.28	21.03
	Mean	76.27	44.99

Discussion

In this nested case-control study, we estimated the associations between occupational X-ray radiation exposure and risk of cancer, especially breast cancer and esophageal cancer among Chinese medical diagnostic X ray workers. We found that the long-term low dose occupational X-ray radiation exposure was significantly associated with cancers, especially breast cancer and esophageal cancer, which may indicate that occupational X-ray radiation play an important role in cancer development.

Epidemiological studies have been carried out in several countries for investigation of cancer risk among medical radiation workers, such as radiologists studied in

Table 5. Logistic regression analyses on associations between different cumulative doses in radiology group and cancer risk

Cumulative dose group (mGy)	Cases	Controls	P	Crude OR (95%CI)	Adjusted OR (95%CI)[f]
Breast cancer					
<16.73[a]	4	5		1	1
16.73~100.08[b]	6	7	0.745[d]	1.07 (0.19-5.91)	1.07 (0.18-6.39)
≥100.08[c]	6	4	0.170[e]	1.88 (0.30-11.63)	1.48 (0.21-10.20)
Esophageal cancer					
<12.10[a]	8	8			
12.10~27.49[b]	16	15	0.944[d]	1.07 (0.32-3.57)	1.02 (0.30-3.45)
≥27.49[c]	10	8	0.224[e]	1.25 (0.32-4.83)	1.26 (0.28-5.55)
Total cancer					
<13.11[a]	11	13		1	1
13.11-63.68[b]	24	26	0.319[d]	1.09 (0.41-2.90)	1.12 (0.42-3.02)
≥63.68[c]	15	8	0.124[e]	2.22 (0.68-7.18)	2.62 (0.66-10.35)

[a]Stratified by the P25% of cumulative dose; [b]Stratified by the P25% ~P75%of cumulative dose; [c]Stratified by the P75% of cumulative dose; [d]Two-sided c2 test for difference in frequency distribution between cases and controls; [e]P trend for cumulative dose between cases and controls; [f]Adjusted for age, gender

the UK(Doll, 2005) and the U.S (Matanoski et al., 2008), radiological technologists studied in the U.S (Little et al., 2014; Moskowitz et al., 2014) and Japan (Yoshinaga et al., 1999), and radiotherapy staff studied in Denmark (Andersson et al., 1991). Breast cancer is believed to be one of the most readily caused by ionizing radiation (Snijders et al., 2012). It seems likely that female breast cancer is related to occupational x-ray exposure, and, as the literature suggests, fractionation of the dose cannot appreciably lower the risk of radiogenic breast cancer (Boice et al., 1991; Howe et al., 1996).

The risk of esophageal cancer was also significantly elevated among the medical x-ray workers, and increased risk of esophageal cancer has been reported among those who exposed to high dose radiation, such as atomic bomb survivors (Little et al., 1999). The elevated OR of esophageal cancer among the medical x-ray workers with long-term low dose external radiation also demonstrated that cumulated and long-term ionizing radiation might bring up cancer risks.

In addition, it has increasingly been recognized that gene mutation may increase cancer risk. A large number of researches show that human peripheral blood lymphocytes hypoxantine-guanine phpsphoribosyl transferase (HPRT) gene, which is a chemical and ionizing radiation sensitive mutagen loci (Nicklas et al., 1991; Zimmer et al., 1997; Hamdan et al., 1999; Helleday et al., 2000), was closely related to the p53 and bcl-2 gene (Liu et al., 1997; Phillips, Gebow et al., 1997), which had been demonstrated strongly association with cancer development (Murray et al., 2012; Zeestraten et al., 2013),especially with breast cancer and esophageal cancer (Bellini et al., 2012; Walerych et al., 2012). Therefore, it is worthy to emphasize that the occupational X-ray radiation exposure might interact with phosphoribosyl gene mutation contribute to cancer susceptibility. Further well-designed large studies, particularly refer to gene-radiation exposure interactions were warranted to confirm the real contribution of occupational X-ray radiation exposure in cancer development.

Although this study has many interesting findings, limitations of this reported study limited our ability to assess cancer risks. First, there were only 79 selected cancer cases. Despite the original cohort had relatively large sample size, the total number of cancer cases is still small, because of the lower cancer incidence rate. This small sample size may limit our ability to detect the correlation between interested exposure and selected cancers, due to the lack of power. Second, our study may be biased by some unmeasured (for example, smoking and drinking, obesity and night shift work) and unknown confounders, which further limited our ability to explore the true correlation between the interested cancers and radiation, even we conducted sensitivity analysis based on literatures.

In conclusion, our present study found that the long-term low dose occupational X-ray radiation was associated with increasing cancer risk, especially for breast cancer and esophageal cancer. This indicated that proper prevention and intervention strategies are needed to bring down the cancer risk among health care workers who exposed to occupational radiation. Further long-follow up time cohort study with completed individual dosimetry data is called to confirm the association between occupational X-ray radiation exposure and cancer risk. In addition, mechanism studies that focus on pathogenesis of radiation carcinogenesis effect, especially on breast cancer and esophageal cancer, and interaction research on radiation and genetic factors to cancer development are needed.

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