Int J Clin Exp Pathol 2016;9(11):11897-11903
www.ijcep.com /ISSN:1936-2625/IJCEP0031563

Original Article

Risk of developing cancers due to low-dose radiation exposure among medical X-ray workers in China-results of a prospective study

Furu Wang[1*], Quanfu Sun[2*], Jin Wang[1], Ningle Yu[1]

[1]Jiangsu Provincial Center for Disease Prevention and Control, 172 Jiangsu Road, Nanjing 210029, China; [2]National Institute for Radiological Protection, China CDC, Beijing 100088, China. [*]Equal contributors.

Received May 2, 2016; Accepted May 20, 2016; Epub November 1, 2016; Published November 15, 2016

Abstract: Previous studies have reported that occupational exposure to radiation has predisposed the workers to various types of cancers. The current study was done to determine the relative risk of developing different types of cancers among medical X-ray workers in China. We adopt cohort study to investigate the incidence of cancer among 3,961 medical diagnostic X-ray workers and 3,742 medical workers who were not engaged in radiation work during 1950~2011 in Jiangsu, and analysis the relative risk (RR) of cancer by Poisson regression model. We found the significant relationship between the risk of malignant tumor and occupational radiation factor (RR = 1.31, 95% *CI*: 1.11-1.55 for solid cancer and RR = 1.33, 95% *CI*: 1.13-1.57 for total malignant tumor). In addition, the risk of lung cancer in medical diagnostic X-ray workers was significantly higher than that in control group (RR = 1.45, 95% *CI*: 1.00-2.09).

Keywords: Cancer, occupational exposure, radiation, risk factor, X-ray

Introduction

Chinese occupational health experts are intensifying efforts to improve workers' health and establish a modern occupational health program. The use of diagnostic and therapeutic procedures in radiology and nuclear medicine in China has increased continuously with the annual per capita dose doubling over the past two decades [1]. Increases in PET imaging and bone scans were the major contributors to the increasing frequency and magnitude of radiation exposure to the population. There is reported increase of the occupational diseases such as occupational lung disease, occupational cancer, heavy metal poisoning, industrial chemical poisoning, and physical factor-induced diseases (noise and heat) have all been on the rise and thus targeted for expanded research, which will serve as a basis for standard setting. Previous studies have shown that occupational exposure to radiation has predisposed the workers to various types of cancers. However, the findings have been inconclusive. Hence, our current study explored to determine the risk of incidence of various types of cancers due to radiation exposure among the health staff working in hospitals. The objective of the study was to determine the relative risk of developing different types of cancers among the health staff working in environments exposed to radiations.

Materials and methods

Recruitment

The study explored to examine correlation between environmental radiation at hospital workplace and different kinds of cancers. In 1981, a total of 7634 eligible healthcare workers from hospitals of Jiangsu province were recruited for a follow-up study. Participants were eligible for enrollment if they started working in the selected hospital between January 1, 1950 and December 31, 1980. The potential participants belonged to the departments of radiology, Internal Medicine, Ear-Nose-Throat (ENT) or Pediatrics. The eligibility criteria included possession of clear medical record, free of

Table 1. Demographic characteristics and exposure status of the recruited medical workers in Jiangsu, China (N = 7703), 1950-2011

Variable		Exposure status	Number	Person-time	Mean	SD
Exposure status		Exposed	3961	149089		
		Unexposed	3742	166220		
		Total	7703	315309		
Gender	Male	Exposed	3299	123622		
		Unexposed	2610	116733		
		Total	5909	240355		
	Female	Exposed	662	25467		
		Unexposed	1132	49487		
		Total	1794	74954		
Age at the end of the study		Exposed			67.4	8.8
		Unexposed			71.6	9.4
		Total			69.4	9.3
Age at the recruitment		Exposed			27.1	6.4
		Unexposed			23.6	5
		Total			25.4	6

any kind of cancers at the time of recruitment or within first five years thereafter. After the recruitment, the participants were divided into two groups based on their working environment. Among them, 3919 persons were involved in the job of diagnostic X-ray imaging in the department of radiology of the selected hospitals and were assigned into exposure group while the other 3715 participants were assigned into non-exposure group. In order to reduce the potential of survival bias, the medical records of those workers, who died or was diagnosed with any kind of cancer between 1950 and 1980 were also collected and used to gather relevant information on socio-demographics, occupational details and exposure to low-dose ionizing radiation. A structured questionnaire was used to collect information regarding socio-demographic, occupational and low dose ionizing radiation exposure, by face-to-face interview.

Follow up

After the baseline survey, all the cancer free participants were encouraged to attend the four follow up surveys which conducted at 1986, 1991, 1996 and 2011 respectively. The current study reported the data collected between 1981 and 2011. During the follow up period, information regarding whether the participants were diagnosed with any kind of cancer was collected. When the participant reported that he/she was diagnosed for any kind of cancer during the study period, information on the tumor type, date of diagnosis and stage of the disease during diagnosis was also collected. If any participants were censored, their medical histories were collected from the selected hospital, to investigate whether they were dead. If they were dead during the study period and censored, their medical history, likely cause of death and date of death were collected from the record system of the corresponding hospital. In our study, loss to follow up was defined as the participant whose contact was lost, and relevant medical and death record could not be accessed/found.

Measures

The person-time of stay in the study for each participant was calculated. If the participants stayed in the study and did not develop any kind of cancers during the study period, their person-times were calculated as the time from joining the work to the last follow up. If a participant were dead for other reasons except cancers, the time periods between the date of joining the work and death were taken as his/her person-time. If a participant was lost to follow up, the time period between the latest follow-up and date of joining the work was treated as his/her person-time.

During the study period, if any participant was diagnosed with any kind of cancer, the first diagnosed cancer was defined as his/her outcome, according to ICD 10 and the details of time, basis and healthcare provider involved in diagnosis were recorded by asking the participants and/or checking the medical records. Mode of diagnosis included: pathological/surgical/radiological/clinical. The time period between the time that the first cancer was diagnosed and date of joining the work was treated as his/her person-time. In our study, solid can-

Table 2. Number of tumor/cancer, death and cancer related death among participants in a cohort that involved in health worker in Jiangsu, China (N = 7703), 1950-2011

Variable	Exposure status	Number	Percentage (%) (%)
Tumor	Exposed	444	11.21
	Unexposed	375	10.02
	Total	819	10.63
Malignant tumor/Cancer	Exposed	415	10.48
	Unexposed	356	9.51
	Total	771	10.00
Death	Exposed	587	14.82
	Unexposed	618	16.52
	Total	1205	15.64
Cancer related death	Exposed	296	7.47
	Unexposed	257	6.87
	Total	553	7.18

Table 3. Tumor diagnosis evidence in a cohort involving health workers in Jiangsu, China (N = 7703), 1950-2011

Diagnosis method	Number	Percentage
Pathological/cellular/surgical evidence	610	74.48
Radiological, CT and ultrasound evidence	195	23.81
Clinical symptoms	14	1.71
Total	819	100

cer was defined as all the malignant tumors that occurred except leukemia.

Statistical analysis

Data was double-entered using the software EpiData 3.0 [2] and multiple logic checks were used to ensure the quality of data. SAS version 9.1 [3] and STATA version 13.0 were used for data analysis. Descriptive analyses were conducted to determine the distribution of the demographic factors, cancer prevalence and the evidence to judge the state of the related cancers. In addition, we performed Poisson regression model to analysis the relative risk (RR) and 95% confidence interval (CI) of the exposure by using the following model: $e^{(\alpha*gender+\beta*age+\gamma*exposed)}$, adjusted by, age, working time and gender. In this model, exposure refers to the exposure status of the participants (1 = exposed, 0 = unexposed).

Since the working environment changed a lot and different kinds of protection equipments were implemented, the interested exposure may have different effect on the participants that started to work at different time, we further performed stratified logistic regression analysis to know the relative risk of working environmental radiation on different kinds of cancers. We stratified on age that started to work (less than 15/15-18/19-24/25-29/30 or more) and the year started to work (before 1960/1960-1969/1970 and later). In stratified analysis, due to the limited number of cancer cases, we only selected lung cancer, solid cancer and all cancers as the outcomes. Gender and aged were further adjusted in the stratified analysis.

Ethical statement

The study process and content were approved by the Ethical Committee of Jiangsu Provincial Center for Disease Prevention and Control (JSCDC). Signed informed consent was obtained from each participant or their legally authorized representatives (if subjects were sick/dead) prior to the interviews/medical record checking. Each of the participants had the discretion to freely decline or withdraw from this survey at any point of time. The filled-in questionnaires, written consent documents and computerized data were properly secured.

Results

Demographic characteristics and exposure status

Between the year of 1950 and 2011, overall of 7703 healthcare workers were recruited and followed up, with a total person-time of 315,309 person years. Among them, 3961 were categorized as exposed to long-term low dose ionizing radiation while 3742 were unexposed. In our study, only 533 participants were lost-to-follow-up (259 among exposed and 274 among unexposed), with an overall retention rate of 93.1% (overall lost-to-follow-up being only about 6.9%).

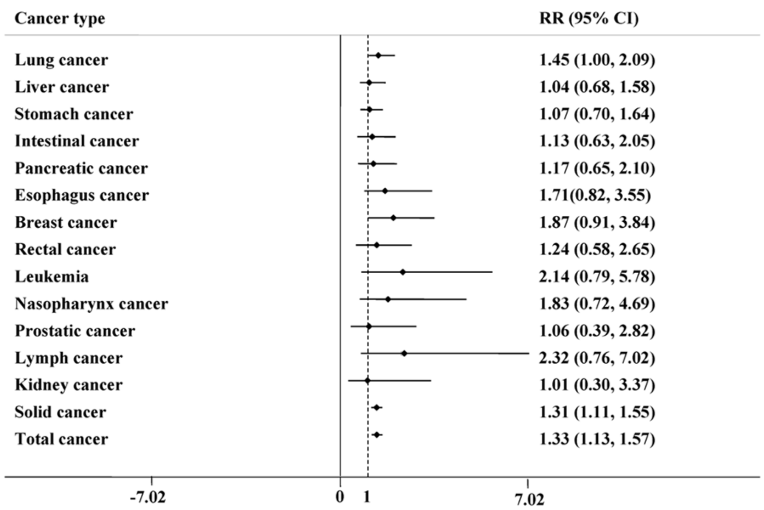

Figure 1. The results of logistic regression of the cancer relative risk (RR).

The mean age of the participants at the time of the recruitment (time of joining the work) was 25.4±6.0 years old, while the mean age in the exposure group was a little higher (27.1±6.4 years old in the exposed group and 23.6±5.0 years old in the unexposed group). However, at the end of the follow up, the mean age of unexposed group was higher than exposed group (71.6±9.4 VS 67.4±8.8), while the overall mean age at the end of the study was 69.4±9.3. **Table 1** presents the demographic information of the participants.

Cancer incidence proportion and tumor diagnosis evidence

In our study, during the follow up period, a total of 819 tumor cases were identified, with an overall tumor incidence proportion of 10.63%. Among these 819 tumor cases, 771 (94.14%) were malignant tumors (cancers) of which, 444 belong to the exposure group (415 malignant tumor/cancer cases), with a tumor incidence proportion of 11.21% (444/3961). A total of 375 tumor cases were identified in non-exposure group (356 malignant tumor cases), with a tumor incidence proportion of 10.02% (375/3742) (**Table 2**). **Table 2** presents the total number of death in both exposed and unexposed group. From the table, we can know that about half (553/1205) of the observed deaths were related to different kinds of cancers. In our study, the detailed evidence to diagnose the cases included pathological, cellular and surgical evidence (610 cases, 74.48%), radiological, CT and ultrasound evidence (195 cases, 23.81%), and clinical symptoms (14 cases, 1.71%) (**Table 3**). Among the cancer cases, the top five cancers were lung cancer (83 VS 71 between exposed and unexposed group), liver cancer (67 VS 55), stomach cancer (60 VS 60), colorectal cancer (22 VS 25) and pancreatic cancer (21 VS 25), which accounted for about 64.72% of the overall malignant tumors. In addition, 34 breast cancer (16 VS 18) and 23 (14 VS 9) leukemia were also found in our study.

Exposure relative risk

The results of logistic regression demonstrated that even after controlling for age, gender, the working age, the exposure group had higher risk in develop lung cancers, with RR of 1.45 (95% CI: 1.00-2.09) (**Figure 1**). In addition, working environmental exposure had a significantly positive association with solid cancers (RR=1.31, 95% CI: 1.11-1.55) and all cancers (RR=1.33, 95% CI: 1.13-1.57). Our study also found that radiation was positively associated with breast cancer, esophagus cancer, leukemia and lymphoma, even though they were not significant.

In stratified analysis, after stratification on the age at which started working, we found that the participants who started to work at about 15-18years of age had the highest relative risk in development of lung cancer (RR = 3.21, 95% CI: 1.25-8.28). For solid cancer and overall cancer, significantly positive associations were found in 25-29 age group, with RR for solid cancers and overall cancers of 1.40 (95% CI: 1.06-1.85) and 1.40 (95% CI: 1.07-1.85), respectively (**Table 4**).

In the models that stratified on the age at which started to work, we found that the interested exposure was significantly positive associated with lung cancer among participants who started to work between the years of 1960-1969. For solid cancer and overall cancer, significantly positive associations were found in the groups of 1960-1969 and 1970 and later (**Table 5**).

Table 4. Relative risk of working environmental radiation on different kinds of cancers after stratified on age at work: results from a cohort involving health workers in Jiangsu, China (N = 7703), 1950-2011

Age at work	Lung Cancer		Solid Cancer		All Cancers	
	Case number	RR (95% CI)	Case number	RR (95% CI)	Case number	RR (95% CI)
<15	0	-	3	3.17 (0.29-34.93)	3	3.17 (0.29-34.93)
15-18	18	3.21 (1.25-8.28)	64	1.18 (0.67-2.10)	66	1.12 (0.63-1.99)
19-24	41	1.70 (0.91-3.17)	238	1.26 (0.97-1.64)	245	1.25 (0.97-1.62)
25-29	42	1.24 (0.66-2.31)	209	1.40 (1.06-1.85)	215	1.40 (1.07-1.85)
≥30	53	0.80 (0.43-1.50)	234	1.18 (0.85-1.64)	242	1.23 (0.89-1.71)

Table 5. Relative risk of working environmental radiation on different kinds of cancers after stratified on the year started to work: results from a cohort involving health workers in Jiangsu, China (N = 7703), 1950-2011

Year at work	Lung Cancer		Solid Cancer		All Cancers	
	Case number	RR (95% CI)	Case number		Case number	RR (95% CI)
<1960	22	-	72	1.39 (0.75-2.58)	77	1.54 (0.86-2.75)
1960-1969	83	1.62 (1.05-2.50)	405	1.28 (1.05-1.67)	415	1.30 (1.07-1.59)
1970-	49	2.57 (0.91-7.22)	271	1.58 (1.12-2.24)	279	1.60 (1.13-2.25)

Discussion

As a potential carcinogen, working environmental radiation has been studied well in many countries [4]. Cardis et al. conducted a cohort studies among radiation workers in 15 countries, and reported that working environment radiation, even at a low dose may increase the risk of developing cancers [4]. One study conducted among workers employed in 15 facilities that generate nuclear power in the United States reported that even though there was no correlation between radiation and different kinds of cancers (May due to the younger age of the participants), a positive correlation was found between radiation and cardiovascular [5].

Several earlier studies have reported the correlation between X-ray radiation and cancers in health working environment [6, 7]. A study by Alice et al., between the years of 1983 and 1998 reported that health staff working in an environment of radiation might increase the potential risk of breast cancers [6]. Another study conducted in Japan and other five countries among 270,000 participants also identified positive correlation between health staff working in a radiation environment and leukemia [7]. Chobanova also reported that the radiology health staff working have increased risk of cancers, particular for breast cancer [8]. Our study has been conducted for more than 30 years, from the time the participants were recruited way back in 1981.

In our study, we found that the majority of the participants were male, particularly in the department of radiology (Male: female = 3.29:1). We also found that the participants in the exposure group were elder than the non-exposure group (27.1±6.4 VS 23.6±5.0). This age difference can be explained by the evolution of health care staff in China between 1950 and 1980. After 1950, many hospitals in China started to establish the department of radiation, while the health workers in the department of radiation were experienced doctors transferred from the other departments in the same hospital.

Overall, 771 developed cancers (415 in exposure group and 356 in control group). After controlling for potential confounders, we found that the exposure was positively correlated with solid cancer and all cancers. These results were similar with the findings of the previous round follow up, which was conducted at 1996 [9]. However, the present study is much stronger than the previous reports, since it has had a longer follow up period, more cases and collected more person-years (215, 355 VS 315, 309 person-years).

Our study also found that the exposure group had significant higher risk in develop lung cancer (RR = 1.45, 95% CI: 1.00-2.09). After performing the stratified analysis, we also found that the participants in the exposure group who started working at a young age (18 or below) or after 1960 also had a higher risk in developing lung cancer. Similar findings were also presented in the group of solid cancers and all cancers. One potential reason for this phenomenon is dose response, since the participants who at the early age were exposed to the radiations than the other health workers, and in turn had higher risk in developing cancers. The correlation between risk of cancer and the time of attending work can be explained by the development of Chinese medical systems. After 1970, X-rays became a popular diagnostic tool and it was widely used by different hospitals in China. However, due to the lack of awareness on protective measures and the lack of protection equipments, the health workers were seldom protected, which may potentially increase their risk for cancers. The long latent period of lung cancer could be the main reason for this, as with the increase of age, the risk of developing lung cancer is also increased.

As rare diseases, limited numbers of cancer cases were identified in our study and this in turn limited our ability to evaluate the correlation between working environmental radiation and different kinds of cancers. In spite of this, we still found out that the majority of the RRs were larger than one. This potentially indicates that the working environmental radiation may increase the risk of develop these specific cancers, particularly for esophagus cancer, breast cancer, leukemia and lymph cancer. As a cohort study, we had certain strengths: large sample size, long term follow up, representative unexposed group, efficient use of existing medical records to reduce the potential for survival bias, allowing for induction time and latency period by using five year cut-point to reduce the potential misclassification of the outcomes, opportunity to study several types of cancers, and the high retention rate of the cohort.

As an observational study, our study also had several limitations, which may have influenced the validity of our study. First, the selection bias induced by loss to follow up may have potentially biased our results. Second, at the beginning of our study, we did not collect information on alcohol drinking, smoking and other potential confounders, which limited our ability to control the potential confounding in our study. In addition, we did not measure the dose of radiation for each participant, which might have introduced some exposure misclassification, and limited our ability to detect the dose-response between the exposure and different kind of cancers. Even with these limitations, we can still conclude that the health staff exposed to a radiation environment at work may potentially increase the risk of lung cancer, solid cancers and total cancers; it may also increase the risk of other specific cancers.

Conclusions

The incidence risk of lung cancer, solid caner and total malignant tumor in medical diagnostic X-ray workers was significantly higher than the control group in China.

Recommendations

Further study by conducting systematic radiation dose estimation and dose-effect analysis is particularly important for epidemiological studies to radiation carcinogenesis. Also, potential intervention methods that can be used to bring down the risks are urgently needed, in order to reduce the potential risk of different cancers.

Acknowledgements

This work was supported by Social development projects and Technology Support Program of Jiangsu Province (NO. BE2009684), “Twelfth Five” Science and Education Health Project “Innovation Platform for Public Health Emergency Preparedness and Response” (NO. ZX20-1109) and National health industry research and special projects (NO. 201002009).

Disclosure of conflict of interest

None.

Address correspondence to: Ningle Yu, Jiangsu Provincial Center for Disease Prevention and Control, 172 Jiangsu Road, Nanjing 210029, China. E-mail: wangfuru@jscdc.cn

References

[1] Yi Y, Zheng J, Zhuo W, Gao L. Trends in radiation exposure from clinical nuclear medicine

procedures in Shanghai, China. Nucl Med Commun 2012; 33: 331-336.
[2] Lauritsen J, Bruus M. EpiData (version 3). A comprehensive tool for validated entry and documentation of data Odense: EpiData Association; 2003.
[3] Institute S. The SAS system for Windows. SAS Institute Cary: NC; 1996.
[4] Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Solano JB, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib R, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ 2005; 331: 77.
[5] Howe GR, Zablotska LB, Fix JJ, Egel J, Buchanan J. Analysis of the mortality experience among US nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Radiat Rese 2004; 162: 517-526.
[6] Mettler FA Jr, Bhargavan M, Faulkner K, Gilley DB, Gray JE, Ibbott GS, Lipoti JA, Mahesh M, McCrohan JL, Stabin MG, Thomadsen BR, Yoshizumi TT. Radiologic and nuclear medicine studies in the United States and worldwide: frequency, radiation dose, and comparison with other radiation sources--1950-2007. Radiology 2009; 253: 520-531.
[7] Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E. Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. Radiology 2004; 233: 313-321.
[8] Chobanova N, Vukov M, Yagova A. Cancer incidence among Bulgarian medical radiation workers: epidemiological study. J BUON 2006; 12: 65-69.
[9] Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY, Aoyama T. Cancer incidence and risk estimation among medical x-ray workers in China, 1950-1995. Health Phys 2002; 82: 455-466.