The Risk of Cataract Associated With Repeated Head and Neck CT Studies: A Nationwide Population-Based Study

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Keywords: cataract, CT, radiation

DOI:10.2214/AJR.12.9652

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Received July 23, 2012; accepted after revision November 20, 2012.

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AJR 2013; 201:626–630

0361–803X/13/2013–626

OBJECTIVE. Medical radiation–induced cataracts, especially those resulting from head and neck CT studies, are an issue of concern. The current study aimed to determine the risk of cataract associated with repeated radiation exposure from head and neck CT.

MATERIALS AND METHODS. This study used information from a random sample of 2 million persons enrolled in the nationally representative Taiwan National Health Insurance Research Database. Exposed cases consisted of patients with head and neck tumor 10–50 years old who underwent at least one CT between 2000 and 2009. The nonexposed control group was composed of subjects who were never exposed to CT studies but who were matched by time of enrollment, age, sex, history of coronary artery disease, hypertension, and diabetes.

RESULTS. There were 2776 patients in the exposed group and 27,761 matched subjects in the nonexposed group. The exposed group had higher overall incidence of cataracts (0.97% vs 0.72%; adjusted hazard ratio [HR], 1.76; 95% CI, 1.18–2.63). Further stratifying the number of CT studies in the exposed group into one or two, three or four, and five or more revealed that cataract incidence increased gradually with increasing frequency of CT studies (0.79%, 0.93%, and 1.45%, respectively) ($p = 0.001$, adjusted for trend). Radiation exposure due to repeated head and neck CT studies was independently associated with an increased risk of developing cataracts when the cumulative CT exposure frequency involved more than four studies (adjusted HR, 2.12; 95% CI, 1.09–4.14).

CONCLUSION. Repeated exposure to head and neck CT is significantly associated with increased risk of cataract.

The increasing use of diagnostic CT has been a worldwide trend in the past decades [1]. In the United States, about 65 million adult and 5 million pediatric CT examinations are performed each year [2]. The United Nations Scientific Committee on the Effects of Atomic Radiation has announced that 20% of the global annual radiation dose for the period 1997–2007 comes from diagnostic medical and dental radiation [3]. In Taiwan, the most updated official information reveals that there are nearly 400 CT scanners and that more than 90% of these operating CT scanners are MDCT scanners. Although CT studies account for only 10% of x-ray examinations, they take up to 50% of the total medical radiation dose [4]. Thus, as the volume of CT increases, the adverse effects of their radiation elicit serious concern.

Radiation hazards to the human body, including increased risk of cancer, have been well established by many large-scale studies from atomic bomb survivors [5]. The lenses of the eyes are the organs most sensitive to radiation injury because of their superficial location and direct contact with the x-ray beam. The relationship of cataract formation after cumulative doses of ionizing radiation is also documented in epidemiologic studies from atomic bomb survivors [6]. The International Commission on Radiologic Protection has published threshold values for detectable lens opacities of 5 Sv for fractionated or protracted exposure and 0.5–2.0 Sv for single brief exposures [7, 8]. In recent years, many articles have discussed radiation-induced cataract among workers in radiologic departments or among patients who have undergone repeated CT [9, 10]. On the basis of current data, the International Commission on Radiologic Protection (ICRP 2011) has provided updated information regarding the lower threshold radiation dose for the lens of the eye. For the induction of deleterious lens opacities, the absorbed dose is about 0.5 Gy. In the recommendations for occupational exposure, the equivalent dose limit for the lens of the eye should be 20 mSv in a year, averaged over a defined period of 5 years, with exposure not exceeding 50 mSv in any single year [11].

Because of the boom in radiologic examinations, medical radiation–induced cataract, especially that resulting from head and neck CT, is an issue that warrants further assessment. This population-based case-control study was conducted using the Taiwan National Health Insurance Research Database (NHIRD) to investigate the association between cataract development and radiation exposure from head and neck CT.

Materials and Methods

Database

The National Health Insurance program in Taiwan, operating since 1995, enrolls nearly all inhabitants of Taiwan (21,869,478 of 22,520,776 population by the end of 2002). The NHIRD at the National Health Research Institutes in Miaoli, Taiwan, is in charge of the entire National Health Insurance claims database and has published numerous extracted datasets for researchers. For instance, the National Health Research Institutes has released cohort datasets comprising 1,000,000 randomly sampled people who were alive in 2000 and collected all of their records from 1995 onward. The database is confirmed by the National Health Research Institutes as representative of the Taiwanese population. It is also one of the largest nationwide population-based databases in the world, with more than 270 scientific articles published using its data [12].

In this cohort dataset, each patient's original identification number has been encrypted for confidentiality. Of note, the encrypting procedure is consistent such that the linkage of claims belonging to the same patient is feasible within the NHIRD datasets. These materials consist of secondary data without identification and released to the public for research. Thus, this study is exempt from full review by the institutional review board.

Subjects

The exposed group ($n = 2776$) was composed of patients with newly diagnosed head, neck, or brain tumors (based on the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 140–1499 and 191–1949) who had undergone CT studies. The patients were identified from two longitudinal health insurance databases from NHIRD. The two data subsets are composed of 2,000,000 randomly sampled beneficiaries and encompass the period 2000–2009 by linkage of these two datasets without overlapping data [13]. Among the CT examination codes registered on the NHIRD, the CT studies performed in the patients with tumors were assumed to have focused on the head and neck region. The scattered radiation doses to the eye lens from head and neck CT were much higher than those from CT studies of other body parts. The exposed group might have undergone repeated CT during the diagnostic, therapeutic, and follow-up period. The nonexposed control group was composed of age- and sex-matched subjects in the National Health Insurance database who never underwent CT, on enrollment or after. Hence, there were no crossover subjects.

Variables included to balance demographic characteristics and to control the confounding risk factor of diabetes mellitus across groups were history of coronary artery disease (ICD-9-CM codes 411.xx–414.xx), diabetes mellitus (ICD-9-CM codes 250.xx), and hypertension (ICD-9-CM codes 401.xx–405.xx). In both groups, subjects who underwent intraocular surgery via procedure coding, preexisting congenital, or trauma-related cataract (ICD-9-CM codes 3660, 3662, 36620, 36621, 36622, and 36623) before enrollment were excluded. Because cataracts were not rare complications in patients with ocular tumors after radiotherapy, those with ocular and orbital region tumors (ICD-9-CM codes 190; 1900–1909) were also excluded to reduce the confounding factor of radiotherapy. Finally, only subjects 10–50 years old were included to minimize the effect of senile cataracts. All patients were followed up until the study endpoint or December 31, 2009.

Cataract Occurrence

The endpoint of the study was the first occurrence of cataract. In this database, the ICD-9-CM codes for cataract (ICD-9-CM codes 366.xx) did not change throughout the whole follow-up period (2000–2009), ensuring the consistency of the disease registry. Subjects who met any of the following two criteria were identified as having cataract: patients who underwent cataract extraction surgery, as identified by procedure codes in the National Health Insurance database; or patients who had at least two clinical visits coded as ICD-9-CM 366.xx combined with therapeutic prescription for cataracts.

Statistical Analysis

An SQL server (2008, Microsoft) was used for data management and computing, and SPSS software (version 15.0, SPSS) was used for statistical analysis. All data were expressed as frequency (percentage) or mean (± SD). Parametric continuous data between the exposed and nonexposed groups were compared by unpaired Student t test, whereas categoric data were compared with the chi-square test and Yates correction or Fisher exact test, as appropriate. Freedom from cataract was assessed using the Kaplan-Meier analysis, with significance based on the log-rank test. The disease-free time was calculated from the date of enrollment to the date of first diagnosis of cataract. Multivariate regression analysis was conducted using Cox proportional hazard regression analysis to evaluate whether CT radiation exposure was an independent factor associated with increased risk of cataract.

Results

A sample size of 30,537 subjects, including 2776 subjects with head, neck, or brain tumor who underwent at least one CT study during the study period (exposed group), and 27,761 matched subjects who never underwent CT (nonexposed group), was obtained. There were no significant differences in age, sex, history of hypertension, diabetes mellitus, and coronary artery diseases between these two groups (Table 1).

During an average follow-up period of 10 years, 27 (0.97%) patients in the exposed group and 201 (0.72%) subjects in the nonexposed group developed cataracts. Patients in the exposed group had a higher risk of developing cataracts (crude hazard ratio [HR], 1.67; 95% CI, 1.12–2.50). After considering variables such as age, sex, hypertension, diabetes mellitus, and history of coronary artery disease, CT exposure remained significantly associated with a higher risk of cataract development (adjusted HR, 1.76; 95% CI, 1.18–2.63). During follow-up, the nonexposed control group had significantly higher cataract-free survival by log-rank test and Kaplan-Meier survival analyses of cataract incidence (Fig. 1).

For elucidating the relationship between CT exposure and cataract risk, the number of CT studies was further stratified into one or two, three or four, and five or more to compare the associated risk of cataract accordingly. The cataract occurrence rate increased gradually with the increasing number of CT studies (0.79%, 0.93%, and 1.45%, respectively) (crude p for trend, 0.0483). After adjusting for these variables, the trend of increased risk of cataract associated with increasing CT frequency was statistically significant (adjusted p for trend, 0.001), indicating that radiation exposure from CT was independently associated with increased risk of cataract (Table 2).

TABLE 1: Demographic Data of Study Population

Demographic Characteristic	Not Exposed to CT Radiation (n = 27,761)	Exposed to CT Radiation (n = 2776)	p
Age (y), mean ± SD	40.00 ± 8.98	40.27 ± 8.38	0.113
Male	20,108 (72.43)	2012 (72.48)	0.959
Hypertension[a]	3139 (11.31)	312 (11.24)	0.914
Diabetes mellitus[b]	1658 (5.97)	165 (5.91)	0.891
Coronary artery disease[c]	961 (3.46)	93 (3.35)	0.759

Note—Except for age and p values, data are no. (%) of patients. The p values for comparisons between the two categoric groups were determined by chi-square test with Yates correction. Continuous data were compared by unpaired Student t test. All chronic conditions were defined by administrative claims using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.
[a]Hypertension: ICD-9-CM codes 401.xx–405.xx.
[b]Diabetes mellitus: ICD-9-CM codes 250.xx.
[c]Coronary artery disease: ICD-9-CM codes 411.xx–414.xx.

To observe the confounding effect of radiotherapy on cataract formation, we further divided the radiation exposure subjects into two groups: subjects exposed to CT radiation only and subjects exposed to both CT radiation and radiotherapy. We respectively compared the cataract incidence of these two groups with nonexposed matched control subjects. The radiation exposure from CT only was independently associated with increased risk of cataract (adjusted HR, 2.20; 95% CI, 1.32–3.66). The cataractogenic effect in this study was mainly derived from CT in the CT radiation exposure without radiotherapy group (Table 3).

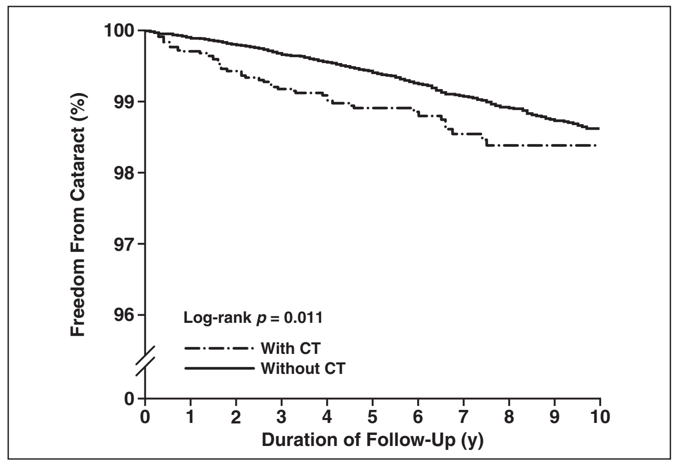

Fig. 1—Kaplan-Meier curves of freedom from cataract in subjects with and without CT radiation exposure. Control group without CT radiation exposure had significantly higher cataract-free survival rate (p = 0.011, log-rank test).

Discussion

The current study shows that patients who undergo CT have a significantly higher risk of developing cataract compared with nonexposed subjects. Subsequent analysis shows that the frequency of CT exposure is strongly associated with increased risk of cataract, further suggesting the positive association between CT exposure and cataract risk.

Cataracts, defined as lens opacity, are the most frequent cause of visual impairment worldwide [14]. Major risk factors include ocular trauma, intraocular surgery, diabetes mellitus, corticosteroid use, and radiation exposure. In the past decades, excessive doses of ionizing radiation have been documented to induce opacities in eye lenses [15]. Recent studies from atomic bomb survivors, Chernobyl clean-up workers, and residents of radiation-contaminated buildings show that the threshold radiation dose for inducing lens opacity is lower than previously reported [16–18]. Dose estimation due to inadequate data in such populations is difficult, whereas subsequent calculated risks in these epidemiologic studies may have limitations in validity. Aside from epidemiologic researches, several smaller studies that examined cataract in relation to self-reported exposure to CT revealed either no association or an association for posterior subcapsular cataracts at relatively low doses (0.1–0.3 Gy) [19]. However, the potential bias of self-reported questionnaires should be considered. Experimental animal studies using molecular analysis showed that the pathogenesis of radiation-induced cataract involves genomic damage to lens epithelium cells [20]. Theoretically, one genetically damaged cell with proliferative potential can be divided into a number of abnormal lens cells. As such, the incidence of cataract increases with radiation dose, and no threshold for induction should be further evaluated (stochastic effect).

Currently, epidemiologic studies also raise the concept of a linear no-threshold model of radiation cataractogenesis [21]. Probably because of the limited numbers of CT procedures and the lack of potential patients with radiation-induced cataract in individual insti-

TABLE 2: Association Between Radiation Exposure From CT and Cataract Incidence

No. of CT Studies	Cataract Incidence, No. (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[a]
0 (n = 27,761)	201 (0.72)	1 (referent)	1 (referent)
1–2 (n = 1512)	12 (0.79)	1.40 (0.78–2.50)	1.61 (0.90–2.88)
3–4 (n = 645)	6 (0.93)	1.71 (0.76–3.85)	1.64 (0.73–3.69)
≥ 5 (n = 619)	9 (1.45)	2.23 (1.14–4.35)	2.12 (1.09–4.14)

Note—p for trend = 0.001.
[a]Adjusted for age, sex, history of hypertension, diabetes mellitus, and coronary artery disease.

TABLE 3: Radiation Exposure From CT and Radiotherapy and Association With Cataract

Hazard Ratio	Exposed to CT Radiation (*n* = 2776)	Exposed to CT Radiation Without Radiotherapy (*n* = 1231)	Exposed to CT Radiation With Radiotherapy (*n* = 1545)	Not Exposed to CT Radiation and Radiotherapy (*n* = 27,761)
Crude Hazard Ratio (95% CI)	1.67 (1.12–2.50)	1.91 (1.15–3.18)	1.43 (0.78–2.62)	1 (referent)
Adjusted Hazard Ratio (95% CI)[a]	1.76 (1.18–2.63)	2.20 (1.32–3.66)	1.38 (0.75–2.53)	1 (referent)

[a]Adjusted for age, sex, history of hypertension, diabetes mellitus, and coronary artery disease.

tutions, few studies discuss the association between repeated head and neck CT and cataract formation [22]. In Taiwan, a large number of CT procedures was performed (1,268,921 CT procedures in 2008) and contributed 50.8% of the annual collective and average effective doses from medical radiation exposure [23]. The current study used two data subsets, composed of 2,000,000 randomly sampled beneficiaries, which provided thousands of CT examinations with the corresponding clinical information. We retrospectively compared these data with an age-, sex-, and comorbidity-matched nonexposed control group. The results reveal a possible linear trend of increasing cataract incidence rate with increasing number of CT studies (i.e., 1–2, 3–4, and ≥ 5 studies, with cataract incidence rate of 0.79%, 0.93%, and 1.45%, respectively, with adjusted p for trend of 0.001). Cox proportional hazard regression model analysis shows that radiation exposure from CT is independently associated with an increased risk of developing cataracts when cumulative CT exposure frequency is five or more (adjusted HR, 2.12; 95% CI, 1.09–4.14).

The typical effective dose of head CT is estimated to be 1–2 mSv for diagnostic single-detector CT and MDCT. The lens of the eye receives considerably high absorbed doses, up to 50 mGy, during head CT examinations [24]. According to this estimated average dose for each head CT, our study results imply that the effective and absorbed radiation threshold doses of head and neck CT to induce cataracts may be as low as 10 mSv and 0.25 Gy. The eye lens is under direct radiation exposure during CT examinations. Most patients undergo head and neck CT without eye shields, because artifacts caused by eye protective shields may affect the quality of images. The current study's results indicate that the risk of radiation-induced cataracts during head and neck CT examination is higher than may be previously expected, and radiology authorities should not ignore this problem. Suggestions such as low-dose head CT using iterative reconstruction and the use of protective shielding materials with minimal artifacts should be encouraged.

The current study has limitations. First, the case group consists of patients with head and neck tumor, and radiotherapy is one of the therapeutic options for these patients. Secondary data from the NHIRD can only provide information about the frequency of radiotherapy. The target area varies with different radiotherapy protocols, and the scattered radiation dose cannot be exactly determined in our study. The modified protocols of imaging-guided or intensity-modulated radiotherapy has substantially reduced scattered radiation dose and complications over nontarget areas. Recent reports of radiotherapy-induced cataracts mainly discuss radiosensitive orbital lymphoma or retinoblastoma [25–27]. Therefore, patients with ocular and orbital tumors are excluded in the case group. Although head and neck radiotherapy may play a role in cataract formation, the percentage of cataracts caused by scattered dose of radiotherapy is expected to be small in the current study. Second, risk factors for cataract such as previous ocular trauma and surgery were excluded, whereas diabetes mellitus was included as a matched characteristic in both the case and control groups. Corticosteroid use was also not assessed in this study because miscellaneous corticosteroid prescriptions in Taiwan are difficult to extract in the NHIRD.

Despite these limitations, the current study is one of the largest population-based studies to focus on the association between cataract and repeated head and neck CT studies. The results will be valuable evidence of the medical radiation hazards to lenses of the human eyes.

In conclusion, in spite of the rapid progress in high-technology CT machines, the radiation dose generated by CT still contributes more than half the medical radiation to human subjects. This 10-year retrospective population-based study using the NHIRD in Taiwan shows the possible dose-dependent relationship between CT examinations and cataract occurrence, because repeated exposure to head and neck CT is significantly associated with increased risk of cataract incidence. Such concerns suggest the need for more efforts to lower the incidence of radiation-induced cataract.

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