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The association between exposure to radiation and the incidence of cataract

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Abstract
Objective To examine the association between exposure to radiation from computed tomography (CT) studies and the incidence of cataract.
Methods In a nested case–control study, all cataract cases and their matched controls were sampled from a retrospective cohort of Israeli residents who underwent CT scans or ultrasonic tests in Soroka Medical Center, Beer-Sheva, Israel, between the years 1996 and 2014. The risk of cataract associated with head, neck or the rest of the body CT was assessed using Poisson survival analysis.
Results The nested matched sample included 3841 cataract cases and their age- and sex-matched controls (n = 228,743). CT radiation exposure was more frequent in the cataract group, with 9.7% head CT, 1.2% neck CT and 6.6% other CT, compared to 5%, 0.7% and 3.7% among person-years without cataract ($p < 0.001$). In a multivariate analysis, a similar increased risk of cataract associated with head (hazard ratio (HR): 1.24, 95% confidence interval (CI): 1.11; 1.38) and other CT (HR: 1.25, 95% CI: 1.10; 1.43) was found. No association with neck CT (HR: 1.07, 95% CI: 0.80; 1.43) was observed.

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Conclusion In our study population, a similar risk of cataract with head, neck or the rest of the body CT was detected.

Keywords Cataract · Computed tomography · Ultrasound · Radiation

Introduction

Cataract is a main ocular problem in the Western world, and its prevalence is rising constantly. According to a report by the National Eye Institute, the number of patients with cataract will increase from 20 million in 2000 to about 50 million in 2050 [1].

The crystalline lens of the eye is known to be one of the most radiosensitive tissues in our body, and ionizing radiation is a reported risk factor for cataract development [2, 3]. Lens opacities in cases of occupational exposure to ionizing radiation have been reported for medical personnel, such as radiology technicians [4] and interventional cardiologists [5–7]. Some studies reported that lens opacities are at least twice more frequent in exposed than in unexposed groups [8, 9].

Within the last 20 years, there has been a fast increase in the population exposure dose from medical radiation, mainly due to the more frequent use of computed tomography (CT). CT is one of the most significant contributors to medical radiation doses. Each year CT examinations are performed in about 65 million adults and 5 million pediatric population in the USA [10]. A large survey in the US has demonstrated a 7.7% annual increase in CT usage resulting in a doubling in the radiation exposure per capita [11].

Data on the association between the type and number of CT tests performed and cataract formation in a general population are scanty and controversy remain mainly due to the problematic research methodology [12–17]. There are inherent difficulties in establishing causality between the exposure and its remote effect [17]. The assessment following large time span between the exposure and proposed effect requires through medical records keeping on a general population level. In addition, variety of biases may affect the estimated association, especially in a view of the expected weak effect. Lastly, the lack of unified exposure scale makes the estimation of the cumulative exposure difficult [12–15, 17].

To overcome all previous limitations, a large population retrospective study was conducted during a long period to examine the association between exposure to radiation from CT studies and the incidence of cataract.

Methods

Study population

The population for this study included Israeli residents who underwent computed tomography (CT) scans in Soroka Medical Center, Beer-Sheva, Israel, or ultrasonic (US) tests between the years 1996 and 2014. Ethical approval was received from the local Helsinki Committee of Soroka Medical Center. No informed consent was required. Since the baseline characteristics of the two exposure groups were very different (Supplementary Table 1), we restricted the analysis to a subsample of people who were diagnosed with cataract between the years 1996 and 2014 and their matched controls. We matched each case with three controls by age at the last year of follow-up and sex. We then included all the follow-up years for these matched persons. Since the inclusion of all follow-up years changed the balancing of the age distributions in the two groups, we additionally added adjustment for age in the regression model. We excluded subjects who underwent SPECT (single-photon emission computerized tomography) or PCI (percutaneous coronary intervention) tests during the studied years and subjects younger than 18 years. For each subject, we retrieved information on the date of cataract diagnosis, age, gender and comorbidities.

Cataract occurrence

The endpoint of the study was defined as the first indication on the cataract occurrence. Subjects were identified as having cataract when any of the following two criteria was present: cataract operation surgery, identified by surgical procedure codes; or patients who had the diagnosis of cataract at the electronic medical record database (ICD-9-CM codes 366.xx).

CT scans and radiation exposure

The scans were grouped into categories according to type of test and the body area scanned. We estimated the eyes exposure to radiation using the x-ray risk calculator developed by Hanley et al. [18]. Basically the web calculator was based on the Biological Effects of Ionizing Radiation (BEIR) VII Phase 2 Report [19]. Taking in account the type of examination, age, gender and number of examinations, the effective dose and cancer risk are calculated.

Statistical analysis

Results are presented by mean ± SD, inter quartile range (IQR) and range for continuous variables and as percentages for categorical data. Student's t test was used for the comparison of normally distributed data, and Mann–Whitney test was used in cases where normality assumption was not met. We used Chi-square test to compare categorical data.

We followed each person through calendar year follow-up periods from 1996 until the year in which they were diagnosed with cataract, died or the last year of follow-up (2014), whichever came first. Because each person had time-varying exposure and confounders, we fit a proportional hazard model using the equivalent Poisson regression. An artificial Poisson observation was generated for each person and each non-censored year with an outcome of zero for all person-years except those experiencing cataract at that time. We added a penalized spline function of year to allow for a piecewise constant hazard for each year. We then used generalized additive Poisson regression with the time-varying predictors (age, hypertension (HTN), diabetes (DM) and coronary heart disease (CHD). The main exposure of interest was a time-varying indicator for whether or not the person underwent US, head CT and/or other CT during each year of follow-up.

To assess modification by personal characteristics, we repeated our models with stratification by the median age (66 years) and sex.

Results are presented as hazard ratios (HR) and 95% confidence intervals (CI).

Results

The original study population included 1,867,776 people, of which 81.7% were exposed to any CT radiation during the study period. The unexposed group comprised of younger people, mostly women. HTN, DM and CHD were less frequent in this group (Supplementary Table 1). The nested matched sample included 3841 cataract cases and their age- sex-matched controls (n = 228,743). The mean age was higher among persons with cataract (72.5 versus 64.1, $p < 0.001$). There were 46.5% males in both groups ($p = 0.792$). Higher proportion of HTN, DM and CHD were observed in the cataract group. CT radiation exposure was more frequent in the cataract group, with 9.7% head CT, 1.2% neck CT and 6.6% other CT, compared to 5%, 0.7% and 3.7% among person-years without cataract ($p < 0.001$) (Table 1).

In a multivariate analysis, we found a similar increased risk of cataract associated with head (HR 1.24, 95% CI 1.11; 1.38) and other CT (HR 1.25, 95% CI 1.10; 1.43). We did not observe an association with neck CT (HR 1.07, 95% CI 0.80; 1.43).

In stratification by age, for younger persons, the risk of CT associated with cataract was higher for head CT exposure (HR 1.61, 95% CI 1.23; 2.10) than for other CT exposure (HR 1.48, 95% CI 1.13; 1.93). For persons older than 66 years, the CT-associated cataract risks were lower and similar for head (HR 1.16, 95% CI 1.02; 1.31) and other CT (HR 1.19, 95% CI 1.03; 1.44). The CT-associated cataract risks were similar for males and females (Table 2).

Discussion

Our study included 3841 cataract cases and their matched controls (n = 228,743). In a multivariate analysis, we found a similar increased risk of cataract associated with head and the rest of the body CT. We did not observe an association with neck CT.

Few studies have examined the possible association between CT and cataract. A nationwide population-based study [12] studied the possible risk of cataract in cases of repeated radiation exposure from head and neck CT. The exposed group comprised of 2776 patients, and the unexposed group comprised of 27,761 matched subjects. There was a higher incidence of cataracts in the exposed group (0.97% vs

Table 1 Population characteristics comparing person-years with and without cataract (n = 232,584 person-years of 15,364 subjects)

	Cataract		
	No 98.4 (228,743)	Yes 1.6% (3841)	*P* value
Age (Mean ± SD)	64.1 ± 11.9	72.5 ± 10.5	< 0.001
Male *n*(%)	105,901 (46.3)	1787 (46.5)	0.792
HTN *n*(%)	114,087 (49.9)	2590 (67.4)	< 0.001
DM %(*n*)	57,459 (25.1)	1442 (37.5)	< 0.001
CHD %(n)	25,997 (11.4)	726 (18.9)	< 0.001
Type of test n(%)			
US	207,911 (90.9)	3196 (83.2)	< 0.001
Head CT	11,362 (5.0)	373 (9.7)	
Neck CT	1711 (0.7)	48 (1.2)	
Other CT	8529 (3.7)	252 (6.6)	

US ultrasonography, *CT* computerized tomography, *HTN* hypertension, *DM* diabetes mellitus, *CHD* coronary heart disease

Table 2 Risk of cataract following exposure to CT radiation

Model	HR (95% CI)	*P* value
All available cases		
Head CT	1.24 (1.11;1.38)	< 0.001
Neck CT	1.07 (0.80;1.43)	0.648
Other CT	1.25 (1.10; 1.43)	< 0.001
By age		
< 66		
Head CT	1.61 (1.23;2.10)	< 0.001
Neck CT	0.58 (0.27;1.23)	0.154
Other CT	1.48 (1.13; 1.93)	0.004
66+		
Head CT	1.16 (1.02;1.31)	0.018
Neck CT	1.27 (0.93;1.74)	0.135
Other CT	1.19 (1.03; 1.44)	0.019
By gender		
Male		
Head CT	1.22 (1.03;1.44)	0.020
Neck CT	1.01 (0.68;1.52)	0.952
Other CT	1.28 (1.07;1.53)	0.007
Male		
Head CT	1.26 (1.09;1.46)	0.002
Neck CT	1.14 (0.75;1.74)	0.530
Other CT	1.22 (1.02; 1.47)	0.033

We modeled the association between cataract and CT scan of different body areas. The model was adjusted for gender and comorbidities (diabetes, hypertension and coronary heart disease). Age (< 35 years, 35–55 years and > 55 years) was inserted as stratification variables, to allow for non-proportionality of survival rates. Ties were treated using the Efron method

0.72%; adjusted hazard ratio [HR], 1.76; 95% CI, 1.18–2.63). After stratifying the number of CT studies in the exposed group, the incidence of cataract was found to increase gradually with increasing number of CT studies. The authors concluded that in cases of repeated exposure to head and neck CT, there is a significant increased risk of cataract. However, results may be biased by not taking into account for the radiation dose to the lens in cases of head and neck cancer patients who undergo radiation therapy [13].

Our results are different to previous reports demonstrating that radiation is a risk factor for cataract development. Children and adolescence are in high risk of radiation-induced cataract [20, 21] and were studied extensively. Nevertheless, only few reports have demonstrated an altered risk among various adult age groups. A recent population study, studying the risk of cataractogenesis following radiation exposure [22], found that gamma knife and CT/angiography study radiation exposure may be independently associated with an increased risk of cataract occurrence. The risk was found to be particularly high in 30–50-year-old adults. The finding of higher risk of cataractogenesis in younger subjects may be related to the fact that, similar to children, the younger lens is more vulnerable and hence prone to radiation-induced cataractogenesis.

Few studied checked for further risk factors for radiation-induced cataract, like diabetes, hypertension and coronary heart disease. Mikryukova and Akleyev [23] have reported that the risk of cataract development is increased in cases of accidentally radiation-exposed residents of the Urals region with arterial hypertension, diabetes and retinal angiosclerosis.

Another study [4] aimed to determine the risk of cataract among radiological technologists. Increased risk of cataract was found when cigarette smoking for $\geq$ 5 pack-years; body mass index of $\geq$ 25 kg/m [2]; and history of diabetes, hypertension, arthritis and hypercholesterolemia at baseline.

Several studies addressed the possible importance of the dose radiation in cataract formation, which may range between 285 and 515 milisievert (mSv) during interventional neuroradiological procedures which may be higher than the threshold of cataract formation [24], to other studies in which no positive dose–response relationship was detected between cataract formation and number of head CT scans [17]. In 2011, the International Commission on Radiological Protection reduced the threshold for lens effects to 0.5 Gy [25]. Biological research suggests that crystalline cells are not necessarily radiosensitive to cell death and there are other mechanisms involved which explain the lack of dose–rate effects [26]. We could not analyze the doses of radiation as were changed over the years without exact documentation, and we were not able to correctly assign the dose to each scan.

The lack of connection between higher of radiation exposure and cataract formation in our study in all age groups might be the results of different methodologies.

Strength of the study includes its population-based retrospective nature. The prolonged nature of the time frame, between the exposure and the possible outcome of cataract, makes such an approach an ideal tool for investigating the possible association. In Soroka Medical Center, where the study took place, three characteristics enabled a large-scale research on this topic: a very large scale of CT scan examinations performed annually; complete computerized medical and administrative patient data; and common computerized medical records with the largest HMO in the area of the hospital (Clalit Health Services), representing more than 500,000 insurers. Establishment of the exposure risks was accomplished by matching the CT examinations, executed in Soroka Medical Center, with cataract development as revealed from patients' records both in the hospital and the community, comparing them to a matching control group of patients who did not have any exposure of medical ionizing radiation. These characteristics are unique and enabled us to develop a comprehensive data based on the population in this research.

Our study has potential limitations. First, we did not have access to CT examinations performed outside Soroka Medical Center, like in the private or in other public hospitals and institutions. Second, other exposures to radiations were only partly known and taken into account (we excluded patients who had PCI, APECT examinations). Third, it is possible that not all patients suffering from cataract were recognized in this study, and conversely, we did not exclude subjects after intraocular surgery, or with preexisting, trauma-related or congenital cataracts before enrollment to the study, and subjects with malignancies which necessitated radiotherapy to the orbital region. Fourth, we did not check the pediatric population, which might be the most vulnerable population to medical-induced radiation. Fifth, there is the lack of analysis of the doses of radiation. Finally, we were not able to account for important potential confounders such as drug history, or systemic illness other than diabetes, heart disease or hypertension, which may affect cataract formation.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical approval Ethical approval was received from the local Helsinki Committee of Soroka Medical Center.

Informed consent No informed consent was needed.

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