Increased risk of ischemic heart disease among subjects with cataracts
A population-based cohort study

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Abstract

Background: Association between cataract and the risk of ischemic heart disease (IHD) development is not completely clear.

Purpose: The primary aim of the study was to evaluate the association between cataract and the risk of incident IHD. The secondary aim was to investigate the subsequent IHD risk of patients with cataracts undergoing cataract surgery.

Methods: Retrospective data from the Longitudinal Health Insurance Database 2000 (LHID2000) was analyzed. Study participants were composed of patients with cataracts (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 366) (n = 32,456), and a comparison cohort without the cataracts (n = 32,456) from 2000 to 2010. Cox proportional hazards regression was used to address the hazard ratio (HR) of IHD associated with cataract.

Results: Within 12 years of follow up, the overall incidence rates of IHD were 24.2 per 1000 person-years in the cataract cohort and 18.2 per 1000 person-years in the noncataract cohort with an adjusted hazard ratio (aHR) of 1.35 (95% CI = 1.29–1.41; $P < 0.001$). Furthermore, the cataract patients undergoing cataract surgery were associated with a higher risk of IHD compared with those cataract patients without surgery (aHR = 1.07, 95% CI: 1.01–1.14; $P < 0.05$).

Conclusions: Our finding suggested that patients with cataracts are at an increased risk of subsequent IHD development.

Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IHD = ischemic heart disease, NHI = National Health Insurance.

Keywords: cataract, cataract surgery, cohort study, incidence, ischemic heart disease

1. Introduction

Ischemic heart disease (IHD) is one of the major causes of mortality in the developed countries; inflammation and oxidative injury are the major players in atherosclerosis.[1–4] Cataract is a common cause of visual impairment in the elderly population; reduced antioxidant and oxidative stress are associated with the pathogenesis of senile cataract.[5–12]

Previous studies have demonstrated the positive correlation between cataract and the risk of IHD separately in specified population.[11,13–16] However, population-based studies addressing the association between cataract and the subsequent IHD risk were limited in the literature.[11,13,16] Furthermore, the effect of cataract surgery on the risk of IHD among patients with cataracts was not well defined.[11,13,16] Therefore, the purpose of the study was to evaluate the association between cataract and the risk of incident IHD. Moreover, the subsequent IHD risk of patients with cataracts undergoing cataract surgery was also investigated.

2. Methods

2.1. Data source

This present study was designed as a population-based retrospective cohort study to focus on the risk of IHD between patients with and without cataracts. The National Health Insurance (NHI) program, a single-payer national insurance system, covers more than 99% of the 23.74 million citizens in Taiwan.[17] In this study, the claim data of the Longitudinal Health Insurance Database 2000 (LHID2000) consisted of claims data by randomly selecting 1,000,000 enrollees from insured people for the period of 1996–2011. LHID2000 was established, maintained, and released by the National Health Research Institutes (NHRI). Data files were linked with the identifications of patients that had been anonymized to protect the privacy of the beneficiaries. The diagnostic codes provided in the LHID2000 for each outpatient visit or hospitalization

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contained up to 5 coded diagnoses according to the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM) classification. The Institutional Review Board of China Medical University and Hospital in Taiwan approved this study (CMUH-104-REC2-115).

2.2. Study population

We identified patients with newly diagnosed cataracts (ICD-9-CM code 366) from 2000 to 2010 as the cataract cohort. The index date for the patient was the date of the first medical visit for cataract. We excluded patients who were diagnosed with IHD (ICD-9-CM codes 410–414) before the index date, and missing information on demographics. The noncataract cohort was selected from the population without a history of cataract documented in the LHID2000. Patients in the cataract and noncataract cohorts were 1:1 matching based upon a propensity score.[18] Using a logistic regression, the propensity score was calculated to measure the probability of the disease status, based upon the baseline variables including year of the index date, age, gender, and comorbidities of hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), chronic renal disease (ICD-9-CM code 585), chronic liver disease (ICD-9-CM code 571), dementia (ICD-9-CM codes 290, 294.1, 331.0), neoplasm (ICD-9-CM codes 140–239), atrial fibrillation (ICD-9-CM code 427), and heart failure (ICD-9-CM code 428). The study outcome was a diagnosis of IHD during the 12-year follow-up. The study patients were followed up from the index date until the date of IHD diagnosis, withdrawal from the NHI program, or the end of 2011 (December 31, 2011).

2.3. Statistical analysis

The distributions of the categorical demographic characteristics and comorbidities were compared between the cataract cohort and the noncataract cohort. The standardized difference was used to quantify the differences in means or prevalence between the cataract and the noncataract cohorts for continuous and categorical matching variables. A value of standardized mean difference equaled 0.05 or less; indicative of a negligible difference in means between the cataract and the noncataract cohorts.[19] To estimate the cumulative incidence of IHD in the cataract and the noncataract cohorts, we performed the Kaplan–Meier method, with significance based on the log-rank test. The incidence densities of IHD were estimated by dividing the number of IHD by the number of person-years stratified by sex, age, and comorbidity. Univariable and multivariable Cox proportion hazard regression models were employed to examine the effect of cataract on the risk of IHD, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariable Cox models were adjusted for age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, stroke, asthma, chronic obstructive pulmonary disease, chronic renal disease, chronic liver disease, dementia, neoplasm, atrial fibrillation, and heart failure. All data analyses were performed using the SAS statistical package (version 9.4 for Windows; SAS Institute, Cary, NC). A 2-tailed P-value of <0.05 indicated the statistical significance level.
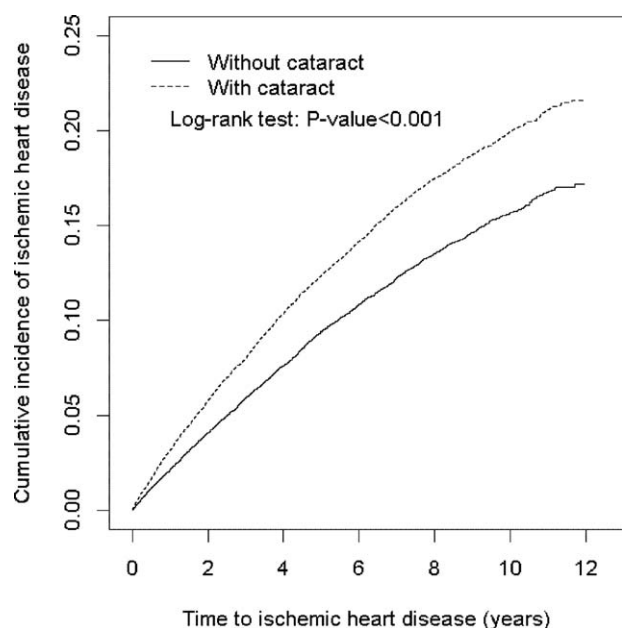
3. Results

Basic characteristics of the cataract patients and their matched noncataract patients are shown in Table 1. The mean ages of the cataract and the noncataract cohorts were 62.3 ($\pm$9.97) and 62.1 years ($\pm$10.9), respectively. The distribution of age, sex, and comorbidity showed similar after propensity score matching. In these 2 cohorts, most people were women (53.9% vs 53.1 %). The major comorbidity was hypertension (40.9% vs 43.2%) in these 2 cohorts. During the mean follow-up period of 5.94 years for the cataract cohort and 5.41 years for the noncataract cohort, the Kaplan–Meier analysis for the cumulative incidence of IHD in the cataract and noncataract cohort demonstrated that the risk of IHD was significantly higher in the cataract cohort than in the noncataract cohort by the end of the 12-year follow up (Fig. 1, log rank test, $P < 0.001$).

The incidence density rate and HR of IHD stratified by sex, age, and comorbidity between patients with and without cataracts are shown in Table 2. Within 12 years of follow up, the overall incidence rates of IHD were 24.2 per 1000 person-years in the cataract cohort and 18.2 per 1000 person-years in

Table 1

Demographic characteristics and comorbidities in patients with and without cataracts.

	Cataract		
Variable	No, N = 32,456, n (%)	Yes, N = 32,456, n (%)	Standard difference
Age (y), mean (SD)	62.1 (10.9)	62.3 (9.97)	0.02
Sex			
Female	17,235 (53.1)	17,506 (53.9)	0.017
Male	15,221 (46.9)	14,950 (46.1)	0.017
Comorbidity			
Hypertension	14,021 (43.2)	13,285 (40.9)	0.05
Diabetes mellitus	4777 (14.7)	4387 (13.5)	0.04
Hyperlipidemia	8872 (27.3)	8118 (25.0)	0.05
Stroke	1334 (4.11)	1251 (3.85)	0.01
Asthma	2502 (7.71)	2299 (7.08)	0.02
Chronic obstructive pulmonary disease	4192 (12.9)	3870 (11.9)	0.03
Chronic renal disease	533 (1.64)	487 (1.50)	0.01
Chronic liver disease	7373 (22.7)	6854 (21.1)	0.04
Dementia	362 (1.12)	330 (1.02)	0.01
Neoplasm	1190 (3.67)	1106 (3.41)	0.01
Atrial fibrillation	2098 (6.46)	1970 (6.07)	0.02
Heart failure	500 (1.54)	471 (1.45)	0.007

Figure 1. Cumulative incidence curves of ischemic heart disease (IHD) for groups with and without cataracts.

The age-specific cataract to noncataract cohorts aHR of IHD were significant higher for all age group (aHR = 1.75, 95% CI = 1.32–2.30 for aged ≤49 years; aHR = 1.56, 95% CI = 1.46–1.67 for aged 50–64 years; aHR = 1.10, 95% CI = 1.03–1.17 for aged ≥65 years). Furthermore, patients with comorbidities had an increased IHD incidence in both cohorts. However, the comorbidity-specific cataract to noncataract cohort relative risk of IHD was significant for patients without comorbidities (aHR = 1.53, 95% CI = 1.38–1.70) and for patients with comorbidities (aHR = 1.27, 95% CI = 1.21–1.34).

To investigate the subsequent IHD risk of patients with cataracts undergoing cataract surgery, we conducted a subgroup analysis. A total of 32,456 cataract patients were included; of them, 16028 patients received cataract surgery, and the remaining 16,428 patients did not receive cataract surgery. The incidence rates of IHD were 18.2 per 1000 person-years in the patients without cataracts, 22.9 per 1000 person-years in the cataract patients without surgery, and 25.5 per 1000 person-years in the cataract patients undergoing cataract surgery. The relative risk of IHD for the cataract patients undergoing cataract surgery to those without cataracts showed significant differences, with an aHR of 1.39 (95% CI = 1.32–1.46). In addition, the relative risk of IHD for the patients with cataracts without surgery to those without cataracts also showed significant differences, with an adjusted HR of 1.31 (95% CI = 1.24–1.38). Furthermore, the cataract patients undergoing cataract surgery were associated with a higher risk of IHD compared with those cataract patients without surgery (aHR = 1.07, 95% CI: 1.01–1.14), as shown in Table 3.

4. Discussion

In this nationwide population-based retrospective cohort study, our results showed that cataract patients are at an increased risk of incident IHD in the future, particularly in the younger population. Furthermore, the cataract patients undergoing cataract surgery were associated with a higher risk of IHD compared with those cataract patients without surgery.

the noncataract cohort with an adjusted hazard ratio (aHR) of 1.35 (95% CI = 1.29–1.41). With the relative risk of 1.33, the estimated population attributable risk (PAR) of IHD associated with cataract patients was 1.04 per 100 or 0.01% for the population. Of 100 cases of IHD, only 1–2 would be prevented if cataract completely disappeared from the general population. The incidence density of IHD was higher in men than in women in both cohorts. The aHR of IHD was significantly higher in the cataract cohort than in the noncataract cohort for both men (aHR = 1.34, 95% CI = 1.26–1.43) and women (aHR = 1.36, 95% CI = 1.28–1.45). The incidence of IHD increased with age in both cohorts.

Table 2

Comparison of incidence and hazard ratio of ischemic heart disease stratified by sex, age, and comorbidity between patients with and without cataracts.

Variable	Without cataract					With cataract				
	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
All	3198	175,566	18.2	1 (Reference)	1 (Reference)	4667	192,703	24.2	1.33 (1.28, 1.40)***	1.35 (1.29, 1.41)***
Sex										
Female	1606	95,841	16.8	1 (Reference)	1 (Reference)	2414	107,141	22.5	1.35 (1.26, 1.43)***	1.36 (1.28, 1.45)***
Male	1592	79,725	20.0	1 (Reference)	1 (Reference)	2253	85,562	26.3	1.33 (1.24, 1.41)***	1.34 (1.26, 1.43)***
Stratify age										
≤49	69	13,351	5.17	1 (Reference)	1 (Reference)	236	19,031	12.4	2.39 (1.83, 3.13)***	1.75 (1.32, 2.30)***
50–64	1534	100,068	15.3	1 (Reference)	1 (Reference)	2176	95,312	22.8	1.51 (1.41, 1.61)***	1.56 (1.46, 1.67)***
≥65	1595	62,147	25.7	1 (Reference)	1 (Reference)	2255	78,359	28.8	1.10 (1.03, 1.17)**	1.10 (1.03, 1.17)**
Comorbidity‡										
No	598	64,108	9.33	1 (Reference)	1 (Reference)	916	65,134	14.1	1.51 (1.36, 1.67)***	1.53 (1.38, 1.70)***
Yes	2600	111,458	23.3	1 (Reference)	1 (Reference)	3751	127,569	29.4	1.28 (1.21, 1.34)***	1.27 (1.21, 1.34)***

Rate, incidence rate, per 1,000 person-years (PY); Crude HR, crude hazard ratio.

† Adjusted HR: Multivariable analysis including age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, stroke, asthma, chronic obstructive pulmonary disease, chronic renal disease, chronic liver disease, dementia, neoplasm, atrial fibrillation, and heart failure.

‡ Comorbidity: Patients with any one of the comorbidities: hypertension, diabetes mellitus, hyperlipidemia, stroke, asthma, chronic obstructive pulmonary disease, chronic renal disease, chronic liver disease, dementia, neoplasm, atrial fibrillation, and heart failure were classified as the comorbidity group.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Incidence and hazard ratio of ischemic heart disease among cataract patients with and without surgery compared to patients without cataracts.

Variable	N	Event	PYs	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
Without cataract	32,456	3198	175,566	18.2	1.00	1.00		
Cataract								
With surgery								
No	16,428	2145	93,754	22.9	1.25 (1.18, 1.32)***	1.31 (1.24, 1.38)***	1.00	1.00
Yes	16,028	2522	98949	25.5	1.41 (1.34, 1.49)***	1.39 (1.32, 1.46)***	1.13 (1.07,1.20)***	1.07 (1.01, 1.14)*

[#] Rate, incidence rate, per 1,000 person-years (PY); Crude HR, crude hazard ratio.
[†] Adjusted HR: Multivariable analysis including age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, stroke, asthma, chronic obstructive pulmonary disease, chronic renal disease, chronic liver disease, dementia, neoplasm, atrial fibrillation, and heart failure.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

The strength of our research is that it is a population-based observational study and there are adequate patients to minimize the confounding factors.[17] Propensity score analysis was used to minimize the observable selection bias with the attempt to simulate the randomization process.[18]

Although cataract is a localized ocular disease, increasing studies support the link between cataract and atherosclerosis.[11,13–16] A variety of mechanisms was involved, including inflammation, accumulation of advanced glycation end products, and oxidative injury.[3–12,20–22] Our finding is consistent with the previous investigations[11,13–16]; furthermore, to our best knowledge, this is the first population-based study to demonstrate the inverse relationship between IHD risk and the advancement of age among patients with cataracts. We believed that less traditional IHD risk factors in the younger subjects, in comparison to those with advanced age, leading to this inverse relationship. This finding is important for cataract patients; additional investigations are necessary to confirm our result and to explore the mechanism involved.

In our study, a subgroup analysis was conducted to further evaluate the subsequent IHD risk of patients with cataracts undergoing cataract surgery. Our findings showed that patients with cataracts undergoing cataract surgery were not associated with a reduced risk of IHD in comparison to those cataract patients without surgery. The possible explanation for our finding is that atherosclerotic process is a continuum, and it cannot be modified by the localized cataract surgery but the IHD risk factors[1–4,11,13–16]; indicating that cataract might be considered as the marker of IHD instead of a direct causative effect.

5. Limitations

First, diagnoses of cataract, IHD, and comorbidity were completely dependent on ICD codes. Therefore, the accuracy of the claims data might influence the results significantly. However, a mechanism to verify the diagnosis has been made by Taiwan's NHI. Second, several IHD risk factors, such as family history of premature IHD, smoking, body mass index, physical inactivity and emotional stress could not be obtained from the LHID2000. However, propensity score matching analysis was used to ensure the validity of the results by reducing selection bias.[18] Third, the severity of cataract cannot be clearly identified due to the limitation of the LHID2000. Fourth, the study was analyzed from Taiwanese database; therefore the result might be inappropriate to apply for other populations. Finally, the

mortality data were not available in our dataset. Therefore, we were unable to conduct the analysis to see whether there is higher mortality in the cataract cohort.

6. Conclusions

In conclusion, our finding suggested that patients with cataracts are at an increased risk of subsequent IHD development, particularly in the younger population.

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