Endophthalmitis Incidence of Cancer Patients After Cataract Surgery: A Nationwide Matched Cohort Study in Taiwan

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• PURPOSE: To compare the incidence rate of endophthalmitis after cataract surgery between cancer cohort and matched noncancer cohort.
• DESIGN: Matched cohort study.
• METHODS: Patients with cataract surgery of both eyes among a nationwide cancer cohort and 1:1 matched noncancer cohort were enrolled from the years 1998 to 2012 in the Taiwan National Health Insurance Research Database. Both the cancer group and the control group were followed for 3 months after the cataract surgery to obtain the rate of endophthalmitis.
• RESULTS: There were 23 362 patients each in the cancer cohort and in the matched noncancer cohort. The mean age of receiving first cataract surgery was 71 years. The mean duration of receiving cataract surgery was 4.3 years after cancer diagnosis. The mean duration between 2 cataract surgeries was 8-9 months. The rate of endophthalmitis within 3 months after cataract surgery was similar between the 2 study groups: 2.4‰ (95% confidence interval = 1.9‰–2.8‰) for the cancer group and 2.3‰ (95% confidence interval = 1.9‰–2.8‰) for the noncancer group, respectively ($P = .892$).
• CONCLUSIONS: Cancer patients have a similar risk of endophthalmitis following cataract surgery as the noncancer population, and the current study suggests that cataract surgery can be considered as appropriately indicated for cancer patients. (Am J Ophthalmol 2019;199:246–254. © 2018 Elsevier Inc. All rights reserved.)

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IMPROVEMENTS IN CANCER TREATMENT HAVE increased the number of long-term cancer survivors. The 5-year survival rate rose from 50.3% in 1975-1977 to 66.4% in 2006-2012.[1] Cancer survivors have higher risks for a number of medical conditions, including cataract, and many cancer survivors with cataract reported that cancer had a lasting effect on their general health.[2] The only effective treatment for cataract is surgery. However, cancer patients are usually older, and their immune function may be diminished because of cancer or cancer treatment.[3,4] In addition, the rate of infectious complications is high in this population.[5] Previous studies reported that infection rates at a number of surgical sites were higher for cancer patients than that for the general population.[6,7] This raises concerns as to whether infection risk after surgical treatment of cataract is higher in cancer survivors.

Infectious endophthalmitis is a serious complication after cataract surgery and may lead to blindness.[8] Although the endophthalmitis rate after cataract surgery is low—between 1.5‰ and 2.2‰ in studies of patients in Canada, Australia, and the United States[9–11]—only 4.2% of cataract surgery patients in a previous study had cancer.[10] Because endophthalmitis incidence is low, there are too few endophthalmitis cases to evaluate the safety of cataract surgery in cancer survivors. Our literature search indicates that the Endophthalmitis Population Study of Western Australia (EPSWA) study in Western Australia was the only study to compare endophthalmitis rates after cataract surgery in patients with and without a history of cancer.[10] To identify risk factors, that study of population-based administrative data pooled results from the whole population. The authors identified 11 endophthalmitis cases out of 4888 cancer patients who underwent cataract surgery. The endophthalmitis incidence rate was 2.3‰ in the cancer group and 1.8‰ in a noncancer group. The difference was not statistically significant.[10]

In the present matched cohort study, we used data from the National Health Insurance (NHI) Research Database of Taiwan to compare the endophthalmitis rates in a cancer cohort and matched noncancer cohort. To our knowledge, this is the first study with a cancer cohort and matched

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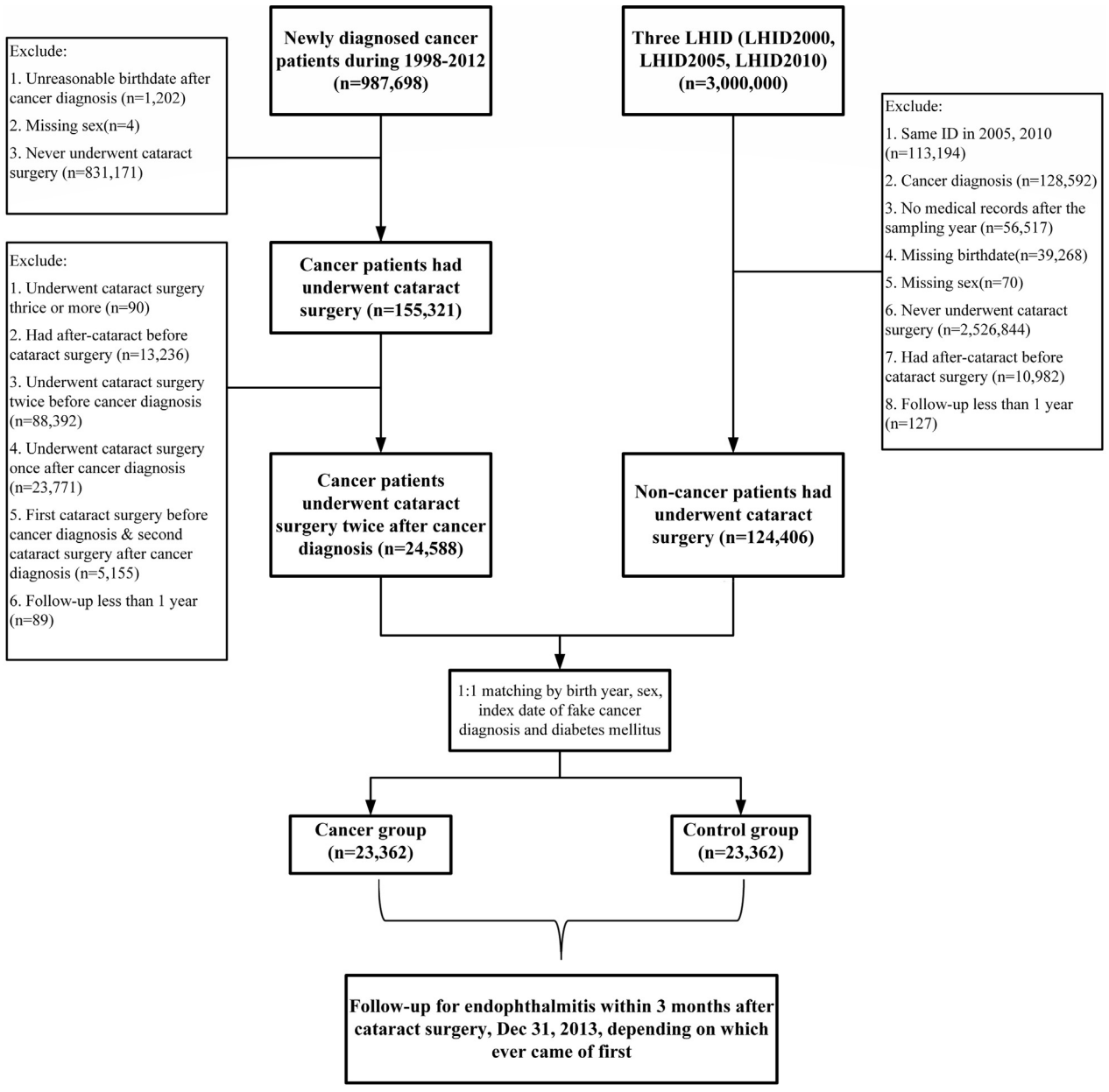

FIGURE 1. Flow chart of subjects included in study.

noncancer cohort to address the safety of cataract surgery in cancer patients. Our experience indicates that a matched cohort study of population-based data is useful for evaluating safety issues in patients with rare diseases.

METHODS

• **DATA SOURCE:** In 1995, Taiwan launched the compulsory single-payer NHI system, which covered 99.9% of the population as of 2014.[12] All claim files and registration files are stored with anonymized identification numbers in the NHI Research Database (NHIRD) and are available for academic use. The Institutional Review Board (IRB) of Chang Gung Medical Foundation, Taiwan, reviewed our research protocol and determined that this study did not require IRB approval because of the lowest risk to subjects' health and use of anonymized personal identification numbers (201702066B1).

• **CANCER COHORT:** The cancer cohort comprised patients with new cancer diagnoses (A codes A090-A141 before the year 2000 or ICD-9-CM codes 140-209 after 2000) during the years 1998-2012. In Taiwan, after histologic confirmation and a review of clinical records by

NHI administrators, cancer patients are provided with a catastrophic illness certificate, which results in a waiver of outpatient and inpatient copayments. A study that used the Taiwan Cancer Registry to validate cancer diagnoses in the NHIRD reported a high positive predictive value (94%), as it is mandatory for oncologists to report details of malignant tumors to the administration.[13]

Patients were excluded if data were questionable (Figure 1), such as a birthdate after the date of cancer diagnosis (n = 1202), or if data on sex were missing (n = 4). Patients who did not undergo cataract surgery were excluded (n = 831 171). We further excluded those who underwent cataract surgery more than twice (n = 90), who had an after-cataract before cataract surgery (n = 13 236), who underwent cataract surgery twice before cancer (n = 88 392), who underwent cataract surgery only once after a cancer diagnosis (n = 23 771), and who underwent cataract surgery once before and once after cancer diagnosis (n = 5155). We also excluded those with less than 1 year of follow-up (n = 89).

Cancer patients who had undergone only 1 cataract surgery were excluded because we were unsure whether this was the first or second eye surgery, and we wanted to compare endophthalmitis rates after first and second eye surgeries. Patients who had undergone only 1 cataract surgery might have undergone cataract surgery before 1995 (the start of the NHI), and such procedures would thus not have been recorded. We excluded patients with less than 1 year of follow-up after cataract surgery. Survival is short for some cancer patients, and endophthalmitis might have been underreported in the NHIRD because such patients would be unlikely to seek treatment for eye problems at the end of life.

In brief, the cancer cohort comprised new cancer patients who had undergone cataract surgeries of both eyes and had been followed for 1 year or longer after surgery during 1998-2012.

• **CONTROL COHORT:** The noncancer cohort was established from 3 NHIRD subsets: Longitudinal Health Insurance Databases (LHID) LHID2000, LHID2005, and LHID2010. The LHID2000 is a subset of longitudinal claims data for 1 million beneficiaries during 1996-2000 and was randomly selected from the entire population of NHI enrollees. The LHID2005 and LHID2010 datasets are 2 separate random samples of 1 million beneficiaries of the NHI program, in 2005 and 2010, respectively. Age, sex, and healthcare costs did not significantly differ between the 3 LHIDs and the entire NHI population.[14]

Control patients with the same ID in the 3 LHID data were excluded to avoid double counting of the same individuals (n = 113 194). We also excluded cancer patients (n = 128 592) and those with no medical records after the sampling year (n = 56 517), a missing birthdate (n = 39 268), missing data on sex (n = 70), and no history of cataract surgery (n = 2 526 844). We further excluded patients who had an after-cataract before cataract surgery (n = 10 982) and those followed for less than 1 year (n = 127).

• **STUDY DESIGN:** For each cancer patient, 1 control was matched 1:1 for sex, calendar year of birth, diabetes mellitus (DM) status, and cancer index date (during the same month). The cancer index date was defined as the date the catastrophic illness certificate for cancer was issued for the cancer patient. Sex, age, and DM are known risk factors for endophthalmitis after cataract surgery.[15–18] The cancer index date (ie, fake cancer index date) for matched noncancer patients was the date of a medical visit for any illness other than cancer during the same month as the cancer index date for matched cancer partners. By matching index dates, we ensured that cancer and noncancer patients survived long enough to receive cataract surgery. In total, 23 362 (95.0%) patients in the cancer group were matched to a patient in the noncancer group. To estimate the rate of endophthalmitis, cancer and noncancer patients were followed for 3 months after cataract surgery or until December 31, 2013, whichever came first.

• **ASCERTAINMENT OF CATARACT SURGERY AND ENDOPHTHALMITIS:** We identified surgical treatment for cataract by using the case payment system codes for cataract (97605K, 97606A, 97607B, 97608C, 97601K, 97602A, 97603B) and the payment code for cataract surgery (86008C). Endophthalmitis was defined as ICD-9-CM code 360.00.[11]

• **STATISTICAL ANALYSIS:** The incidence rate of endophthalmitis was calculated as the number of endophthalmitis cases within 3 months after cataract surgery divided by the cataract procedures performed. A 2-year moving average of the endophthalmitis incidence rate was calculated to determine how the rate varied with time after cancer diagnosis.[19] Two-year moving averages avoid fluctuations owing to rare annual events, and most patients with new cancer diagnoses finished their cancer treatment within 2 years. The 95% confidence interval (CI) was computed based on the relationship between the F distribution and binomial distribution.[20] Because of the enormous sample size for the 2 study groups, standardized mean difference (SMD) was used to compare data between the 2 study groups, and an SMD larger than 0.1 was considered statistically significant.[21] The χ^2 test and McNemar test were used to compare endophthalmitis outcomes between and within study groups, respectively. Subgroup analysis was used to determine how endophthalmitis rates differed in relation to cancer site and type of cancer treatment. Statistical significance was defined as a P value of $<.05$.

TABLE 1. Demographic Characteristics and Diabetes Status in Cancer and Matched Noncancer Cohorts, Taiwan, 1998-2012

	Cancer (n = 23 362 Subjects)	Non-cancer[a] (n = 23 362 Subjects)	
	n (%)	n (%)	SMD
Age at cancer diagnosis, years			.000
Mean ± SD	67.1 ± 8.7	67.1 ± 8.7	
<65	8969 (38.4%)	8964 (38.4%)	
≥65	14 393 (61.6%)	14 398 (61.6%)	
Age at first cataract surgery, years			.000
Mean ± SD	71.5 ± 8.3	71.6 ± 8.3	
<65	5036 (21.6%)	5022 (21.5%)	
≥65	18326 (78.4%)	18340 (78.5%)	
Age at second cataract surgery, years			.006
Mean ± SD	72.3 ± 8.3	72.52 ± 8.3	
<65	4524 (19.4%)	4473 (19.2%)	
≥65	18 838 (80.6%)	18 889 (80.8%)	
Sex			.000
Female	12 139 (52.0%)	12 139 (52.0%)	
Male	11 223 (48.0%)	11 223 (48.0%)	
Diabetes mellitus			.000
No	16 676 (71.4%)	16 676 (71.4%)	
Yes	6656 (28.6%)	6656 (28.6%)	
Urbanization level			.067
Urban	12 824 (54.9%)	12 108 (51.8%)	
Suburban	7648 (32.7%)	7884 (34.2%)	
Rural	2230 (9.6%)	2569 (11.0%)	
Not specified	660 (2.8%)	691 (3.0%)	
Monthly income (TWD)			.071
≥40 000	1442 (6.2%)	1392 (6.0%)	
20 000-39 999	7695 (32.9%)	8486 (36.3%)	
<20 000 or dependent	14 225 (60.9%)	13 484 (57.7%)	
Region			.026
Subtropical	14 998 (64.2%)	14 911 (63.8%)	
Intermediate	1409 (6.0%)	1556 (6.7%)	
Tropical	6715 (28.8%)	6651 (28.5%)	
Missing	240 (1.0%)	241 (1.0%)	

SMD = standardized mean difference.

[a]The noncancer group was matched 1:1 for sex, calendar year of birth, diabetes status, and cancer index date (within the same month). In the noncancer cohort, the cancer index date was defined as the date (during the same month as the cancer group) they presented for treatment of an illness other than cancer.

RESULTS

BECAUSE OF THE 1:1 MATCHED DESIGN, THERE WAS NO SIGnificant difference in age at cancer diagnosis (fake cancer index date for the control group), age at cataract surgery, sex, or DM status. There were slightly more women (52%) than men, and 28.6% of patients had DM. Mean age at first cataract surgery was 71 years, the mean interval between cancer diagnosis and cataract surgery was 4.3 years, the mean age at second cataract surgery was 72.3 years, and the mean interval between cataract surgeries was 8-9 months. There was no significant difference in urbanization level, monthly income, or region (Table 1).

There were 23 362 patients and 46 724 cataract procedures in each cohort. Endophthalmitis developed within 3 months after 110 cataract procedures in the cancer cohort and after 108 procedures in the noncancer cohort. The rate of endophthalmitis was 2.4‰ (95% CI = 1.9‰–2.8‰) in the cancer cohort and 2.3‰ (95% CI = 1.9‰–2.8‰) in the noncancer cohort ($P = .892$). The rate of endophthalmitis after the first and second cataract surgeries was similar between cohorts ($P = .658$ and $P = .864$, respectively; Table 2). Interestingly, the endophthalmitis rate after the second cataract surgery was higher than that after the first cataract surgery in both the cancer and noncancer cohorts ($P = .018$ and $P = .003$, respectively; Table 3).

Figure 2 shows the 2-year moving averages for endophthalmitis rate after the cancer index date in the cancer cohort and matched noncancer cohort. The 95% CIs for endophthalmitis rates in the cancer cohort and matched

TABLE 2. Rate of Endophthalmitis Within 3 Months After Cataract Surgery in the Cancer Cohort and Matched Noncancer Cohort, Taiwan, 1998-2012

	Cancer (n = 23 362 Subjects/46 724 Eyes)			Noncancer (n = 23 362 Subjects/46 724 Eyes)			
	Endophthalmitis	Incidence Rate	(95% CI)	Endophthalmitis	Incidence Rate	(95% CI)	*P* Value[a]
Endophthalmitis							
Eyes	110	2.4‰	(1.9‰–2.8‰)	108	2.3‰	(1.9‰–2.8‰)	.892
After first cataract surgery	43	1.8‰	(1.3‰–2.5‰)	39	1.7‰	(1.2‰–2.3‰)	.658
After second cataract surgery	67	2.9‰	(2.2‰–3.6‰)	69	3.0‰	(2.3‰–3.7‰)	.864

[a]χ^2 test.

TABLE 3. Endophthalmitis Rate After First and Second Cataract Surgeries in the Cancer Cohort and Matched Noncancer Cohort, Taiwan, 1998-2012

			P Value[a]
Cancer cohort			.018
		After second cataract surgery	
		No	Yes
After first cataract surgery	No	23 256	63
	Yes	39	4
Noncancer cohort			.003
		After second cataract surgery	
		No	Yes
After first cataract surgery	No	23257	66
	Yes	36	3

[a]McNemar test.

noncancer cohort overlap in all time periods, which indicates that the rates were similar. The difference was of borderline significance ($P = .065$) only at 1-2 years after cancer diagnosis between the 2 study groups.

Subgroup analyses of endophthalmitis rate with regard to cancer site and type of cancer treatment (Figure 3) showed no significant difference in relation to cancer site, as indicated by the overlapping 95% CIs. With respect to cancer treatment, surgery alone was most common (42.6%), followed by surgery combined with chemotherapy (17.1%). Endophthalmitis rate did not significantly differ in relation to cancer therapy.

DISCUSSION

IN THIS NATIONWIDE MATCHED COHORT STUDY, THE INCIdence rate of endophthalmitis after cataract surgery was 2.4‰ (95% CI = 1.9‰–2.8‰) for the cancer cohort, and the rate did not significantly differ in relation to cancer site or type of cancer treatment. The rates were similar for the cancer cohort and a control cohort matched for age, sex, DM status, and cancer index date. In sum, these results indicate that cataract surgery is safe for cancer patients.

Postoperative endophthalmitis was investigated in a number of large-scale studies of cataract surgery. A retrospective study at Farabi Eye Hospital in Iran reported 112 endophthalmitis cases out of 480 104 cataract surgeries during 2006-2014 (0.2‰).[15] DM and age older than 81 years were preoperative risk factors for postoperative endophthalmitis. A French nationwide study identified 6668 endophthalmitis cases out of 6 371 242 cataract surgeries (1.0‰) during 2005-2014.[16] The preoperative risk factor identified was male sex. A meta-analysis of 42 studies including 8963 endophthalmitis cases out of 6 686 169 patients (1.3‰) found that male sex and age older than 85 years were preoperative risk factors.[17] However, none of these studies analyzed endophthalmitis rate in cancer patients. The EPSWA study comparing endophthalmitis rates after cataract surgery in cancer and noncancer patients identified 11 endophthalmitis cases

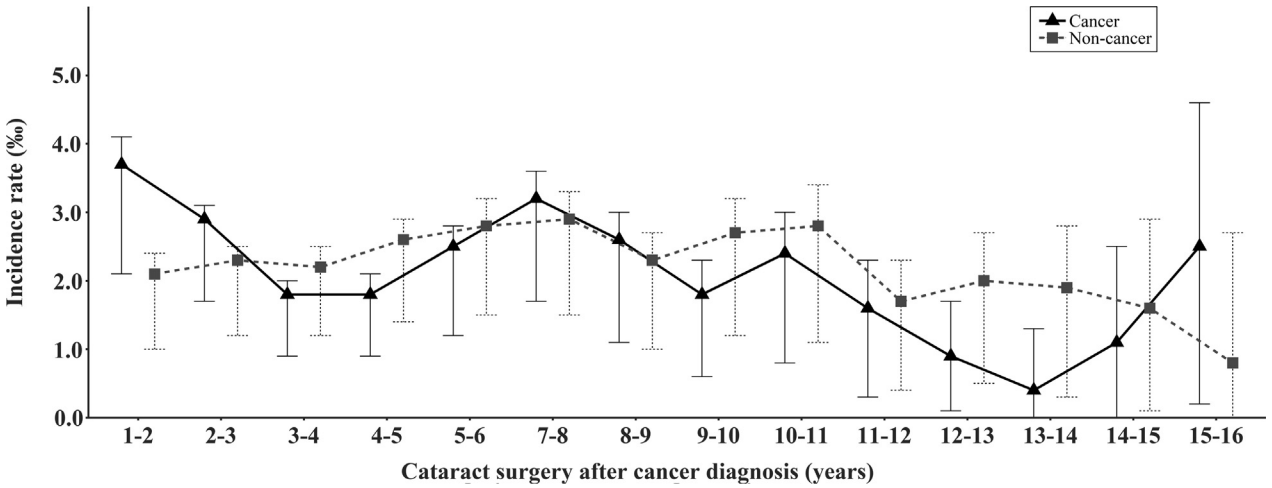

FIGURE 2. Two-year moving average of incidence rate of endophthalmitis within 3 months after cataract surgery in the cancer cohort and matched noncancer cohort, by interval after cancer diagnosis, Taiwan, 1998-2012. The noncancer group was matched 1:1 for sex, calendar year of birth, diabetes status, and cancer index date (within the same month). In the noncancer cohort, the cancer index date was defined as the date (during the same month as the cancer group) they presented for treatment of an illness other than cancer.

out of 4888 cataract surgeries (2.2‰) for patients with any cancer except skin cancer.[10] The odds ratio for endophthalmitis was 1.23 in cancer patients but was not statistically significant.

The present study identified 110 endophthalmitis cases out of 46 724 cataract surgeries for cancer patients. This is the first study to compare endophthalmitis rates in cancer patients and a cohort matched for the previously identified preoperative risk factors of age, sex, and DM status.[15–18] To eliminate bias owing to recent improvements in medical technology, the date of cancer diagnosis was matched by month. Cataract surgery during the previous year was associated with a higher endophthalmitis rate.[16,22] The annual incidence rate of endophthalmitis after cataract surgery in France decreased from about 1.4‰ in 2005-2007 to about 0.5‰ in 2013-2014.[16] The rate in Sweden decreased from around 0.6‰ in 2000-2002 to approximately 0.2‰ in 2018-2019.[22] The reduction in endophthalmitis incidence after cataract surgery may be attributable to improvement of surgical instruments, which reduces operation time, and adoption of antiseptic prophylaxis procedures, such as topical povidone-iodine and topical or intracameral antibiotics.[23–25] Our results show that the endophthalmitis rate after cataract surgery did not differ between cancer patients and a matched cohort.

Because the immune response to infection might be diminished and delayed in cancer patients, we analyzed postoperative endophthalmitis within 3 months after cataract surgery instead of within 6 weeks or a shorter interval. Almost all cases of postoperative endophthalmitis were reported within a 3-month period. Granulocyte, humoral, and T-cell function can be affected by cancer progression and chemotherapy.[3,4] This extension of the diagnostic window for endophthalmitis may partly explain why the present endophthalmitis incidence rate was slightly higher than those in other studies. Because the immune response in cancer patients was a concern, the endophthalmitis rate was also calculated by using ICD-9-CM codes 3600, 3601, 36403, 36405, and 36423, to investigate incidence rates of infectious and noninfectious endophthalmitis, combined, after cataract surgery in the cancer and noncancer cohorts. Using theses codes, we found that endophthalmitis rates during the 3 months after cataract surgery were similar between the groups: 5.4‰ (95% CI = 4.5‰–6.4‰) for the cancer cohort and 5.0‰ (95% CI = 4.1‰–6.0‰) for the noncancer cohort ($P = .521$).

In studies that classified surgical wounds from clean wounds to dirty wounds, rates of surgical infection at all body sites were higher for cancer patients than for noncancer patients.[6,7] In the present study, the endophthalmitis rate after cataract surgery was similar between cancer patients and noncancer patients. According to a guideline for prevention of surgical site infection, the risk factors for surgical site infection are DM, duration of the operation, hemostasis, obliteration of dead spaces, and presence of foreign bodies at the surgical site.[26] Several factors in the current cataract procedures prevented surgical site infection, including short operative duration (usually less than 30 minutes), absence of bleeding in most cases, and absence of remaining dead space. Cataract is not life threatening, and cataract surgery can usually be postponed until the end of cancer treatment. However, the possibility of cataract complications may sometimes make postponement impossible. In addition, because of the complexity of cancer therapy, cataract

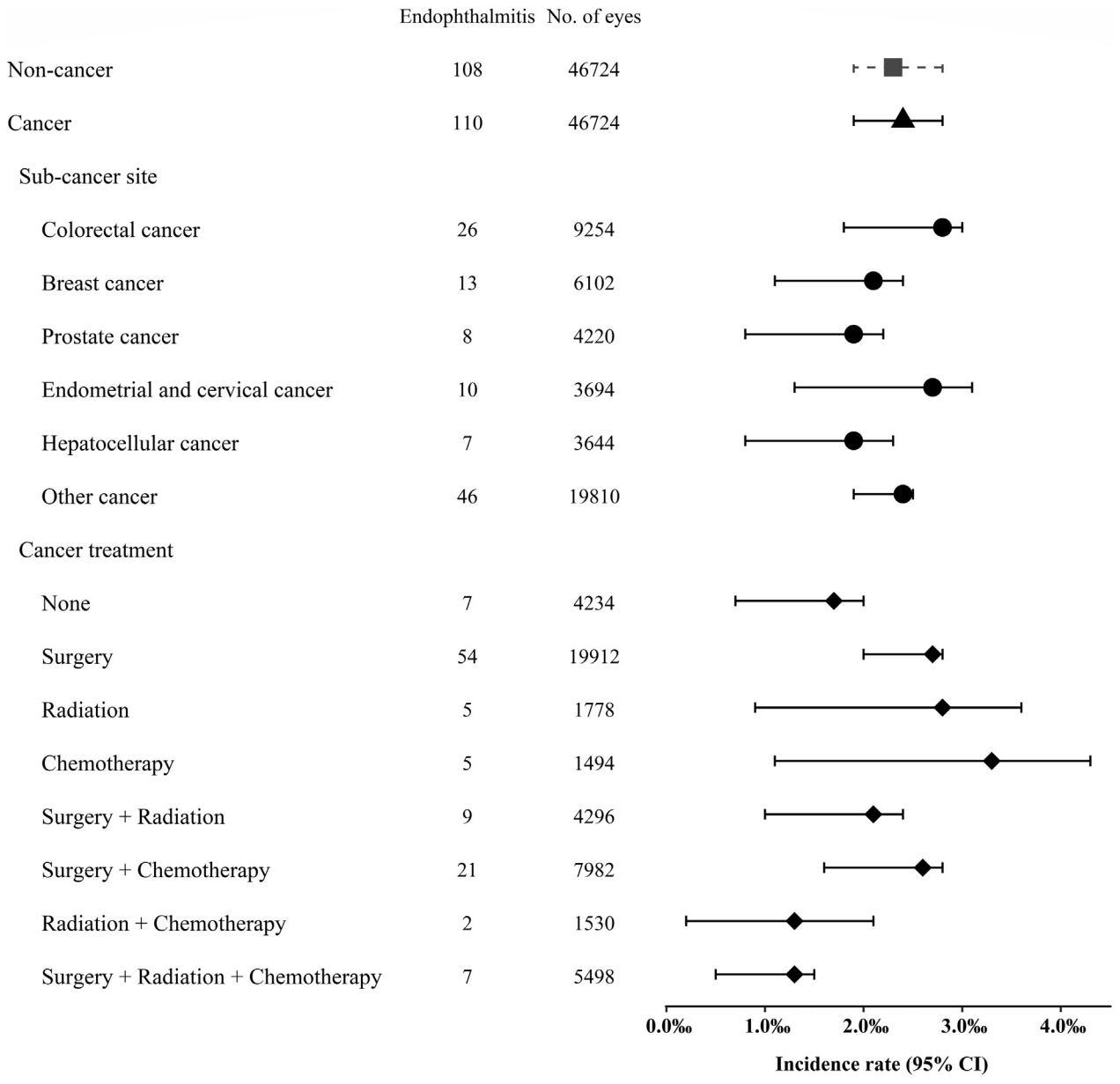

FIGURE 3. Incidence rate of endophthalmitis within 3 months after cataract surgery in the cancer cohort and matched noncancer cohort, by cancer site and type of cancer treatment, Taiwan, 1998-2012. Because of the very low incidence of endophthalmitis, the 5 most common cancer sites are listed, and the others are combined in the "other" category.

surgery may need to be done during or between treatments. We compared endophthalmitis rates after cataract surgery during various intervals after cancer diagnosis. Because aggressive treatment for cancer is usually started after the disease is diagnosed, the patient's general condition might be suboptimal in the early months or years after diagnosis. However, we found no significant difference in endophthalmitis rate between the cancer and noncancer cohort for any period after cancer diagnosis.

The rate of endophthalmitis after the second cataract surgery was higher than that after the first cataract surgery. A possible explanation for this finding is that patients strictly followed postoperative care instructions after the first cataract surgery but were less meticulous after the second eye surgery. Another explanation is that we only included patients with a record of 2 cataract surgeries. Those who developed endophthalmitis after the first cataract surgery might have been reluctant to consent to a second cataract surgery and would thus have been excluded from this study. The NHIRD did not indicate if a cataract surgery was the first, or merely the first recorded in the database, because it was begun in 1995 and surgical records

before that time were not included in the database. Therefore, we only included patients with a record of 2 cataract surgeries in this study.

The study was carefully designed to address the safety of cataract surgery among cancer patients. We assigned a fake cancer index date to the control group and matched the cancer group and control group by birth year and cancer index date, to ensure that both groups survived long enough to undergo cataract surgery. Second, patients who developed endophthalmitis after cataract surgery for the first eye might have postponed cataract surgery for the other eye. As we lacked data on cataract surgery procedures before 1995, we included only patients who had cataract surgery twice after a cancer diagnosis, in the cancer cohort, or fake cancer diagnosis, in the noncancer cohort. Third, financial constraints in seeking treatment for cancer or cataract were not a concern in this study because of the compulsory single-payer NHI system in Taiwan, which provides almost 100% coverage and affordable copayments.

Nevertheless, this study has limitations. First, disease codes might have been incorrectly entered by clinicians. To minimize this type of error, the Taiwan NHI Administration conducts regular reviews and assesses penalties when necessary. Second, noninfectious postoperative inflammation might have been treated and coded as endophthalmitis in our study. Endophthalmitis is sometimes a clinical diagnosis, and the positive rate for tissue culture is usually 50% or less.[15] This was the case in our study and in previous population-based reports.[9–11,16] We compared rates of combined infectious and noninfectious endophthalmitis in these 2 cohorts and found no difference, which suggests that miscoding was minimal in this study. Third, the details of surgical procedures are not available in the NHIRD. Thus, we could not analyze intraoperative risk factors such as antisepsis with povidone-iodine, wound position or size, duration of surgery, use of topical or intracameral antibiotics, posterior capsule integrity, or type of implanted intraocular lens. Surgical procedures vary by time period and country. We did not match the study groups by date of cataract surgery because too many records would have been excluded, but there was no difference in age at first cataract surgery or age at second cataract surgery between groups. The cancer and noncancer cohorts were matched by age and index date of cancer, and bias in intraoperative factors attributable to the calendar year of surgery was therefore minimized. We collected data from a very large number of cases (110 endophthalmitis cases out of 46 724 cataract surgeries in cancer patients), and we believe this substantially overcomes the limitations of our study. Fourth, we could not separate our cancer cohort into a stable, or "cured," group and a cancer progression group because of lack of data in the Taiwan NHIRD. The status of cancer patients is often unstable while they are receiving treatment during the first few years after diagnosis, and no significant difference in endophthalmitis rate was noted during these periods in this study.

In conclusion, cancer patients have a similar risk of endophthalmitis following cataract surgery as the noncancer population, and the current study suggests that cataract surgery can be considered as appropriately indicated for cancer patients.

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