Risk of Leukemia after Dengue Virus Infection: A Population-Based Cohort Study

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ABSTRACT

Background: Infections account for about 15% of human cancers globally. Although abnormal hematologic profiles and bone marrow suppression are common in patients with dengue, whether dengue is associated with a higher risk of leukemia has not been investigated.

Methods: We conducted a nationwide population-based cohort study by analyzing the National Health Insurance Research Databases in Taiwan. Laboratory-confirmed dengue patients between 2002 and 2011 were identified; five matched non-dengue controls were randomly selected for each patient. Follow-up ended on December 31, 2015. Multivariate Cox proportional hazard regression models were used to evaluate the effect of dengue virus infection on the risk of leukemia. Cancers other than leukemia were used as falsification endpoints to evaluate the validity of this study.

Results: We identified 12,573 patients with dengue and 62,865 non-dengue controls. Patients with dengue had a higher risk of leukemia [adjusted HR, 2.03; 95% confidence interval (CI), 1.16–3.53]. Stratified analyses by different follow-up periods showed that dengue virus infection was significantly associated with a higher risk of leukemia only between 3 and 6 years after infection (adjusted HR, 3.22; 95% CI, 1.25–8.32). There was no significant association between dengue and the risk of other cancers.

Conclusions: This study provides the first epidemiologic evidence for the association between dengue virus infection and leukemia.

Impact: Considering the rapidly increasing global incidence of dengue and the burden of leukemia, further studies are required to verify this association and to unravel the potential mechanisms of pathogenesis.

Introduction

According to recent statistics, there are approximately 17.2 million new cancer cases and 8.9 million cancer-related deaths worldwide per year (1). Among them, infections account for about 15% of human cancer cases (2). Several pathogens have been recognized by the International Agency for Research on Cancer as Group 1 carcinogens, which mean that there is sufficient evidence of carcinogenicity in humans or there is both strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens and sufficient evidence of carcinogenicity in experimental animals (3). Hepatocellular carcinoma caused by hepatitis virus B or hepatitis virus C, cervical cancer caused by human papillomavirus, nasopharyngeal carcinoma caused by Epstein–Barr virus, and Kaposi sarcoma caused by human herpesvirus-8 are all well-known infection-attributable cancers (2). For hematologic malignancies, examples of such causal relationships include those between human T-cell leukemia virus type I and adult T-cell leukemia, Epstein–Barr virus and Burkitt lymphoma and Hodgkin lymphoma, human immunodeficiency virus and Hodgkin lymphoma and non-Hodgkin lymphoma, hepatitis C virus and non-Hodgkin lymphoma, and *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue lymphoma (2).

Dengue fever is an important mosquito-borne infectious disease (4). Over the past decades, the incidence of dengue has dramatically increased worldwide with significant geographical expansion to new countries and regions, which probably results from rapid urbanization, increasing frequency of travel, and global climate change (5). An estimated 390 million people are infected by dengue virus every year, of which 25% are symptomatic (5, 6).

Abnormal hematologic profiles, such as leukopenia, thrombocytopenia, and atypical lymphocytes, are hallmark laboratory findings in patients with dengue (5). Bone marrow suppression is also commonly observed in patients with dengue in the early stage of infection (7–9). Moreover, dengue virus can be recovered from bone marrows of both fatal and survival human subjects (10). In-line with these clinical observations, cumulative laboratory evidence suggests that hematopoietic progenitor cells in bone marrow, in both *in vitro* and *ex vivo* systems, as well as *in vivo* nonhuman primates, are highly infectable by dengue virus (11–15). Furthermore, case reports of acute myeloid leukemia precipitated by dengue virus infection (16) and dengue virus infection–mimicking plasma cell leukemia (17) have been documented. These clues guided us to hypothesize that dengue virus infection might be associated with leukemia.

Here we investigated whether the risk of leukemia was increased after dengue virus infection by analyzing nationwide population databases in Taiwan. In dengue hyperendemic countries, most of the

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people have been infected by dengue virus multiple times (18), making the selection of uninfected people for comparison challenging. The availability of comprehensive nationwide databases (19, 20), as well as the low incidence of dengue in Taiwan provided us unique and valuable resources to test this hypothesis.

Materials and Methods

Data sources and study population

A population-based cohort study was conducted by analyzing the National Health Insurance Research Databases (NHIRD) and the Notifiable Disease Dataset of Confirmed Cases (19). The former database contains detailed medical insurance claims from the National Health Insurance (NHI) program, which covers >99.6% of the total population of over 23 million in Taiwan (19). All information for each person in NHIRD was linked through an encrypted unique personal identification number, which also allowed linkage to multiple national databases including registries of birth, deaths, and reportable infectious diseases (19, 20). In Taiwan, reporting suspected patients with dengue is mandatory by law. Blood samples from suspected cases should be tested by certified laboratories approved by the Taiwan Centers for Disease Control to confirm the diagnosis of dengue during the study period. The laboratory criteria for confirmed dengue infection evolved over the study period but generally included the following: (i) virus isolation; (ii) detection of RNA by real-time reverse transcription PCR; (iii) 4-fold rise in IgG titer in paired acute- and convalescent-phase samples; and (iv) detection of dengue-specific IgM and IgG antibody in single serum samples (21).

We identified newly confirmed dengue cases between 2002 and 2011 from the Notifiable Disease Dataset of Confirmed Cases. The date of symptom onset recorded in this database for each patient was defined as the index date; those who had a missing ID or were not enrolled in the NHI Program were excluded. Five non-dengue controls were randomly selected from the NHIRD for each dengue case by matching on age, sex, area of residence (Tainan, Kaohsiung, Pingtung, and others), and the calendar year of the index date. The matched controls had the same index date as the corresponding case. Participants who had cancer before the index dates or died within 60 days after the index dates were excluded from both the dengue group and non-dengue group (**Fig. 1**).

Study outcome and follow-up

The primary outcome of interest of this study was leukemia, defined as at least three outpatient visits or one hospital admission with relevant ICD-9-CM codes (Supplementary Table S1) plus the use of at least one chemotherapy drug for hematologic malignancies suggested in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. The death dates of the study participants were retrieved by linking to the Cause of Death Data in Taiwan. Participants in both groups were followed from the index date until the diagnosis of leukemia, death, or the end of follow-up on December 31, 2015, whichever occurred first.

Covariates

The sociodemographic variables considered in this study included age, sex, area of residence, urbanization level, and monthly income level. Dengue epidemics usually occurred in southern Taiwan, especially in Tainan, Kaohsiung, Pingtung, and only sporadic cases or small clusters could be found in the remaining parts of Taiwan. All city districts and towns in Taiwan were classified into seven urbanization levels, in which one was the most urbanized and seven was the least urbanized according to Liu and colleagues (22). Because only a small percentage of people lived in levels four to seven, we combined these four levels into a single urbanization stratum, we referred to as level 4. The monthly income was classified into three levels (unemployed, low, and high). Several lifestyle-related diseases, including chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, diabetes mellitus, and peptic ulcer disease, were considered as potential confounders. These comorbidities for each subject were defined as at least three outpatient visits or one hospital admission with relevant ICD-9-CM codes (Supplementary Table S2) between January 1, 2000 and the index date.

Statistical analysis

The baseline characteristics between dengue and non-dengue groups were compared using standardized mean differences, and a meaningful difference between groups was considered when the standardized mean difference was greater than 0.1 (23). The incidence rate of leukemia was calculated as the number of patients diagnosed during follow-up divided by total follow-up time in person-year for both groups (24). We constructed multivariable Cox proportional hazard regression models to estimate HRs and 95% confidence intervals (CI) for leukemia among dengue virus–infected people compared with uninfected people, adjusting for potential confounders as listed above. The proportional hazard assumption was checked by using log–log survival plots. Because the majority of dengue cases were adults, many of whom were the elderly, and the follow-up time in our study was long, subdistribution hazard models proposed by Fine and Grey were also used to account for the competing risk of death for sensitivity analyses (25).

In addition, it usually takes at least 2–3 years for leukemia to develop (26–29); therefore, we investigated HRs of leukemia in different follow-up periods after dengue virus infection (<3 years and $\geq$3 years; follow-up time $\geq$ 3 years was further categorized into 3–6 years and >6 years). To investigate whether dengue virus infection was specifically associated with leukemia, we additionally examined the association between dengue virus infection and lymphoma, as well as other non-hematologic cancers as defined in Supplementary Table S1. These cancers, furthermore, could serve as prespecified falsification end points, also known as negative controls, which have been reported as a useful tool to validate findings from observational studies (30, 31). Stratified analyses by age (<18 and $\geq$18 years old) were also performed to evaluate whether the association between dengue virus infection and leukemia differed between children and adults. All analyses were performed using SAS 9.4 (SAS Institute). Results were considered statistically significant for two-tailed $P < 0.05$.

Ethics statement

This study used national databases obtained from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare in Taiwan. All data obtained were anonymized and deidentified by the HWDC. The data used in this study must be accessed and analyzed in the HWDC under its regulation after filling out an application and thus cannot be shared. This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (approval no. B-ER-106-184).

Results

We identified 12,573 eligible cases of confirmed dengue virus infection and 62,865 matched non-dengue controls. The median follow-up time was 8.22 years [interquartile range (IQR)

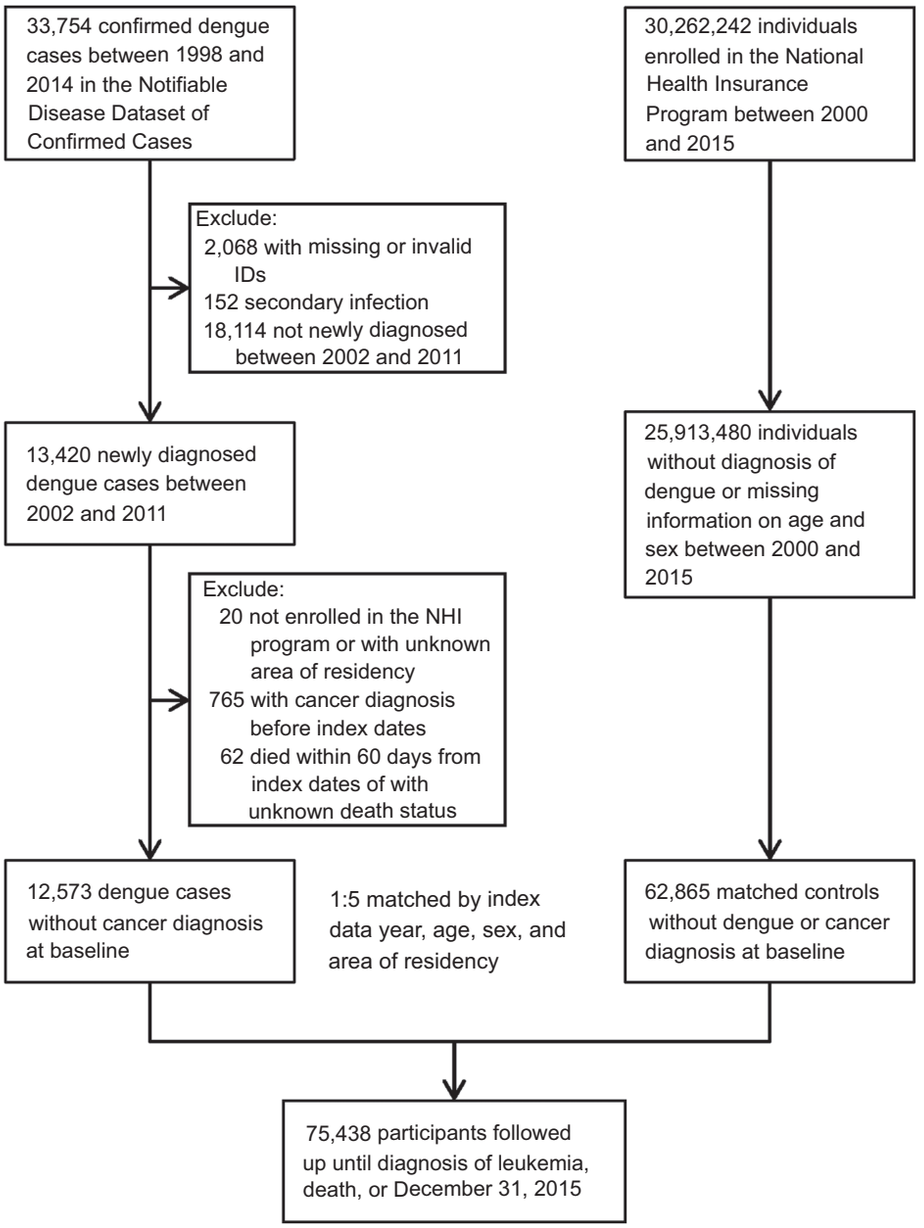

Figure 1.
Flow diagram for identifying the study population.

5.30–13.15] in dengue virus–infected people and 8.22 years (IQR 5.28–13.15) in the control group. The demographic and clinical characteristics of the study population are tabulated in **Table 1**. There was no meaningful difference in the prevalence of five selected comorbidities between the two groups, but dengue cases seemed to live in more urbanized areas than the controls did (**Table 1**).

The overall incidence rate of leukemia was 17.20 (95% CI, 10.35–26.86) and 7.85 (95% CI, 5.68–10.57) per 100,000 person-years in dengue cases and non-dengue groups, respectively. After adjusted for age, sex, area of residence, urbanization level, monthly income level, and comorbidities, previous dengue virus infection was associated with a higher risk for leukemia (adjusted HR 2.03; 95% CI, 1.16–3.53; $P = 0.013$; **Table 2**). Further classification of leukemia suggested positive associations between previous dengue virus infection and all leukemia subtypes, although the associations were not statistically significant, probably due to the low case number for each subtype. Sensitivity analyses using subdistribution hazard models showed similar results. The characteristics of the leukemia cases are shown in Supplementary Table S3.

Time is an important element in cancer formation. Considering different follow-up periods, previous dengue virus infection was associated with a higher risk of leukemia only after 3 years of infection (adjusted HR 2.13; 95% CI, 1.15–3.93; $P = 0.016$; **Table 3**), particularly between 3 and 6 years after infection (adjusted HR 3.22; 95% CI, 1.25–8.32; $P = 0.016$; **Table 3**). We also investigated the association between dengue virus infection and the risk of lymphoma and other non-hematologic malignancies, but no significant association was found (**Table 4**).

Stratified analyses by age were also performed to evaluate whether the association between dengue and leukemia differed between

Table 1. Demographic and clinical characteristics of the study population by dengue virus infection status.

	Dengue cohort ($n = 12,573$)	Non-dengue cohort ($n = 62,865$)	Standardized mean difference
Sex			
Female	6,250 (49.7)	31,250 (49.7)	—
Male	6,323 (50.3)	31,615 (50.3)	—
Age			
0–17	1,222 (9.7)	6,110 (9.7)	—
18–35	2,829 (22.5)	14,145 (22.5)	—
36–50	3,279 (26.1)	16,395 (26.1)	—
51–65	3,635 (28.9)	18,175 (28.9)	—
≧66	1,608 (12.8)	8,040 (12.8)	—
Area of residence			
Tainan	2,408 (19.2)	12,040 (19.2)	—
Kaohsiung	8,479 (67.4)	42,395 (67.4)	—
Pingtung	678 (5.4)	3,390 (5.4)	—
Others	1,008 (8.0)	5,040 (8.0)	—
Urbanization level			
1 (highest)	4,462 (35.5)	15,700 (25.0)	0.2372
2	5,609 (44.6)	21,677 (34.5)	0.2111
3	1,757 (14.0)	15,049 (23.9)	0.2378
4–7 (lowest)	745 (5.9)	10,439 (16.6)	0.2929
Monthly income level			
Unemployed	5,183 (41.2)	22,873 (36.4)	0.1001
Low	3,537 (28.1)	20,982 (33.4)	0.1120
High	3,853 (30.7)	19,010 (30.2)	0.0088
Comorbidity			
COPD	690 (5.5)	3,070 (4.9)	0.0278
Hypertension	2,663 (21.2)	11,566 (18.4)	0.0711
Hyperlipidemia	1,731 (13.8)	6,826 (10.9)	0.0914
Peptic ulcer disease	2,055 (16.3)	8,844 (14.1)	0.0647
Diabetes	1,291 (10.3)	5,668 (9.0)	0.0432

children and adults. However, only 1,222 (9.7%) of the dengue cases in this study were <18 years of age, none of whom subsequently develop leukemia. Therefore, the association in children could not be explored because of the small sample size and low leukemia incidence. After excluding children, dengue virus infection was associated with a higher risk of leukemia among adults (adjusted HR 2.05; 95% CI, 1.17–3.58; $P = 0.012$). All the HRs obtained in adults were very close to HRs obtained in the original analyses.

Discussion

In this nationwide population-based cohort study, we found that the risk of developing leukemia was significantly higher in people with previous dengue virus infection. Unlike solid cancers which usually take at least 10 years to develop (32), the minimum latent period of leukemia after a detrimental exposure is generally considered to be around 2–3 years (26–29). In this study, the adjusted HR reached to 3.22 with statistical significance between 3 and 6 years after dengue virus infection, but the HRs within 3 years and after 6 years were smaller and not statistically significant (**Table 3**), suggesting a temporal relationship and potential causation between single decisive dengue virus exposure and leukemia with a peak incidence occurring between 3 and 6 years (33). The effect of dengue virus infection on cancers seems to be very specific to leukemia, not to lymphoma or other non-hematologic cancers.

Classical symptoms of dengue include sudden onset of high fever and chills, malaise, headache, retro-orbital pain, arthralgia, myalgia, bone pain, nausea, vomiting, and rash (5). While dengue can proceed to life-threatening complications including severe bleeding and shock in a small proportion of people, most of the affected individuals recover spontaneously as fever resolves (5). Therefore, dengue has traditionally been viewed as an acute febrile illness without long-term sequela. However, persistent dengue symptoms lasting for months or even years have been reported in Cuba, Peru, and Brazil (34–37). For example, Garcia and colleagues reported that over half of patients with dengue had persistent dengue symptoms in the 2-year follow-up after dengue virus infection, and autoimmune marker alterations were commonly found in these patients (36). In addition, one recent retrospective cohort study using NHIRD in Taiwan showed that patients with dengue had a higher risk of developing autoimmune diseases after acute dengue virus infection (38). Therefore, there is increasing evidence suggesting that dengue may not be just an acute illness and may have some long-term effects on the affected people.

Bone marrow examination studies in previous decades have shown that bone marrow transient cell suppression is a salient finding in patients with dengue during the early febrile stage (7–9). Despite these early discoveries, bone marrow biopsies were rarely done in later studies probably due to the increased bleeding risk in performing such

Table 2. Comparison of the incidence of leukemia by dengue virus infection status.

	Dengue cohort		Non-dengue cohort							
Cancer	No. of events	Incidence rate (per 100,000 person-years)	No. of events	Incidence rate (per 100,000 person-years)	Crude HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Adjusted SHR[a] (95% CI)	*P*
All leukemia	19	17.20	43	7.85	2.19 (1.28–3.76)	0.004	2.03 (1.16–3.53)	0.013	2.06 (1.21–3.49)	0.008
Lymphocytic leukemia[b]	6	5.43	15	2.74	1.98 (0.77–5.11)	0.156	2.04 (0.77–5.40)	0.150	2.06 (0.78–5.43)	0.144
Myeloid leukemia	10	9.05	28	5.11	1.77 (0.86–3.64)	0.122	1.62 (0.77–3.42)	0.203	1.65 (0.83–3.30)	0.156
AML	6	5.43	19	3.47	1.56 (0.63–3.92)	0.340	1.25 (0.49–3.20)	0.638	1.28 (0.53–3.09)	0.589
CML	3	2.72	9	1.64	1.65 (0.45–6.09)	0.453	2.04 (0.52–8.05)	0.310	2.06 (0.58–7.38)	0.266

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; No., number; SHR, subdistribution HR.
[a]Adjusted for age, sex, area of residence, urbanization level, monthly income level, and comorbidities.
[b]Lymphocytic leukemia was not further classified into acute lymphoblastic leukemia and chronic lymphocytic leukemia because results less than three individuals were not allowed to be exported under the regulations of the HWDC in Taiwan.

Table 3. Comparison of the incidence of leukemia by dengue virus infection status, stratified by follow-up period.

	Dengue cohort		Non-dengue cohort							
Year	No. of events	Incidence rate (per 100,000 person-years)	No. of events	Incidence rate (per 100,000 person-years)	Crude HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Adjusted SHR[a] (95% CI)	*P*
<3	3	8.01	9	4.82	1.66 (0.45–6.13)	0.447	1.69 (0.44–6.48)	0.446	1.70 (0.48–6.00)	0.414
≥3	16	21.91	34	9.41	2.33 (1.29–4.22)	0.005	2.13 (1.15–3.93)	0.016	2.14 (1.19–3.85)	0.011
3–6	8	24.31	10	6.13	3.97 (1.57–10.05)	0.004	3.22 (1.25–8.32)	0.016	3.25 (1.30–8.11)	0.012
>6	8	19.94	24	12.11	1.65 (0.74–3.67)	0.221	1.60 (0.70–3.65)	0.267	1.59 (0.72–3.49)	0.249

Abbreviations: No., number; SHR, subdistribution HR.
[a]Adjusted for age, sex, area of residence, urbanization level, monthly income level, and comorbidities.

a procedure for patients with dengue. *In vitro* and *ex vivo* experimental studies have demonstrated that dengue virus can efficiently infect hematopoietic progenitor cells (11, 12, 15) and only replicates in leukocytes derived from the bone marrow and not from lymph nodes, spleen, or thymus (39). Very recently, studies in nonhuman primates have revealed that intravenous injection of dengue virus results in infection of bone marrow cells where dengue virus can be recovered (13, 14). These laboratory data together with results from the aforementioned long-term follow-up studies of patients with dengue (34–38) and our study suggest that hematopoietic stem cells infected by dengue virus may cause aberrations in hematopoietic and immune systems in some individuals for a long period of time, which, to some extent, may result in persistent symptoms, as well as increased risk of leukemia and autoimmune diseases after acute infections.

This study has a number of strengths. The use of nationwide population-based databases with very high coverage rates makes selection bias and loss of follow-up unlikely. Also, all the dengue cases were laboratory confirmed and leukemia was defined using ICD-9 codes plus the use of chemotherapy drugs, minimizing misclassification bias for both exposure and outcome. Furthermore, the main strength of this study is that cancers other than leukemia were used as falsification end points, which were prespecified negative outcomes that were not expected to be affected by dengue virus exposure (30, 31). Current clinical and laboratory evidence shows that dengue virus can infect hematopoietic stem cells in bone marrow (11–15), suggesting a possible link to leukemia, but not to other cancers. As anticipated, our results showed that dengue virus infection was associated with a higher risk of leukemia, but was not associated with cancers other than leukemia, suggesting that the observed association between dengue virus and leukemia in our study is consistent with current evidence and is less likely due to a result of unmeasured confounders, detection bias, or other sources of bias (30, 31). Moreover, considering the general latent period of leukemia (26–29), within 3 years after dengue virus infection could serve as a falsification period (31) when dengue virus was expected to show no association with leukemia. We did find that the risk of leukemia did not differ between dengue and non-dengue groups within 3 years after dengue virus infection, thus further strengthening the validity of this study.

There are also several limitations to this study. First, approximately 75% of dengue virus infections are asymptomatic (5), and some symptomatic cases do not seek medical care and therefore cannot be detected by the surveillance system. As a result, the dengue virus infection status of some people in the non-dengue group might have been misclassified. However, because dengue incidence was

Table 4. Comparison of the incidence of other cancers by dengue virus infection status.

	Dengue cohort		Non-dengue cohort							
Cancer[a]	No. of events	Incidence rate (per 100,000 person-years)	No. of events	Incidence rate (per 100,000 person-years)	Crude HR (95% CI)	*P*	Adjusted HR[b] (95% CI)	*P*	Adjusted SHR[b] (95% CI)	*P*
All lymphoma	16	14.48	75	13.69	1.06 (0.62–1.81)	0.839	0.87 (0.51–1.52)	0.632	0.89 (0.51–1.56)	0.680
Nasopharynx	9	8.14	42	7.66	1.06 (0.52–2.18)	0.868	1.21 (0.58–2.52)	0.620	1.28 (0.58–2.56)	0.604
Esophagus	11	9.95	87	15.87	0.63 (0.33–1.17)	0.144	0.60 (0.32–1.14)	0.119	0.61 (0.33–1.15)	0.128
Stomach	32	28.98	161	29.39	0.99 (0.67–1.44)	0.940	0.96 (0.65–1.42)	0.829	0.98 (0.66–1.46)	0.930
Colon, rectum, and anus	127	115.33	562	102.85	1.12 (0.92–1.36)	0.247	1.09 (0.89–1.32)	0.420	1.11 (0.91–1.36)	0.318
Liver and intrahepatic bile ducts	90	81.57	539	98.50	0.83 (0.66–1.04)	0.097	0.84 (0.67–1.05)	0.129	0.86 (0.68–1.08)	0.193
Lung, trachea, and bronchus	110	99.68	529	96.65	1.03 (0.84–1.27)	0.772	0.96 (0.77–1.18)	0.685	0.98 (0.79–1.21)	0.831
Female breast	66	118.14	366	132.08	0.89 (0.69–1.16)	0.401	0.84 (0.64–1.10)	0.199	0.85 (0.65–1.11)	0.228
Cervix	8	14.26	67	24.07	0.59 (0.29–1.23)	0.161	0.57 (0.27–1.21)	0.143	0.58 (0.28–1.21)	0.146
Prostate	52	95.96	200	74.40	1.29 (0.95–1.75)	0.104	1.13 (0.82–1.56)	0.454	1.16 (0.83–1.62)	0.380

Abbreviations: No., number; SHR, subdistribution HR.
[a]Results for brain tumors were not reported because results of fewer than three individuals were not allowed to be exported under the regulations of HWDC in Taiwan.
[b]Adjusted for age, sex, area of residence, urbanization level, monthly income level, and comorbidities.

extremely low in most parts of Taiwan before 2011 and the overall seroprevalence of dengue virus infection remains low (40), misclassification bias of exposure status in this study should be very small. In addition, because we found that people with previous dengue virus infection had a higher risk of leukemia, this misclassification should result in bias toward the null, indicating that the true HR regarding the association between dengue virus and leukemia should be even higher than estimated in our study. Therefore, this misclassification bias should not affect our conclusion. Second, we were unable to control several risk factors for leukemia, including lifestyles (e.g., smoking, obesity, and dietary intake) and environmental exposures (e.g., radiation, chemicals, and air pollution; ref. 41), because the NHIRD does not contain such information. However, we included several lifestyle-related diseases and demographic variables, which could serve as proxies for lifestyles and environmental exposures for confounding control. Third, under the regulations of the HWDC in Taiwan, individual data and results of fewer than three individuals were not allowed to be exported to prevent reidentification (19). Therefore, some analyses (**Tables 2** and **4**) and a more detailed description of the 19 possible dengue virus–associated leukemia cases (Supplementary Table S3) could not be reported. Fourth, we only identified 12,573 confirmed dengue cases over 10 years in Taiwan, and the incidence of leukemia was low; therefore, the number of leukemia cases occurring during the follow-up period in the dengue group was low. As a result, further analyses of the association between dengue virus infection and specific leukemia subtypes lacked statistical power. Finally, leukemia is the most common cancer in children (42) and most of the patients with dengue in hyperendemic countries are also children. However, we failed to examine the association between dengue and leukemia in children because less than 10% of the dengue cases were children in Taiwan.

Our study provides the first epidemiologic evidence of the association between dengue virus and the risk of leukemia. The results need to be validated in other countries where population-based health information databases are available. In addition, southern Taiwan experienced two successive severe dengue outbreaks in 2014 and 2015, which caused more than 58,000 confirmed dengue cases. Investigating the risk of leukemia among these cases a few years later when the follow-up time is sufficient and their data are available in NHIRD can further confirm the findings of this study.

If prior dengue virus infection really increases the risk of leukemia, this would profoundly alter the disease burden attributable to dengue virus. The mechanisms of oncogenic viruses include the integration of viral genome into the host genome, promotion of host cell replication, chronic inflammation, and immunosuppression (43). In our study, we found a more than 3-fold increase in the risk of leukemia overall between 3 and 6 years after dengue virus infection, but did not identify a leukemia subtype specifically associated with dengue virus. Although different leukemia subtypes are generally considered to be biologically distinct disorders associated with different genetic lesions, previous studies have shown that dengue virus can infect $CD133^+$ or $CD34^+$ cells (15), marker for primitive or multipotential hematopoietic stem cells, respectively, in bone marrow which can differentiate into a variety of blood cells. Therefore, it is possible that dengue virus infection contributes to the pathogenesis of many different types of leukemia. Although the potential mechanisms remain to be explored, our preliminary observations suggest that transcriptional factors are affected in hematopoietic stem cells upon dengue virus infection. Considering the increasing global incidence of dengue and the burden of leukemia, further studies are urgently needed to verify our findings and to investigate how dengue virus infection may affect and manipulate the transcriptional factors in hematopoietic stem cells, and whether there are other mechanisms which may contribute to the development of leukemia after dengue virus infection.

Infection-associated cancers account for a significant portion of the global cancer burden and are potentially preventable by effective vaccines, screening programs, and other preventive measures. Here we conducted a population-based cohort study using NHIRD in Taiwan and found that dengue virus infection was associated with a higher risk of leukemia, particularly after 3 years of infection, but was not associated with other cancers. Although this study provides epidemiologic evidence for the association between dengue virus infection and leukemia, further epidemiologic and experimental studies are required to verify this association and to unravel the potential mechanisms of pathogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y.-W. Chien, C.-Y. Lee, G.C. Perng
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