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# Cancer Risk in Patients With Chronic Urticaria

## A Population-Based Cohort Study

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**Objective:** To investigate the relative risk of cancer among patients with chronic urticaria in the Taiwanese population.

**Design:** Retrospective population-based cohort study.

**Setting:** The National Health Insurance Research Database of Taiwan from January 1, 1996, through December 31, 2008.

**Participants:** A total of 12 720 patients with chronic urticaria, with long-term antihistamine use and no history of malignant tumors, autoimmune diseases, atopy, or allergic diseases.

**Main Outcome Measure:** Relative cancer risk calculated by standardized incidence ratios.

**Results:** There were 704 cancers among chronic urticaria patients. An increased risk of cancer (standardized incidence ratio, 2.2; 95% CI, 2.0-2.3), especially hematologic malignant tumor (4.1; 3.1-5.4), was observed. The relative risk of cancer varied by age and was highest among those aged 20 to 39 years in comparison with the general population. Most cancer cases were detected within the first year of diagnosis. The risk of non-Hodgkin lymphoma was greatest (standardized incidence ratio, 4.4; 95% CI, 3.0-6.1) among the hematologic cancers.

**Conclusions:** Patients with chronic urticaria are at increased risk of cancer, especially hematologic malignant tumors. Further studies are needed to delineate the associations.

*Arch Dermatol.* 2012;148(1):103-108

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CHRONIC URTICARIA IS A common and frustrating disorder, characterized by a diverse and heterogeneous presentation. The pathogenic mechanisms of chronic urticaria remain elusive. *Chronic urticaria* is defined as urticaria that persists for more than 6 weeks with daily or nearly daily symptoms. More than 50% of patients continue to experience chronic urticaria 10 years after initial diagnosis,<sup>1</sup> and most of these patients need long-term treatment. In contrast to acute urticaria, there is no evidence of an exogenous allergen as a cause of this disorder. On the basis of different clinical presentations, chronic urticaria can be classified as ordinary urticaria, physical urticaria, angioedema, contact urticaria, or urticarial vasculitis.

Although there have been case reports of urticaria associated with malignant tumor, a study of more than 1000 patients showed no association between chronic ur-

ticaria and malignant tumor.<sup>2</sup> Urticarial vasculitis sometimes occurs in patients with lymphoproliferative disease, such as mixed cryoglobulinemia and IgM gammopathy.<sup>3</sup> Urticarial vasculitis with IgM gammopathy or Schnitzler syndrome has been associated with a higher frequency of hematologic malignant tumors.<sup>4,5</sup> Only limited epidemiologic information is available about the exact extent of the association between chronic urticaria and cancer. Our aim was to evaluate the relative risk of cancer occurrence among chronic urticaria patients who have received long-term antihistamine treatment by means of a nationwide population-based database of Taiwan.

## METHODS

### DATA SOURCES

This study was based on data from the National Health Insurance Research Database

(NHIRD) released by the National Health Research Institute. Taiwan began its National Health Insurance program in 1995 to finance health care for all of its residents. There are presently more than 23 million enrollees in the program, representing approximately 99% of Taiwan's population. The NHIRD contains registration files and original claims data for reimbursements for all enrollees, making it one of the largest and most complete nationwide population-based health care services data sets in the world. In this database, the diagnostic codes of the patients, in the format of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, were established by the board-certified physicians in the corresponding specialties. The accuracy of diagnosis of major diseases in the NHIRD, such as diabetes mellitus and stroke, has been validated,<sup>6,7</sup> and this database has been used extensively in many epidemiologic studies in Taiwan.<sup>8-12</sup> Personal information, including family history, lifestyle, and habits such as smoking and alcohol use, was not available from the NHIRD.

## STUDY PATIENTS

This retrospective population-based cohort study made use of data from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD that contains all the original claims data from 1 000 000 individuals randomly sampled from the Registry of NHIRD in 2000. A total of 17 206 patients with a diagnosis of urticaria (ICD-9-CM code 708) who had received long-term antihistamines (ie, use of antihistamine for a total of 6 months during 2 years) were identified. The antihistamines included second- and third-generation antihistamines, such as cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, levocetirizine dihydrochloride, loratadine, and traditional sedating antihistamines. To minimize the possible effect of personal allergy history on cancer occurrence, patients with coexisting atopic dermatitis (ICD-9-CM code 691.8, diagnosed by dermatologists, pediatricians, or immune-rheumatologists), asthma (ICD-9-CM code 493, diagnosed by internists or immune-rheumatologists), or allergic rhinitis (ICD-9-CM code 477, diagnosed by immune-rheumatologists or otolaryngologists), who may need long-term antihistamine treatment, were excluded. Patients with a history of malignant tumors or with coexisting rheumatoid arthritis (ICD-9-CM code 714), systemic lupus erythematosus (ICD-9-CM code 710.0), or Sjögren syndrome (ICD-9-CM code 710.2) were also excluded. The diagnoses of coexisting autoimmune diseases were based on the records from the registry of Catastrophic Illness Patient Database, which includes only those meeting the diagnostic criteria of diseases, as described previously.<sup>13,14</sup> Finally, a total of 12 720 chronic urticaria patients were enrolled as the study cohort. All study patients were included between January 1, 1996, and December 31, 2006, and followed up until December 31, 2008, to ensure that each patient was observed for at least 2 years.

## WAIVER OF REVIEW

The data set used in this study consisted of deidentified secondary data released to the public for research purposes. Therefore, the institutional review board of Taichung Veterans General Hospital waived a review of this study.

## IDENTIFICATION OF CANCER CASES

We identified the diagnoses of cancers in the study cohort by linking to the records of the Catastrophic Illness Patient Database. To apply for a cancer catastrophic illness certificate, one must provide cytologic or pathologic reports or evidence,

such as additional laboratory and imaging studies, that support the diagnosis of cancer, including tumor marker surveys, radiographs, bone scans, computed tomography scans, or magnetic resonance imaging scans. At least 2 oncologists carefully examine the medical records, laboratory information, and results of imaging studies. Only those patients who meet the criteria of diagnoses are issued certificates. We excluded those with in situ malignant tumors because in situ malignant diseases do not qualify for a catastrophic illness certificate. The diagnostic codes of malignant tumors were defined as those from 140 to 208.91 in the ICD-9-CM format. We categorized these cancer cases into hematologic cancers and nonhematologic cancers. Hematologic cancers were subcategorized into leukemias (coded 204-208) and lymphomas (including non-Hodgkin lymphoma [coded 200 or 202-203] and Hodgkin lymphoma [coded 201]), according to the methods of the Cancer Registry in Taiwan.

## STATISTICAL ANALYSIS

All study subjects were followed up until a first-time diagnosis of cancer, the end of follow-up in the medical records, or the end of 2008. We examined the association between chronic urticaria and specific cancer types using standardized incidence ratios (SIRs). Standardized incidence ratios were calculated as the number of cancer cases among chronic urticaria patients divided by the expected number of cancer cases according to national age-specific, sex-specific, and period-specific cancer rates. The CIs are based on the Byar approximation of the exact Poisson distribution, which is extremely accurate even for small numbers.<sup>15</sup>

Yearly reports of cancer rates were obtained from the Taiwan National Cancer Registry. Hospitals with greater than 50-bed capacity that provide outpatient and inpatient cancer care participate in reporting all newly diagnosed malignant neoplasia to the registry. Cancer incidence data appear each year in a special bulletin and in an annual registry report published by the Ministry of Health. Analyses and observed trends are published in annual reports. The registry also provides a database of cancer-related data for various research efforts. We adopted the 2003 Cancer Registry Report of Taiwan as a standard.

To assess the effect of age on the relative risk of malignant tumors, we analyzed the relative risk among patients younger than 20, those aged 20 to 39, 40 to 59, and 60 to 79, and those 80 years or older at diagnosis of chronic urticaria. Analysis was also performed to determine whether the association of malignant tumors varied according to the length of time after diagnosis of chronic urticaria. We divided follow-up times into 6 periods: less than 1 year, 1 to less than 2 years, 2 to less than 4 years, 4 to less than 6 years, 6 to less than 8 years, and 8 years or more.

The SAS statistical package, version 9.1 (SAS Institute, Inc), and the Stata statistical package, version 9.1 (StataCorp), were used to perform analyses of the data in this study.

## RESULTS

### DEMOGRAPHIC DATA

The age and sex distribution of study subjects are presented in **Table 1**. Among 12 720 study patients, 10 720 (84.3%) received systemic corticosteroids, with a median duration of 10 days per year (mean [interquartile range], 30.7 [3.4-29.6] days per year). There were 186 patients (1.5%) receiving other immunosuppressants, including methotrexate sodium, cyclosporine, and azathioprine so-

**Table 1. Demographic Characteristics of 12 720 Patients With Chronic Urticaria**

| Characteristic           | Value           |
|--------------------------|-----------------|
| Age at diagnosis, y      |                 |
| Mean                     | 37.9            |
| Median (IQR)             | 41.5 (5.9-63.0) |
| Length of observation, y |                 |
| Mean                     | 5.5             |
| Median (IQR)             | 5.6 (3.4-7.6)   |
| Sex, No. (%)             |                 |
| Male                     | 6468 (50.8)     |
| Female                   | 6252 (49.2)     |
| Age, y, No. (%)          |                 |
| <20                      | 4393 (34.5)     |
| 20-39                    | 1790 (14.1)     |
| 40-59                    | 2922 (23.0)     |
| 60-79                    | 3187 (25.1)     |
| ≥80                      | 428 (3.4)       |

Abbreviation: IQR, interquartile range.

dium, with a median duration of 28 days per year (mean [interquartile range], 98.1 [6.5-120.6] days per year).

### OVERALL CANCER RISK ANALYSIS

During the observation period of 69 305 person-years, 704 cancers were identified after the diagnosis of chronic urticaria. The incidence was 1016 cases per 100 000 person-years. An increased overall cancer risk in chronic urticaria was observed (SIR, 2.2; 95% CI, 2.0-2.3). Female and male patients showed similar risks of developing cancer (**Table 2**). After we excluded the 186 patients who received immunosuppressants other than antihistamines or corticosteroids, the risk of malignant tumor remained elevated (SIR, 2.2; 95% CI, 2.0-2.4).

The relative risk of cancer was greatest among young and middle-aged patients with chronic urticaria (Table 2). Malignant diseases in chronic urticaria were mostly detected in the first year following diagnosis (SIR, 4.3; 95% CI, 3.8-4.9). The risk ratios gradually decreased over time (Table 2). After 8 years of follow-up, the SIR of malignant tumors in chronic urticaria remained elevated (SIR, 1.5; 95% CI, 1.0-2.2).

### ASSOCIATION OF HEMATOLOGIC CANCERS WITH CHRONIC URTICARIA

Among all malignant diseases, there were 58 hematologic malignant tumors (8.2%), including 35 cases of non-Hodgkin lymphoma, 1 case of Hodgkin lymphoma, and 22 cases of leukemia. A significantly elevated risk for hematologic malignant tumors in chronic urticaria was observed (SIR, 4.1; 95% CI, 3.1-5.4) (**Table 3**). The risk of cancer varied by age. Young patients (<20 years) were at greatest relative risk for hematologic cancers compared with the age-matched general population (Table 3).

The risks for hematologic cancers were highest following the first year of diagnosis (SIR, 16.5; 95% CI, 11.4-23.2). The relative risk of hematologic cancer remained elevated after long-term observation (Table 3).

**Table 2. Standardized Incidence Ratios (SIRs) of Overall Cancer Occurrence in Chronic Urticaria<sup>a</sup>**

| Characteristic                      | No.      |                  | SIR (95% CI)  |
|-------------------------------------|----------|------------------|---------------|
|                                     | Observed | Expected         |               |
| Total No. with cancer               | 704      | 324 <sup>b</sup> | 2.2 (2.0-2.3) |
| Sex                                 |          |                  |               |
| Male                                | 420      | 202              | 2.1 (1.9-2.3) |
| Female                              | 284      | 122              | 2.3 (2.1-2.6) |
| Age, y                              |          |                  |               |
| <20                                 | 10       | 4                | 2.5 (1.2-4.6) |
| 20-39                               | 35       | 6                | 5.8 (4.1-8.1) |
| 40-59                               | 211      | 56               | 3.8 (3.3-4.3) |
| 60-79                               | 396      | 210              | 1.9 (1.7-2.1) |
| ≥80                                 | 52       | 39               | 1.3 (1.0-1.7) |
| Time from diagnosis to detection, y |          |                  |               |
| <1                                  | 243      | 56               | 4.3 (3.8-4.9) |
| 1-<2                                | 116      | 56               | 2.1 (1.7-2.5) |
| 2-<4                                | 156      | 100              | 1.6 (1.3-1.8) |
| 4-<6                                | 105      | 73               | 1.4 (1.2-1.7) |
| 6-<8                                | 58       | 45               | 1.3 (1.0-1.7) |
| ≥8                                  | 26       | 17               | 1.5 (1.0-2.2) |

<sup>a</sup>Based on the 2003 Cancer Registry Report of Taiwan.

<sup>b</sup>The sum may not equal to the overall expected number because of the different observation times in each stratification.

**Table 3. Standardized Incidence Ratios (SIRs) of Hematologic Cancers in Chronic Urticaria<sup>a</sup>**

| Characteristic                      | No.      |                 | SIR (95% CI)     |
|-------------------------------------|----------|-----------------|------------------|
|                                     | Observed | Expected        |                  |
| Total No. with cancer               | 58       | 14 <sup>b</sup> | 4.1 (3.1-5.4)    |
| Sex                                 |          |                 |                  |
| Male                                | 37       | 9               | 4.1 (2.9-5.7)    |
| Female                              | 21       | 5               | 4.2 (2.6-6.4)    |
| Age, y                              |          |                 |                  |
| <20                                 | 7        | 1               | 7.0 (2.8-14.4)   |
| 20-39                               | 6        | 1               | 6.0 (2.2-13.1)   |
| 40-59                               | 12       | 2               | 6.0 (3.1-10.5)   |
| 60-79                               | 30       | 8               | 3.8 (2.5-5.4)    |
| ≥80                                 | 3        | 2               | 1.5 (0.3-4.4)    |
| Time from diagnosis to detection, y |          |                 |                  |
| <1                                  | 33       | 2               | 16.5 (11.4-23.2) |
| 1-<2                                | 4        | 2               | 2.0 (0.5-5.1)    |
| 2-<4                                | 10       | 4               | 2.5 (1.2-4.6)    |
| 4-<6                                | 11       | 3               | 3.7 (1.8-6.6)    |

<sup>a</sup>Based on the 2003 Cancer Registry Report of Taiwan.

<sup>b</sup>The sum may not equal to the overall expected number because of the different observation times in each stratification.

Ten occurrences of malignant tumors were observed in those younger than 20 years. Among them were 7 lymphohematopoietic cancers (5 acute or chronic lymphocytic leukemias and 2 leukemias of monocytic cells or unspecified cell types). Of the 3 remaining malignant diseases, 2 were brain tumors and 1 was a tumor of ovarian origin. In regard to specific cancer types, the risk of non-Hodgkin lymphoma (including other lymphosarcoma, reticulosarcoma, multiple myeloma, and other immunoproliferative neoplasms) was greatest

**Table 4. Standard Incidence Ratios (SIRs) of Specific Types of Hematologic Malignant Tumors in Chronic Urticaria<sup>a</sup>**

| Type                 | No.      |          | SIR<br>(95% CI) |
|----------------------|----------|----------|-----------------|
|                      | Observed | Expected |                 |
| Total                | 58       | 14       | 4.1 (3.1-5.4)   |
| Non-Hodgkin lymphoma | 35       | 8        | 4.4 (3.0-6.1)   |
| Hodgkin lymphoma     | 1        | 0        | ...             |
| Leukemia             | 22       | 6        | 3.7 (2.3-5.6)   |

<sup>a</sup>Based on the 2003 Cancer Registry Report of Taiwan.

(SIR, 4.4; 95% CI, 3.0-6.1), followed by leukemia (3.7; 2.3-5.6) (**Table 4**).

## ASSOCIATION OF NONHEMATOLOGIC CANCERS WITH CHRONIC URTICARIA

An increased risk of various nonhematologic malignant tumors (SIR, 2.1; 95% CI, 1.9-2.3) was also observed in chronic urticaria patients (**Table 5**). The most significantly associated cancers were those originating from the brain, retroperitoneum, vulva, and kidney.

## COMMENT

Various causes of urticaria, including food, infection, and drugs, have been reported. However, the cause is unknown in more than 80% of cases.<sup>16</sup> The association of malignant tumor and chronic urticaria remains controversial. Several cases of malignant tumors have been reported in association with urticaria, including leukemias and lymphomas,<sup>17,18</sup> myeloma,<sup>19</sup> testicular cancer,<sup>20</sup> ovarian carcinoma,<sup>21</sup> lung cancer,<sup>22</sup> colon cancer,<sup>23</sup> and thyroid carcinoma.<sup>24</sup> Nevertheless, 1 population-based study showed no associations between chronic urticaria and malignant tumor.<sup>2</sup> Our study provided nationwide population-based evidence that chronic urticaria patients may be at increased risk of cancer occurrence, especially hematologic cancers.

A point prevalence of 0.5% to 1% of chronic urticaria in the general population has been reported.<sup>25</sup> However, to our knowledge, no epidemiologic data regarding chronic urticaria have been published in Taiwan. We identified 3357 patients with chronic urticaria in 2000, with an estimated prevalence of 0.4% (data not shown). This is comparable with reports from other countries. A comprehensive prospective surveillance for chronic urticaria in Taiwan is needed for further studies.

A link between chronic urticaria and hematologic malignant tumor has rarely been reported. *Schnitzler syndrome* is defined as chronic urticaria and monoclonal gammopathy, in combination with at least 2 of the following features: fever, arthralgia or arthritis, bone pain, hepatomegaly and/or splenomegaly, palpable lymph node, elevated erythrocyte sedimentation rate, and leukocytosis. Rarely, patients progress to develop lymphoplasmacytic neoplasia, particularly Waldenstrom macroglobulinemia.<sup>26</sup> Most of these patients present with gammopathy and hematologic disorder in their 40s to 60s after 4 to 9 years of chronic urticaria.<sup>27-29</sup>

**Table 5. Standard Incidence Ratios (SIRs) of Nonhematologic Cancers in Chronic Urticaria<sup>a</sup>**

| Cancer Type                         | No.      |                  | SIR (95% CI)   |
|-------------------------------------|----------|------------------|----------------|
|                                     | Observed | Expected         |                |
| Total                               | 646      | 310 <sup>b</sup> | 2.1 (1.9-2.3)  |
| Oral cavity                         | 49       | 24               | 2.0 (1.5-2.7)  |
| Tongue, gingiva                     | 25       | 11               | 2.3 (1.5-3.4)  |
| Oropharynx, hypopharynx, and others | 8        | 4                | 2.0 (0.9-3.9)  |
| Larynx                              | 4        | 3                | 1.3 (0.4-3.4)  |
| Nasopharynx                         | 10       | 5                | 2.0 (1.0-3.7)  |
| Nose, sinus, and ear                | 2        | 1                | 2.0 (0.2-7.2)  |
| Hepatogastroenterologic system      | 303      | 135              | 2.2 (2.0-2.5)  |
| Esophagus                           | 19       | 7                | 2.7 (1.6-4.2)  |
| Stomach                             | 42       | 20               | 2.1 (1.5-2.8)  |
| Small intestine                     | 1        | 2                | 0.5 (0.0-2.8)  |
| Colorectum, cecum, and anus         | 78       | 46               | 1.7 (1.3-2.1)  |
| Liver and gallbladder               | 146      | 53               | 2.8 (2.3-3.2)  |
| Pancreas                            | 12       | 7                | 1.7 (0.9-3.0)  |
| Retroperitoneum and others          | 5        | 1                | 5.0 (1.6-11.7) |
| Lungs and mediastinum               | 105      | 46               | 2.3 (1.9-2.8)  |
| Lungs and trachea                   | 102      | 45               | 2.3 (1.8-2.8)  |
| Mediastinum including heart, thymus | 3        | 1                | 3.0 (0.6-8.8)  |
| Skin                                | 14       | 10               | 1.4 (0.8-2.3)  |
| Melanoma                            | 1        | 1                | 1.0 (0.0-5.6)  |
| Nonmelanoma                         | 13       | 9                | 1.4 (0.8-2.5)  |
| Female genitalia                    | 33       | 16               | 2.2 (1.5-3.1)  |
| Uterus                              | 5        | 3                | 1.7 (0.5-3.9)  |
| Cervix including ovary              | 24       | 12               | 2.0 (1.3-3.0)  |
| Vulva, placenta, and others         | 4        | 1                | 4.0 (1.1-10.2) |
| Female breast                       | 32       | 19               | 1.7 (1.2-2.4)  |
| Male genitalia                      | 29       | 17               | 1.7 (1.1-2.4)  |
| Prostate                            | 26       | 16               | 1.6 (1.1-2.4)  |
| Testis, penis, and others           | 3        | 1                | 3.0 (0.6-8.8)  |
| Genitourinary system                | 45       | 20               | 2.3 (1.6-3.0)  |
| Bladder                             | 15       | 11               | 1.4 (0.8-2.2)  |
| Kidney, urinary system, and others  | 30       | 9                | 3.3 (2.2-4.8)  |
| Others                              | 28       | 8                | 3.1 (2.1-4.5)  |
| Brain                               | 10       | 2                | 5.0 (2.4-9.2)  |
| Other neural systems                | 1        | 0                | ...            |
| Bone, joint, and soft tissue        | 4        | 2                | 2.0 (0.5-5.1)  |
| Thyroid gland                       | 11       | 4                | 2.8 (1.4-4.9)  |
| Endocrine system other than thyroid | 2        | 0                | ...            |
| Ill-defined sites                   | 2        | 0                | ...            |
| Unknown origin                      | 6        | 6                | 1.0 (0.4-2.2)  |

<sup>a</sup>Based on the 2003 Cancer Registry Report of Taiwan. All data were rounded to a whole number.

<sup>b</sup>The sum may not equal to the overall expected number because of the different observation times in each stratification.

To our knowledge, no previous studies have examined the effect of age at onset of chronic urticaria on cancer occurrence. Our study demonstrated that younger patients (aged <40 years) tend to have the greatest risk of cancer development, especially for hematologic cancers. These results suggest that thorough and periodic assessment may be needed in younger patients.

An association of hematologic malignant tumors in urticarial vasculitis has been described. Urticarial vasculitis, comprising approximately 2% of chronic urticaria,<sup>30,31</sup> often presents clinically as persistent urticaria lesions and microscopically as leukocytoclastic vasculi-

tis. Multisystem involvement in urticarial vasculitis, such as severe angioedema, arthritis, and pulmonary involvement, has been frequently described. Various neoplastic conditions have been reported to be associated with hypocomplementemic urticarial vasculitis, such as polycythemia rubra vera,<sup>32</sup> IgA myeloma,<sup>33</sup> megakaryocytic leukemia,<sup>34</sup> and non-Hodgkin lymphoma.<sup>5,35</sup> However, the diagnosis of urticarial vasculitis is sometimes underinvestigated by physicians, and there is no specific diagnostic code for urticarial vasculitis in the ICD-9 coding system.

This study demonstrated associations of cancers of various origins with chronic urticaria. Significant elevated risks of cancers originating from the brain, retroperitoneum, vulva, and kidney were observed. At present, it is not known whether the coexistence of chronic urticaria and various malignant tumors is merely a coincidence or whether there are shared etiologic factors. In some case reports, removal of the tumor leads to prompt resolution of urticarial lesions,<sup>17,18,21,23,24</sup> suggesting a pathogenetic relationship between these diseases. The SIRs of most cancers were very modest and the case numbers were small for certain tumor types, which limited subset analyses. Further studies are needed to address these relationships.

The effect of medications commonly used for chronic urticaria on cancer development has not been explored in detail. To our knowledge, no studies have reported an association between corticosteroid use and cancer development in other autoimmune diseases, such as systemic lupus erythematosus.<sup>36</sup> Long-term use of common immunosuppressants, except cyclophosphamide, does not increase the cancer risk in systemic lupus erythematosus.<sup>36</sup> An association between cancer and chronic urticaria remained unchanged in our study after we excluded patients receiving long-term immunosuppressants other than corticosteroids. This implied that the effect of corticosteroid-sparing immunosuppressants is not strong in regard to cancer risk in chronic urticaria patients.

There are 3 main limitations to our study. First, we did not have personal patient information, such as family history of cancer, lifestyle, body mass index, or smoking and alcohol use. There was also no information regarding signs or symptoms, other than urticaria, or laboratory abnormalities that would suggest the need for an evaluation for cancer. Second, to diminish the likelihood of a misdiagnosis of common urticaria based on the administrative database, we used additional pharmaceutical information (long-term use of oral antihistamines) to select our case patients. Thus, the prevalence of chronic urticaria may have been underestimated. Third, we were not able to separate out possible cases of urticarial vasculitis from cases of common chronic urticaria because of the lack of a distinct diagnostic code for urticarial vasculitis. Because internal malignant tumors have been reported more frequently in patients with vasculitis, this may have distorted the findings.

Our study provides some valuable information. We demonstrated a possible link between cancer and chronic urticaria on the basis of a nationwide database in Taiwan. Most cancers were detected within 1 year of diagnosis. The possible association between cancer and chronic urticaria deserves further study.

**Submitted for Publication:** February 23, 2011; final revision received September 9, 2011; accepted September 22, 2011.

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**Author Contributions:** Drs Chen and Wu contributed equally to this study. Drs Chen, Wu, and Chang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Y.-J. Chen, Wu, and Chang. **Acquisition of data:** Y.-J. Chen, Wu, Shen, T.-T. Chen, and Chang. **Analysis and interpretation of data:** Y.-J. Chen, Wu, and Chang. **Drafting of the manuscript:** Y.-J. Chen. **Critical revision of the manuscript for important intellectual content:** Y.-J. Chen, Wu, Shen, T.-T. Chen, and Chang. **Statistical analysis:** Y.-J. Chen and T.-T. Chen. **Obtained funding:** Y.-J. Chen, Wu, and Shen. **Administrative, technical, and material support:** Y.-J. Chen, Wu, and Shen. **Study supervision:** Wu and Chang.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was partly supported by grants TCVGH-996801B and TCVGH-996802C from Taichung Veterans General Hospital.

**Disclaimer:** This study is based in part on data from the NHIRD provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institute. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or the National Health Research Institute.

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### Notable Notes

#### Charles Bukowski and Sylvia Plath on Moles and Melanoma

In his poem "a threat to my immortality," Charles Bukowski (1920-1994), lying in bed with a bottle of beer, watches a girlfriend getting undressed.<sup>1</sup> Something on her buttock arouses his interest: "where'd you get that wart on/your ass? I asked./ that's no wart, she said./that's a mole, a kind of/birthmark./ that thing scares me, I said./let's call/it off." The girlfriend, who wants to carry on, tries to distract Bukowski by referring to his own appearance thusly: "you've got warts and scars and/all kinds of things all over/you. I do believe you're the ugliest/old man/I've ever seen." Fascinated and scared but refusing to be distracted, Bukowski just answers "forget that, . . . tell me some more/about that/mole on your butt." The poem title and Bukowski's reaction suggest that he considered the mole to be life-threatening.

About 10 years earlier, Sylvia Plath (1932-1963), in her autobiographical story *The Bell Jar*, refers to a mole as well.<sup>2</sup> Attending a lecture with a friend who was a medical student at a university hospital, she writes, "One slide I remember showed a beautiful laughing girl with a black mole on her cheek. Twenty days after that mole appeared the girl was dead,

the doctor said, and everybody went very quiet for a minute and then the bell rang, so I never really found out what the mole was or why the girl died." One could get the impression that the lack of certainty regarding the mole being the cause of death was somewhat reassuring for Plath.

At the time that Plath wrote her story, the medical profession was acquainted only somewhat with moles and melanoma. About 10 years later, melanoma already had been brought into the focus not only of professionals but also of the public. Since then, melanoma has been feared as a particularly malignant lesion, even though about 80% of all patients affected survive.

Both Plath and Bukowski show marked interest in skin. However, in her work, Plath uses the skin not only as a physiological entity but also as a psychological construct in a powerful symbolic order.<sup>3</sup> In contrast, Bukowski, who had suffered from extremely severe acne during puberty, is more concerned with the appearance of his scarred facial skin as well with the discrepancy between his look and his success as ladies' man.<sup>4</sup>

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