Increased risk of bladder cancer in young adult men with hyperlipidemia
A population-based cohort study
Hung-Jen Shih, MD, PhDa,b,c, Ke-Hsun Lin, MDCd, Yu-Ching Wen, MD, PhDc,d, Yen-Chun Fan, PhDc,e, Pei-Shan Tsai, PhDg,h,i, Chun-Jen Huang, MD, PhDj,k,"*

Abstract
A high-cholesterol diet increases the risk of bladder cancer. The purpose of this nationwide longitudinal population-based retrospective cohort study is to investigate whether hyperlipidemia is a risk factor for bladder cancer.

Data from Taiwan National Health Insurance Database were analyzed. The primary study end point was the occurrence of newly diagnosed bladder cancer. The relative risk of bladder cancer in a hyperlipidemia cohort was compared with that in an age- and gender-matched non-hyperlipidemia cohort by using the Cox proportional hazards regression model. Cox regression analyses were further adjusted by the propensity score.

Our data revealed that the hyperlipidemia cohort (n = 33,555) had a significantly higher subsequent risk of bladder cancer than did the non-hyperlipidemia cohort (n = 33,555) (adjusted hazard ratio [HR] = 1.37, P = .005) after propensity score adjustment. Subgroup analyses revealed that men in the hyperlipidemia cohort had a significantly higher subsequent risk of bladder cancer than those in the non-hyperlipidemia cohort (adjusted HR = 1.36, P = .040). However, the risk of bladder cancer was not significantly different between women in the hyperlipidemia cohort and those in the non-hyperlipidemia cohort. Subgroup analyses further revealed that the risk of bladder cancer was significantly higher in men aged 20 to 39 years in the hyperlipidemia cohort than in those in the non-hyperlipidemia cohort (adjusted HR = 5.45, P = .029).

In conclusion, hyperlipidemia is a risk factor for bladder cancer in young adult men.

Abbreviations: ATC = anatomical therapeutic chemical, CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2010 = Longitudinal Health Insurance Database 2010, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NSAIDs = nonsteroidal anti-inflammatory drugs.

Keywords: bladder cancer, gender, hyperlipidemia, lipid

Editor: Wen-Wei Sung.

TPS and HCJ contributed equally to this work.

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Taipei Medical University (Protocol Number: N201803071). The study was performed in accordance with the Declaration of Helsinki.

Availability of data and materials: The data in this publication are commercially confidential. Data requests should be made to the Corresponding Author.

This study was supported by grants from Taipei Medical University (TMU107-AE1-B32), which was awarded to HJS, and Wan Fang Hospital (110-wf-eva-30), which was awarded to HCJ.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

a Division of Urology, Department of Surgery, Changhua Christian Hospital, Changhua, Taiwan, b Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei Medical University, Taipei, Taiwan, c Department of Urology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, d School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan, e School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan, f Department of Nursing, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, g Research Center of Big Data and Meta-analysis, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, h Department of Anesthesiology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, i Integrative Research Center for Critical Care, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, j Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

Correspondence: Chun-Jen Huang, Department of Anesthesiology, Wan Fang Hospital, Taipei Medical University, 111 Xinglong Rd., Sec. 3, Wenshan Dist., Taipei 11696, Taiwan (e-mail: huangcj1112@gmail.com).

Copyright © 2021 the Author[s]. Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Shih HJ, Lin KH, Wen YC, Fan YC, Tsai PS, Huang CJ. Increased risk of bladder cancer in young adult men with hyperlipidemia: a population-based cohort study. Medicine 2021;100:48(e28125). Received: 20 May 2020 / Received in final form: 14 April 2021 / Accepted: 15 November 2021 http://dx.doi.org/10.1097/MD.00000000000028125
1. Introduction

In 2012, bladder cancer was the ninth most commonly diagnosed cancer worldwide.\textsuperscript{[1]} Globally, the bladder cancer age-standardized incidence rates (per 100,000 person-years) are 9 for men and 2.2 for women and the age-standardized mortality rates (per 100,000 person-years) are 3.2 for men and 0.9 for women, respectively.\textsuperscript{[1,2,3]} Similar pictures are observed in Taiwan.\textsuperscript{[1,2,3]} In non-muscle-invasive bladder cancer, adjuvant treatment and long-term regular follow-up after transurethral resection of the bladder tumor are required to detect tumor recurrence and progression.\textsuperscript{[3]} In muscle-invasive bladder cancer, patients should receive radical cystectomy or tri-modality treatment for organ preservation.\textsuperscript{[4]} During 2007 to 2011, the survival rate for bladder cancer in Taiwan was approximately 67%.\textsuperscript{[2]} Identifying risk factors for bladder cancer is important and has profound clinical and epidemiological impacts.

The identified risk factors for bladder cancer include tobacco smoking,\textsuperscript{[5]} occupational exposure to aromatic amines and other chemicals,\textsuperscript{[1]} arsenic in drinking water,\textsuperscript{[2]} aristolochia-based herbal medicines,\textsuperscript{[2]} radiotherapy,\textsuperscript{[6]} and genetic factors.\textsuperscript{[7]} Tobacco smoking is a major risk factor for bladder cancer.\textsuperscript{[8]} A meta-analysis showed that tobacco smoking causes abnormalities in serum lipids, including an increase in triglycerides and a decrease in the high-density lipoprotein cholesterol level.\textsuperscript{[9]} A high-cholesterol diet increases the risks of various cancers, including bladder cancer.\textsuperscript{[9]} In a hospital-based case-control study, patients with metabolic syndrome had a 2-fold higher risk of bladder cancer than did patients without metabolic syndrome.\textsuperscript{[10]} Increase body mass index was associated with increased risk of recurrence and progression in patients with high grade non-muscle-invasive bladder cancer administered intravesical Bacillus Calmette-Guérin (BCG) immunotherapy.\textsuperscript{[11]} Collectively, these data indicate a possible association between hyperlipidemia and the subsequent risk of bladder cancer. However, the relationship between hyperlipidemia and bladder cancer has not fully elucidated.

To elucidate this association, we conducted this population-based study and hypothesized that patients with hyperlipidemia may have a higher subsequent risk of bladder cancer than do patients without hyperlipidemia. Furthermore, hyperlipidemia in young adults increases the risk of coronary heart disease,\textsuperscript{[12]} and lipid metabolism differs by gender.\textsuperscript{[13]} Hyperlipidemia may have differential impacts in adults with different ages and genders. In this study, the risk of bladder cancer was thus further examined through subgroup analyses stratified by age and gender to determine whether the subsequent risk of bladder cancer is significantly different between men and women with hyperlipidemia.

2. Methods

2.1. Data sources

In this nationwide longitudinal population-based retrospective cohort study, data retrieved from the Longitudinal Health Insurance Database 2010 (LHID2010) was analyzed. The single-payer National Health Insurance (NHI) program was established in Taiwan in 1995. Approximately 99.9% of the population of Taiwan is covered in the NHI program. The longitudinal medical records of all insurants in the NHI program are included in the National Health Insurance Research Database (NHIRD). One million people from the Registry of Beneficiaries of the NHIRD in 2010 (approximately 27.38 million individuals) were randomly sampled to create the LHID2010. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are used for diagnoses in the database. The diagnostic accuracy of the NHI claims data with ICD-9-CM diagnostic codes have been validated by the National Health Research Institute, Taiwan.\textsuperscript{[14]} If malignancy is diagnosed, insurants can apply for a Catastrophic Illness Certificate, and the medical records, pathology, and imaging reports are validated by a panel of specialists. The LHID2010 includes the Registry of the Catastrophic Illness Patient Database and thus provides disease information for the purpose of research. Because the LHID2010 contains anonymous data, no patient consent is required. This study was approved by the Institutional Review Board of Taipei Medical University (Protocol Number: N201803071).

2.2. Study design

This study included individuals with at least 2 separate inpatient or outpatient medical records with hyperlipidemia diagnoses (ICD-9-CM code 272.x) between January 2000 and December 2012. The validity of ICD-9-CM code for hyperlipidemia in the NHIRD (sensitivity 69.1% and positive predictive value 89.5%) has been evaluated.\textsuperscript{[15]} In Taiwan, according to the diagnostic criteria for hyperlipidemia, physicians diagnose hyperlipidemia and prescribe medications for hyperlipidemia.\textsuperscript{[16]} In this study, the index date for the hyperlipidemia cohort was defined as the date of hyperlipidemia diagnosis. Individuals without hyperlipidemia were matched by age, gender, and the index date to patients with hyperlipidemia (index date ± 90 days) in a 1:1 ratio and were included in the control cohort. Patients who were aged younger than 20 years or older than 99 years, diagnosed as having hyperlipidemia or bladder cancer for only one occasion, or diagnosed as having hyperlipidemia or bladder cancer before the index date were excluded. Medical diagnoses were identified using ICD-9-CM codes, and medication use was identified according to Anatomical Therapeutic Chemical (ATC) classification system codes. The primary end point of this study was the occurrence of newly diagnosed bladder cancer. To identify all patients with bladder cancer, each patient was tracked from the index date until the end of 2013. To ensure the accuracy of bladder cancer diagnosis, the diagnosis code of bladder cancer (ICD-9-CM code 188.x) should be identified in at least 2 separate inpatient or outpatient medical records.

The confounders considered in this study were identified within 1 year before the index date. The comorbidities related to the risk of bladder cancer considered in this study were diabetes mellitus (DM) (ICD-9-CM code 250),\textsuperscript{[17]} hypertension (ICD-9-CM codes 401–405),\textsuperscript{[18]} obesity (body mass index > 27) (ICD-9-CM codes 278 and 278.0),\textsuperscript{[19]} chronic obstructive pulmonary disease (COPD) (as a proxy of smoking; ICD-9-CM codes 490–496),\textsuperscript{[20]} and uremia (ICD-9-CM code 586).\textsuperscript{[21]} Medications related to the risk of bladder cancer were aspirin (ATC codes B01AC06 and N02BA01),\textsuperscript{[22]} nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC code M01A),\textsuperscript{[23]} metformin (ATC code A10BA02),\textsuperscript{[24]} rosiglitazone (ATC code A10BG02),\textsuperscript{[23]} and pioglitazone (ATC code A10BG03).\textsuperscript{[23]}

2.3. Statistical analyses

Distributions of patient characteristics, comorbidities, and medications as well as the incidence of bladder cancer were compared between the hyperlipidemia and non-hyperlipidemia
cohorts by using chi-squared tests. Differences in the mean duration of bladder cancer development and median time of follow-up between these two cohorts were determined using the Mann–Whitney U test. A P value of <.05 indicated statistical significance. The relative subsequent risk of bladder cancer in the hyperlipidemia cohort was compared with that in the non-hyperlipidemia cohort by using the Cox proportional hazards regression model. Cox regression analyses were further adjusted by the propensity score. The SPSS statistical package (SPSS 21.0, SPSS Inc., IBM Corporation, Somers, NY) was used for data analyses.

3. Results

3.1. Demographics of study population

A total of 67,110 patients were identified, with 33,555 patients in the hyperlipidemia cohort and 33,555 in the non-hyperlipidemia cohort (Fig. 1). The variables of DM, hypertension, obesity, COPD, uremia, aspirin use, NSAID use, metformin use, and rosiglitazone use were significantly different between these 2 cohorts (Table 1).

3.2. Hyperlipidemia is associated with a higher subsequent risk of bladder cancer

The median follow-up time was not significantly different between the hyperlipidemia and non-hyperlipidemia cohorts (8.02 years vs 7.96 years, \( P = .105 \)). The mean duration from the index date to the date of bladder cancer occurrence was not significantly different between the hyperlipidemia and non-hyperlipidemia cohorts (mean ± standard deviation: 5.31 ± 3.48 years vs 4.67 ± 3.16 years, \( P = .116 \)).

During the 1 to 14 years of follow-up, 217 patients in the hyperlipidemia cohort (n = 33,555) and 143 patients in the non-hyperlipidemia cohort (n = 33,555) were diagnosed with bladder cancer. The incidence of bladder cancer in the hyperlipidemia cohort matched by age, sex, and index date at a ratio of 1:1.
3.3. Men, but not women, with hyperlipidemia show a higher subsequent risk of bladder cancer

Subgroup analyses were performed to evaluate the association between gender and the risk of bladder cancer between the hyperlipidemia and non-hyperlipidemia cohorts. Men in the hyperlipidemia cohort (n = 15,023) had a significantly higher subsequent risk of bladder cancer than did those in the non-hyperlipidemia cohort (n = 15,023) (adjusted HR = 1.36, 95% CI = 1.01–1.82, P = .040; Table 3). However, the subsequent risk of bladder cancer was not significantly different between women in the hyperlipidemia cohort and those in the non-hyperlipidemia cohort (both n = 18,532) (Table 3). These data indicated that for men but not for women, hyperlipidemia were associated with an increased risk of bladder cancer.

Subgroup analyses were also performed to evaluate the association between gender and the risk of bladder cancer in the hyperlipidemia cohort. Notably, the incidence of bladder cancer was significantly higher in men than in women in the hyperlipidemia cohort (0.8% vs 0.4%, P < .001). Men in the hyperlipidemia cohort also had a significantly higher subsequent risk of bladder cancer comparing to women in the hyperlipidemia cohort (adjusted HR = 1.97, 95% CI = 1.51–2.59, P < .001; Table 3). These data indicated that men with hyperlipidemia were associated with an increased risk of bladder cancer.

3.4. Hyperlipidemia increases the subsequent risk of bladder cancer in young adult men

Subgroup analyses were also performed to evaluate the association between age and the risk of bladder cancer between the hyperlipidemia and the non-hyperlipidemia cohorts. In the age group of 20 to 39 years, the risk of bladder cancer was significantly higher in the hyperlipidemia cohort than that in the non-hyperlipidemia cohort (adjusted HR = 4.38, 95% CI = 1.23–15.62, P = .023; Table 4). Similar results were observed in the age group of 40 to 49 years (adjusted HR = 2.1, 95% CI = 1.11–3.95, P = .022; Table 4) but not in the age groups of 50 to 99 years (Table 4). These data indicated that young adult patients (20–49 years) with hyperlipidemia were associated with an increased risk of bladder cancer.

The subsequent risk of bladder cancer was further explored in analyses stratified by age in both men and women. The risk of bladder cancer was significantly higher in men aged 20 to 39 years in the hyperlipidemia cohort than in those in the non-hyperlipidemia cohort (HR = 5.45, 95% CI = 1.19–25.07, P = .029; Table 3). However, the risk of bladder cancer was not significantly different between men aged 40 to 99 years in the hyperlipidemia cohort and those in the non-hyperlipidemia cohort (Table 4). Moreover, in all age groups, the risk of bladder cancer was not significantly different between women in the hyperlipidemia cohort and those in the non-hyperlipidemia cohort (Table 4). These data indicated that only men aged 20 to 39 with hyperlipidemia were associated with an increased risk of bladder cancer.

4. Discussion

Data regarding the association between hyperlipidemia and cancer risk are heterogeneous.

Higher risks of colon, prostate, and testicular cancers have been reported in patients with hyperlipidemia in previous research. By contrast, studies have
reported that patients with hyperlipidemia have lower risks of stomach, liver, and hematopoietic/lymphoid tissue cancers.\textsuperscript{[26]} This population-based cohort study demonstrated that patients with hyperlipidemia exhibited a 37\% to 51\% increased risk of bladder cancer compared with their non-hyperlipidemia counterparts. The incidence of hyperlipidemia is high in adults (37\% for men and 40\% for women).\textsuperscript{[27]} The data from this study thus should have profound clinical impact.

The association of hyperlipidemia with the risks of some types of cancer differs between men and women.\textsuperscript{[26]} A large population-based study (Metabolic syndrome and Cancer project) showed that hyperlipidemia has an inverse relationship with the risks of liver cancer, pancreas cancer, nonmelanoma of the skin, and lymph/hematopoietic tissue cancer among men and with the risks of gallbladder cancer, breast cancer, melanoma of the skin, and lymph/hematopoietic tissue cancer among women.\textsuperscript{[27]} In the present study, subgroup analyses revealed that men with hyperlipidemia had a 36\% to 54\% increased risk of bladder cancer compared with men without hyperlipidemia. Notably, the risk of bladder cancer was not significantly different between women with hyperlipidemia and women without hyperlipidemia. These data further highlight that hyperlipidemia increases the subsequent risk of bladder cancer in men but not in women. Therefore, gender has different impacts on the risk of cancer, including bladder cancer, in hyperlipidemia patients. The possible mechanisms may relate to the distinct body fat distribution and energy utilization patterns between men and women, and the storage of fat in visceral adipose tissue and visceral obesity in men have been linked to carcinogenesis.\textsuperscript{[13,29]} Although bladder cancer is not defined as an endocrine-related cancer, the association of the androgen/androgen receptor with bladder cancer development has been reported.\textsuperscript{[30]} The androgen receptor has been found in bladder tissue, and the down-regulation of androgen receptor expression suppresses bladder

### Table 2

| Cohorts             | Bladder cancer: n (%) | \( P \) value |
|---------------------|-----------------------|---------------|
| Hyperlipidemia (n = 33,555) | 217 (0.6)                     | <.001\textsuperscript{†} |
| Non-hyperlipidemia (n = 33,555) | 143 (0.4)                     |               |

| Cohorts             | Un-adjusted hazard ratio   | 95\% confidence intervals | \( P \) value |
|---------------------|----------------------------|---------------------------|---------------|
| Hyperlipidemia (n = 33,555) | 1.51                         | 1.22–1.86                  | <.001\textsuperscript{†} |
| Non-hyperlipidemia (n = 33,555) | 1.00                         |                           |               |

| Cohorts             | Adjusted hazard ratio    | 95\% confidence intervals | \( P \) value |
|---------------------|--------------------------|---------------------------|---------------|
| Hyperlipidemia (n = 33,555) | 1.37                         | 1.10–1.71                  | .005\textsuperscript{†} |
| Non-hyperlipidemia (n = 33,555) | 1.00                         |                           |               |

\textsuperscript{†} Tested by the chi-squared tests.
\textsuperscript{†} Tested by Cox proportional hazard regression.

\textsuperscript{†} Adjusted for propensity score, which was calculated using the logistic regression to estimate the hyperlipidemia status and baseline characteristics (age, gender, diabetes mellitus, hypertension, obesity, COPD, uremia, aspirin use, NSAIDs use, metformin use, rosiglitazone use, and pioglitazone use).

### Table 3

| Cohort | Unadjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|--------|-------------------------|---------------------------|---------------|
| Hyperlipidemia men | 1.54                         | 1.16–2.04                  | .003\textsuperscript{†} |
| Non-hyperlipidemia men | 1.00                         |                           |               |

| Cohort | Adjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|--------|-----------------------|---------------------------|---------------|
| Hyperlipidemia men | 1.36                         | 1.01–1.82                  | .040\textsuperscript{†} |
| Non-hyperlipidemia men | 1.00                         |                           |               |

| Cohort | Unadjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|--------|-------------------------|---------------------------|---------------|
| Hyperlipidemia women | 1.47                         | 1.07–2.02                  | .019\textsuperscript{†} |
| Non-hyperlipidemia women | 1.00                         |                           |               |

| Cohort | Adjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|--------|-----------------------|---------------------------|---------------|
| Hyperlipidemia women | 1.39                         | 1.00–1.93                  | .053\textsuperscript{†} |
| Non-hyperlipidemia women | 1.00                         |                           |               |

| Hyperlipidemia cohort | Unadjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|-----------------------|-------------------------|---------------------------|---------------|
| Men | 1.68                         | 1.28–2.20                  | <.001\textsuperscript{†} |
| Women | 1.00                         |                           |               |

| Hyperlipidemia cohort | Adjusted hazard ratio | 95\% confidence intervals | \( P \) value |
|-----------------------|-----------------------|---------------------------|---------------|
| Men | 1.97                         | 1.51–2.59                  | <.001\textsuperscript{†} |
| Women | 1.00                         |                           |               |

\textsuperscript{†} Tested by Cox proportional hazard regression.
\textsuperscript{†} Adjusted for propensity score.
cancer growth in vitro and in vivo. Thus, the association between the androgen/androgen receptor and bladder cancer has been evaluated. Shiota et al. demonstrated that androgen deprivation therapy decreases the risk of bladder cancer in patients with prostate cancer. In a prospective cohort study, dihydrotestosterone level, was associated with a reduced risk of bladder cancer,

Hyperlipidemia development in young adulthood (aged 20–39 years) increased the subsequent risk of bladder cancer. According to previous studies, many factors in adolescent obesity have been linked to an increased risk of bladder cancer,

Hyperlipidemia cohort vs non-hyperlipidemia cohort

| Age groups | Hazard ratio | 95% confidence intervals | P value |
|------------|-------------|--------------------------|--------|
| 20–39      | Un-adjusted | 5.32 | 1.55–18.25 | .008*  |
|            | Adjusted    | 4.38 | 1.23–15.62 | .023†  |
| 40–49      | Un-adjusted | 2.13 | 1.13–3.99 | .019†  |
|            | Adjusted    | 2.1  | 1.11–3.95 | .002†  |
| 50–59      | Un-adjusted | 1.39 | 0.91–2.14 | .127‡  |
|            | Adjusted    | 1.41 | 0.92–2.17 | .015†  |
| 60–69      | Un-adjusted | 1.13 | 0.77–1.66 | .520†  |
|            | Adjusted    | 1.14 | 0.78–1.67 | .495†  |
| 70–99      | Un-adjusted | 1.25 | 0.80–1.96 | .332‡  |
|            | Adjusted    | 1.25 | 0.79–1.97 | .336‡  |

Hyperlipidemia men vs non-hyperlipidemia men

| Age groups | Hazard ratio | 95% confidence intervals | P value |
|------------|-------------|--------------------------|--------|
| 20–39      | Un-adjusted | 6.98 | 1.59–30.72 | .010*  |
|            | Adjusted    | 5.45 | 1.19–25.07 | .029†  |
| 40–49      | Un-adjusted | 2.16 | 0.97–4.83 | .061‡  |
|            | Adjusted    | 2.12 | 0.94–4.77 | .068‡  |
| 50–59      | Un-adjusted | 1.16 | 0.63–2.15 | .631†  |
|            | Adjusted    | 1.17 | 0.63–2.17 | .629†  |
| 60–69      | Un-adjusted | 1.48 | 0.86–2.54 | .157‡  |
|            | Adjusted    | 1.47 | 0.85–2.53 | .167‡  |
| 70–99      | Un-adjusted | 0.93 | 0.53–1.63 | .791†  |
|            | Adjusted    | 0.92 | 0.53–1.62 | .776†  |

Hyperlipidemia women vs non-hyperlipidemia women

| Age groups | Hazard ratio | 95% confidence intervals | P value |
|------------|-------------|--------------------------|--------|
| 20–39      | Un-adjusted | 1.99 | 0.18–21.97 | .574†  |
|            | Adjusted    | 2.21 | 0.19–25.33 | .523†  |
| 40–49      | Un-adjusted | 2.02 | 0.73–5.6 | .176‡  |
|            | Adjusted    | 2.08 | 0.75–5.78 | .159‡  |
| 50–59      | Un-adjusted | 1.68 | 0.93–3.06 | .087‡  |
|            | Adjusted    | 1.71 | 0.94–3.12 | .078†  |
| 60–69      | Un-adjusted | 0.84 | 0.49–1.45 | .536†  |
|            | Adjusted    | 0.85 | 0.50–1.47 | .572†  |
| 70–99      | Un-adjusted | 2.03 | 0.9–4.57 | .087‡  |
|            | Adjusted    | 2.01 | 0.89–4.52 | .092†  |

* Tested by Cox proportional hazard regression.
† Adjusted for propensity score.

Adolescent obesity has been linked to an increased subsequent risk of cancer. Metabolic dysregulation in early life plays an integral role in carcinogenesis. The results of our study reveal that hyperlipidemia development in young adulthood (aged 20–39 years) increased the subsequent risk of bladder cancer. According to our finding, early-onset hyperlipidemia is a risk factor for bladder cancer in men.

According to previous studies, many factors influence the risk of bladder cancer. For example, DM is associated with an increased incidence and mortality of bladder cancer in both men and women. In patients on dialysis for end-stage renal disease, the risk of bladder cancer is increased and is higher in women. Obesity increases the risk of bladder cancer linearly according to the body mass index. COPD is associated with poor survival in elderly patients with bladder cancer.

Female patients with hypertension are at an increased risk of bladder cancer, and untreated hypertension is associated with a decreased risk of bladder cancer. Aspirin is associated with a decreased recurrent risk of bladder cancer. NSAIDs, especially ibuprofen, and metformin are associated with reduced bladder cancer risk. Rosiglitazone and pioglitazone are associated with an increased risk of bladder cancer in patients with diabetes. In this study, the aforementioned confounders significantly differed between the 2 cohorts, except for
hyperlipidemia increases the risk of bladder cancer in men but not in women. Young men (aged 20–39 years) with hyperlipidemia show a 5.45-fold increased risk of bladder cancer compared with men without hyperlipidemia. The results of this study provide evidence to indicate that hyperlipidemia is a risk factor for bladder cancer, especially in young men.

Author contributions

Authorship: Hung-Jen Shih, Ke-Hsun Lin, Yu-Ching Wen, Yen-Chun Fan, Pei-Shan Tsai, and Chun-Jen Huang have made substantial contributions to the conception of the work, data acquisition, data analysis and interpretation, drafting the work, reviewed the manuscript, and final approval of the submitted version.

Conceptualization: Hung-Jen Shih, Ke-Hsun Lin, Yu-Ching Wen, Pei-Shan Tsai, Chun-Jen Huang.

Data curation: Hung-Jen Shih, Yen-Chun Fan, Chun-Jen Huang.

Formal analysis: Yen-Chun Fan, Chun-Jen Huang.

Investigation: Hung-Jen Shih, Pei-Shan Tsai, Chun-Jen Huang.

Methodology: Hung-Jen Shih, Yen-Chun Fan, Pei-Shan Tsai, Chun-Jen Huang.

Project administration: Chun-Jen Huang.

Software: Yen-Chun Fan.

Supervision: Chun-Jen Huang.

Validation: Hung-Jen Shih, Ke-Hsun Lin, Yu-Ching Wen, Yen-Chun Fan, Pei-Shan Tsai.

Writing – original draft: Hung-Jen Shih.

Writing – review & editing: Hung-Jen Shih, Pei-Shan Tsai, Chun-Jen Huang.

References

[1] Montella M, Di Maso M, Crispo A, et al. Metabolic syndrome and the risk of bladder cancer increases subsequent risk of bladder and rectal cancer: a population-based cohort study Comparative Study. J Urol 2008;180: 2005–9.
[2] Rothman N, Garcia-Closas M, Chatterjee N, et al. A multi-stage genomewide association study of bladder cancer identifies multiple susceptibility loci. Research Support, N. I. H., Extramural Research Support, N. I. H., Intramural. Nat Genet 2010;42:978–84.
[3] Hata Y, Nakajima K. Life-style and serum lipids and lipoproteins. Research Support, Non-U. S. Gov’t. Review. J Atheroscler Thromb 2000;7:177–97.
[4] Ha J, La Vecchia C, de Groh M, et al. Dietary cholesterol intake and cancer. Research Support, Non-U. S. Gov’t. Ann Oncol 2012;23: 491–500.
[5] Montella M, Di Maso M, Crispo A, et al. Metabolic syndrome and the risk of urothelial carcinoma of the bladder: a case-control study. Research Support, Non-U. S. Gov’t. BMC Cancer 2015;15:720.
[6] Ferro M, Vartolomei MD, Russo GI, et al. An increased body mass index is associated with a worse prognosis in patients administered BCG immunotherapy for T1 bladder cancer. World J Urol 2019;37:507–14.
[7] Navar-Boggan AM, Peterson ED, D’Agostino RBSr, Neely B, Snidman ND, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. Research Support, N. I. H., Extramural Research Support, U. S. Gov’t, P.H.S. Circulation 2015;131:451–8.
[8] Varlamov O, Bethel CL, Roberts CTJr. Sex-specific differences in lipid and glucose metabolism. Front Endocrinol 2014;5:241.
[9] Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Research Support, Non-U.S. Gov’t. Pharmacoepidemiol Drug Saf 2011;20:236–42.
[10] Sung SF, Hsieh CY, Lin HJ, Chen YW, Yang YH, Li CY. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. Int J Cardiol 2016;215:277–82.
[11] Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk of coronary heart disease. Research Support, N. I. H., Extramural Research Support, U. S. Gov’t, P.H.S. Circulation 2015;131:451–8.
[12] Varlamov O, Bethel CL, Roberts CTJr. Sex-specific differences in lipid and glucose metabolism. Front Endocrinol 2014;5:241.
[13] Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Research Support, Non-U.S. Gov’t. Pharmacoepidemiol Drug Saf 2011;20:236–42.
[14] Sung SF, Hsieh CY, Lin HJ, Chen YW, Yang YH, Li CY. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. Int J Cardiol 2016;215:277–82.
[15] Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk of coronary heart disease. Research Support, N. I. H., Extramural Research Support, U. S. Gov’t, P.H.S. Circulation 2015;131:451–8.
[16] Varlamov O, Bethel CL, Roberts CTJr. Sex-specific differences in lipid and glucose metabolism. Front Endocrinol 2014;5:241.
[17] Jiang X, Castelo JE, Yuan JM, et al. Hypertension, diuretics and anti hypertensives in relation to bladder cancer. Comparative Study Research Support, N. I. H., Extramural. Carcinogenesis 2010;31:1964–71.
[18] Qin Q, Xu X, Wang X, Zheng XY. Obesity and risk of bladder cancer: a meta-analysis of cohort studies. Meta-Analysis Research Support, Non-U. S. Gov’t, Ann Oncol 2012;23: 491–500.
van de Schans SA, Janssen-Heijnen ML, Biesma B, et al. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. Multicenter Study. Eur J Cancer 2007; 43:2194–202.

Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. Research Support, Non-U.S. Gov’t. J Am Soc Nephrol 2003;14:197–207.

Gee JR, Jarrard DF, Bruskewitz RC, et al. Reduced bladder cancer recurrence rate with cardioprotective aspirin after intravesical bacille Calmette-Guérin. BJU Int 2009;103:736–9.

Baris D, Karagas MR, Koutros S, et al. Nonsteroidal anti-inflammatory drugs and other analgesic use and bladder cancer in northern New England. Research Support, N.I.H., Extramural. Int J Cancer 2013; 132:162–73.

El-Araby AA. New insight for metformin against bladder cancer. Genes Environ 2017;39:13.

Hsiao FY, Hsieh PH, Huang WF, Tsai YW, Gau CS. Risk of bladder cancer in diabetic patients treated with rosiglitazone or pioglitazone: a nested case-control study. Drug Saf 2013;36:643–9.

Radisauskas R, Kuzmiacki I, Milinaviciene I, Everatt R. Hypertension, serum lipids and cancer risk: a review of epidemiological evidence. Medica (Kaunas) 2016;52:89–98.

Venkitachalam L, Wang K, Porath A, et al. Global variation in the prevalence of elevated cholesterol in outpatients with established vascular disease or 3 cardiovascular risk factors according to national indices of economic development and health system performance. Research Support, U S Gov’t, Non-P H S. Circulation 2012;125:1838–69.

Strohmaier S, Edlinger M, Manjer J, et al. Total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer Project (MeCan). Multicenter Study Research Support, Non-U.S. Gov’t. PLoS One 2013;8:e54242.

Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. Research Support, Non-U.S. Gov’t. Proc Nutr Soc 2012;71:181–9.