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Increased risk of bladder cancer in young adult men with hyperlipidemia

A population-based cohort study

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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 did 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.

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TPS and HCJ contributed equally to this work.

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1. Introduction

In 2012, bladder cancer was the ninth most commonly diagnosed cancer worldwide.[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.[1,2] Similar pictures are observed in Taiwan.[1,2] 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.[3] In muscle-invasive bladder cancer, patients should receive radical cystectomy or tri-modality treatment for organ preservation.[4] During 2007 to 2011, the survival rate for bladder cancer in Taiwan was approximately 67%.[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,[5] occupational exposure to aromatic amines and other chemicals,[1] arsenic in drinking water,[2] aristolochia-based herbal medicines,[2] radiotherapy,[6] and genetic factors.[7] Tobacco smoking is a major risk factor for bladder cancer.[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.[8] A high-cholesterol diet increases the risks of various cancers, including bladder cancer.[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.[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.[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,[12] and lipid metabolism differs by gender.[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.[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.[15] In Taiwan, according to the diagnostic criteria for hyperlipidemia, physicians diagnose hyperlipidemia and prescribe medications for hyperlipidemia.[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 $\pm$ 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),[17] hypertension (ICD-9-CM codes 401–405),[18] obesity (body mass index $>$ 27) (ICD-9-CM codes 278 and 278.0),[19] chronic obstructive pulmonary disease (COPD) (as a proxy of smoking; ICD-9-CM codes 490–496),[20] and uremia (ICD-9-CM code 586).[21] Medications related to the risk of bladder cancer were aspirin (ATC codes B01AC06 and N02BA01),[22] nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC code M01A),[23] metformin (ATC code A10BA02),[24] rosiglitazone (ATC code A10BG02),[25] and pioglitazone (ATC codeA10BG03).[25]

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

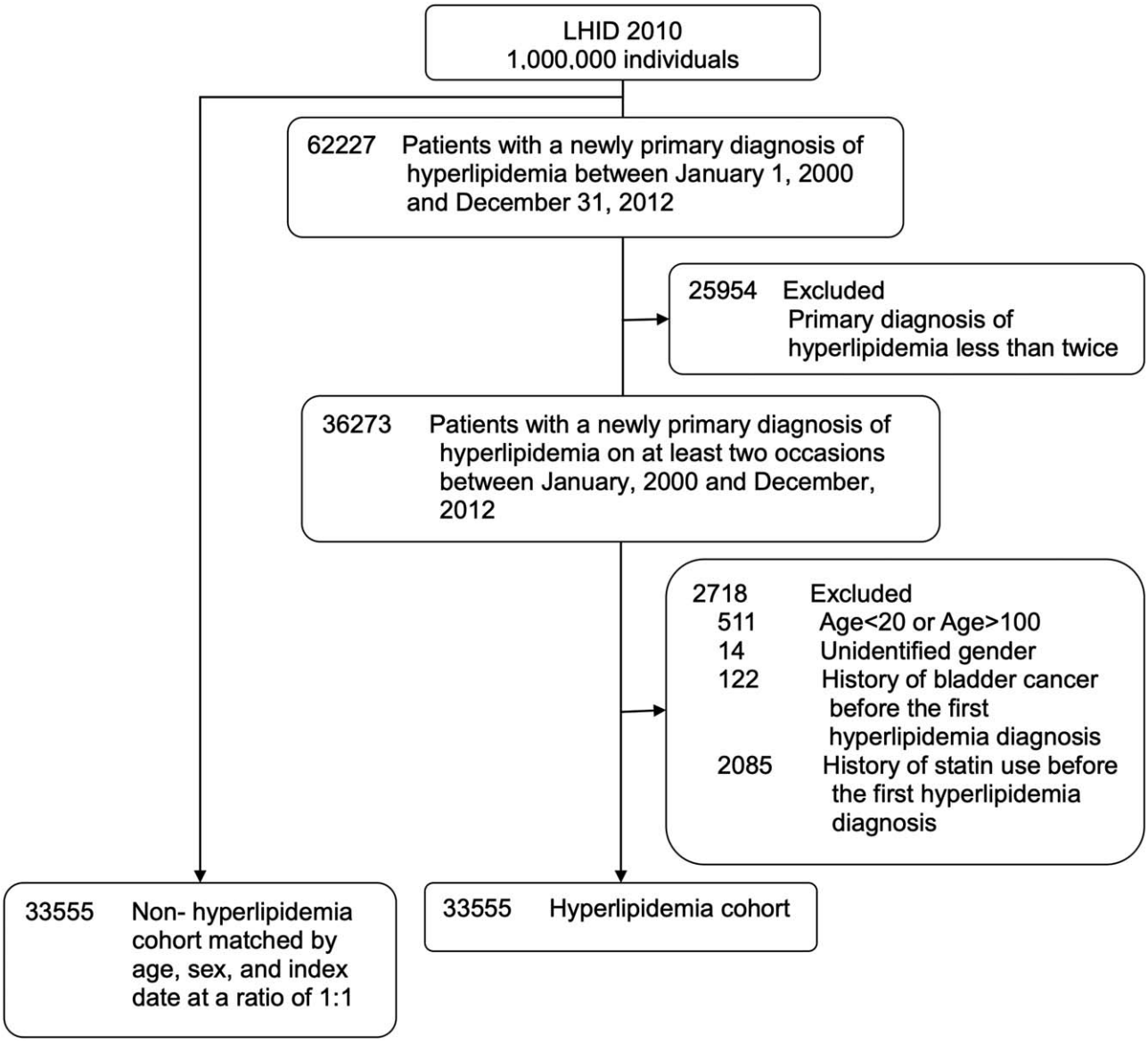

Figure 1. Flowchart of patient selection in the study cohort. LHID = Longitudinal Health Insurance Database.

Table 1

Distribution of characteristics in hyperlipidemia and non-hyperlipidemia cohorts.[†]

	Cohort		
	Hyperlipidemia (n = 33,555)	Non-hyperlipidemia (n = 33,555)	*P* value[*]
Age, n (%)			1.000
20–29	1598 (4.8)	1598 (4.8)	
30–39	4544 (13.5)	4544 (13.5)	
40–49	9220 (27.5)	9220 (27.5)	
50–59	10,149 (30.2)	10,149 (30.2)	
60–69	5259 (15.7)	5259 (15.7)	
70–99	2785 (8.3)	2785 (8.3)	
Gender, n (%)			1.000
Male	15,023 (44.8)	15,023 (44.8)	
Female	18,532 (55.2)	18,532 (55.2)	
Diabetes mellitus, n (%)			<.001
Yes	3744 (11.2)	1158 (3.5)	
No	29,811 (88.8)	32,397 (96.5)	
Hypertension, n (%)			<.001
Yes	8044 (24)	4205 (12.5)	
No	25,511 (76)	29,350 (87.5)	
Obesity, n (%)			<.001
Yes	386 (1.2)	42 (0.1)	
No	33,169 (98.8)	33,513 (99.9)	
COPD, n (%)			<.001
Yes	3472 (10.3)	2597 (7.7)	
No	30,083 (89.7)	30,958 (92.3)	
Uremia, n (%)			<.001
Yes	283 (0.8)	189 (0.6)	
No	33,272 (99.2)	33,366 (99.4)	
Aspirin use, n (%)			<.001
Yes	4388 (13.1)	2924 (8.7)	
No	29,167 (86.9)	30,631 (91.3)	
NSAIDs use, n (%)			<.001
Yes	25,852 (77)	23,302 (69.4)	
No	7703 (23)	10,253 (30.6)	
Metformin use, n (%)			<.001
Yes	907 (2.7)	529 (1.6)	
No	32,648 (97.3)	33,026 (98.4)	
Rosiglitazone use, n (%)			.002
Yes	56 (0.2)	27 (0.1)	
No	33,499 (99.8)	33,528 (99.9)	
Pioglitazone use, n (%)			.576
Yes	43 (0.1)	37 (0.1)	
No	33,512 (99.9)	33,518 (99.9)	

COPD = chronic obstructive pulmonary disease, as a proxy of smoking, NSAIDs = nonsteroidal anti-inflammatory drugs.

[*] Tested by the chi-square test.

[†] The hyperlipidemia cohort was matched by age and gender at a 1:1 ratio with the non-hyperlipidemia cohort.

cohort was significantly higher than that in the non-hyperlipidemia cohort (0.6% [217/33555] vs 0.4% [143/33555], $P < .001$; Table 2). The relative risk of bladder cancer in the hyperlipidemia cohort was significantly higher than that in the non-hyperlipidemia cohort (unadjusted hazard ratio [HR] = 1.51, 95% confidence interval [CI] = 1.22–1.86, $P < .001$; Table 2). The trend remained the same after adjustment for the propensity score (adjusted HR = 1.37, 95% CI = 1.10–1.71, $P = .005$) (Table 2). These data indicated that patients with hyperlipidemia were associated with an increased risk of bladder cancer comparing to non-hyperlipidemia patients.

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.[26] Higher risks of colon, prostate, and testicular cancers have been reported in patients with hyperlipidemia in previous research.[26] By contrast, studies have

Table 2

The prevalence rate and relative risk of having bladder cancer in hyperlipidemia cohort compared with those in non-hyperlipidemia cohort.

Cohorts	Bladder cancer: n (%)		*P* value
Hyperlipidemia (n = 33,555)	217 (0.6)		<.001*
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†
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‡
Non-hyperlipidemia (n = 33,555)	1.00		

* Tested by the chi-squared tests.

† Tested by Cox proportional hazard regression.

‡ 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).

reported that patients with hyperlipidemia have lower risks of stomach, liver, and hematopoietic/lymphoid tissue cancers.[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).[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.[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.[28] 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.[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.[30] The androgen receptor has been found in bladder tissue, and the down-regulation of androgen receptor expression suppresses bladder

Table 3

The relative risk of having bladder cancer in hyperlipidemia cohort compared with that in non-hyperlipidemia cohort stratified by gender.

Cohort	Unadjusted hazard ratio	95% confidence intervals	*P* value
Hyperlipidemia men	1.54	1.16–2.04	.003*
Non-hyperlipidemia men	1.00		
Cohort	**Adjusted hazard ratio**	**95% confidence intervals**	***P* value**
Hyperlipidemia men	1.36	1.01–1.82	.040†
Non-hyperlipidemia men	1.00		
Cohort	**Unadjusted hazard ratio**	**95% confidence intervals**	***P* value**
Hyperlipidemia women	1.47	1.07–2.02	.019*
Non-hyperlipidemia women	1.00		
Cohort	**Adjusted hazard ratio**	**95% confidence intervals**	***P* value**
Hyperlipidemia women	1.39	1.00–1.93	.053†
Non-hyperlipidemia women	1.00		
Hyperlipidemia cohort	**Unadjusted hazard ratio**	**95% confidence intervals**	***P* value**
Men	1.68	1.28–2.20	<.001*
Women	1.00		
Hyperlipidemia cohort	**Adjusted hazard ratio**	**95% confidence intervals**	***P* value**
Men	1.97	1.51–2.59	<.001†
Women	1.00		

* Tested by Cox proportional hazard regression.

† Adjusted for propensity score.

Table 4

Subgroup analyses of the relative risk of having bladder cancer in hyperlipidemia cohort compared with that in non-hyperlipidemia cohort.

Age groups		Hazard ratio	95% confidence intervals	*P* value
Hyperlipidemia cohort vs non-hyperlipidemia cohort				
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	.022†
50–59	Un-adjusted	1.39	0.91–2.14	.127*
	Adjusted	1.41	0.92–2.17	.115†
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				
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				
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	.178*
	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	.535*
	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.

cancer growth in vitro and in vivo.[30,31] Thus, the association between the androgen/androgen receptor and bladder cancer has been evaluated. Shiota et al[32] demonstrated that androgen deprivation therapy decreases the risk of bladder cancer in patients with prostate cancer. In a prospective cohort study, finasteride, a 5-alpha reductase inhibitor that reduces the dihydrotestosterone level, was associated with a reduced incidence of bladder cancer.[33] According to the findings of previous studies and our study, sex hormones may play a role in the different risks of bladder cancer in hyperlipidemia patients. Additional studies are required to ascertain the underlying mechanisms.

Subgroup analyses further revealed that young adult men aged 20 to 39 years in the hyperlipidemia cohort exhibited an up to 5.45-fold increased risk of bladder cancer compared with those in the non-hyperlipidemia cohort. However, the risk of bladder cancer was not significantly different between men aged older than 40 years in the hyperlipidemia cohort and those in the non-hyperlipidemia cohort. These data further highlight that hyperlipidemia increases the subsequent risk of bladder cancer, especially in young adult men. A hyperlipidemia diagnosis in young adults increases the subsequent risk of coronary heart disease due to the increased duration of exposure to hyperlipidemia.[12] Cancer often takes years to be diagnosed after initial exposure to a carcinogen.[34] Obesity and a high-fat, low-vegetable diet may represent risk factors for carcinogenesis.[35] Adolescent obesity has been linked to an increased subsequent risk of cancer.[36] Metabolic dysregulation in early life plays an integral role in carcinogenesis.[36] 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.[17] In patients on dialysis for end-stage renal disease, the risk of bladder cancer is increased and is higher in women.[21] Obesity increases the risk of bladder cancer linearly according to the body mass index.[19,37] COPD is associated with poor survival in elderly patients with bladder cancer.[20] Female patients with hypertension are at an increased risk of bladder cancer,[38] and untreated hypertension is associated with a decreased risk of bladder cancer.[18] Aspirin is associated with a decreased recurrent risk of bladder cancer.[22] NSAIDs, especially ibuprofen, and metformin are associated with reduced bladder cancer risk.[23,24] Rosiglitazone and pioglitazone are associated with an increased risk of bladder cancer in patients with diabetes.[25] In this study, the aforementioned confounders significantly differed between the 2 cohorts, except for

pioglitazone. The impact of these confounders was controlled for through propensity score adjustment. After controlling for these potential confounders, the risk of bladder cancer was higher in the hyperlipidemia cohort than in the non-hyperlipidemia cohort and in men than in women in the hyperlipidemia cohort.

Our population-based study showed the association of hyperlipidemia with the risk of bladder cancer. Whether controlling the serum lipid level can prevent the risk of bladder cancer is unclear; further evaluation is thus required. Furthermore, this study has some limitations. First, smoking is a major risk factor for bladder cancer[5]; this information is lacking in the NHIRD. Because smoking is the most important causative factor for COPD,[39] we used COPD as a confounder to decrease the bias of this study. Other possible confounding factors, such as occupational exposure to aromatic amines,[1] arsenic in drinking water,[2] herbal remedies containing aristolochic acids,[2] radiotherapy,[6] and schistosomiasis infection[40] were not included in this study. Second, the dietary factor is important for the risk of bladder cancer[41]; information on lifestyle, physical activity, and dietary habits are lacking in the NHIRD. Third, data on the serum lipid level (such as low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) are unavailable in the NHIRD. Fourth, the medications for hyperlipidemia and medications treatment duration were not evaluated in this study. Fifth, direct evidence is lacking for the cause–effect relationship between hyperlipidemia and the risk of bladder cancer in this retrospective study. Prospective randomized clinical trials should be conducted to obtain more precise information. Sixth, the association between hyperlipidemia and disease prognosis was not included in this study. Seventh, the diagnosis of hyperlipidemia was made by the record of ICD-9-CM in the NHIRD, the impact of misclassification bias should be further elucidated. Eighth, the diagnosis codes made by ICD-9-CM in the LHID2010 (from the year 2000 to 2012) were validated in the many previous studies.[42] However, the validation study for ICD-10 diagnosis codes adopted after the year 2016 in the NHIRD is limited.[42] The results of this study should be further evaluated in the future with validated new database.

5. Conclusions

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.

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