# Multi-factorial Etiology of Gallbladder Cancer: A USA Case-Control Population Study


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## Introduction & Objectives

**Gallbladder Cancer (GBC) in USA**

- Globally rare, asymptomatic, lethal cancer known for late diagnosis and poor prognosis[1,2]
- Between 2007-2011, 3,700 GBC cases and 2,000 deaths (1.13 cases and 0.62 deaths per 100,000) [1]
- 5-20% five-year survival rate and mean survival of 2-52 months [3]
- Possible risk factors include: cholecystitis, gallstones, smoking, alcohol, female gender, race, and environmental toxins [3,4]

**Research Question**

1. **Is GBC incidence dependent on specific demographic characteristics?**
2. **What are the main environmental factors associated with GBC risk?**
3. **Which female factors contribute to the risk of GBC?**
4. **What chronic conditions are associated with GBC?**
5. **Is there an association between GBC and steatosis after adjustment for potential cofounders?**

## Methods

- Hospital-based case - control study conducted at UT MD Anderson Cancer (2017-2021).

**Inclusion Criteria**

- **Cases:** 79 patients with confirmed GBC diagnosis who reside in the US, without previous history of other cancers
- **Controls**: 660 healthy individuals without prior history of cancer, who are spouses of cancer patients (excluding GI or smoking-related cancer)
- No restrictions by age, gender, or race
- All participants interviewed for prior history of GBC were reviewed for evidence of GBC and other GI Cancers (radiologically and clinically).

**Statistical Analysis**

- SPSS and STATA statistical softwares used to perform multivariable logistic regression to estimate odds ratios.
- Assess the independent effect and significance ($p < 0.05$) of multiple risk factors including cigarette smoking, alcohol drinking, diabetes, thyroid diseases, obesity, hormones, and family history of cancer
- Adjusted OR (AOR) and 95% Confidence Interval (95% CI) values calculated for each factor
- All AORs were adjusted for age, gender, race, educational level and marital status
- Analyses were performed in men and women separately and all populations.

## Responsible Conduct of Research

Under IRB approval of MD Anderson, cases and controls were personally interviewed for different GBC risk factors. Protocol was strictly followed for data acquisition, management, ownership, and sharing to ensure patient privacy.

## Results

**Table 1: Demographic Characteristics of the Study Populations [79 cases and 660 controls]**

| Demographic Variables | Gallbladder Cases N=79 (%) | Controls N=660 (%) | P value |
|---|---|---|---|
| **Sex** | | | **0.03** |
| Male | 35 (44.3) | 403 (61.1) | |
| Female | 44 (55.7) | 257 (38.9) | |
| **Race** | | | **<0.001** |
| White | 56 (70.9) | 596 (90.3) | |
| African American | 8 (10.1) | 19 (2.9) | |
| Hispanics | 9 (11.4) | 41 (6.2) | |
| Asian/Pacific Islander | 6 (7.6) | 4 (0.6) | |
| **Age (Years)** | | | 0.849 |
| <=40 | 3 (3.8) | 25 (3.8) | |
| 41-50 | 13 (16.5) | 101 (15.3) | |
| 51-60 | 20 (25.3) | 209 (31.7) | |
| 61-70 | 30 (38) | 224 (33.9) | |
| >70 | 13 (16.5) | 101 (15.3) | |
| **Education Level** | | | 0.150 |
| <= High School | 22 (27.8) | 145 (22) | |
| >High School | 57 (72.2) | 515 (78) | |
| **Marital Status** | | | **<0.001** |
| Single | 17 (21.5) | 44 (6.7) | |
| Married | 62 (78.5) | 616 (93.3) | |
| **Resident State** | | | **<0.001** |
| Texas & Adjacent States | 43 (54.4) | 487 (73.8) | |
| Other States | 36 (45.6) | 173 (26.2) | |

*Adjacent states include Louisiana, Arkansas, Oklahoma, and New Mexico

**Table 2: Estimated Odds Ratios (OR), 95% Confidence Interval (CI) of different exposures: Multivariable Logistic Regression Analysis**

| Exposure | Case N=79 (%) | Controls N=660 (%) | OR (95% CI) | P value |
|---|---|---|---|---|
| **Age** | | | | 0.231 |
| Above age of 50 | 63 (79.7) | 534 (80.9) | 1 (reference) | |
| Below age of 50 | 16 (20.3) | 126 (19.1) | 1.02 (0.99-1.05) | |
| **Race** | | | | **<0.001** |
| Non-white | 23 (29.1) | 596 (90.3) | 1 (reference) | |
| White | 56 (70.9) | 64 (9.7) | 0.21 (0.11-0.42) | |
| **Gender** | | | | **0.005** |
| Male | 35 (44.3) | 403 (61.1) | 1 (reference) | |
| Female | 44 (55.7) | 257 (38.9) | 1.97 (1.23-3.16) | |
| **Cigarette Smoking** | | | | 0.151 |
| Nonsmokers | 49 (62) | 353 (53.5) | 1 (reference) | |
| Smokers | 30 (38) | 307 (46.5) | 0.70(0.44-1.14) | |
| **Marital Status** | | | | **0.005** |
| Not Married | 17 (21.5) | 44 (6.7) | 1 (reference) | |
| Married | 62 (78.5) | 616 (93.3) | 0.26 (0.14- 0.48) | |
| **Alcohol History** | | | | **0.027** |
| Non-drinkers | 34 (43) | 295 (44.7) | 1 (reference) | |
| Drinkers | 45 (57) | 365 (55.3) | 1.97 (1.08-3.58) | |
| **Education** | | | | 0.997 |
| >Highschool | 57 (72.2) | 515 (78) | 1 (reference) | |
| <=Highschool | 22 (27.8) | 145 (22) | 1.00 (0.55-1.84) | |
| **Diabetes History** | | | | 0.406 |
| Non-diabetic | 67 (84.8) | 581 (88) | 1 (reference) | |
| Diabetic | 12 (15.2) | 079 (12) | 0.70(0.30-1.62) | |
| **Adulthood history of Obesity** | | | | 0.666 |
| Non-obese | 55 (69.6) | 458 (69.4) | 1 (reference) | |
| Obese | 24 (30.4) | 202 (30.6) | 0.87(0.48-1.59) | |
| **Gallstone Inflammation History** | | | | **<0.001** |
| No | 38 (48.1) | 585 (88.6) | 1 (reference) | |
| Yes | 41 (51.9) | 75 (11.4) | 7.97(4.52-14.06) | |
| **Family History of Cancer** | | | | 0.158 |
| No | 20 (25.3) | 228 (34.5) | 1 (reference) | |
| Yes | 59 (74.7) | 432 (65.5) | 1.53(0.85-2.77) | |
| **History of Hypothyroidism** | | | | 0.533 |
| No | 72 (91.1) | 600 (90.9) | 1 (reference) | |
| Yes | 7 (8.9) | 60 (9.1) | 0.74(0.29-1.88) | |

**Summary Statistics for Tables 1 & 2:**

- **Table 1:** Significance variation was observed in race, gender, marital status, and the resident state of Texas and its adjacent states.
- **Table 2:** Increase of GBC risk was observed in the female-gender, non-white race, non-married marital status, alcohol history, and gallstone history.

## Results

**Table 3: Estimated Odds Ratios (OR), 95% Confidence Interval (CI) of Female Factors: Multivariable Logistic Regression Analysis**

| Variable | Cases N=44 (%) | Controls N=253 (%) | OR (95% CI)* | *P* value |
|---|---|---|---|---|
| **Birth Control History** | | | | 0.084 |
| No | 9 (20.9) | 63 (24.9) | 1 (reference) | |
| Yes | 34 (79.1) | 190 (75.1) | 2.89(0.87-9.64) | |
| **Hysterectomy History** | | | | 0.161 |
| No | 30 (68.2) | 123 (48.6) | 1 (reference) | |
| Yes | 14 (31.8) | 130 (51.4) | 0.45(0.15-1.37) | |
| **History of ever Estrogen use** | | | | **<0.001** |
| No | 37 (84.1) | 96 (37.4) | 1 (reference) | |
| Yes | 7 (15.9) | 161 (62.6) | 0.06(0.02-0.22) | |
| *=< 2 years of Estrogen use* | 3 (6.8) | 29 (11.3) | 0.15(0.04-0.66) | **.012** |
| *>2 years of Estrogen use* | 4 (9.1) | 132 (51.4) | 0.04(0.01-0.15) | **<0.001** |
| **History of ever Progesterone use** | | | | |
| No | 39 (88.6) | 200 (77.8) | 1 (reference) | |
| Yes | 5 (11.4) | 57 (22.2) | 1.09(0.27-4.48) | |

*ORs are adjusted for age, race, alcohol drinking, menopausal age, gallbladder stones or inflammation, and marital status

**Summary Statics for Table 3:**

- 94% decrease in the risk of GBC among women who have had estrogen exposure
- Females who used estrogen for less than or equal to two years have an 85% decrease in risk of GBC
- GBC protection increased when estrogen was used for 2+ years, decreasing risk by 96%
- Other female factors were not significantly associated with GBC such as birth control history, hysterectomy history, and progesterone use.

**Prevalence of Various Chronic Medical Conditions in Patients with GBC**

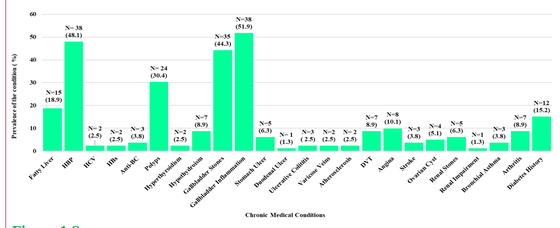


**Figure 1 Summary:**

- **High prevalence of chronic medical conditions:** gallbladder inflammation (51.9%), HBP or high blood pressure (48.1%), gallbladder stones (44.3%), and polyps (30.4%).
- **Medium prevalence of chronic medical conditions:** fatty liver (18.9%), diabetes history (15.2%), angina or ischemic chest pain (10.1%), DVT or deep vein thrombosis (8.9%), and hypothyroidism (8.9%)
- **Low prevalence of chronic medical conditions:** renal stones (6.3%), ovarian cysts (5.1%), stroke (3.8%), atherosclerosis (3.8%), bronchial asthma (3.8%), anti-BC (3.8%), HBs (2.5%), HCV (2.5%), varicose veins (2.5%), ulcerative colitis (2.5%), hyperthyroidism (2.5%), renal impairment (1.3%), and duodenal ulcer (1.3%).

**Mean & Standard Deviation of Female Factors**

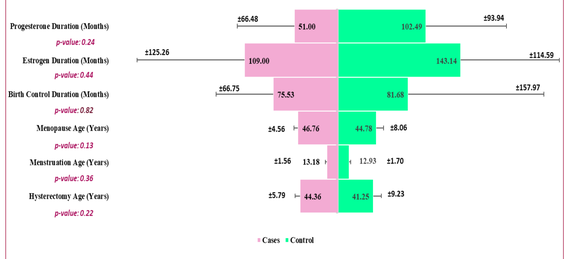


**Figure 2 Summary:**

- No significant variation between cases and controls in terms of duration of female factors such as the duration of progesterone, estrogen, birth control, menopause age, menstruation age, and hysterectomy age.

## Results

- GBC was more common in females, non-white races, and non-married individuals. The geographical variation observed was most likely due to the referral pattern of patients.
- Gallbladder inflammation was related to 8 times higher risk for GBC.
- Alcohol users had approximately two-fold higher risk for GBC.
- Restricted analysis among 44 women cases and 257 women controls yielded 94% reduction in GBC risk among estrogen users (the reduction was associated with the duration of estrogen intake).
- Despite that 19% of the GBC patients had pathological evidence of steatosis, obesity and diabetes was not significantly related to GBC risk.
- The most prevalent chronic medical conditions in patients with GBC were high blood pressure, polyps, gallbladder stones, gallbladder inflammation, and fatty liver. *(Note: Prevalence of chronic medical conditions was not studied in control group)*

## Conclusions & Future Implications

- GBC is multi-factorial in origin
- Control of environmental exposures (alcohol use) may reduce GBC susceptibility and promote primary prevention
- Patients with high risk factors such as GBD and cholecystitis should be considered for early GBC prevention and screening programs
- Mechanistic pathway for GBC with GBD and cholecystitis needs to be further explored
- Limitation of this study was small sample size due to GBC rarity
- Further validation of GBC risk factors is necessary as it will help confirm findings and develop diagnostic markers and early treatments of GBC.
- Strategic planning of prevention and management of GBC should be further investigated and developed by healthcare providers.

## References


1. Henley SJ, Weir HK, Jim MA, Watson M, Richardson LC. Gallbladder Cancer Incidence and Mortality, United States 1999–2011. *Cancer Epidemiology Biomarkers & Prevention*. 2015;24(9):1319-1326. doi:10.1158/1055-9965.epi-15-0199
2. Kanlioz M, Ekici U, Ayva Y. Analysis of Incidental Gallbladder Cancer in Cholecystectomies. *Cureus*. Published online September 20, 2019. doi:10.7759/cureus.5710
3. Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. *Clinical and Experimental Hepatology*. 2019;5(2):93-102. doi:10.5114/ceh.2019.85166
4. Shaffer EA. Gallbladder cancer: the basics. Gastroenterol Hepatol (N Y). 2008;4(10):737-741.


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