# Relationship Between GERD-Associated Comorbidities and Gastrointestinal Cancer Outcomes

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## ABSTRACT

Gastrointestinal (GI) cancers have high incidence and mortality rates. Obesity and obesity-related disorders such as gastroesophageal reflux disease (GERD) and type 2 diabetes (T2D) are associated with increased risk of GI cancers. We examined the possible correlation between GI cancer type and GERD-associated comorbidities in T2D patients. All eligible adult T2D patients diagnosed with GI cancer at Roswell Park Cancer Institute (January 1, 2003-December 31, 2010) were included in this retrospective analysis (n = 222). Patient demographic information, clinical, and pharmaceutical histories were documented. The overall survival (OS) and disease-free survival (DFS) comparisons utilizing univariate and multivariate analyses were determined using Kaplan-Meier log-rank tests and Cox proportional hazards models. We report here that T2D patients with GI cancer and GERD had significantly lower OS and DFS than patients without GERD ($P$ = .0010; $P$ = .0022; respectively). We found that GERD was highly prevalent in patients with cancer diagnoses in the upper GI compared to the lower GI ($P$ = <.0001). Upper GI cancer patients had a 4.25 fold increase in odds ($P$ = <.0001) of having a metastatic cancer diagnosis than those with lower GI cancer. Additionally, OS and DFS was significantly higher when patients used metformin to treat T2D ($P$ = .0177 and $P$ = .0476 respectively). Reducing the incidence of GERD, improving management of GERD-associated risk factors, and using metformin therapy will contribute to the current focus of decreasing GI cancer incidence and mortality in patients with T2D.

## INTRODUCTION

- Gastrointestinal (GI) cancers are among the most common and deadliest cancers in the United States.
  - 5-year survival rates: esophageal (18%); gastric cancers (28%)
  - Colorectal cancer: 2nd most commonly diagnosed cancer in females; 3rd most commonly diagnosed cancer in males.[1]
- GI cancers have a strong association with obesity and obesity-related disorders such as type 2 diabetes (T2D) and gastroesophageal reflux disease (GERD), alcohol consumption, and smoking.[2,3]
- T2D is a well-known risk factor for both cancer occurrence and mortality. However, the correlation between T2D and cancer is very complex and insufficiently understood. Thus, antidiabetic therapy, comorbidities associated with T2D (i.e. GERD), alcohol consumption, and smoking may influence the risk of acquiring cancer.
- Metformin is the most commonly used oral glucose-lowering therapy:
  - Decreases hepatic glucose production, intestinal absorption.
  - Increases glucose utilization by reducing hyperinsulinemia associated with insulin resistance.[4]
  - Associated with weight reduction in T2D patients with obesity,[5] reductions of circulating lipids,[6] reduced cancer risk[7,8] and mortality.[7,9]
- Because of the worldwide diabetes epidemic, the incidence of GI cancers will continue to rise unless the diabetes rate is controlled, including its associated risk factors, weight gain, alcohol consumption, and smoking. Association of these factors with specific GI tract location of cancer occurrence was evaluated in this study. We aimed to clarify whether any specific correlation exists between specific GI cancer type and any of these conditions.

## METHODS

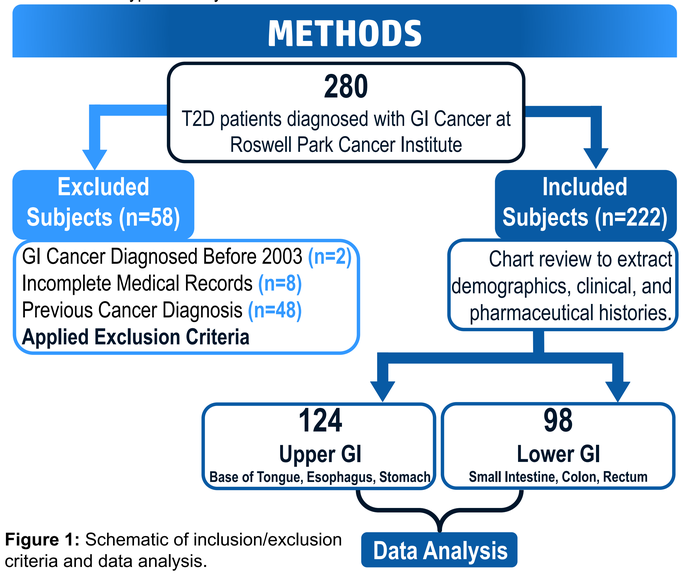


**Figure 1:** Schematic of inclusion/exclusion criteria and data analysis.

## RESULTS

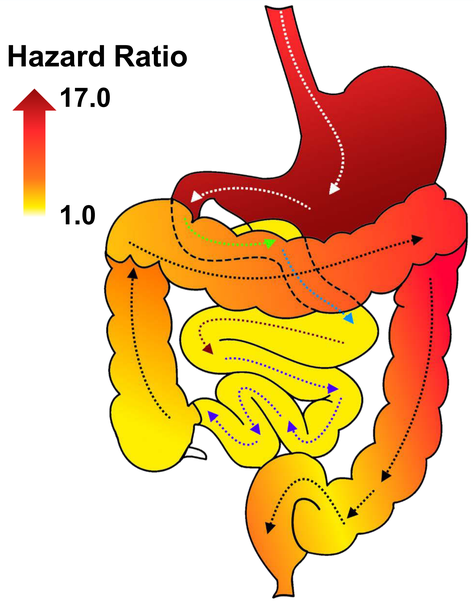


**Figure 2:** Risk of mortality specific to anatomical site.

| Table 1: Demographics by Tumor Location | Upper GI % (No.) | Lower GI % (No.) |
|---|---|---|
| **Age (Years)** | | |
| Younger than 50 | 4.0 (5) | 5.1 (5) |
| 50 to 59 | 16.1 (20) | 18.4 (18) |
| 60 to 69 | 39.5 (49) | 38.8 (38) |
| 70 to 79 | 29.9 (37) | 30.6 (30) |
| 80 or Older | 10.5 (13) | 7.1 (7) |
| **BMI Category (CDC Classification)** | | |
| Underweight | 2.4 (3) | 2.0 (2) |
| Healthy Weight | 13.7 (17) | 8.2 (8) |
| Overweight | 25.8 (32) | 32.7 (32) |
| Obese | 38.7 (48) | 45.9 (45) |
| Unknown | 19.4 (24) | 11.2 (11) |
| **Gender** | | |
| Male | 72.6 (90) | 60.2 (59) |
| Female | 27.4 (34) | 39.8 (39) |
| **Ethnicity** | | |
| African American | 5.7 (7) | 7.1 (7) |
| Caucasian | 83.9 (104) | 87.8 (86) |
| Other | 10.4 (13) | 5.1 (5) |
| **Smoking History** | | |
| Non-Smoker | 19.4 (24) | 60.2 (39) |
| Smoker (Past or Current) | 80.6 (100) | 39.8 (59) |
| **Alcohol History** | | |
| No Alcohol Use | 28.2 (35) | 65.3 (64) |
| Alcohol Use (Past or Current) | 71.8 (89) | 34.7 (34) |
| **Family History of Cancer** | | |
| Absent | 39.5 (49) | 53.1 (52) |
| Present | 60.5 (75) | 46.9 (46) |
| **Metastatic at Diagnosis** | | |
| Not Metastatic | 54.0 (67) | 82.7 (81) |
| Metastatic | 46.0 (57) | 17.3 (17) |
| **Presence of GERD** | | |
| No GERD | 49.2 (61) | 93.9 (92) |
| GERD | 50.8 (63) | 6.1 (6) |

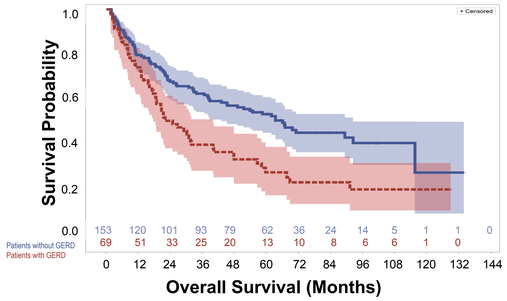


**Figure 3:** Overall survival of T2D patients with incident GI cancers having or not GERD at the time of cancer diagnosis. ($P$ = .0010 [$X^2$ = 10.77], 95% CI).

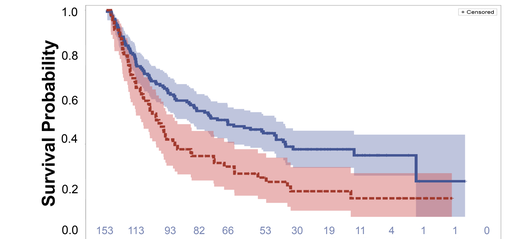


**Figure 4:** Disease-free survival of T2D patients with incident GI cancers having or not GERD at the time of cancer diagnosis. ($P$ = .0022 [$X^2$ = 9.348], 95% CI).

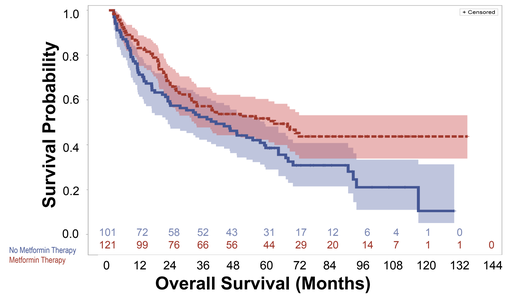


**Figure 7:** Overall survival of GI cancer patients with metformin treatment is higher than those without ($P$ = .0177 [$X^2$ = 5.62], 95% CI).

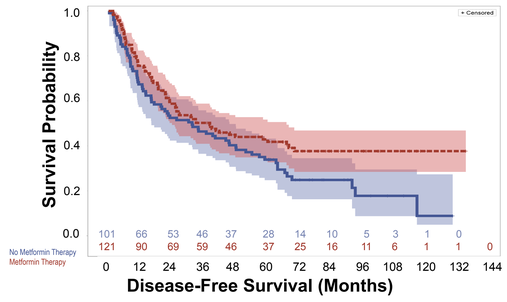


**Figure 8:** Disease-free survival of GI cancer patients with metformin treatment is higher than those without ($P$ = .0476 [$X^2$ = 3.9245], 95% CI).

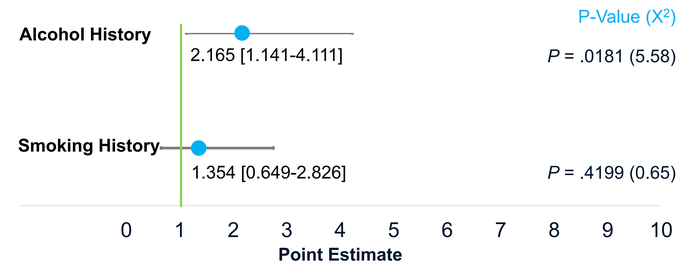


**Figure 5: Association of Alcohol and Smoking History and Presence or Absence of GERD in T2D Patients with Incident GI Cancers.** Performed analysis accounted for the contribution of age and weight (in kilograms).

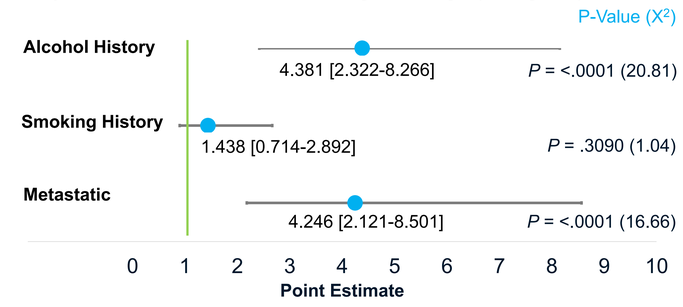


**Figure 6: Alcohol and Smoking History in T2D Patients with Incident Upper vs. Lower GI Cancers.** Performed analysis accounted for the contribution of age and weight (in kilograms).

## CONCLUSIONS

- Our study evaluated any relationship between specific GI cancer type and GERD risk factors in a retrospective hospital cohort with T2D. We report here that the site of GI tumor development is associated with cancer outcome, with stomach having a HR significantly higher as compared to the base of the tongue (Fig. 2).
- T2D patients with GI cancer and GERD had significantly lower OS and DFS than patients without GERD (Fig. 3, $P$ = .0010; Fig. 4, $P$ = .0022 respectively). GERD was associated with history of alcohol consumption and smoking, with respective fold increase in odds of 2.17 (95% CI 1.141-4.111, $P$ = .0101) and 1.35 (95% CI 0.649-2.826, $P$ = .4199) compared to those without GERD (Fig. 5). Previous analysis including subsequent excluded subjects found smoking to be significant.
- When stratifying by upper and lower GI cancers, our data further indicates that T2D patients who develop GERD also have an increased risk of developing upper GI cancer (table 1). An interesting finding from our study revealed a strong correlation between upper GI cancer and history of alcohol consumption (odds ratio 4.38, 95% CI 2.322-8.266, $P$ = <.0001), smoking (odds ratio 1.44, 95% CI 0.714-2.892, $P$ = <.3090), and metastatic diagnosis (odds ratio 4.25, 95% CI 2.121-8.501, $P$ = <.0001), (Fig. 6, table 1). Previous analysis including subsequent excluded subjects found smoking to be significant. A contributing factor to the reduced risk of a metastatic lower GI cancer may be due to early cancer detection using colonoscopy screening.
- Obesity is a risk factor for both GI cancer and GERD, however, BMI was not predictive of GERD in our population and it did not correlate with GI cancer site, with 64.5% of the upper GI cancer patients and 78.6% of the lower GI cancer patients (table 1). The lack of association of obesity with GERD may have been due to under-reporting of GERD by patients or patient's self-management of GERD.
- We also report that receiving metformin therapy is associated with improved GI cancer prognosis. T2D patients on any metformin therapy had significantly higher OS and DFS than patients with no metformin (Fig. 7, $P$ = .0177; Fig. 8, $P$ = .0476 respectively).
- In summary, this study supports the ongoing effort to decrease GI cancer incidence and mortality in patients with T2D by reducing the incidence of GERD, improving management of GERD-associated risk factors, and using metformin therapy.

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