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# Increased Colorectal Cancer Rate in Turner Syndrome: A Case Control Study

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**Abstract:** Female sex hormonal supplementation had been shown to be protective against Colorectal cancer (CRC). Turner syndrome (TS) is a rare X lined chromosomal disorder associated with sex hormonal deficiency. Hence, we hypothesized that that females with TS would be at an increased risk of CRC. From the Truven Health Marketscan Commercial Claims and Encounters Database, female patients who had colonoscopy with TS were compared to aged matched to controls. For these patients we obtained demographic variables, risk factors (diabetes, morbid obesity, smoking, use of non-steroidal anti-inflammatory drugs and statins) and endoscopic results (adenoma and cancer detection) from the database. Multivariate logistic regression analysis was performed to compare the cancer detection rates in both groups. Of the 7,77,36,681 patients of age 35 or older in the database 3265 had TS. Of those 546 (17%) patients had a colonoscopy that was reported. These patients were compared to 1059 age matched controls. Prevalence of diabetes (14.3 vs 8.4, P<0.001), and smoking (2.6 vs 0.9, p=0.01) was higher in patients with TS. Cancer detection rate was higher in patients with TS (1.1% vs 0.2%, p=0.01). After adjustment for the above variables, patients with TS have an adjusted odds ratio of 9.5 for CRC at any colonoscopy (95% CI 1.7-52.8, p =0.008). Hence, we concluded that in the studied cohort of TS patients there was a higher colorectal cancer detection rate at any colonoscopy when compared to their age matched female counterparts. TS patients represent a 'disparity group' who warrant enhanced CRC screening.

**Keywords:** Colorectal Cancer, Turner Syndrome, Disparity Group, Case Control Study, Truven Marketscan Database

## 1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer related deaths (men and women combined) in the United States [1]. The American Cancer Society estimated that approximately 150,000 people will be diagnosed with colorectal cancer in the year 2020. Although the overall death rates from colorectal cancer continue to decrease over the last few decades, the number of deaths from CRC in patients younger than age 55 have increased by 2% from 2007 to 2016 [2]. Inherited pathogenic germline mutations are present in 10% of all patients with CRC [3] and up to 20% of patients with early onset CRC [4]. Thus, a significant proportion of patients have no discernable inherited genetic risk factors.

A few non-modifiable risk factors influence the need for early screening of CRC. These include having a personal history of hereditary cancer syndromes, inflammatory bowel disease, or any first degree relative with CRC and/or advanced adenoma [5]. According to the United States Multi-Society Taskforce on Colorectal Cancer, individuals who have a first degree relative with CRC or an advanced adenoma are recommended to have a screening colonoscopy at age 40 (or the earliest of 40 years of age vs. 10 years prior to the event occurrence if the event occurred in first degree relative aged<65 years). The estimated lifetime risk of CRC is 4.4% and 4.1% for men and women respectively [1, 6]. Gender despite being a non-modifiable risk factor for CRC does not currently influence the need for early screening colonoscopy.

Turner syndrome (TS) is a rare non-inherited X chromosomal disorder that occurs in 1 in 2500 female liver births [7]. Patients with this condition have congenital ovarian hypoplasia and hence a deficiency of female sex hormones. Most patients with TS are unable to conceive naturally or with fertility support. Few studies elucidated the fact that gravidity is protective against colon cancer [8]. Female sex hormone supplementation for post-menopausal females was also demonstrated to be protective against CRC in large cohort studies [9, 10]. Hence in theory patients with TS have an increased risk of CRC due to lower fertility rate and deficiency of sex hormones. Registry based studies from Europe on patients with TS demonstrated conflicting results with regards to the risk for CRC [11-13]. These studies were limited by having inherent study flaws, absence of an appropriate control group, and lack of adjustment for other co-variables.

We hypothesized that patients with TS will have a higher CRC detection rates at colonoscopy when compared to their age matched controls. As the prevalence of TS is rare we decided to undertake this study using a large nationwide insurance database.

## 2. Methods

### *2.1. Patients and Eligibility Criteria*

We performed a retrospective matched case control study using Truven Health Marketscan Commercial Claims and Encounters Database (Truven Health Analytics Inc, Ann Arbor, MI) [14]. This database encompassed of claims submitted from 2005 to 2017. It had information of all insurance claims that were submitted for a particular patient that included inpatient, outpatient, prescription drug, and other health care resource utilization.

We included female patients who were aged 35 or older for the purpose of our analysis. We created a 1: N matched case control study where N can range from 1 to 4 for increased power. International Classification of Diseases, 9$^{th}$ revision (ICD-9) code and International Classification of Diseases, 10$^{th}$ revision (ICD-10) codes had been used to define the presence of specific disease in the database. Patients with TS were defined as those who had the following codes: ICD-9 code 758.6 or ICD-10 codes of Q96.0 -Q96.4, Q96.8 or Q96.9. Patients with a diagnosis of inflammatory bowel disease (IBD) were excluded. (Crohn's disease defined as ICD9 of 555.xx or ICD 10 of k50.xx; Ulcerative Colitis defined as ICD9 is 556.xx or ICD10 is k51.xx).

### *2.2. Case-Control*

The crude incidence of CRC by age was calculated in patients with and without TS and also was stratified by every decade starting at age 35. Patients who had performance of colonoscopy during the study time were included in the final analysis. Performance of colonoscopy was defined by a Current Procedural Terminology (CPT) codes of 45378-45386, 45388-45393, 45398. Case was defined as an individual with a diagnosis of TS and had a colonoscopy done during the study period whereas control was one without TS. The control group was created to mirror the average risk female population for CRC.

### *2.3. Outcomes Ascertainment*

The two main outcomes of interest were the presence of colorectal adenoma and CRC detected on index colonoscopy in both the groups. These were obtained using the appropriate ICD-9 or ICD-10 coding as noted in the supplemental table 1. Adenoma detection rate (ADR) is defined as percentage of patients in a group with at least one adenoma found on colonoscopy.

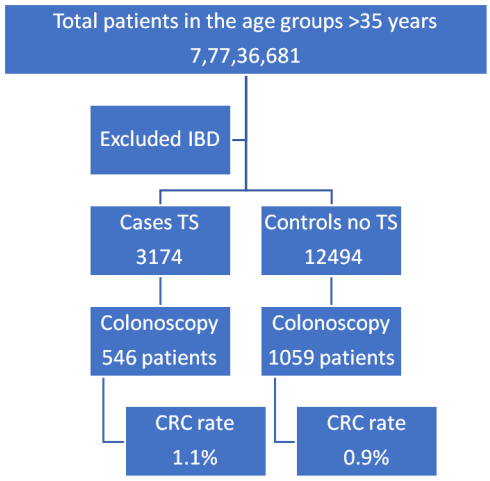


***Figure 1.*** *Study design.*

***Table 1.*** *Crude incidence of CRC per 100,000 population.*

| Age | Colorectal cancer prevalence in patients with TS<br>Number per 100,000 Total patients: 3174 | Colorectal cancer prevalence in patients without TS<br>Number per 100,000 Total patients: 12494 |
|---|---|---|
| 35-45 | 300 | 240 |
| 46-55 | 1125 | 830 |
| 56-64 | 150 | 1150 |
| Total | 720 | 530 |

### *2.4. Assessment of Covariates*

The variables obtained for our study included age, geographical area, smoking status, presence of morbid obesity, presence of diabetes, Non-steroidal anti-inflammatory drug (NSAID) use and 3-hydroxy-3-methylglutaryl coenzyme A reductase (statin) medication use. As this is a commercial insurance database it does not have information regarding patients who are older than 64

years of age. Smoking was defined as presence of any code pertaining to smoking or intervention done to help with smoking cessation as per a prior study [15]. Morbid obesity was defined as the presence of the disease code [16]. Similarly, diabetes was defined by the appropriate disease code. These ICD-9, ICD-10 and CPT codes are also summarized in the table 4. As the database had information on the prescription medications we deduced if the patients were on NSAIDs or statins. The medications are included in table 5.

***Table 2.*** *Demographic table.*

| Demographic variable | Cases (Turner Syndrome) Number (Percentage) | Controls (No Tuner Syndrome) Number (Percentage) | P value |
|---|---|---|---|
| AGE GROUP, Y | | | |
| 35-44 | 79 (14.5) | 103 (9.73) | |
| 45-54 | 288 (52.8) | 567 (53.54) | 0.01 |
| 55-64 | 179 (32.8) | 389 (36.73) | |
| REGION OF USA | | | |
| Northeast | 86 (15.8) | 84 (7.9) | |
| North central | 134 (24.5) | 262 (24.7) | |
| South | 227 (41.6) | 674 (63.6) | |
| West | 93 (17.03) | 37 (3.5) | |
| Unknown | 6 (1.1) | 2 (0.2) | |
| COMORBIDITES | | | |
| Diabetes | 78 (14.3) | 89 (8.4) | <.0001 |
| Morbid Obesity | 12 (2.2) | 11 (1.04) | 0.06 |
| Smoking | 14 (2.6) | 9 (0.85) | 0.01 |
| Medications | | | |
| NSAID use | 86 (15.8) | 194 (18.3) | 0.20 |
| Statin Use | 97 (17.8) | 160 (15.11) | 0.17 |
| OUTCOMES | | | |
| Number of patients with at least one adenoma | 177 (32.42) | 355 (33.52) | 0.66 |
| Number of patients with cancer | 6 (1.1) | 2 (0.19) | 0.01 |

***Table 3.*** *Multivariate regression model for odds of having CRC.*

| Odds Ratio Estimates and Wald Confidence Intervals | | | | |
|---|---|---|---|---|
| **Variable** | **Estimate** | **95% Confidence Limits** | | **P value** |
| Colorectal cancer (CRC) | 9.46 | 1.71 | 52.48 | 0.01 |
| Adenoma | 0.95 | 0.74 | 1.22 | 0.66 |
| Diabetes | 2.11 | 1.45 | 3.08 | <.0001 |
| Morbid Obesity | 2.38 | 0.90 | 6.28 | 0.08 |
| Smoking | 2.34 | 0.94 | 5.80 | 0.07 |
| NSAID use | 0.88 | 0.64 | 1.21 | 0.44 |
| Statin use | 1.24 | 0.89 | 1.72 | 0.20 |

***Table 4.*** *ICD codes used.*

| Outcomes and Covariates | ICD-9 code | ICD-10 codes | CPT codes |
|---|---|---|---|
| Colorectal cancer or CRC | 153.x, 154.x | C18.0, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C 18.9, C19, C20 | |
| Benign colorectal neoplasms (or adenoma) | 211.3, 211.4 | D12.1, D12.2, D12.3, D12.4, D12.5, D12.6, D12.7, D12.8, D12.9 | |
| Smoking | V15.82, 305.1X, 649.0X, 989.84 | F17.2, F17.20, F17.200, F17.201, F17.203, F17.208, F17.209, F17.21, F17.210. F17.211, F17.213, F17.218, F17.219, F17.22, F17.220, F17.221, F17.223, F17.228, F17.229, F17.29, F17.290, F17.291, F17.293, F17.298, F17.299, Z71.6, Z72.0, Z72.0, Z87.891, 099.33, Z87, Z87.8 or Z87.891. | 99406, 99407, G0375, G0376, G0436, G0437, G8402, G8403, G8453, G8454, S4990, S4991, S4995, S9075, S9453, 4000F or 4001F |
| Morbid obesity | 278.01, V85.4 | E66.01, E66.2, Z68.4 | |
| Diabetes | 250.0 | E11.9 | |

***Table 5.*** *Medication specific search.*

| Medications | |
|---|---|
| Non-steroidal anti-inflammatory drug (NSAID) | Aspirin, Diclofenac, Diflunisal, Ibuprofen, Indomethacin, Etodolac, Fenoprofen, Flurbiprofen, Indomethacin, Mefenamic Acid, Ketorolac, Naproxen, Oxaprozin, Piroxicam, Meloxicam, Nabumetone, Sulindac, Tolmetin, Celecoxib, Valdecoxib or Rofecoxib |
| Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase medications | Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin or Simvastatin |

### *2.5. Statistical Analysis*

Analysis was conducted using SAS version 9.4 software (SAS Institute, Cary, NC). Univariate analysis was conducted to assess statistical significance of differences in proportions using a Chi-Square test for categorical variables. The statistical tests were reported as significant if the level of significance (p-value) was less than 0.05 (two-sided). Conditional logistic regression was used to estimate the adjusted odds ratios (aOR) and 95% CI adjusting for diabetes, obesity, smoking, region in the United States, NSAID, and statins.

## 3. Results

Of the 7,77,36,681 patients aged 35 or older, 3265 had TS. After excluding those patient's with IBD, 3174 patients remained in the study. These patients were compared to 12494 average risk female counterparts. The estimated crude incidence of CRC (for a population of 100,000) in both the groups is depicted in Table 1. There was a higher overall incidence of CRC in patients with TS when compared to those without (720 vs 520 per 100,000 population). When stratified by decade the younger population of patients (age 35-55) with TS had higher CRC detection rate when compared to the average risk female counterparts. This was the opposite in patients aged 56-64 were higher incidence of CRC is seen in average risk females.

Of these 3174 patients with TS, 546 (17%) patients had a colonoscopy during our study period. These patients were compared to 1059 controls (patients had a colonoscopy and no TS). Age was stratified by decade: 35-44, 45-54 and 55-64 years. The majority of the patients were in the 45-54 age group range. Compared to the age matched controls, patient's with TS had a higher prevalence of diabetes (14.3 vs 8.4, $P<0.001$) and smoking (2.6 vs 0.9, $p=0.01$). There was no difference in the prevalence of obesity, use of statins, or use of NSAIDs between the groups. The ADR was 32% in the patients with TS when compared to 36% in patients without TS ($p=0.66$). Six patients of the 546 with TS had CRC detected on the colonoscopy (cancer detection rate 1.1%), in comparison to 2 of the 1059 without TS (cancer detection rate 0.2%) ($p=0.01$). The demographic table is represented in table 2. Of the 6 CRC found in patients with TS, five were located at the sigmoid colon while one was in an unspecified location. In patients without TS one had CRC diagnosed in the transverse colon while another is in the cecum.

On multivariate logistic regression analysis to determine the odds of detecting CRC at colonoscopy in patients with and without TS, we found that after adjustment for diabetes, smoking, morbid obesity, NSAIDs use and statin use patients with TS had an aOR of 9.46 (95% CI 1.7-52.8, $p =0.008$). This is depicted in table 3.

## 4. Discussion

In a large insurance-based database study from United States we found a higher CRC detection rate in patients with TS, when compared with their age matched controls.

Patients with TS have hypergonadotropic hypogonadism and hence have amenorrhea. They are usually supplemented by hormonal replacement therapy for induction of puberty and maintenance of a healthy reproductive growth [17]. Despite this, only 2% of patients with TS have natural pregnancies [18]. In a well-designed retrospective study performed in Washington state gravidity was shown to be protective against CRC [8] and there was a 40%-60% increased risk of CRC in nulligravid and nulliparous women. Estrogen receptor-beta (ERB) is found on the colonic epithelium, but the expression of this receptor is lost during progression of normal colonic mucosa to colorectal cancer [19]. Loss of ERB from the colonic mucosa in mice was found to promote inflammation, higher grade of dysplasia and early phase of tumor development [20]. A human study performed on 1262 patients with CRC showed that when the tumor samples were analyzed for ERB expression by immunohistochemistry, lack of expression is associated with advanced cancer stage and poor survival [21]. Although not related to the current patient population, Women Health Initiative study noted an incidental decrease of CRC with hormonal supplementation in post-menopausal females [22]. We hypothesize that sex hormone deficiency and nulli-gravidity might contribute to the increase risk of CRC in patients with TS.

There were three European registry studies the investigated the incidence of various cancers in patients with TS. These studies retrospectively looked at crude life time incidence rate of various cancers and compared the numerical value to the expected crude incidence of general population. While the study from Denmark [11] showed seven fold increase in CRC in patients with TS when compared to the general population, others studies from Sweden [12] and Great Britain [13] demonstrated no increased risk. Our study's unique design helped in comparing this risk with the average risk population. Patients with TS had a higher prevalence of obesity and diabetes when compared to general population [25]. A Danish cohort on patients with TS pointed a similar high risk of having diabetes in this population. Diabetes has been shown to be a risk factor for CRC in various studies [26]. Similarly, morbid obesity and smoking were shown to be risk factors for development of CRC [27, 28]. The cancer detection rate is high after adjustment for these above-mentioned risk factors. Our study found similar ADR in both groups. Some genetic conditions like Lynch syndrome have lower adenoma prevalence rate when compared to other genetic cancer syndromes, despite having high cancer detection rates [29]. It is postulated that these patients might have a rapid adenoma-carcinoma progression due to chromosomal microsatellite instability (MSI) [30-32]. Women are less likely to have MSI positive tumors at a younger age [33]. This was attributed to gravidity or use of hormonal supplementation. We speculate that patients with TS may have an MSI positive type tumor biology with rapid

adenoma-carcinoma progression. However, no study to date including ours was designed to look at the mutation profile of TS associated CRC.

This is a large database study which was not only able to capture a low prevalent condition but also some associated risk factors. By virtue of being a claims data it is directly linked to financial incentives and is carefully scrutinized for inaccuracies. Hence, we assumed that the primary outcomes (CRC and adenomas) might be accurately captured. Considering the CRC diagnosed within the 3-month time frame of colonoscopy improves the sensitivity as there could be delays with code submission. As TS is only seen in females, age matched controls minimized the potential for any confounders. The findings are generalizable to the entire population of the United States irrespective of geography or type of health care setting the colonoscopy was performed.

Our study has several limitations. CRC diagnosis is restricted to those obtained from an endoscopy. However, endoscopy with biopsy is the only way to diagnose localized CRC. We do not have any information on the extent and staging of the diagnosed CRC. Misrepresentation of covariates is possible as the database relies on appropriate submission by the providers. Non-availability of data on numerical BMI, over the counter medication use, and labs restricted us in modelling the analysis more precisely. Lack of some endoscopic data including the quality indicators related to colonoscopy prevented us from performing a well devised subgroup analysis. It only has data from commercial health insurances and does not include other types of insurances. Another major limitation was the unavailability of data on presence of CRC or advanced adenoma in a first degree relative which as discussed above is one of the important non-modifiable risk factors. Hence the study conclusions should be interpreted in the context of these limitations.

Certain groups of patients who required enhanced CRC screening have been identified. A systematic review and meta-analysis of 42 case control studies showed an increased risk of CRC in patients with one first degree relative having CRC with a further increase in that risk if the diagnosis of cancer was before age 50 [23]. Hence the Canadian Association of Gastroenterology Banff Consensus recommended enhanced screening and surveillance colonoscopy in patients with such history of having a first degree relative with colon cancer or advanced adenoma [24].

# 5. Conclusion

Our large insurance-based study showed a higher CRC detection rates at colonoscopy in patients with TS aged 35-64 years when compared to their age matched female counterparts. Similarly, we propose that patients with TS are a “disparity” group at increased risk for CRC and would benefit from early screening (start at age 40 years) and frequent surveillance (every 5-year interval). Further studies are needed to investigate possible differential tumor biology of CRC in patients with TS.

# Abbreviations

ADR: Adenoma Detection Rate
aOR: adjusted Odds Ratios
CPT: Current Procedural Terminology
CRC: Colorectal cancer
ERB: Estrogen receptor-beta
IBD: Inflammatory Bowel Disease
ICD-9: International Classification of Diseases, 9$^{th}$ revision
ICD-10: International Classification of Diseases, 10$^{th}$ revision
MSI: MicroSatellite Instability
NSAID: Non-steroidal anti-inflammatory drug
TS: Turner syndrome

# Conflict of Interest

All the authors do not have any possible conflicts of interest.

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