



Obesity and Biliopancreatic Cancers: Exploring Current Evidence

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ABSTRACT

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Background: Pancreatic cancer (PC) is among foremost causes of cancer related deaths worldwide due to generic symptoms and lack of screening. The risk of developing pancreatic cancer in obese or overweight individuals is 1.5 times higher than individuals with a normal BMI. Bariatric Surgery has been associated with a reduction of obesity-related cancer, however, the number of cases that developed pancreatic cancer post Bariatric surgery is not known.

Aim: Examine the relationship between Bariatric Surgery and Pancreatic cancer and identify reported cases of pancreatic cancer after bariatric surgery.

Materials and Methods: A narrative review of the literature was conducted. A MEDLINE database search was performed using the following Medical Subject Headings (MeSH) terms: pancreatic cancer, bariatric surgery, weight reduction surgery, pancreatic adenocarcinoma. These were combined with the following: postoperative, after surgery, and during surgery. A WebScience search was then performed using similar terms. Additional references were then identified by manual search of the articles obtained from the MEDLINE and Web of Science. Cancer cases that were identified at the pre-operative period or intra-operatively were excluded. The searches covered the period from January 2000 to November 2020.

Results/Review: Epidemiological evidence has shown that obesity as a risk factor for the development of PC is a dose dependent risk. The review found that the risk of developing pancreatic cancer in obese or overweight individuals is 1.5 times higher than individuals with a normal BMI. At the same time, evidence from literature demonstrated that weight reduction by dietary restriction, physical activities, pharmacotherapy or weight reduction surgery reduces risk of PDAC. A total of 24 cases of pancreatic cancer were identified and reported post Bariatric Surgery in the literature. The average age at diagnosis was 57.2 years and onset from surgery to diagnosis ranged from 2 months to 25 years. Of the identified cases, 23 cases were post Roux-en-Y Gastric Bypass and one case post Duodenal Switch. The review found that PDAC was the commonest reported pancreatic cancer post bariatric surgery accounting for 58.3%, followed by Neuroendocrine Tumours (NET) 16.7%.

Conclusions: Along with weight reduction and improving comorbidities, Bariatric surgery reduces risk of obesity-related carcinogenesis. Given the variation in onset of diagnosis, bariatric surgery did not increase cancer risk but rather accelerated the diagnosis of pancreatic cancer.

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1. BACKGROUND

Obesity is an epidemic disease that is in the rise around the world with increasing associated complications. Along this, obesity increases risk of cardiovascular, respiratory, and liver disease with increase in risk of overall mortality. In addition, it has been reported that obesity is associated with increased risk of cancers including Gastrointestinal cancers.

The number of Bariatric Surgery across the globe has increased in the last three decades and currently among the most common gastrointestinal procedures performed. This is due to the sustained long-term results with reduction of both weight and related comorbidities ¹. Several procedures have been approved and been used worldwide for weight reduction with well-defined postoperative complications. However, the

risk of cancer in general and biliopancreatic cancer post bariatric surgery remains unclear.

Currently, pancreatic cancer is the third leading cause of cancer related mortality with lifetime risk of 1.6% of developing in any person ². Pancreatic cancer is usually diagnosed late where 85% of cases are inoperable due to distant metastases indicating a poor prognosis with less overall survival rate. Previous Gastric or Bariatric surgery presents a diagnostic and management challenge for the treating surgeon ³.

Recent observation found that there is a shift in the epidemiology of certain cancers where they are happening more in younger patient that previously known i.e >50 years ⁴. Similar results were found by Sung et al with the incidence of six cancers including three gastrointestinal cancers: Gallbladder, Pancreatic, and Colorectal) ⁵.

Treatment options for obesity include lifestyle changes (including diet and physical activities), pharmacotherapy, behavioral counselling and bariatric surgery. Among these options, bariatric surgery is the only option that offers long term reduction in both weight and obesity related comorbidities ⁶. However, life-long commitment to post surgery management is mandatory. It has been estimated that on an annual basis, there are more than 580,000 bariatric procedures performed worldwide ⁷.

The role of bariatric surgery on reducing or increasing pancreatic cancer risk remains unclear. A Canadian study by Christou et al (2008) analyzed data on 1035 patient post bariatric surgery and 5746 control group. Pancreatic cancer was found in 0.1% in post- surgery group and 0.33% in control group (RR 0.29) ⁸.

Aim: To evaluate current evidence on association between Obesity and Biliopancreatic cancers and summarise reported cases of cancer post Bariatric Surgery.

2. MATERIALS AND METHODS

2.1 Scope

This study reviewed the available literature on the relationship between obesity and cancer and focus on the reported cases of Biliopancreatic cancers post Bariatric Surgery.

2.2 Search Criteria

To achieve the objectives of this study the available data on the literature were searched using PubMed, Google Scholar, Embase Database, Cochrane database, and Science direct with one or more of the key words. Database of all published articles between January 1990 and July 2020 in English language were searched. Relevant articles were identified by scanning the title and the abstracts initially followed by review of the full article. Cited references in the published articles were identified and then assessed for relevance. Studies from peer-reviewed journals were included with key words including obesity, weight gain, weight loss, cancer, gastrointestinal cancer, GI cancer, GI neoplasm, pancreatic

cancer, gallbladder cancer, cholangiocarcinoma, Bariatric surgery, metabolic surgery, Obesity surgery, adjustable gastric band, sleeve gastrectomy (LSG), Roux-Y Gastric Bypass (RYGB), One anastomosis (OAGB, OMG), and duodenal switch (DS).

2.3 Exclusion Criteria

Non-English language studies and animal model or in vivo studies were excluded. Along these criteria, studies that presented cancers that were identified at surgery or pre surgery were also excluded.

2.4 Data Extraction

Identified articles that met the inclusion criteria were further grouped and analyzed accordingly. The second part of the study will explore the role of bariatric surgery on biliopancreatic cancer risk (Increase and decrease).

3. RESULTS (REVIEW)

3.1 Obesity and risk of Cancer

3.1.1 Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest types of cancer with an estimated incidence of 8 per 100,000 person-years and mortality of 7 per 100,000 person-years worldwide⁹.

Epidemiological evidence in the literature has shown that obesity as a risk factor for the development of PDAC is a dose dependent risk ¹⁰. This increased risk was also evident for early adulthood adiposity and suggests that the population burden of PDAC will increase worldwide due to childhood and adolescent obesity ¹⁰. At the same time, evidence from literature demonstrated that weight reduction by dietary restriction, physical activities, pharmacotherapy or weight reduction surgery reduces risk of PDAC ¹¹.

Accumulation of fat in the pancreas causes nonalcoholic fatty pancreas and has been suggested to promote pancreatic endocrine dysfunction which is linked via insulin resistance and type 2 diabetes with the development of PDAC ¹². Along with this, a significant contributor for the development of obesity associated PDAC is adipose tissue inflammation and raised levels of leptin ¹³. Genkinger and colleagues (2011) found that the risk of developing pancreatic cancer in obese or overweight individuals is 1.5 times higher than individuals with a normal BMI ¹⁴.

3.1.2 Gallbladder Cancer

People with obesity and overweight have an increased risk of developing gallbladder cancer (60% and 20% respectively) ¹⁵. A meta-analysis by Tan et al (2015) found an associated risk between obesity overweight and cancer of 56% and 14% respectively ¹⁶. This risk is higher in females than males. The relationship between BMI and risk of gallbladder cancer is a positive dose response relationship with relative risk of 1.2 with overweight and 1.6 with obesity (WCRF, 2015).

Mechanisms through which obesity is linked to gallbladder cancer have been hypothesized. One of these is that obesity is

associated with an increased risk of gallstones which indirectly can increase risk of gallbladder cancer¹⁷. Another mechanism is the link between obesity and metabolic syndrome, which is characterized by hyperglycemia, hypertension, dyslipidemias and insulin resistance. Alterations in circulating levels of insulin, and adipokines, along with inflammatory cytokines results in inflammation, growth signaling and vascular alteration leading to the development of gallbladder cancer and other types of cancer. Female sex hormones may be the reason for the higher risk of gallbladder cancer in female as they can affect gallbladder function and liver bile secretion¹⁸. The impaired gallbladder emptying caused by progesterone and increased cholesterol secretion affect bile secretion and cause stasis and increase gallstone formation.

A prospective study by Beghdadi et al (2020) reported the incidence of cholangiocarcinoma post Roux-en-Y Gastric bypass to be 0.16%¹⁹. Along with this, there was a low incidence of hepatocellular cancer post bariatric surgery (0.15%-1.13%). Similar results were reported by Yang (2016)²⁰ and Adams et al (2009)²¹. Upper GI cancers post bariatric surgery present late at an advanced stage. This is usually due to the common upper GI symptoms (nausea, vomiting, oral intolerance, and weight loss) that can also be related to post op symptoms.

3.2 Reported Cases Post Bariatric Surgery

The review found 11 authors that reported pancreatic and cholangiocarcinoma with total 27 reported cases^{3,19, 22-31}

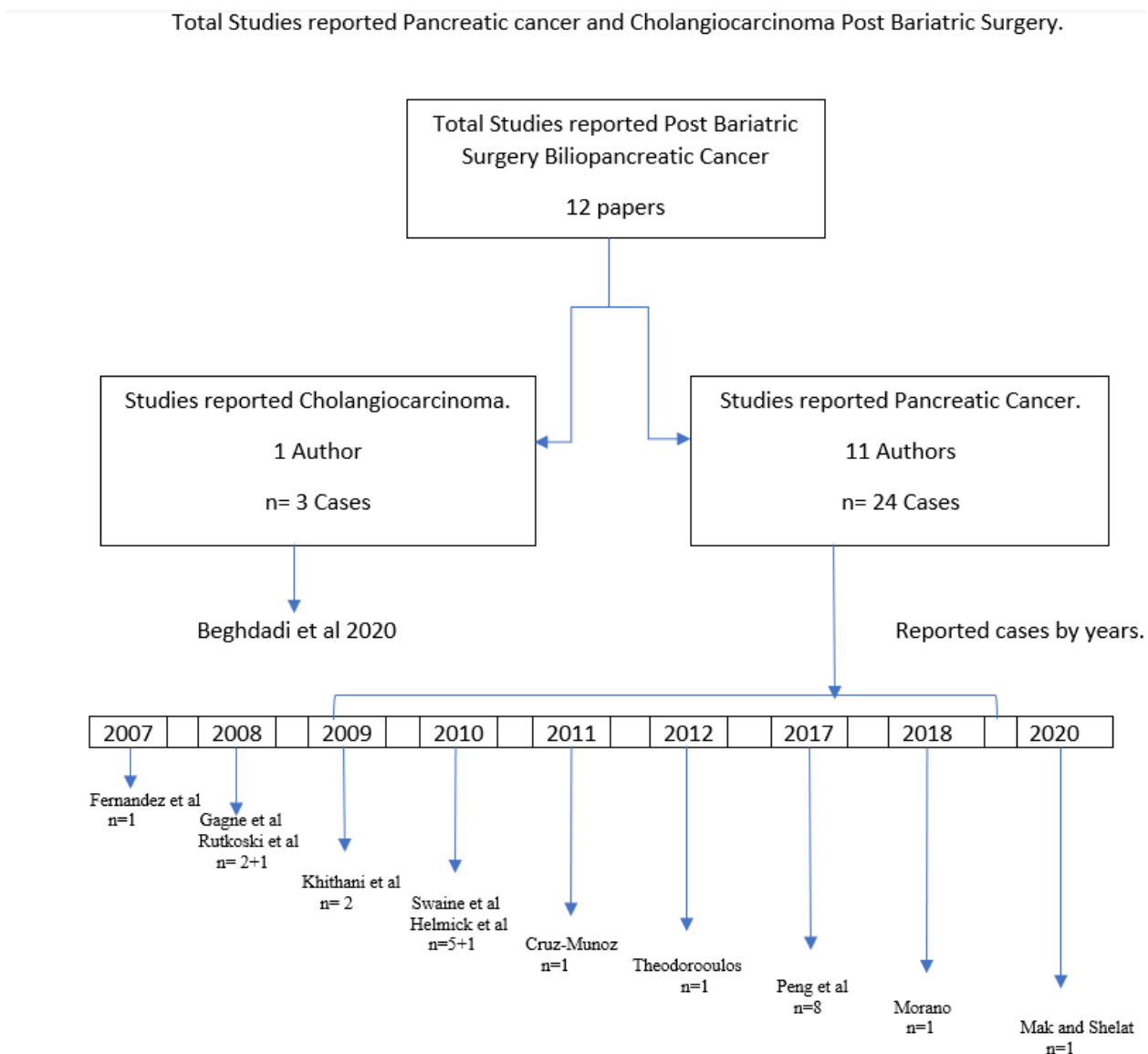


Figure 1. Reported Cases in the Literature

Pancreatic cancer cases accounted for 88.9% of the cases. Cholangiocarcinoma cases were found only with Roux-Y Gastric bypass procedure. At the same time, Roux-Y Gastric Bypass was the procedure performed in almost 96% of pancreatic cancers (1 case following Duodenal Switch).

Table 1. Distribution of Reported Cases by procedure

Procedure	Cholangiocarcinoma	Pancreatic	Total by procedure
<i>Adjustable Gastric Banding</i>			
<i>Vertical Gastroplasty</i>			
<i>Sleeve Gastrectomy</i>			
<i>RY Gastric Bypass</i>	3	23	26
<i>MGB/ OAGB/ Mason Loop</i>			
<i>BP Diversion</i>		1	1
Total by Cancer Type	3	24	27

3.2.1 Cholangiocarcinoma

Although bariatric surgery has been reported to reduce the risk of obesity related cancers, data on cholangiocarcinoma remains limited ³². There are three reported cases of cholangiocarcinoma in the literature, all three patients underwent RYGB. However, given the short delay between surgery and time of diagnosis (0.7-1.1 years), the oncogenic process is unlikely to have been triggered by the procedure. On the other hand, surgery could have accelerated the

development of undiagnosed cholangiocarcinoma through signalling modification of bile acid.

Recent study by Deutschmann et al (2018) highlighted the link between RYGB induced bile acid metabolism modification and development of cholangiocarcinoma via activation of liver TGR5 receptors ³³. Although the incidence cholangiocarcinoma post bariatric surgery appeared low, the three reported cases of cholangiocarcinoma were diagnosed at an advanced stage (Beghdadi, 2020).

Table 2: Data Reported on Cholangiocarcinoma

Author	Year	Gender	Bariatric Procedure	Onset Since Surgery (Years)	Type of Cancer	Site	Age
Beghdadi et al	2020	Female	RYGB	1	Cholangiocarcinoma	Gallbladder perihilar	58
Beghdadi et al	2020	Female	RYGB	0.7	Cholangiocarcinoma	Gallbladder perihilar	58
Beghdadi et al	2020	Female	RYGB	1.1	Cholangiocarcinoma	Gallbladder intra hepatic	55

3.2.2 Pancreatic cancer

Globally, there are 24 reported cases of pancreatic cancer post bariatric surgery. The average age at diagnosis was 57.2 years and onset from surgery to diagnosis ranged from 2 months to 25 years. Eight cases have missing data on age and onset from surgery to diagnosis. Of the available data, more than 2 thirds

of cases were female (68.75%). The review found that pancreatic ductal adenocarcinoma (PDAC) was the commonest reported pancreatic cancer post bariatric surgery accounting for 85.3%. This was followed by Neuroendocrine Tumours (NET) with 4 cases.

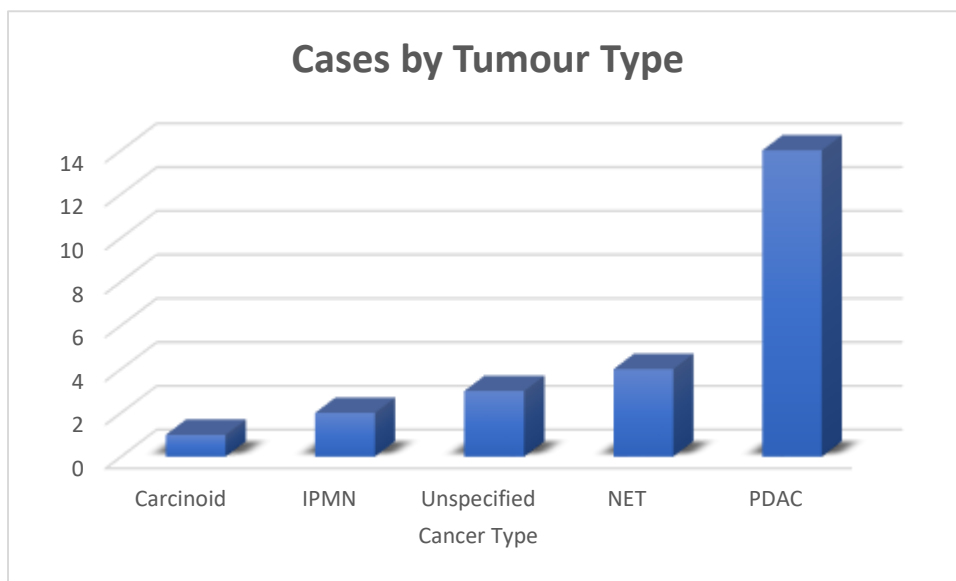


Figure 2. Number of Pancreatic cancer cases by tumour type

Table 3: Data Reported on Pancreatic Cancer

Author	Year	Gender	Bariatric Procedure	Onset Since Surgery (Years)	Type of Cancer	Site	Age
<i>Gagne et al</i>	2008	Female	RYGB	5	Pancreas	Pancreas	54
<i>Gagne et al</i>	2008	Female	RYGB	2.5	Pancreas	Pancreas	56
<i>Fernandez</i>	2007	Female	BPD	3	Pancreas (Carcinoid)	Pancreas	58
<i>Peng et al</i>	2017		RYGB		Pancreas Invasive IPMA		
<i>Swain et al</i>	2010	Female	RYGB	0.75	Pancreatic ampullary cancer	Pancreas	56
<i>Helmick et al</i>	2010	Male	RYGB	4	Pancreatic IPMN	Pancreas	71
<i>Mak and Shelat</i>	2020	Male	RYGB	12	Pancreatic NET	Head of pancreas	59
<i>De la Cruz-Munoz</i>	2011	Male	RYGB	0.18	Pancreatic NET	Pancreas	61
<i>Swain et al</i>	2010	Female	RYGB	2	Pancreatic NET	Pancreas	55
<i>Swain et al</i>	2010	Male	RYGB	10	Pancreatic NET	Pancreas	51
<i>Morano et al</i>	2018	Female	RYGB	12	Pancreatic PDAC	Pancreas	63
<i>Theodorooulos</i>	2012	Female	RYGB	14	Pancreatic PDAC	Pancreas	53
<i>Rutkoski</i>	2008	Female	RYGB	5	Pancreatic PDAC	Pancreas	49
<i>Khithani</i>	2009	Male	RYGB	NR	Pancreatic PDAC	Pancreas	61
<i>Khithani</i>	2009	Female	RYGB	NR	Pancreatic PDAC	Pancreas	57
<i>Swain</i>	2010	Female	RYGB	1.75	Pancreatic PDAC	Pancreas	50
<i>Swain</i>	2010	Female	RYGB	25	Pancreatic PDAC	Pancreas	61
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		
<i>Peng et al</i>	2017		RYGB		Pancreatic PDAC		

Pancreatic cancer can be asymptomatic or present with symptoms. In this review, clinical presentations were recorded for 13^{3, 24-28, 31} of the 24 cases. These were distributed as follow; Pain (4), Pain and Jaundice (3), Jaundice and Weight loss (1), Jaundice (1), and Incidental finding (4). With regards to surgical management of the pancreatic cancer, majority of authors reported the option of gastrectomy of the remnant stomach and when not feasible gastrostomy was the option of choice. The remnant stomach was spared in six cases where pancreaticoduodenectomy with other with reconstruction was performed^{3,24,26-28,31}.

4. CONCLUSION

With current rise in obesity, the number of performed bariatric surgery and intervention will increase. Epidemiological evidence suggests a dose dependent association between obesity and risk of pancreatic cancer. Weight reduction through Bariatric Surgery has been shown to reduce risk of cancer. Although cases of pancreatic and cholangiocarcinoma have been reported post bariatric surgery, the number is small comparing to the number of bariatric procedures performed. The short duration between surgery and diagnosis of cancer indicates that bariatric

surgery unlikely to be the cause of the tumorigenesis process, however, it may have accelerated the development of undiagnosed cholangiocarcinoma though signalling modifications.

LIST OF ABBREVIATIONS

- BMI: Body Mass Index
- BPD: Biliopancreatic Diversion
- GI: Gastrointestinal
- IPMN: Intraductal Papillary Mucinous Neoplasm
- LSG: Laparoscopic Sleeve Gastrectomy
- NET: Neuroendocrine Tumour
- OAGB: One Anastomosis Gastric Bypass
- PC: Pancreatic Cancer
- PDAC: Pancreatic Ductal Adenocarcinoma
- RR: Risk Ratio
- RYGB: Roux-Y- Gastric Bypass

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