“Gastrointestinal cancer after bariatric surgery: What do we know?”

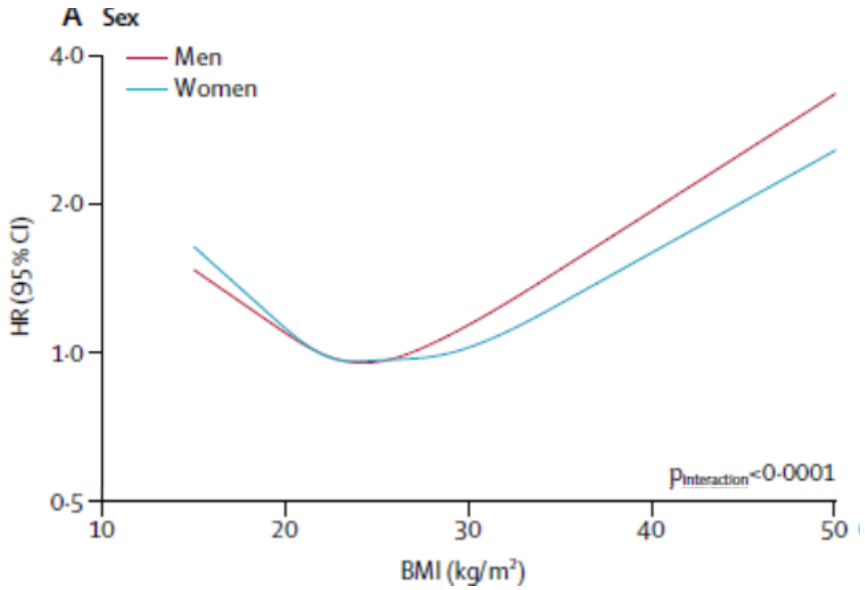
Tom Mala

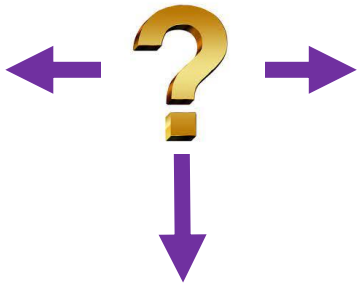
Oslo University Hospital/University of Oslo

Oslo universitetssykehus

Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK

Krishnan Bhaskaran, Isabel dos-Santos-Silva, David A Leon, Ian J Douglas, Liam Smeeth





Agenda

1. Obesity - associations with cancer

2. Cancer risk (general) after bariatric surgery

3. Gastrointestinal cancer risk after bariatric surgery

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

1. Obesity and associations with cancer

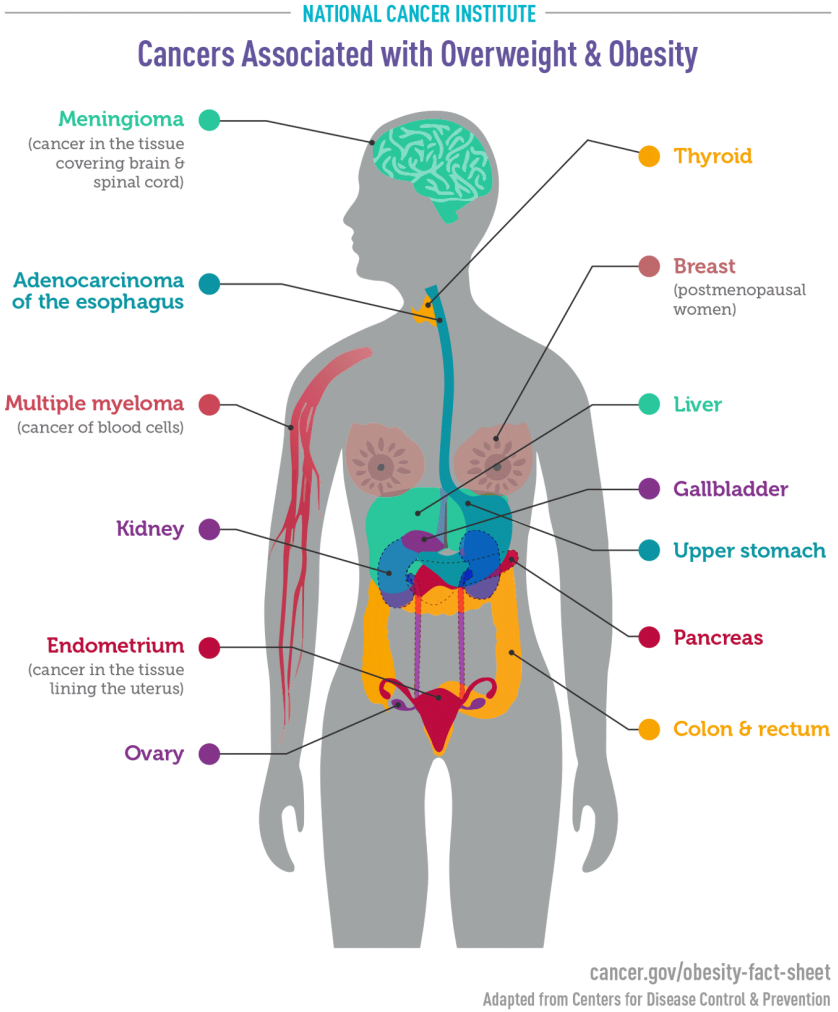


Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

Adiposity and cancer at major anatomical sites: umbrella review of the literature

Maria Kyrgiou,[1,2] Ilkka Kalliala,[1] Georgios Markozannes,[3] Marc J Gunter,[4] Evangelos Paraskevaidis,[5] Hani Gabra,[1,2] Pierre Martin-Hirsch,[6,7] Konstantinos K Tsilidis[3,8]

Conclusions:

……. the association of adiposity with cancer risk for 11 cancers **esophageal** adenocarcinoma, multiple myeloma, cancers of the **gastric cardia**, **colon**, **rectum**, **biliary tract system**, **pancreas**, breast, endometrium, ovary, and kidney were supported by strong evidence.

The Role of Mendelian Randomization Studies in Deciphering the Effect of Obesity on Cancer

Zhe Fang, MBBS, BS,[1] Mingyang Song, MBBS, ScD,[1,2,3,4] Dong Hoon Lee, MS, ScD,[2]
Edward L. Giovannucci, MD, ScD[1,2,5,*]

The reported associations **may be causal** for some malignancies but are susceptible to potential **confounding bias**, as obesity co-occurs with various risk factors of cancer, and reverse causality.

7/11

For gastrointestinal cancers till present association:
esophageal adenocarcinoma
colorectal cancer
pancreatic cancer

Body mass index and pancreatic adenocarcinoma: A nationwide registry-based cohort study

Usman Saeed, Tor Å. Myklebust, Trude E. Robsahm, Bjørn Møller, Tom Mala, Bjørn S. Skålhegg and Sheraz Yaqub

Scandinavian Journal of Surgery
2023, Vol. 112(1) 11–21

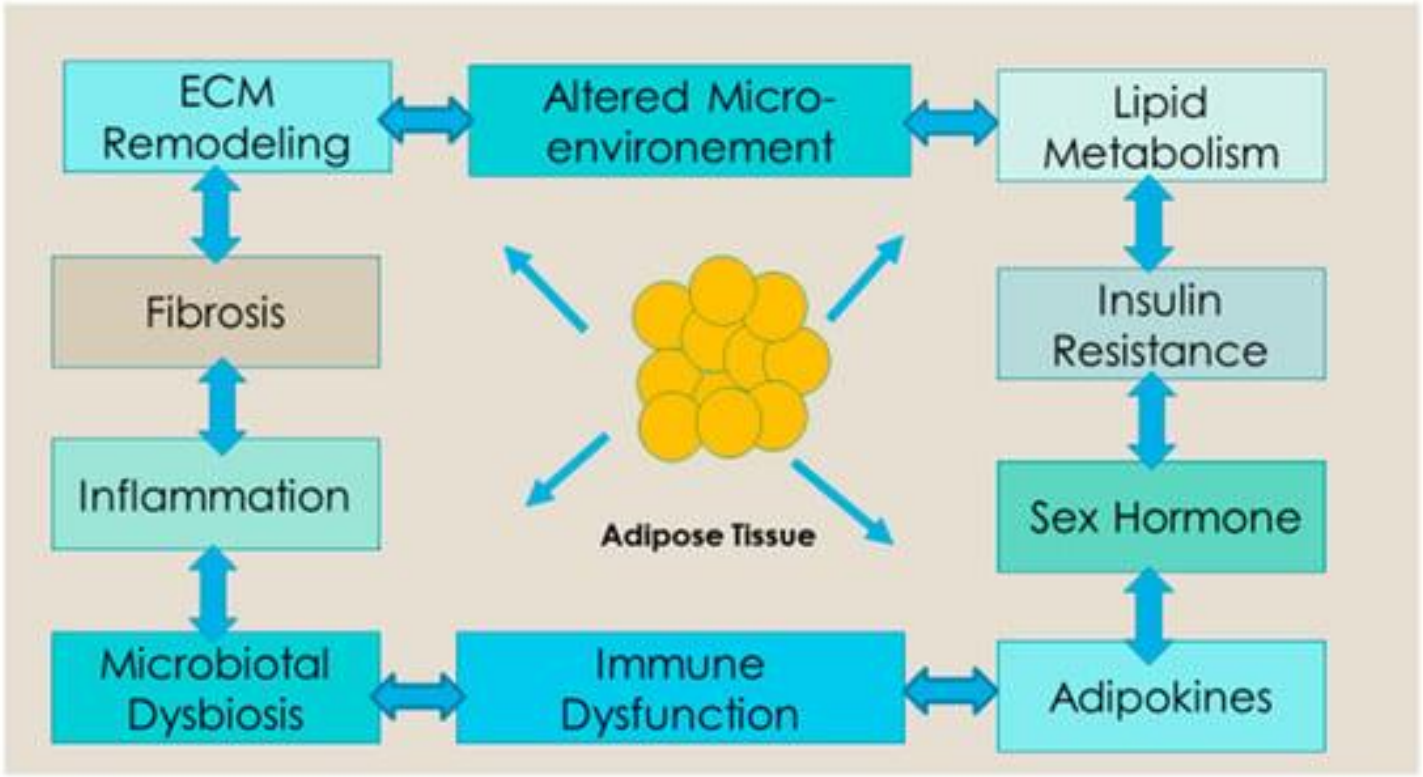
Risk and survival in colorectal cancer with increasing body mass index: A nationwide population-based cohort study

Usman Saeed[1] | Tor Å. Myklebust[2,3] | Trude E. Robsahm[4] | Marlene F. Kielland[5] | Bjørn Møller[2] | Bjørn S. Skålhegg[5] | Tom Mala[1,6] | Sheraz Yaqub[1,6]

Colorectal Disease. 2023;25:375–385.

Association with higher BMI and risk of cancer
Higher risk of cancer related death

Plausible biological mechanisms for the association



Pati S et al., Cancers **2023**

1. Convincing evidence of association between obesity and several cancers

1. Convincing evidence of association between obesity and several cancers

Gastrointestinal cancer:

Esophagus
Colon/Rectum
Pancreas

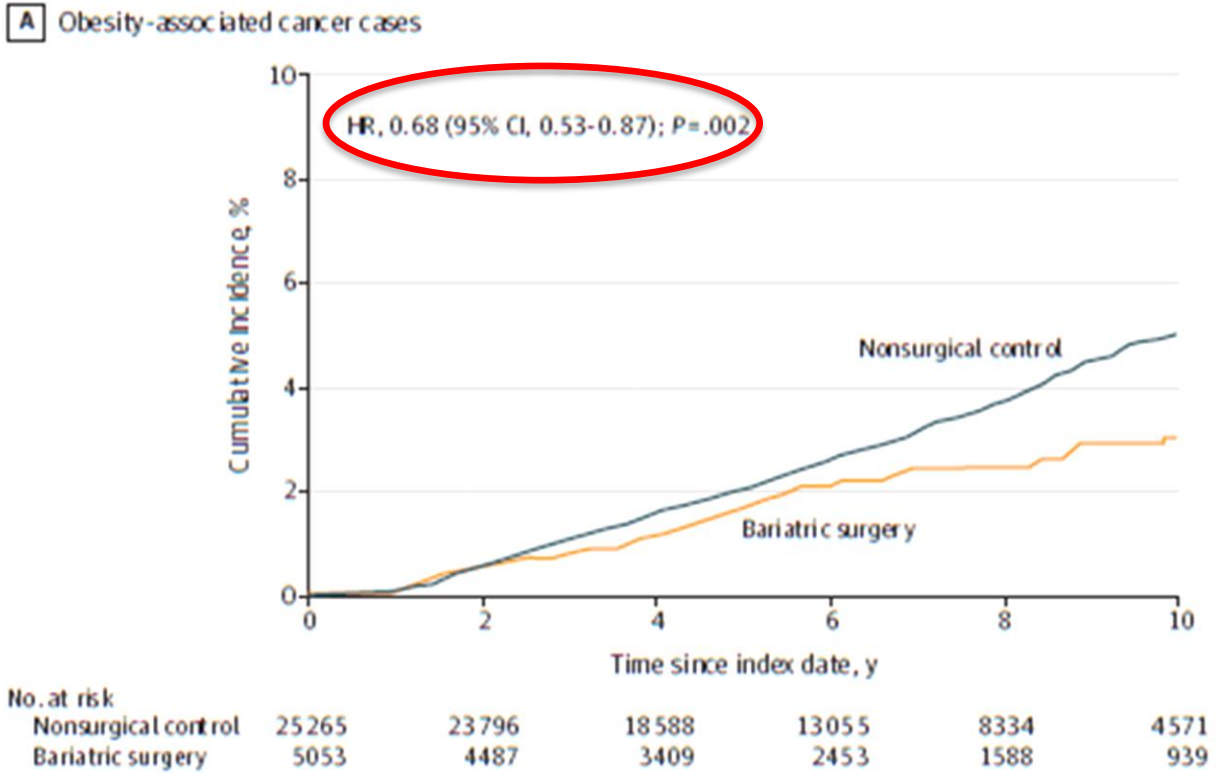
Cardia cancer
Liver
Gallbladder

2. Cancer risk after bariatric surgery

JAMA | Original Investigation

Association of Bariatric Surgery With Cancer Risk and Mortality in Adults With Obesity

Ali Aminian, MD; Rickesha Wilson, MD; Abbas Al-Kurd, MD; Chao Tu, MS; Alex Milinovich, BA; Matthew Kroh, MD; Raul J. Rosenthal, MD; Stacy A. Brethauer, MD; Philip R. Schauer, MD; Michael W. Kattan, PhD; Justin C. Brown, PhD; Nathan A. Berger, MD; Jame Abraham, MD; Steven E. Nissen, MD



JAMA | Original Investigation

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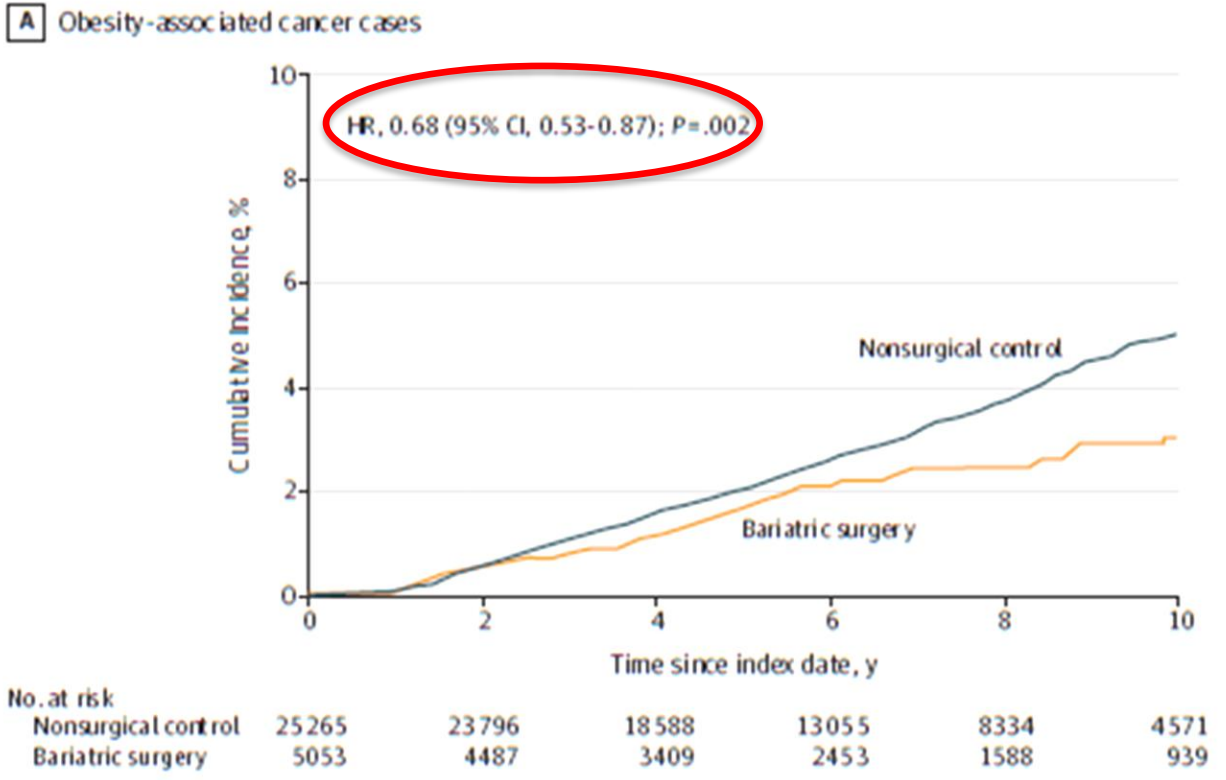
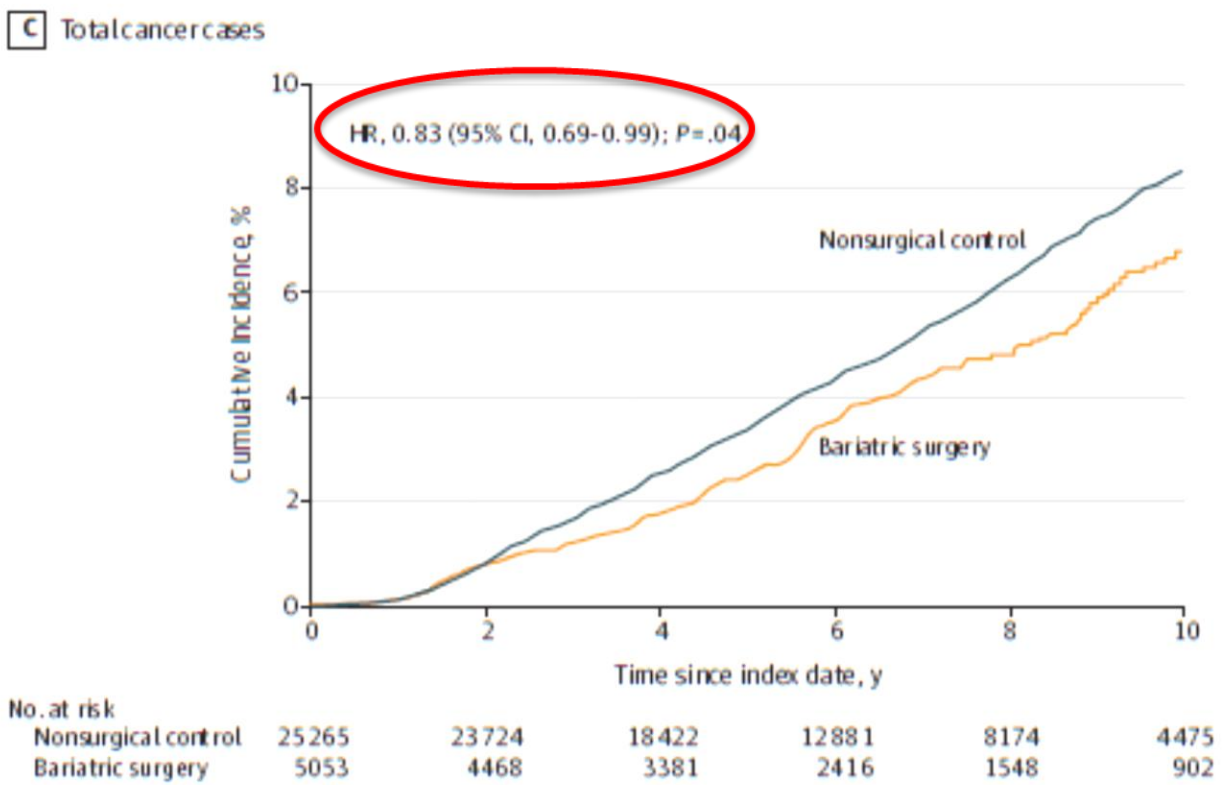
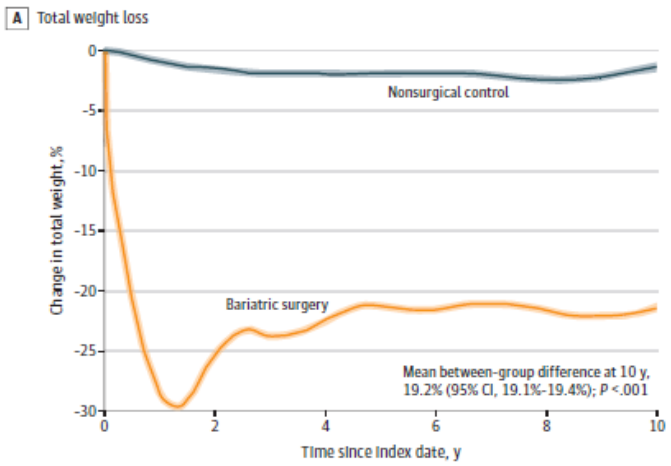
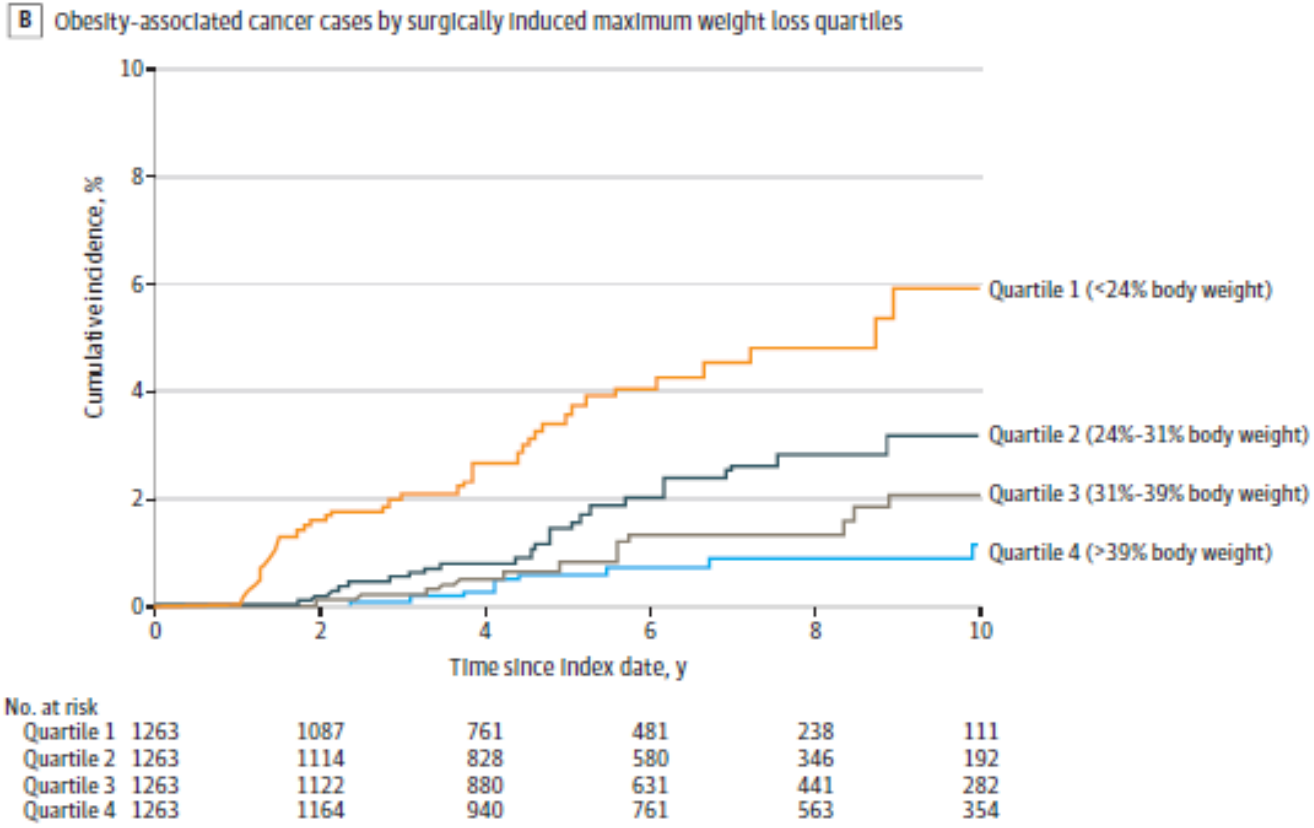




Dose-dependent response (risk reduction)





No. at risk

Quartile 1	1263	1087	761	481	238	111
Quartile 2	1263	1114	828	580	346	192
Quartile 3	1263	1122	880	631	441	282
Quartile 4	1263	1164	940	761	563	354

Risk of non-hormonal cancer after bariatric surgery: meta-analysis of retrospective observational studies

Benjamin Clapp[1], Ray Portela[2], Ishna Sharma[3], Hayato Nakanishi[4], Katie Marrero[5], Philip Schauer[6], Thorvardur R. Halfdanarson[7], Barham Abu Dayyeh[8], Michael Kendrick[2] and Omar M. Ghanem[2,*]

Total of 947 787 bariatric patients, 17 635 690 controls

The bariatric group lower incidence of non-hormonal cancer

OR 0.65 (95% CI 0.53 to 0.80)

Cohort series

Lazzati A et al. Br J Surg 2022	Decreased risk obesity-related cancer (HR 0.89, 95% CI 0.83-0.95)
Khalid SI et al. Ann Surg 2022	Lower rates of any cancers after sleeve and bypass
Feigelson HS. Ann Surg 2020	Reduced risk premenopausal breast cancer (HR 0.72, 95% CI, 0.54-0.94) Reduced risk postmenopausal breast cancer (HR 0.55, 95% CI, 0.42-0.72)
Mackenzie H et al. Br J Surg 2018	Decreased risk of hormone-related cancers (OR 0.23, 95% CI 0.18-0.30) Increased risk of colorectal cancer (OR 2.63, 95% CI 1.17-5.95)
Schauer DP et al. Ann Surg 2019	Decreased overall risk (HR 0.67, 95% CI 0.60, 0.74) Obesity-associated cancers (HR 0.59, 95% CI 0.51, 0.69)
Sjøstrom L et al. Lancet Oncol 2009	Lower number first-time cancers (n=117/169)(HR 0.67, 95% CI 0.53-0.85)

Systematic reviews

Wilson RB et al. Int J Mol Sci 2023	Reduced overall cancer risk (RR 0.62, 95% CI 0.46-0.84)
Clapp B et al. Br J Surg 2022	Reduced overall cancer risk (OR 0.65, 95% CI 0.53-0.80)
Ishihara BP, Surg Obes Relat Dis 2020	Reduced risk (breast/ovarian/endometrial) (RR 0.41, 95% CI 0.31-0.56)
Zhang K et al. Obes Surg 2020	Reduced risk overall cancer risk (OR 0.56, 95% CI 0.48-0.66)
Wiggins T et al. Obes Surg 2019	Decreased overall cancer risk (POR = 0.72; 95% CI 0.59-0.87) Obesity-related cancer (POR = 0.55; 95% CI 0.31-0.96)

Original article

What is currently known about the association between bariatric surgery and cancer

Daniel P. Schauer, M.D., M.Sc.*

Table 1
Key studies on the impact of bariatric surgery on cancer risk

Study	Publication dates	Type of study	Number	Follow-up	Results
SOS study	2009–2021	Prospective matched cohort	2007 bariatric patients 2040 matched controls	>16 yr (median)	Any cancer: HR = .67; 95% CI, .53–.85
Utah cohorts	2007–2009	Retrospective matched cohort	6956 bariatric patients 9422 matched controls	12.5 yr (mean)	Any cancer: HR = .76; 95% CI, .65–.89
Kaiser Permanente	2017–2020	Retrospective matched cohort	22,198 bariatric patients 66,427 matched controls	4 yr (mean)	Any cancer: HR = .67; 95% CI, .60–.74
SPLENDID	2022	Retrospective matched cohort	5053 bariatric patients 25,265 matched controls	6 yr (median)	Obesity-associated cancers: HR = .68; 95% CI, .53–.87

SOS = Swedish Obese Subjects; HR = hazard ratio; CI = confidence interval.

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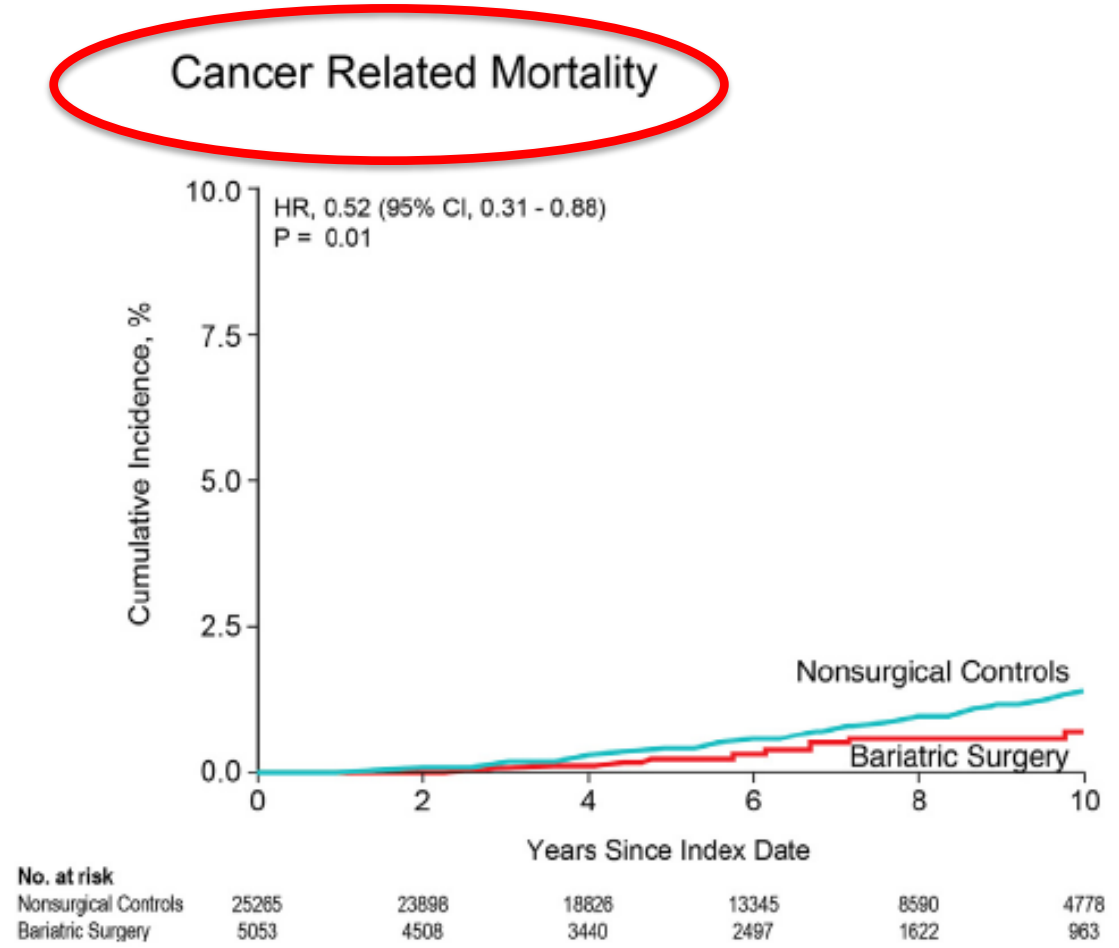


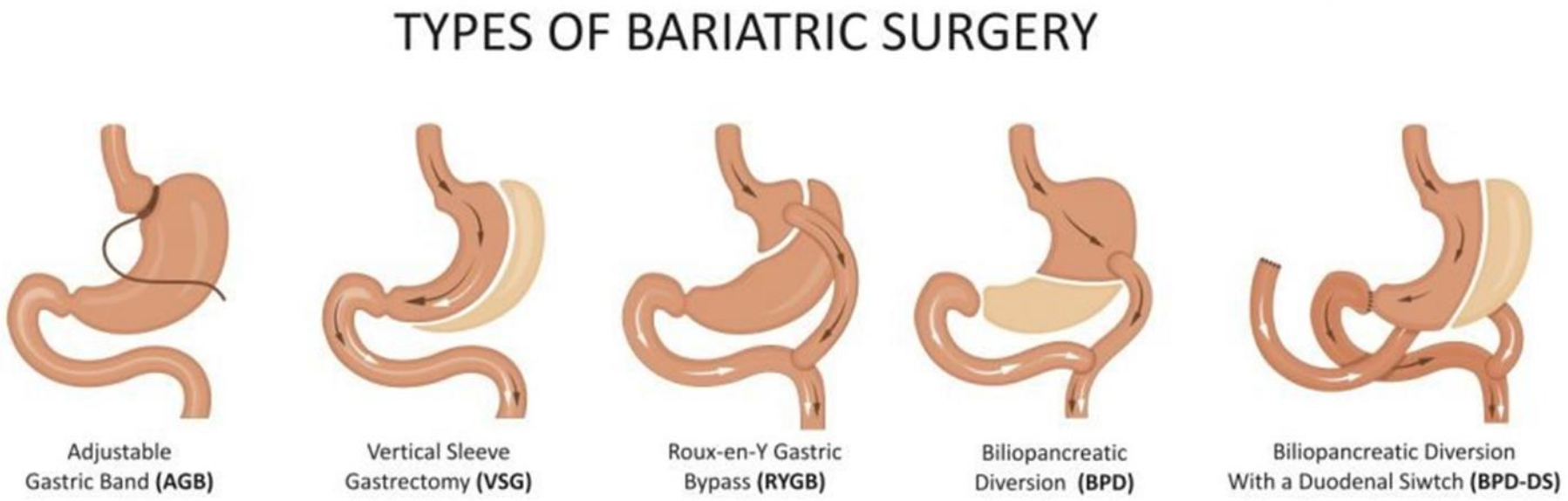
Fig. 6. Ten-year cumulative incidence estimates (Kaplan-Meier) of cancer-related mortality. HR = hazard ratio. Adapted and modified from Aminian et al. [1] with permission.

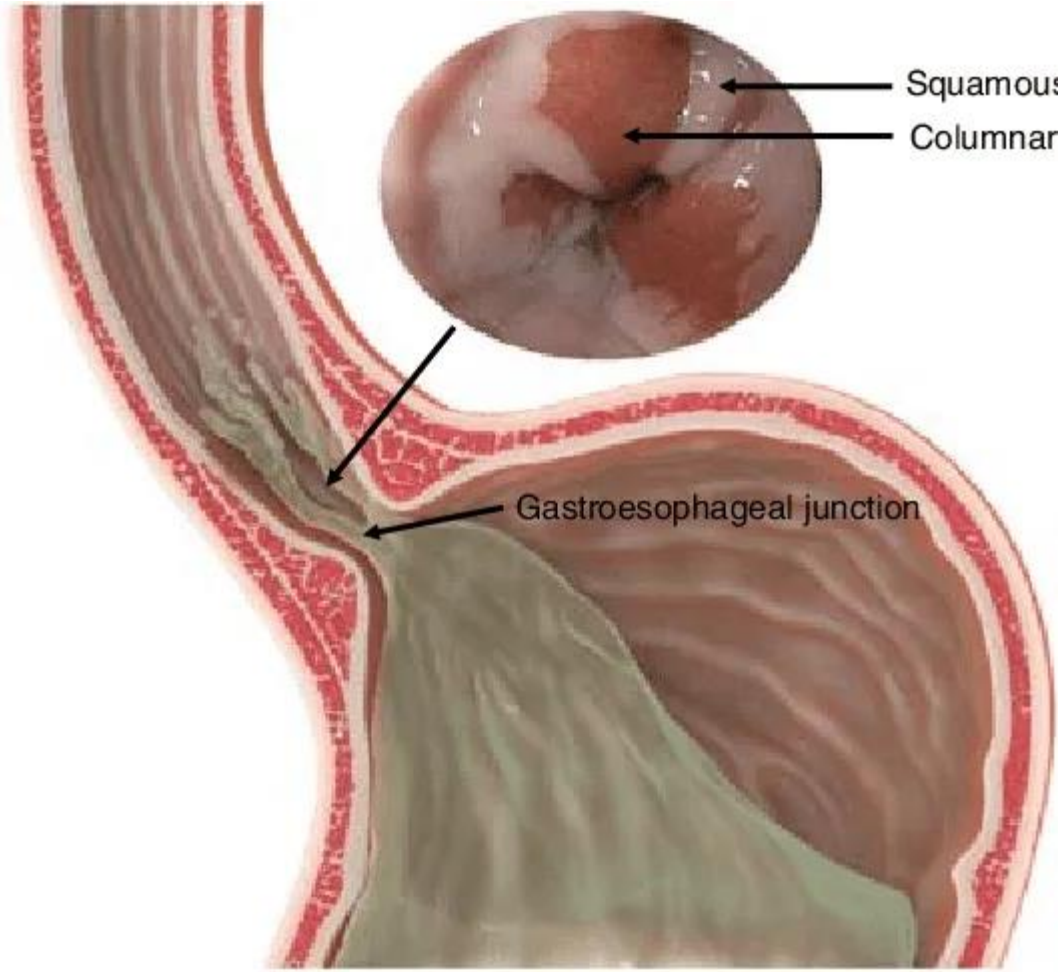
Cum. incidence 10 years: 0.8% vs. 1.4%,
48% reduction cancer-related mortality

Wilson R et al,
Surg Obes Relat Dis 2023

2. Substantial evidence from observational studies of reduction in general cancer risk after bariatric surgery

3. Gastrointestinal cancer risk after bariatric surgery

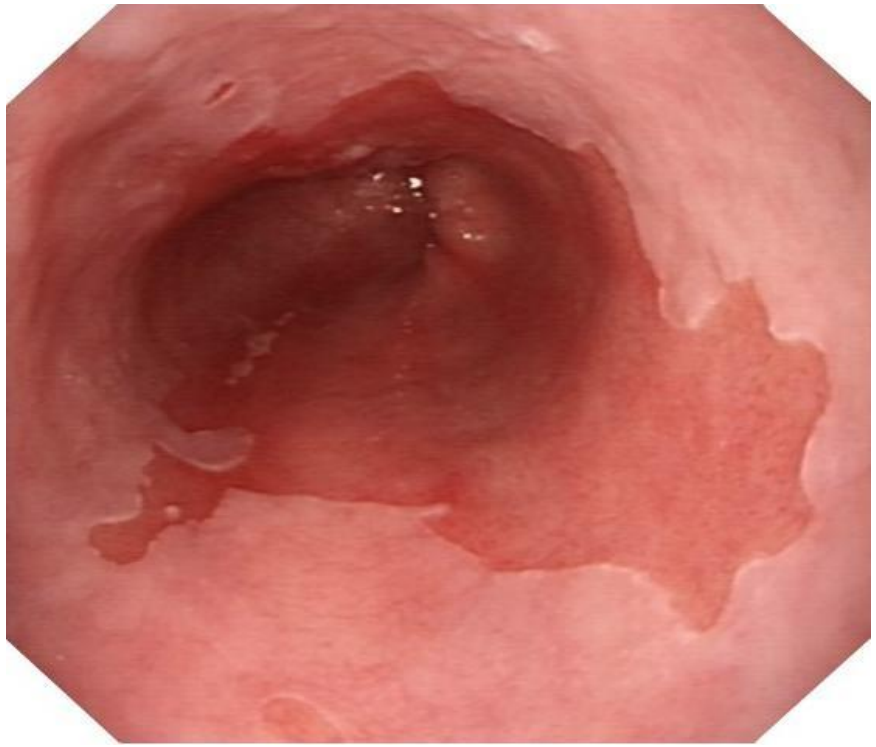



Squamous
Columnar
Gastroesophageal junction

SYSTEMATIC REVIEW AND META-ANALYSIS

Barrett's esophagus after sleeve gastrectomy: a systematic review and meta-analysis CME

Bashar J. Qumseya, MD, MPH,[1] Yazan Qumsiyeh, MD,[2] Sandeep A. Ponniah, MD,[3] David Estores, MD,[1] Dennis Yang, MD,[1] Crystal N. Johnson-Mann, MD,[4] Jeffrey Friedman, MD,[4] Alexander Ayzengart, MD, MPH,[4] Peter V. Draganov, MD[1]



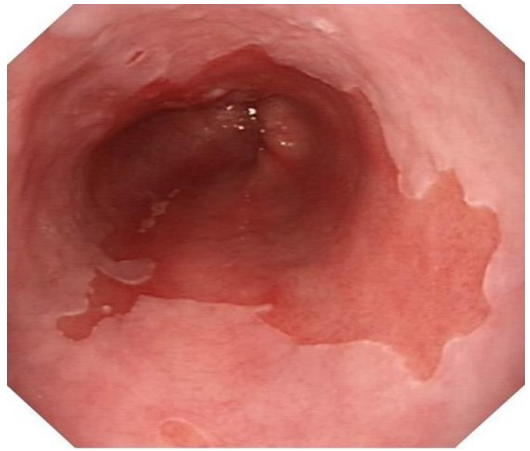
10 studies, 680 patients
Gastroscopy 6 months to 10 years

Pooled prevalence
11.6% (95% CI, 8.1%-16.4%)

Most observed **after 3 years** of follow-up

Controversies in definition of Barretts
Dysplasia
Length of Barretts

Tubularized and Effaced Gastric Cardia Mimicking Barrett Esophagus Following Sleeve Gastrectomy
Johari Y et al., Ann Surg 2022



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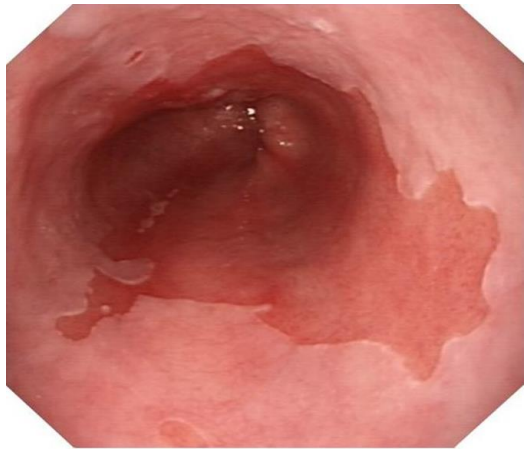


Passion and personal believes:

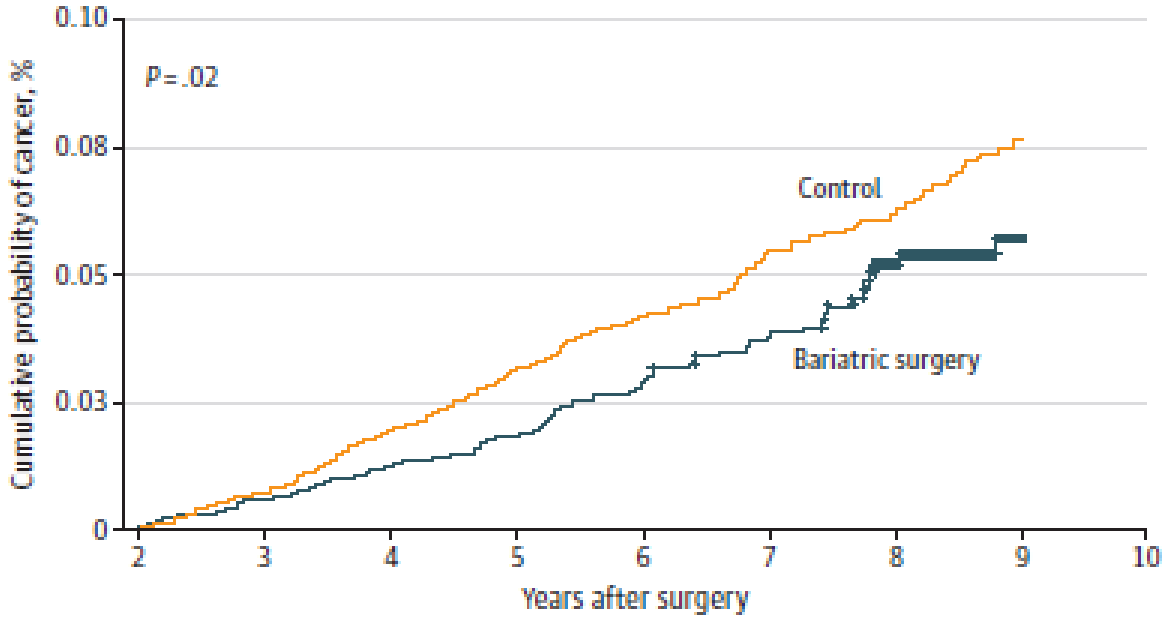
Alarmists at the Gates: Esophageal Adenocarcinoma after Sleeve Gastrectomy is Not Different than with Other Bariatric/Metabolic Surgeries.
M Gagner Obes Surg 2022

JAMA Surgery | Original Investigation

Risk of Esophageal and Gastric Cancer After Bariatric Surgery

Andrea Lazzati, MD, PhD; Tigran Poghosyan, MD, PhD; Marwa Touati, MS; Denis Collet, MD, PhD; Caroline Gronnier, MD, PhD

Figure 1. Cumulative Incidence of Esophagogastric Cancer by Group



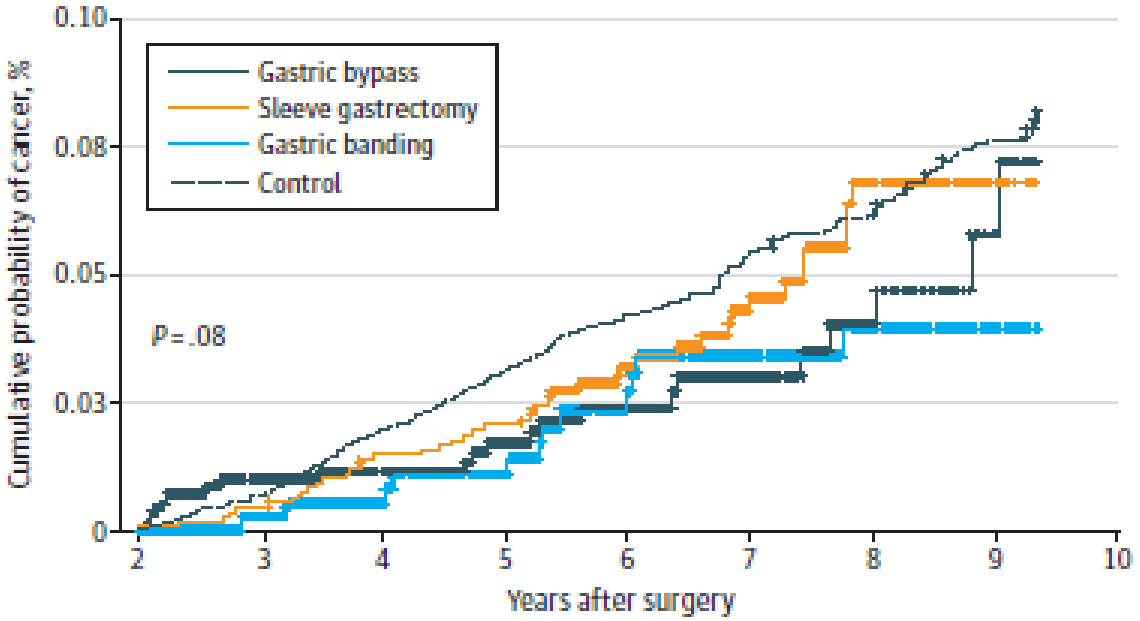
No. at risk								
Control	605 140	530 527	451 518	374 256	298 378	222 953	146 612	74 705
Bariatric surgery	303 709	258 599	210 907	167 159	124 525	85 680	51 551	23 825

JAMA Surgery | Original Investigation

Risk of Esophageal and Gastric Cancer After Bariatric Surgery

Andrea Lazzati, MD, PhD; Tigran Poghosyan, MD, PhD; Marwa Touati, MS; Denis Collet, MD, PhD; Caroline Gronnier, MD, PhD

Figure 2. Cumulative Incidence of Esophagogastric Cancer by Bariatric Procedure



No. at risk

Control	605 140	530 527	451 518	374 256	298 378	222 953	146 612	74 705
Gastric banding	39 453	37 847	35 495	32 633	28 365	22 982	16 098	8580
Sleeve gastrectomy	178 912	147 022	114 266	85 586	59 149	37 017	19 816	7780
Gastric bypass	84 187	72 720	60 250	48 153	36 292	25 042	15 096	7072

JAMA Surgery | Original Investigation

Risk of Esophageal and Gastric Cancer After Bariatric Surgery

Andrea Lazzati, MD, PhD; Tigran Poghosyan, MD, PhD; Marwa Touati, MS; Denis Collet, MD, PhD; Caroline Gronnier, MD, PhD

Overall a **decrease in the incidence of esophagogastric cancer** from 6.9 to 4.9 per 100 000 population/year

No statistical significant difference of esophagogastric cancer risk between procedures

Risk of non-hormonal cancer after bariatric surgery: meta-analysis of retrospective observational studies

Benjamin Clapp[1], Ray Portela[2], Ishna Sharma[3], Hayato Nakanishi[4], Katie Marrero[5], Philip Schauer[6], Thorvardur R. Halfdanarson[7], Barham Abu Dayyeh[8], Michael Kendrick[2] and Omar M. Ghanem[2,*]

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Total of 947 787 bariatric patients, 17 635 690 controls

Reduced risk of esophageal cancer overall after bariatric surgery

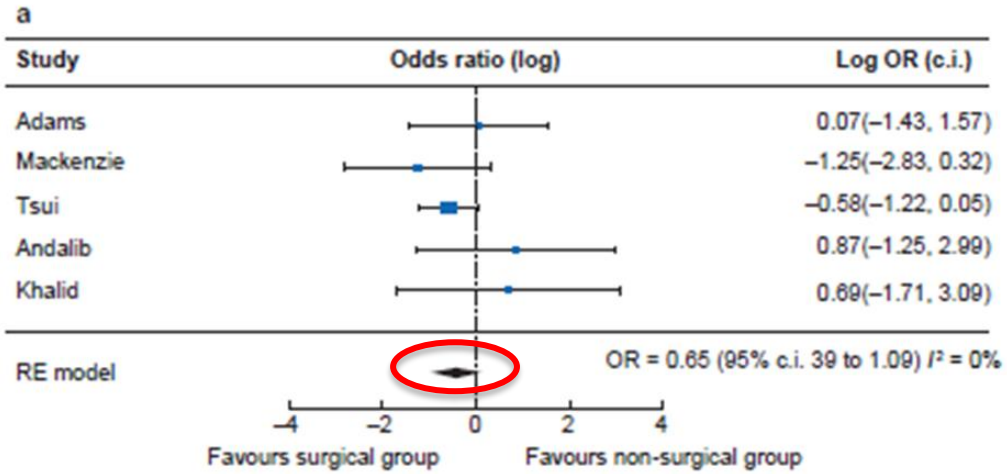
The risk of gastric cancer comparable (with/without bariatric surgery)

Risk of non-hormonal cancer after bariatric surgery: meta-analysis of retrospective observational studies

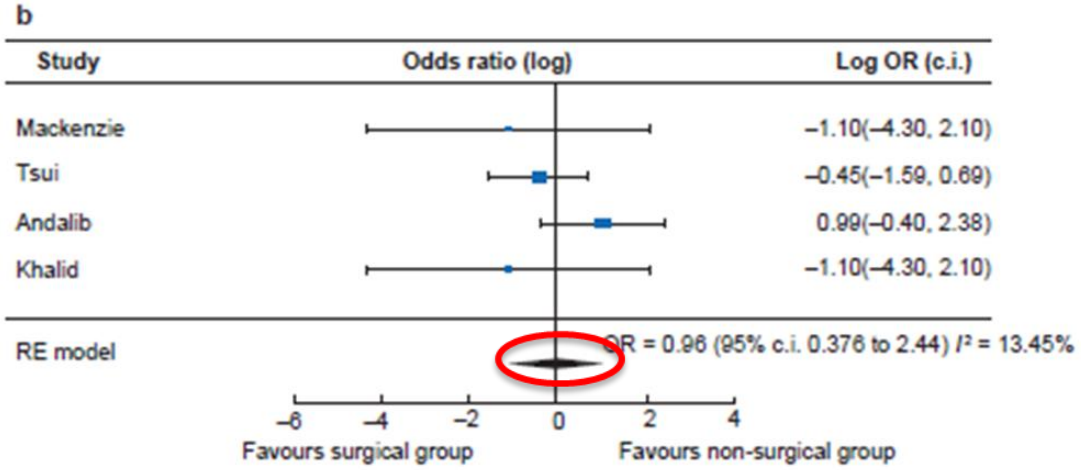
Benjamin Clapp[1], Ray Portela[2], Ishna Sharma[3], Hayato Nakanishi[4], Katie Marrero[5], Philip Schauer[6], Thorvardur R. Halfdanarson[7], Barham Abu Dayyeh[8], Michael Kendrick[2] and Omar M. Ghanem[2,*]

Decreased risk of esophageal cancer after RYGB, not SG (did not achieve statistical significance)

RYGB



GS

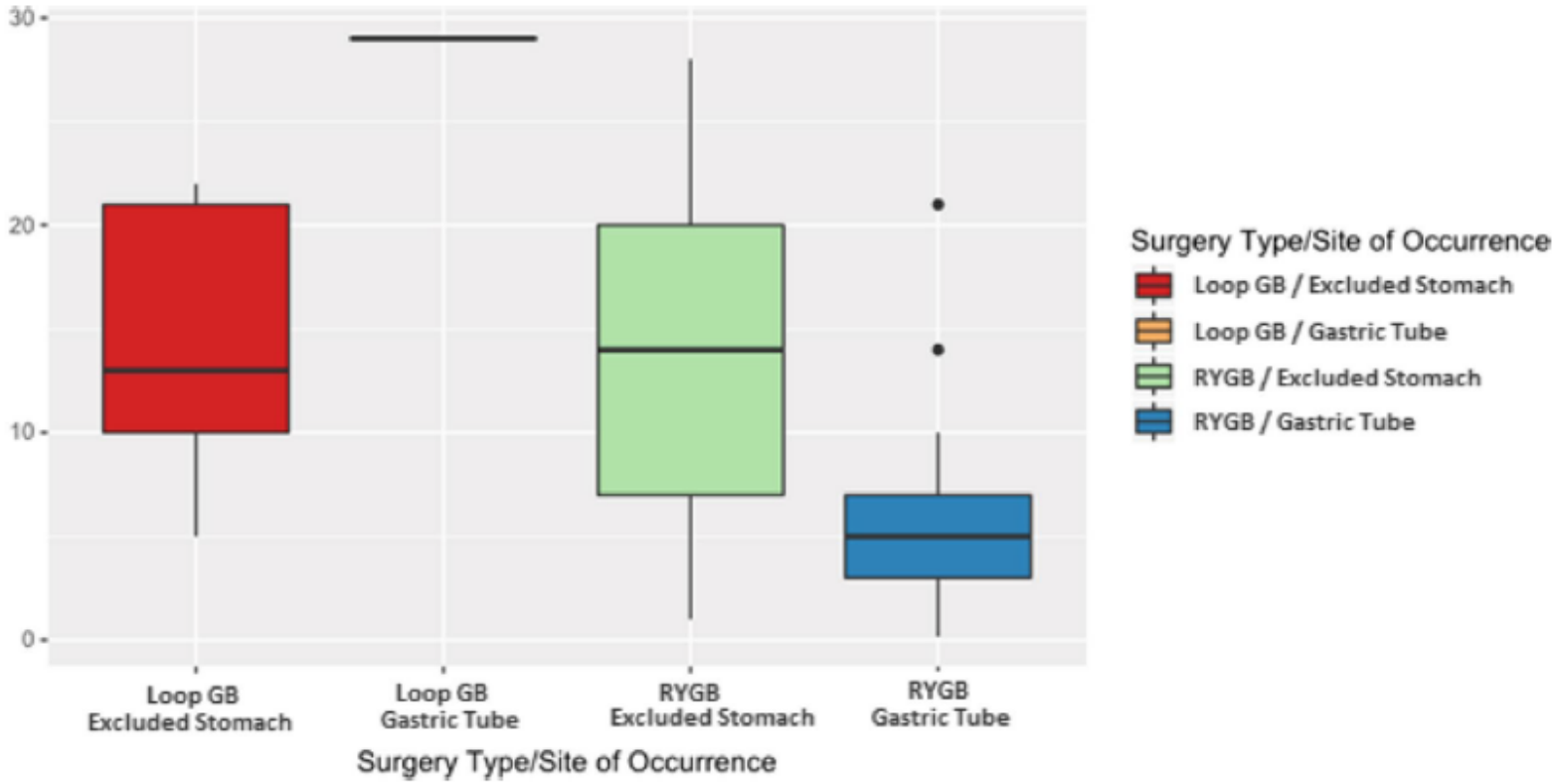


Obesity Surgery (2022) 32:1300–1311
https://doi.org/10.1007/s11695-022-05921-4

REVIEW

Gastroesophageal Cancer After Gastric Bypass Surgeries: a Systematic Review and Meta-analysis

Rodrigue Chemaly[1,2] · Samer Diab[1] · Georges Khazen[3] · Georges Al-Hajj[1,2]



Other gastrointestinal cancers

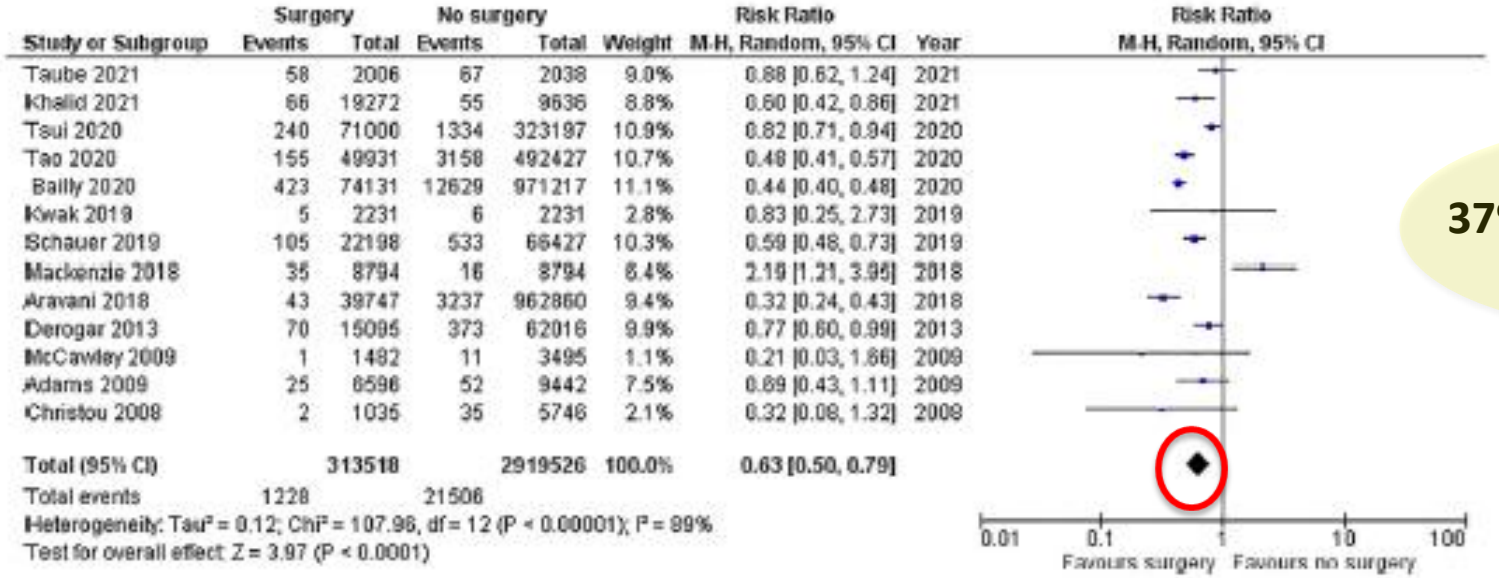
Original article

The effect of bariatric surgery on reducing the risk of colorectal cancer: a meta-analysis of 3,233,044 patients

Michał R. Janik, M.D.[a,*], Benjamin Clapp, M.D.[b], Przemysław Sroczyński, M.D.[a], Omar Ghanem, M.D.[c]

Mean follow-up 9.5 years

RR 0.63 (95% CI 0.50-0.79)



Study or Subgroup	Surgery Events	Surgery Total	No surgery Events	No surgery Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taube 2021	58	2006	67	2038	9.0%	0.88 [0.62, 1.24]	2021
Khalid 2021	66	19272	55	9636	8.8%	0.60 [0.42, 0.86]	2021
Tsui 2020	240	71000	1334	323197	10.9%	0.82 [0.71, 0.94]	2020
Tao 2020	155	49931	3158	492427	10.7%	0.48 [0.41, 0.57]	2020
Bailly 2020	423	74131	12629	971217	11.1%	0.44 [0.40, 0.48]	2020
Kwak 2019	5	2231	6	2231	2.8%	0.83 [0.25, 2.73]	2019
Schauer 2019	105	22198	533	66427	10.3%	0.59 [0.48, 0.73]	2019
Mackenzie 2018	35	8794	16	8794	6.4%	2.19 [1.21, 3.95]	2018
Aravani 2018	43	39747	3237	962860	9.4%	0.32 [0.24, 0.43]	2018
Derogar 2013	70	15095	373	62016	9.9%	0.77 [0.60, 0.99]	2013
McCawley 2009	1	1482	11	3495	1.1%	0.21 [0.03, 1.66]	2009
Adams 2009	25	6596	52	9442	7.5%	0.69 [0.43, 1.11]	2009
Christou 2008	2	1035	35	5746	2.1%	0.32 [0.08, 1.32]	2008
Total (95% CI)		**313518**		**2919526**	**100.0%**	**0.63 [0.50, 0.79]**	
Total events	1228		21506				

Heterogeneity: Tau² = 0.12; Chi² = 107.96, df = 12 (P < 0.00001); I² = 89%

Test for overall effect: Z = 3.97 (P < 0.0001)

37% Risk reduction

Fig. 2. Forest plot of colorectal cancer in patients who had bariatric surgery and those who did not.

JAMA Surgery | Original Investigation

Colorectal Cancer Risk Following Bariatric Surgery in a Nationwide Study of French Individuals With Obesity

Laurent Bailly, MD, PhD; Roxane Fabre, MSc; Christian Pradier, MD, PhD; Antonio Iannelli, MD, PhD

JAMA Surg. 2020;155(5):395-402.

34% risk reduction

Systematic Review

Does Bariatric Surgery Reduce the Risk of Colorectal Cancer in Individuals with Morbid Obesity? A Systematic Review and Meta-Analysis

Andrea Chierici [1,†], Paolo Amoretti [1,†], Céline Drai [1,2], Serena De Fatico [1], Jérôme Barriere [3], Luigi Schiavo [4] and Antonio Iannelli [1,2,5,*]

54% risk reduction (19% reduction in HR)

Colorectal cancer after bariatric surgery

Data heterogeneity
Need for:
- Gender differentiation
- Differentiation colon/rectum
- Duration of obesity

Bariatric surgery reduces the risk of pancreatic cancer in individuals with obesity before the age of 50 years: A nationwide administrative data study in France

Julie Bulsei [a], Andrea Chierici [b], Marco Alifano [c, d], Antonio Castaldi [f], Céline Drai [f, g], Serena De Fatico [f], Edoardo Rosso [e], Eric Fontas [a], Antonio Iannelli [f, g, h, *]

160 129 bariatric pts
1 263 804 controls

FU: 5.2 vs. 6 years

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Bariatric surgery **protective effect** against pancreatic cancer in the 18-50 years population

HR: 0.567 (95% CI 0.467-0.689)
Crude rate 0.07% vs 0.35%

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The Impact of Bariatric Surgery on Pancreatic Cancer Risk: a Systematic Review and Meta-Analysis

Hongdan Fan[1] · Qingsong Mao[1] · Wenfeng Zhang[1] · Qinghua Fang[2] · Qu Zou[1] · Jianping Gong[1]

Obesity Surgery Accepted: 28 March 2023

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But not all studies on pancreatic cancer risk after bariatric surgery support the association ……..

Risk of non-hormonal cancer after bariatric surgery: meta-analysis of retrospective observational studies

Benjamin Clapp[1], Ray Portela[2], Ishna Sharma[3], Hayato Nakanishi[4], Katie Marrero[5], Philip Schauer[6], Thorvardur R. Halfdanarson[7], Barham Abu Dayyeh[8], Michael Kendrick[2] and Omar M. Ghanem[2,*]

BJS, 2023, **110**, 24–33

Gastroenterology 2021;161:171–184

CLINICAL—LIVER

Bariatric Surgery Reduces Cancer Risk in Adults With Nonalcoholic Fatty Liver Disease and Severe Obesity

Vinod K. Rustgi,[1,2] You Li,[1,2] Kapil Gupta,[1,2] Carlos D. Minacapelli,[1,2] Abhishek Bhurwal,[1,2] Carolyn Catalano,[1,2] and Mohamed I. Elsaid[1,2]

98 090 pts (NAFLD) total
33 435 after bariatric

Decreased risk of liver (hepatocellular carcinoma) cancer after bariatric surgery

Original article

What is currently known about the association between bariatric surgery and cancer

Daniel P. Schauer, M.D., M.Sc.*

Reduced rectum cancer risk
No risk changes for colon cancer

Table 1
Key studies on the impact of bariatric surgery on cancer risk

Study	Publication dates	Type of study	Number	Follow-up	Results
SOS study	2009–2021	Prospective matched cohort	2007 bariatric patients 2040 matched controls	>16 yr (median)	Any cancer: HR = .67; 95% CI, .53–.85
Utah cohorts	2007–2009	Retrospective matched cohort	6956 bariatric patients 9422 matched controls	12.5 yr (mean)	Any cancer: HR = .76; 95% CI, .65–.89
Kaiser Permanente	2017–2020	Retrospective matched cohort	22,198 bariatric patients 66,427 matched controls	4 yr (mean)	Any cancer: HR = .67; 95% CI, .60–.74
SPLENDID	2022	Retrospective matched cohort	5053 bariatric patients 25,265 matched controls	6 yr (median)	Obesity-associated cancers: HR = .68; 95% CI, .53–.87

SOS = Swedish Obese Subjects; HR = hazard ratio; CI = confidence interval.

Original article

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No risk changes for colon cancer

Reduced risk colon and pancreatic cancer and esophageal adenocarcinoma

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".. no evidence to date that any cancers are increased following bariatric surgery, and no studies have been adequately powered to compare procedure types……"

3. Sum up for gastrointestinal cancer risk after bariatric surgery

Esophagus
Colon/Rectum
Pancreas

Cardia cancer
Liver
Gallbladder

Association vs. causality

Association vs. causality

Limitations

Heterogeneity

Strength of the association (?)

Different types of cancers

Controls

Short period of follow-up

Risk exposure may vary across geographic/ethnical groups/genders

Strengths

Consistency

Strong association (?)

Dose response

Potential biological mechanisms

Weight reduction reduces risk

Sir Bradford-Hill

“The world is richer in associations than meanings,
and it is the part of wisdom to differentiate the two”

Lessons from history

Gastric stump carcinoma following gastric resection

The **average latency time 20-27 years** (up to 40 years). Steep increase in the risk of developing gastric stump cancer from the 20th year after partial gastrectomy

THE LANCET, AUGUST 30, 1986

Occasional Survey

RISK OF CARCINOMA FOLLOWING GASTRIC OPERATIONS FOR BENIGN DISEASE

A Historical Cohort Study of 3470 Patients

A. VISTE
P. OPHEIM
J. THUNOLD
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Departments of Surgery, University of Bergen, County Hospital at Voss, Diakonissehjemmets Sykehus, and Hospitalet Betanien; Department of Pathology, the Gade Institute; Section for Medical Informatics and Statistics, University of Bergen; and Cancer Registry of Norway, Oslo, Norway

At 5-10 years postoperatively comparable cancer risk to general (total) population

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At 5-10 years postoperatively comparable cancer risk to general (total) population

After 40-50 years it was 7.3 fold higher

Original article

Esophageal and gastric malignancies after bariatric surgery: a retrospective global study

Chetan Parmar, M.S., D.N.B., F.R.C.S.[a,*,†], Roxanna Zakeri, M.R.C.S.[a,b,†], Mohamed Abouelazayem, M.Sc., M.R.C.S.[c], Thomas H. Shin, M.D., Ph.D.[d], Ali Aminian, M.D., F.A.S.M.B.S[d], Tala Mahmoud, M.D.[e], Barham K. Abu Dayyeh, M.D., M.P.H.[e], Melissa Y. Wee[f], Laura Fischer, M.D.[g], Freek Daams, M.D., Ph.D.[h], Kamal Mahawar, F.R.C.S.Ed.[i], on behalf of OGMOS Study Group

Cancer diagnosed a **mean of 9.5 years** (1-44 years) after bariatric surgery


HEADLINE
STORY
?

“Gastrointestinal cancer after bariatric surgery: What do we know?”

We know something

Bariatric surgery and (gastrointestinal) cancer

Conclusions

Obesity is associated with increased (gastrointestinal) cancer risk

Substantial observational data related to (reduced) cancer risk after bariatric surgery that is fairly consistent but not yet definitive

Need for more knowledge and particularly prolonged observation time

At large current findings hold promise for potential benefits of bariatric surgery on overall and gastrointestinal cancer risk