

# XXVIII IFSO World Congress

9-12 September 2025 | Santiago, Chile



Asim Shabbir

# IFSO 2025 Santiago

Combined Therapies, The Dawn of a New Era

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# Disclosure Slide



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|                                     |                         |
|-------------------------------------|-------------------------|
| <input checked="" type="checkbox"/> | No, nothing to disclose |
| <input type="checkbox"/>            | Yes, please specify:    |



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# **Relationship between Cancer and Metabolic Surgery**

# Introduction

- Obesity & Cancer
- Mechanisms
- Pre MBS screening of Cancer
- MBS & Cancer outcomes
- Procedure Specific outcomes
- Future direction
- Conclusion



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# Relationship between high BMI & Types of cancer



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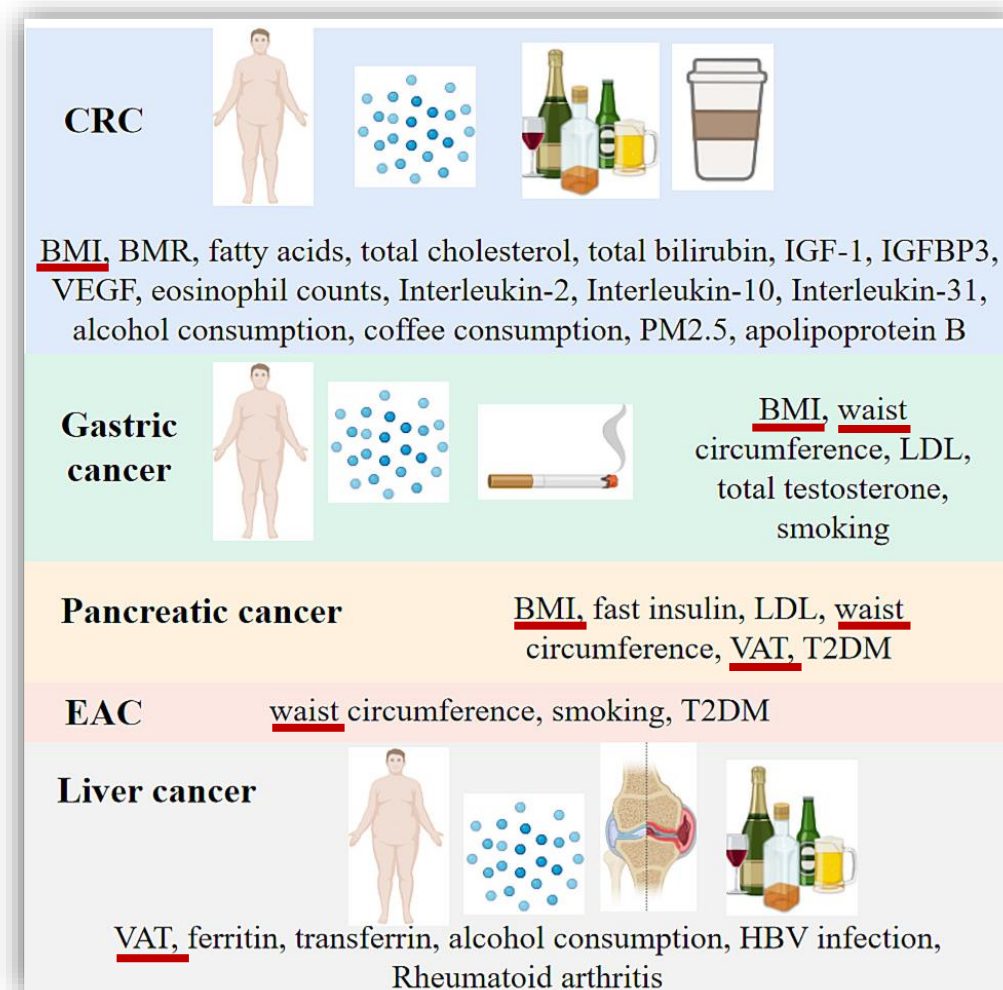
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| Strength of evidence for a cancer-preventive effect of the absence of excess body fat according to the site or type of cancer |                                |   |
|---|--------------------------------|---|
| Location or type of cancer  | Strength of evidence in humans | Relative risk of higher versus normal BMI (95%CI) |
| Esophagus adenocarcinoma  | Sufficient                     | 4.8 (3.0-7.7)                                     |
| Cardia  | Sufficient                     | 1.8 (1.3-2.5)                                     |
| Colorectal  | 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, post-menopausal   | Sufficient                     | 1.1 (1.1-1.2)                                     |
| Uterus (body)   | 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)                                     |
| Myeloma   | Sufficient                     | 1.5 (1.2-2.0)                                     |
| Male Breast Cancer  | Limited                        | Not applicable                                    |
| Prostate Cancer (fatal)   | Limited                        | Not applicable                                    |
| Diffuse Large B-cell Lymphoma   | Limited                        | Not applicable                                    |



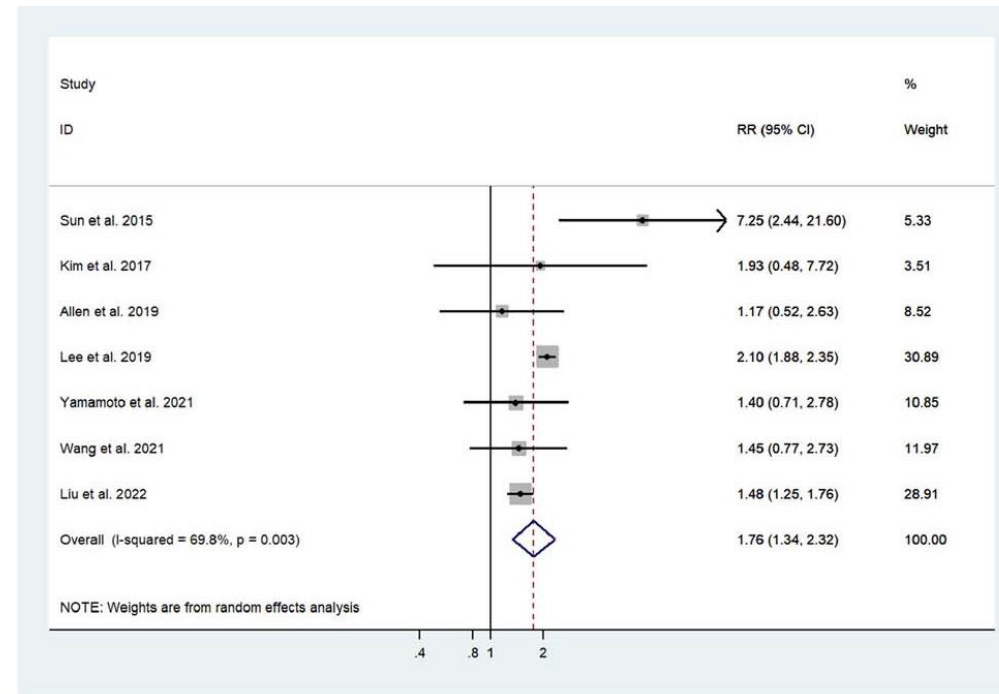
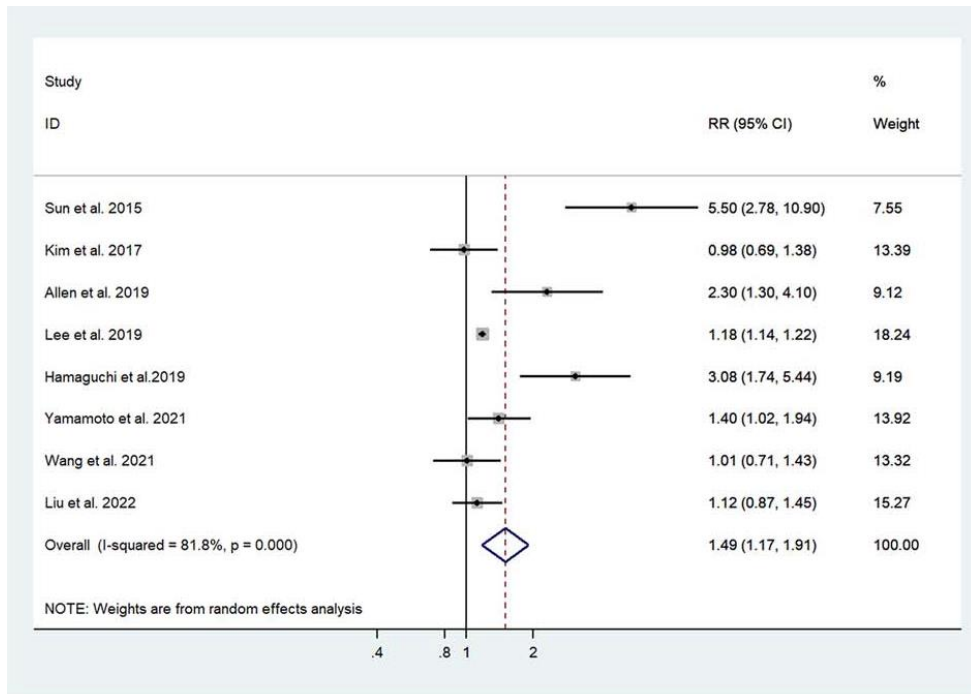
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# Risk factors for Gastrointestinal Cancers from Mendelian Randomization studies

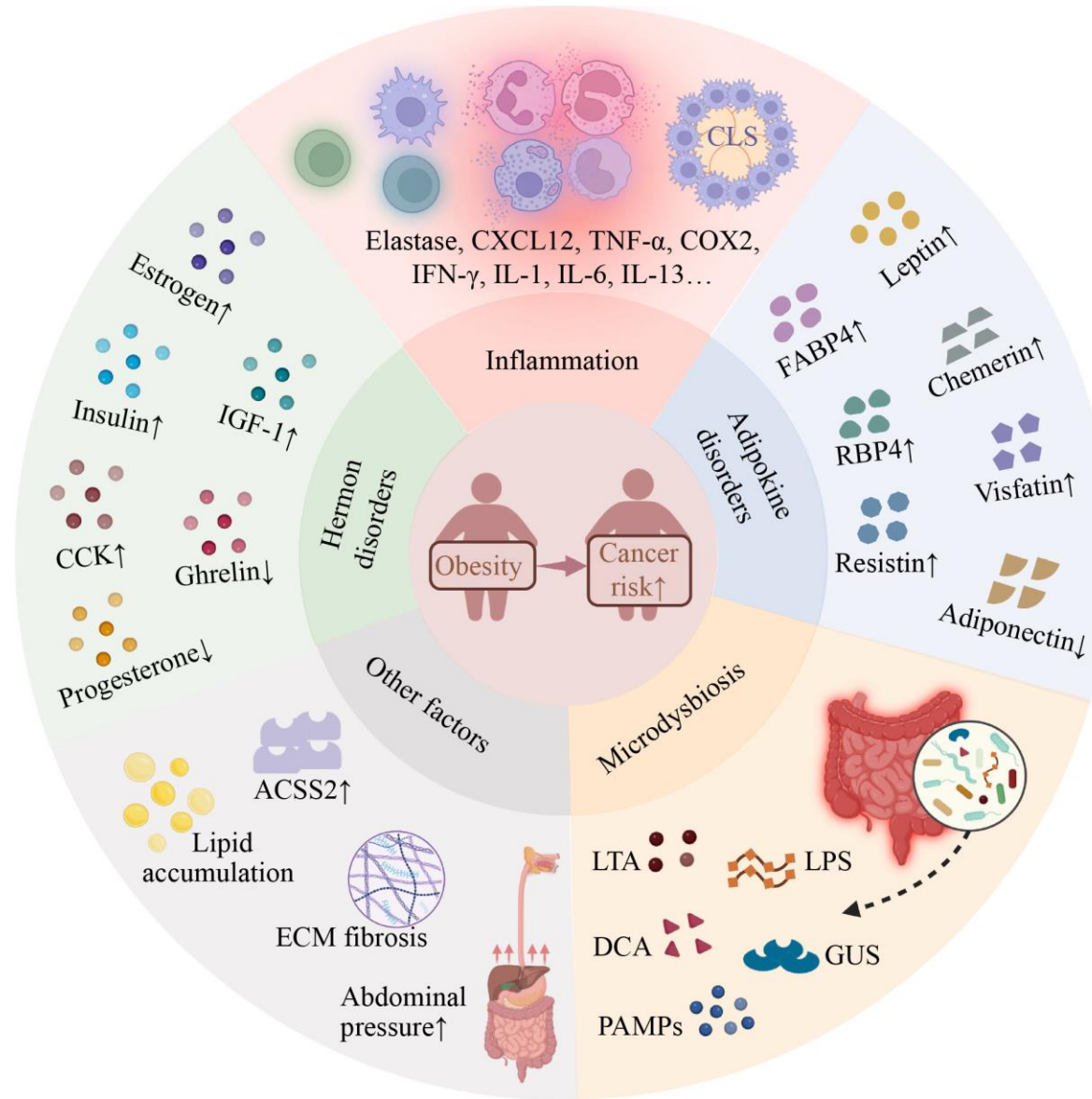


# MAFLD and GC / EC cancer

- 8 studies comprising a total of 8629525 participants
- Pooled RR values for the risk of
  - GC in patients with MAFLD was 1.49 (95%CI:1.17–1.91)
  - EC in patients with MAFLD was 1.76(95%CI:1.34–2.32)



# Mechanisms linking Obesity & Cancer risk



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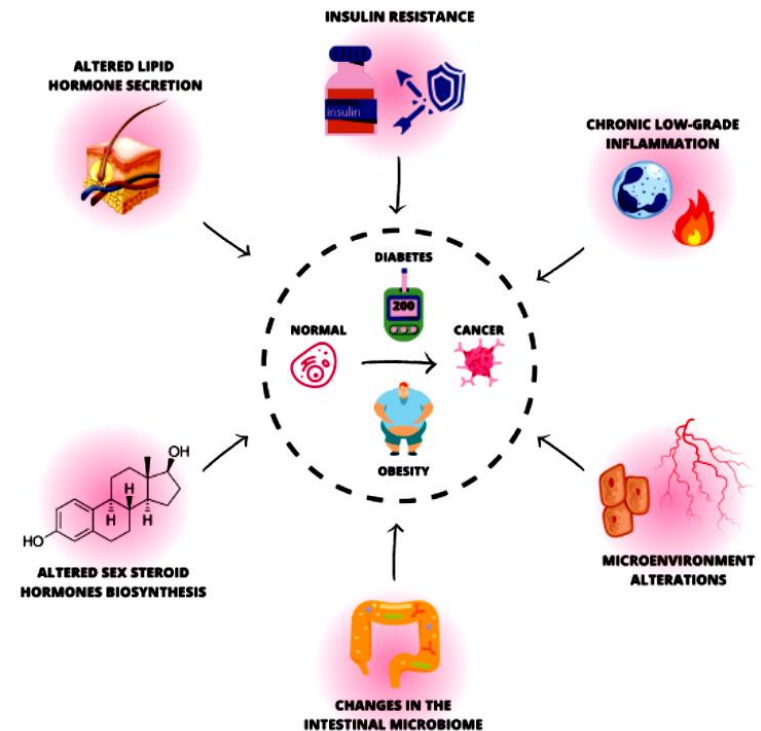
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# T2DM Obesity & Cancer

- Increased risk for cancer in patients with T2DM
- Hyperglycemia induces oxidative stress and DNA damage, initiating tumorigenesis
- Endogenous hyperinsulinemia - reduced insulin sensitivity activates insulin receptors, IGF-1 receptors, and hybrid insulin/IGF-1 receptors, promoting cancer cell proliferation, survival, and metastasis
- Women with T2DM & HbA1C  $\geq$  8% appear to have an increased risk of developing a tumor than men
- Endocrine interactions between the insulin signaling & gonadal axis leading to increased estrogen levels are thus higher in premenopausal women than in men



# Impact of MBS on Diabetes

- Direct mechanisms
  - Reduced circadian blood glucose fluctuations
  - Reduced or even discontinued insulin therapy
- Similar effects for LSG VS RYGB
- Indirect mechanisms that lead to a risk reduction for cancer
  - increased postprandial secretion of satiety hormones such as GLP-1, PYY, and oxyntomodulin
  - Increased postop GLP-1 levels and their effect on insulin are discussed as a possible mediator of angiogenesis and cell growth
  - Accordingly, to these mechanisms, this effect is increased in insulin-dependent type 2 diabetes mellitus patients



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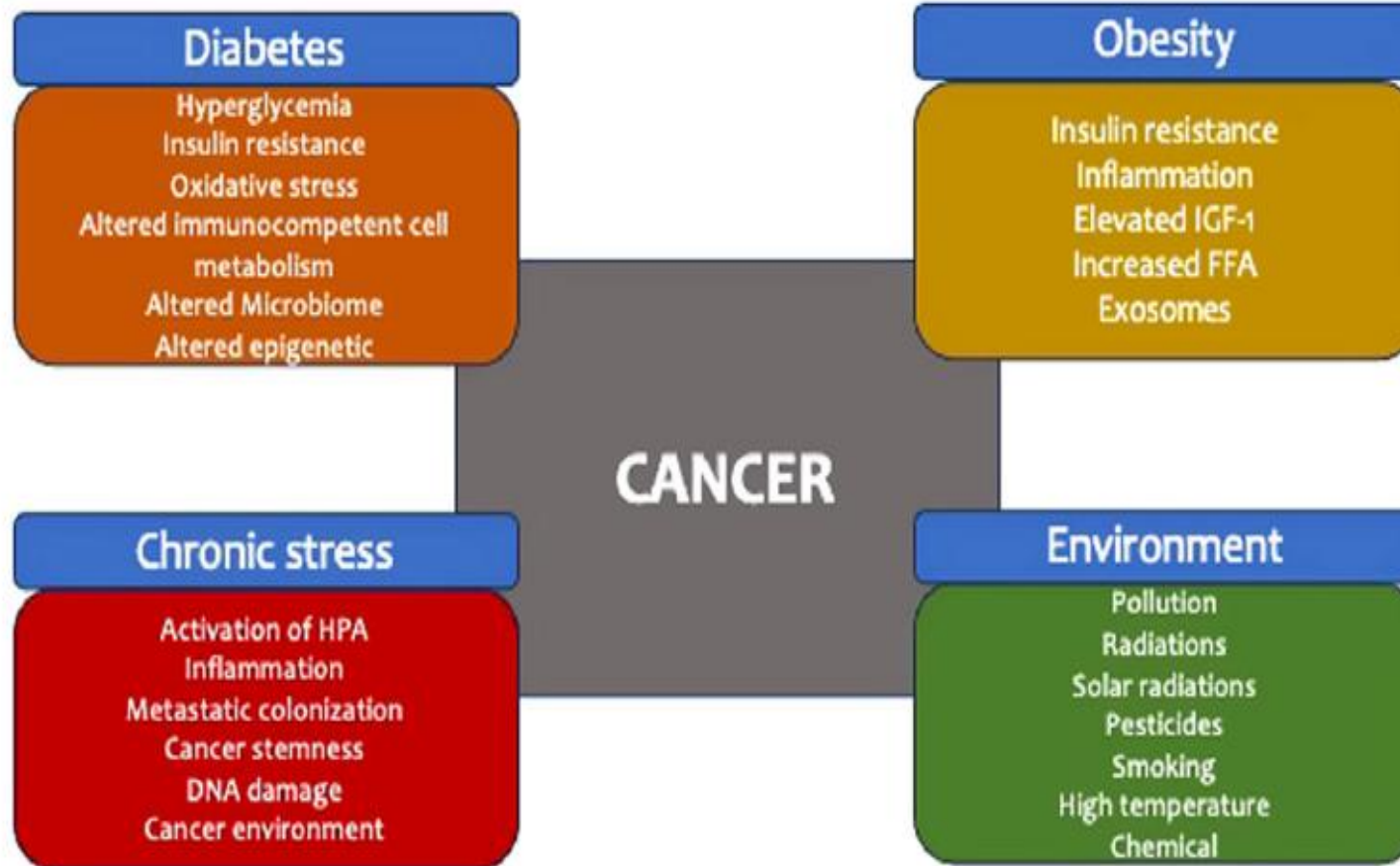


# T2DM Obesity & Cancer



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# Preop Screening for Cancer

An age & family history-related, risk-based tumor screening before MBS is recommended - *American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), The Obesity Society (TOS), the American Society for Metabolic and Bariatric Surgery (ASMBS), the Obesity Medicine Association (OMA), and the American Society of Anesthesiologist (ASA)*



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# Preop Screening for Cancer

- Absolute necessity of OGD is debatable
  - Preoperative gastroscopy reveals not only an HP- and reflux-related esophagitis or Barrett's metaplasia, but also other asymptomatic gastrointestinal pathologies, which has a great impact on the choice of the bariatric and metabolic procedure
  - High costs & only 0.4% of surgery was delayed or cancelled
- Colonoscopy, CT scans, ultrasound or other screening examinations for cancer are not routinely recommended
  - Tremendous effort required for the patient and the associated additional health costs



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# MBS and Cancer



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- 1035 MBS patients vs 5000 non-operated patients
- Cancer incidence decrease 4 fold
  - 2.03% [MBS], while in the non-surgical group was 8.49%
- Decrease in the number of hospitalizations for cancer
  - 54.95/1,000 person-years in the non-operated group *versus* only 11.80 in the operated group

# MBS and Cancer Risk Reduction

- Retrospective cohort study 2005 - 2012 with follow-up through 2014.  
Data from a large integrated health insurance and care delivery systems
- 22,198 subjects who had MBS & 66,427 non-surgical subjects matched on sex, age, study site, BMI and Elixhauser comorbidity index.
- Incidence of cancer up to 10 years



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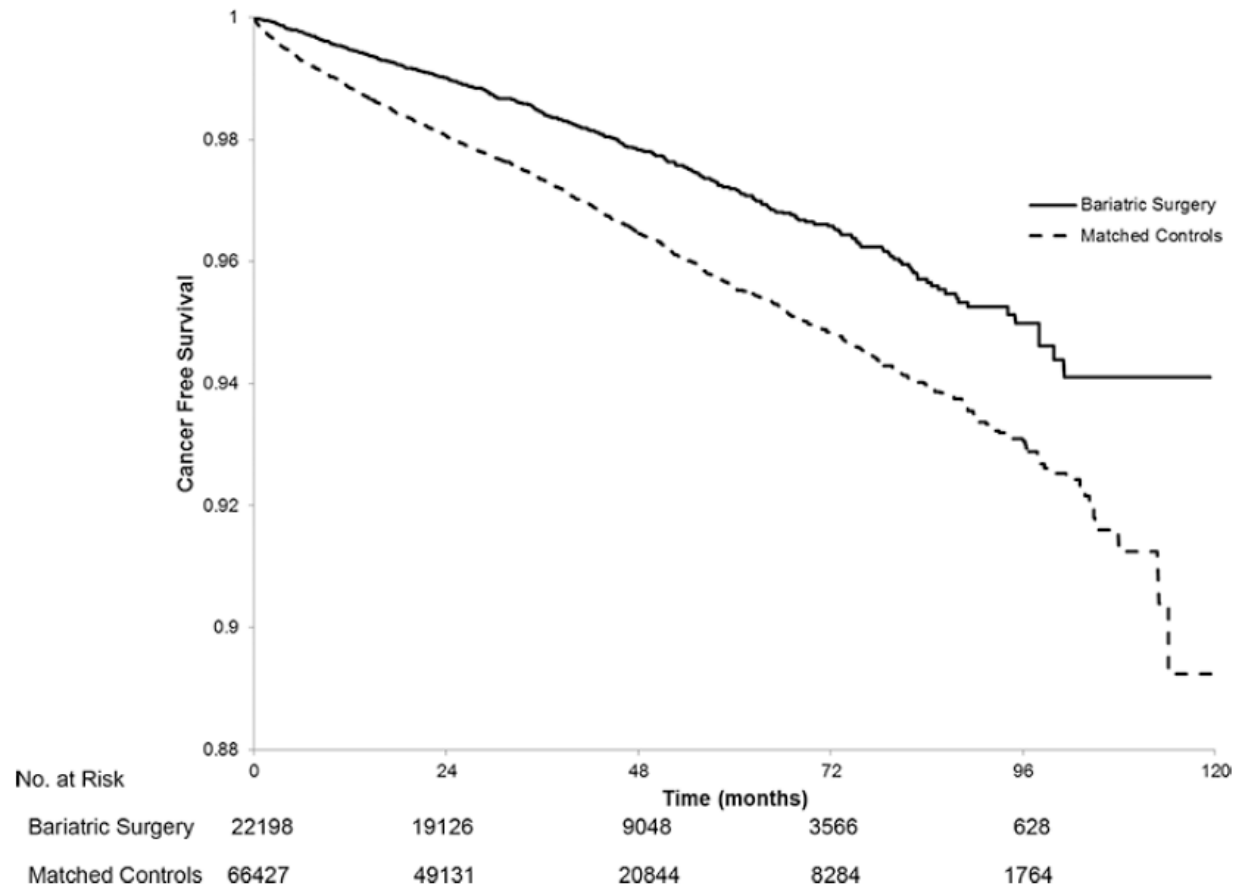
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# All Cancers Outcome



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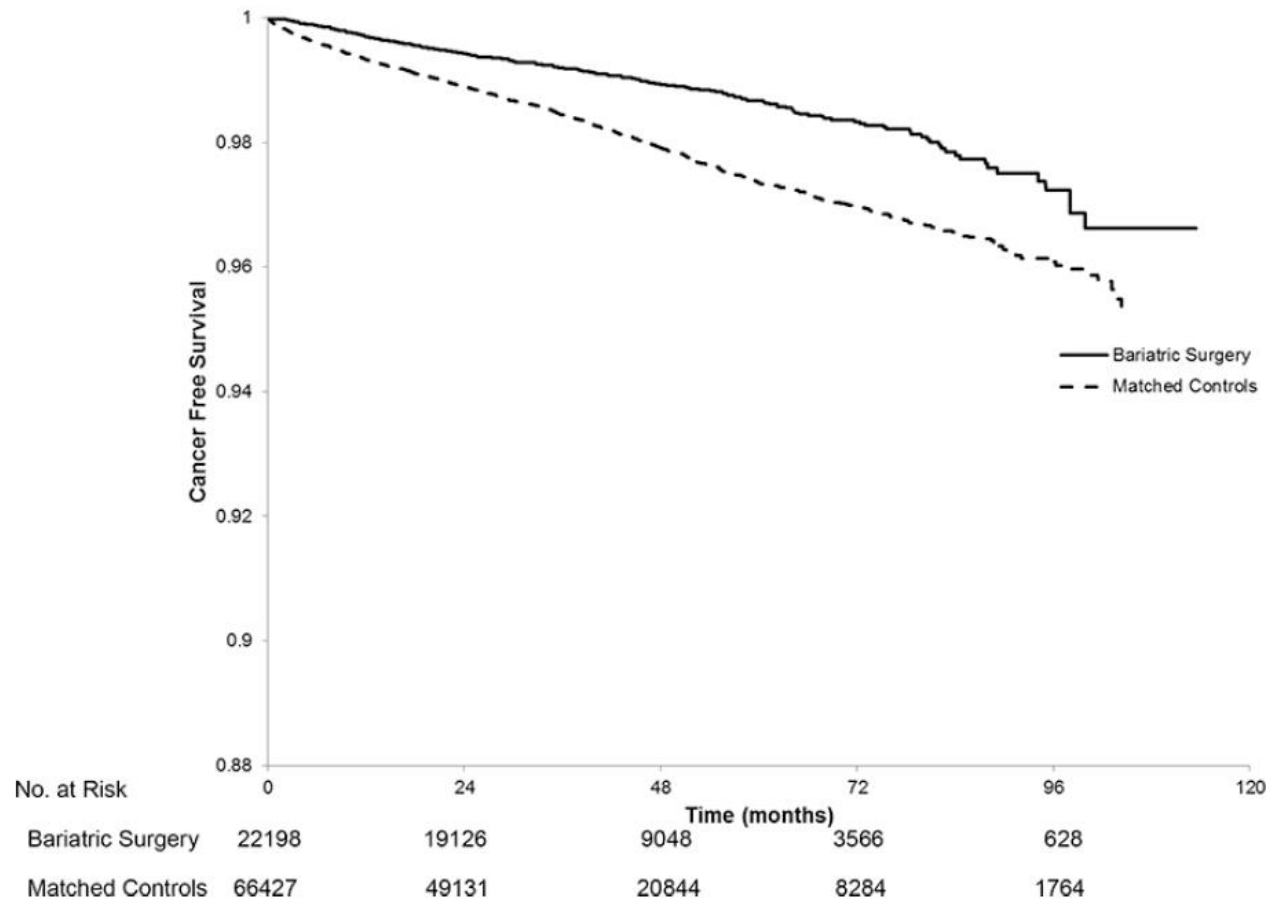
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# Obesity Associated Cancer Outcome



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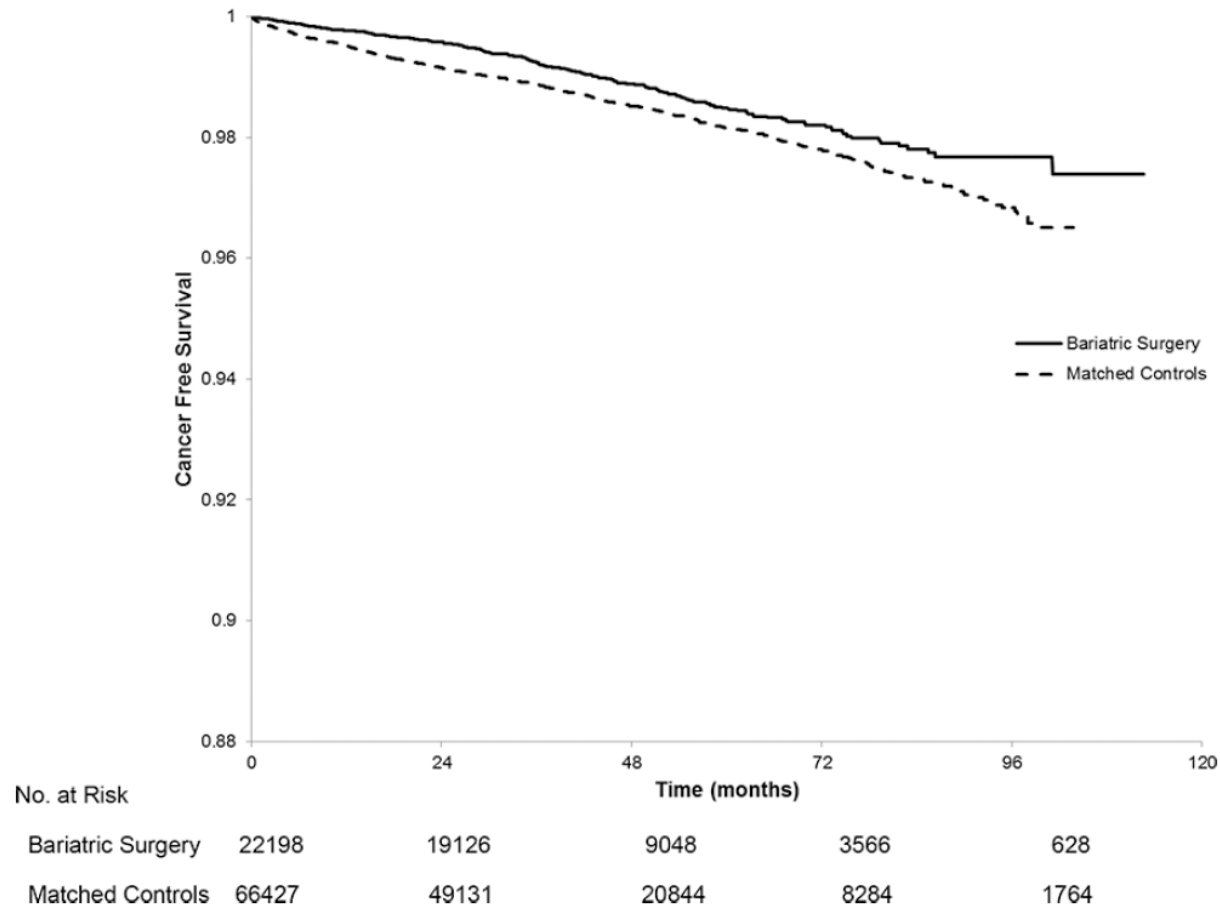
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# Cancers not associated with obesity Outcome



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# MBS and Cancer Risk Reduction

- MBS pts had a 33% lower hazard of developing any cancer (HR 0.67, 95% C.I. 0.60, 0.74)
- Obesity-associated cancers 41% lower hazard (HR 0.59, 95% C.I. 0.51, 0.69)
  - Postmenopausal breast 42% (HR 0.58, 95% C.I. 0.44, 0.77)
  - Colon 41% (HR 0.59, 95% C.I. 0.36, 0.97)
  - Endometrial 50% (HR 0.50, 95% C.I. 0.37, 0.67)
  - Pancreatic cancer 54%(HR 0.46, 95% C.I. 0.22, 0.97)



# MBS & Cancer

- Systematic review and meta-analysis demonstrated that BS is associated with a reduced
  - Overall incidence of cancer (RR 0.62, 95% CI 0.46–0.84)
  - Obesity-related cancer (RR 0.59, 95%CI 0.39–0.90)



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# Post MBS Recurrent Weight Gain & Cancer

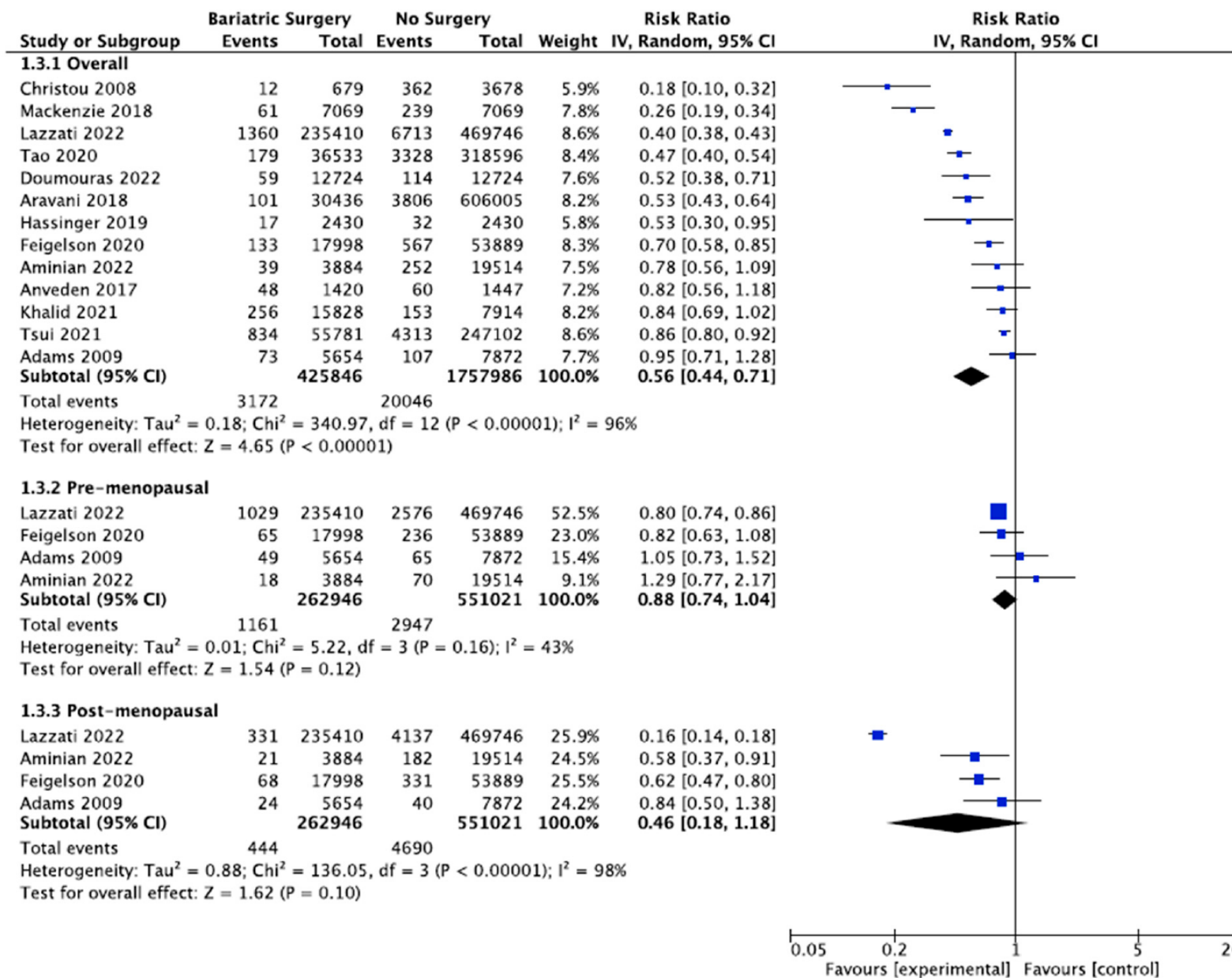


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- Multi-center population-based study
- Cumulative incidence of cancers among patients with weight recurrence was significantly lower (52%) in the MBS compared to the nonsurgical control group (HR 0.48, 95%CI 0.459–0.507)
- This protective effect extends to specific cancers such as breast, endometrial, & colorectal cancers



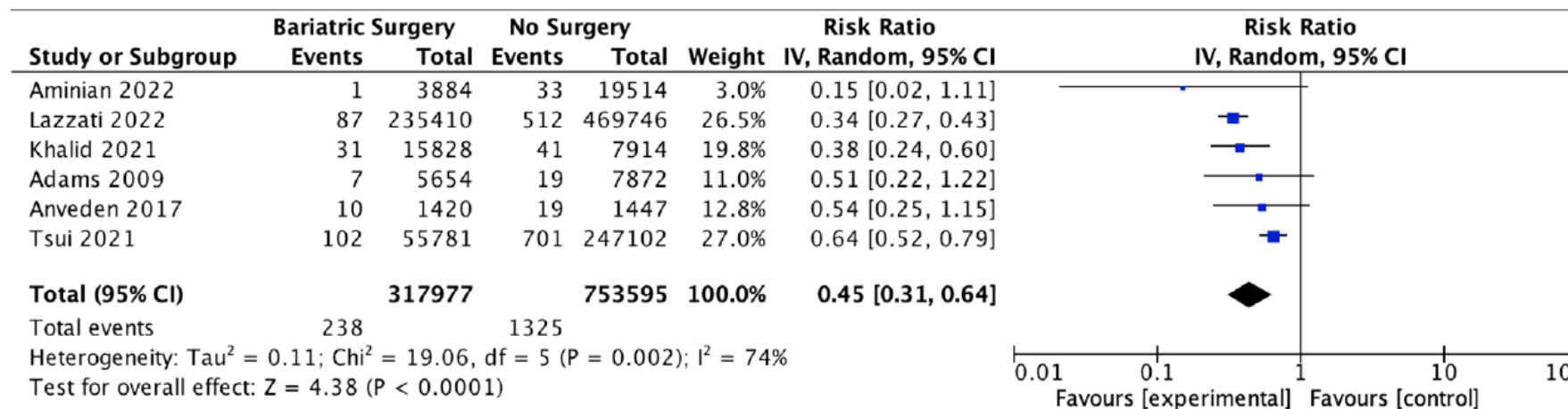
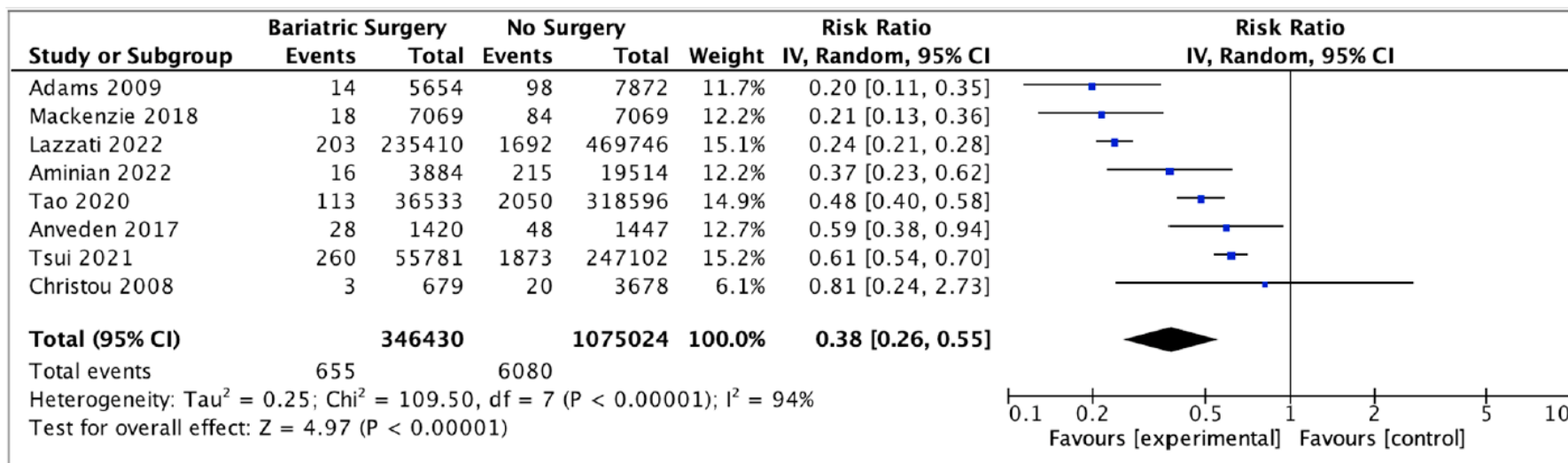


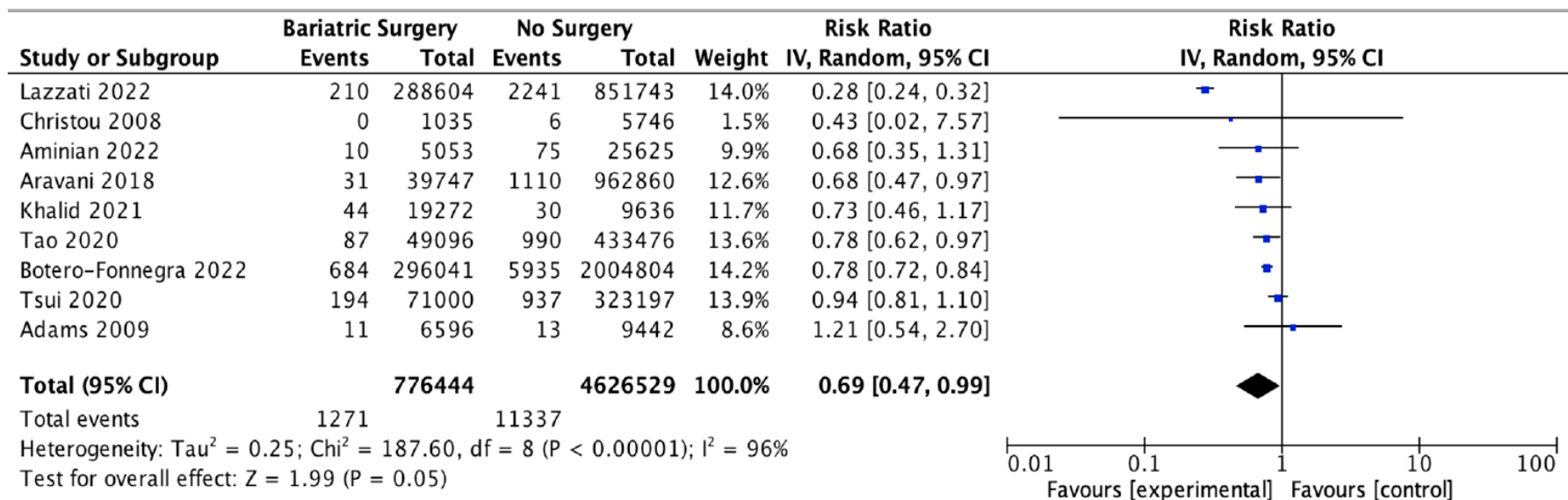
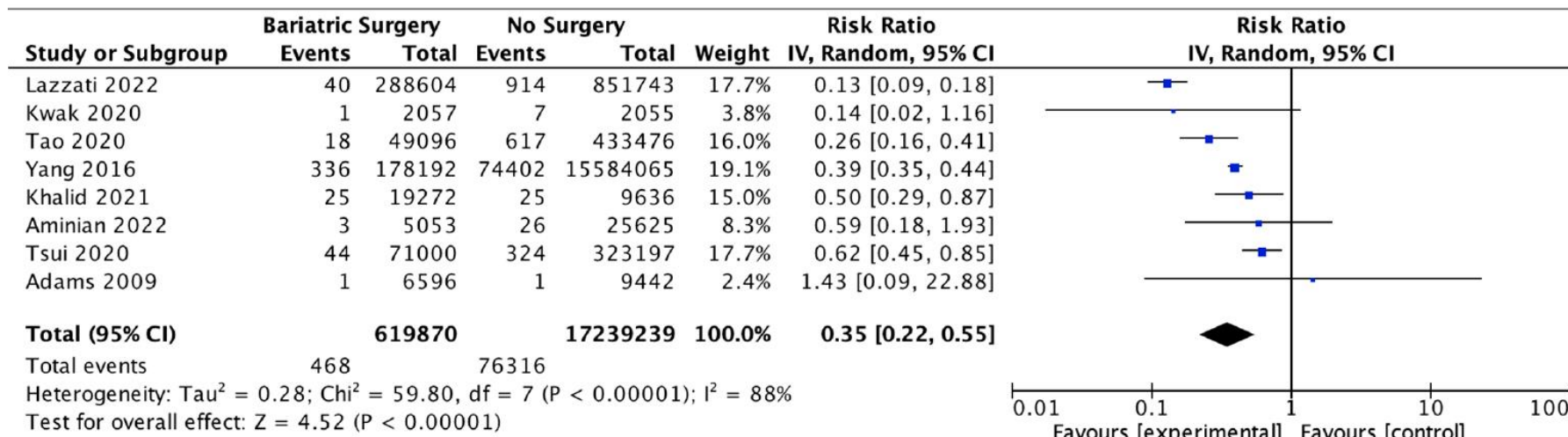
# MBS Endometrial Ovarian and Cancers



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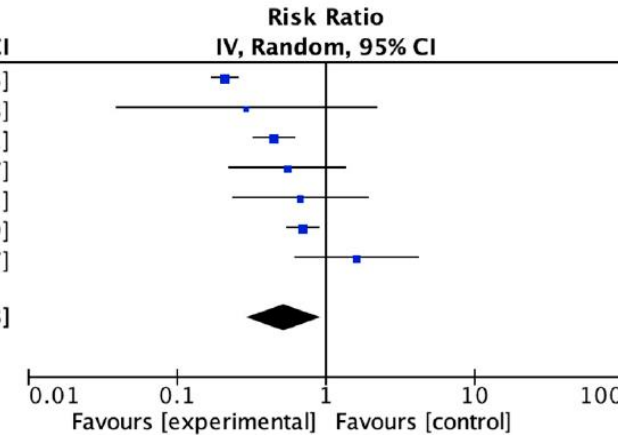
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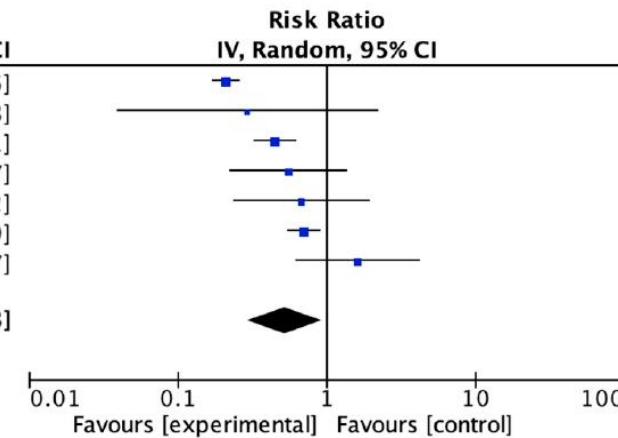




| Study or Subgroup  | Bariatric Surgery |               | No Surgery |                | Weight        | Risk Ratio               |
|--|-------------------|---------------|------------|----------------|---------------|--------------------------|
|  | Events            | Total         | Events     | Total          |               | IV, Random, 95% CI       |
| Lazzati 2022   | 98                | 288604        | 1382       | 851743         | 19.0%         | 0.21 [0.17, 0.26]        |
| Christou 2008  | 1                 | 1035          | 19         | 5746           | 5.8%          | 0.29 [0.04, 2.18]        |
| Tao 2020   | 41                | 49096         | 808        | 433476         | 18.4%         | 0.45 [0.33, 0.61]        |
| Khalid 2021  | 10                | 19272         | 9          | 9636           | 13.2%         | 0.56 [0.23, 1.37]        |
| Aminian 2022   | 4                 | 5053          | 30         | 25625          | 11.9%         | 0.68 [0.24, 1.92]        |
| Tsui 2020  | 74                | 71000         | 481        | 323197         | 18.8%         | 0.70 [0.55, 0.89]        |
| Adams 2009   | 9                 | 6596          | 8          | 9442           | 12.7%         | 1.61 [0.62, 4.17]        |
| <b>Total (95% CI)</b>  |                   | <b>440656</b> |            | <b>1658865</b> | <b>100.0%</b> | <b>0.52 [0.29, 0.93]</b> |
| Total events   | 237               |               | 2737       |                |               |                          |
| Heterogeneity: Tau <sup>2</sup> = 0.44; Chi <sup>2</sup> = 68.39, df = 6 (P < 0.00001); I <sup>2</sup> = 91% |                   |               |            |                |               |                          |
| Test for overall effect: Z = 2.20 (P = 0.03)   |                   |               |            |                |               |                          |



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# MBS and Specific Cancers



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- MBS was associated with a reduction in the future incidence of
  - Hepatocellular carcinoma (RR 0.35, 95%CI 0.22–0.55)
  - Colorectal cancer (RR 0.63, 95%CI 0.50–0.81)
  - Pancreatic cancer (RR 0.52, 95%CI 0.29–0.93)
  - Gallbladder cancer (RR 0.41, 95%CI 0.18–0.96)
  - Breast cancer (RR 0.56, 95%CI 0.44–0.71)
  - Endometrial cancer (RR 0.38, 95%CI 0.26–0.55,
  - Ovarian cancer (RR 0.45, 95%CI 0.31–0.64)



# MBS and Specific Cancers

- No significant reduction in the incidence of
  - Esophageal
  - Gastric
  - Thyroid
  - Renal
  - prostate cancer
  - Multiple myeloma



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# MBS & UGI cancer

- 748,932 pts with obesity, of whom 91,731 underwent MBS
- Predominantly RYGB (n=70,176; 76.5%)
- Adjusted risk of esophageal cancer decreased over time from 2.2 after 2 to 5 years to 0.6 after 10 to 40 years
- RYGB was followed by a strongly decreased adjusted risk of esophageal adenocarcinoma (HR 0.3, 95%CI 0.1–0.8) but not of cardia adenocarcinoma (HR 0.9, 95%CI 0.5–1.6)



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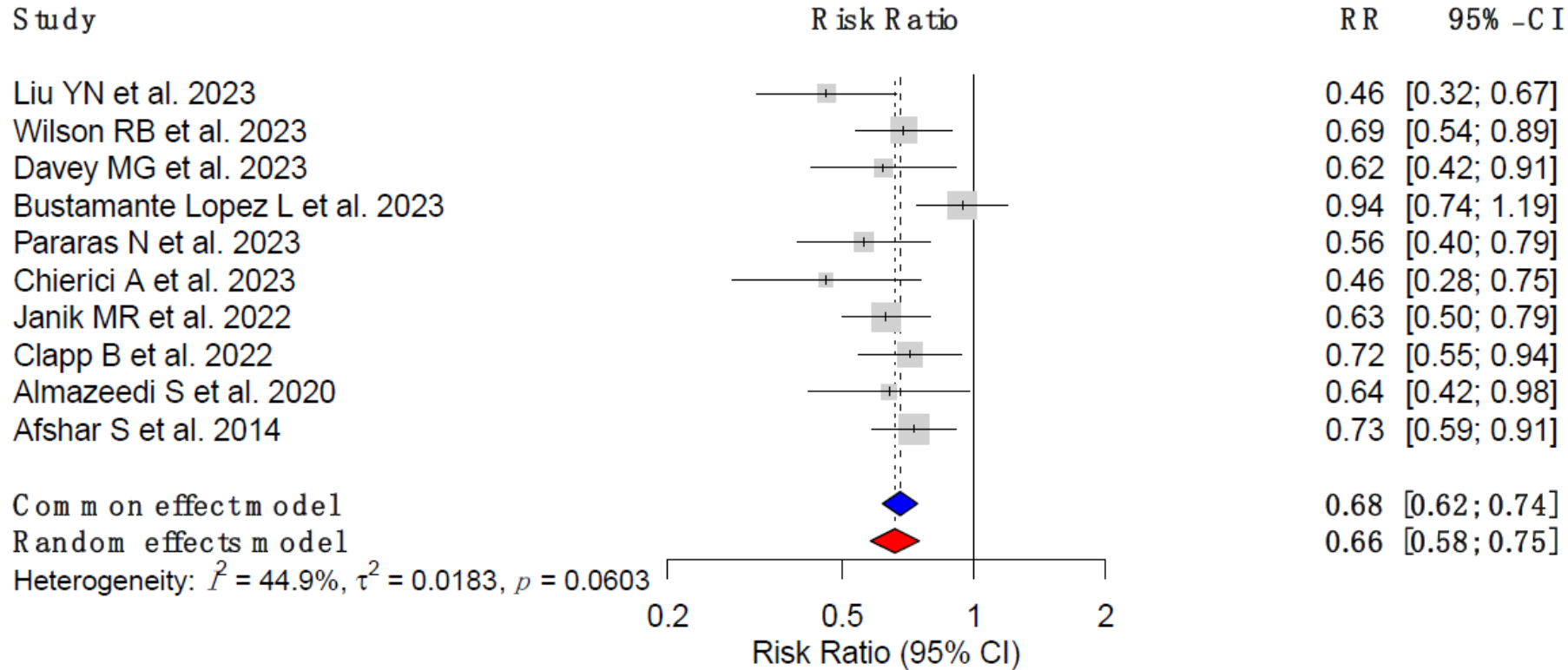


Figure 2. Forest plot depicting the reduction in the risk of colorectal cancer (CRC) following metabolic bariatric surgery (MBS)



# LSG and Cancer



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- Reduction in overall cancer incidence compared to nonsurgical treatment in patients undergoing SG was 0.44 (OR) (95%CI 0.27–0.70)
- Notable concern for esophageal cancer due to increased GERD (41%) and Barrett's esophagus (18%)
- SG is generally lower for most cancer types, vigilance for esophageal cancer remains necessary.

Chen ZW et al. Surg Obes Relat Dis. 2024;20(5):467-81

Sebastianelli L et al. Obes Surg. 2019;29(5):1462-9



# RYGB & Cancer

- Systematic review
  - Post-RYGB gastroesophageal cancer in 27/44 occur in the gastric tube

Chemaly R et al. *Obes Surg.* 2022;32(4):1300-11.

- 21 cases of remnant gastric cancer after RYGB, with a median time to diagnosis of 11 years postoperatively

Dong SL et al. <https://doi.org/10.3760/cma.j.cn441530-20211221-00515>

- Gastric cancer in the excluded stomach post-RYGB - 77% of these cancers diagnosed at an advanced stage

Doukas SG et al. *Obes Surg.* 2023;33(6):1876-88.



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# MBS – OAGB

- Gastroesophageal cancer incidence similar to RYGB
- Systematic review and meta-analysis
  - 37.5% of gastroesophageal cancers after OAGB were located in the gastric tube vs 61% after RYGB OR of 0.38
  - Indicating no significant increase in cancer occurrence in the gastric tube after OAGB compared to RYGB
- The arguments that bile reaches the terminal ileum diluted are unfounded, since physiology studies show that 90% of bile reaches that location intact, where it is later reabsorbed
- OAGB should be used with great caution, since the potential harmful effects, such as the development of cancer in the gastric remnant and esophagus, may only become apparent 30 to 40 years postoperatively



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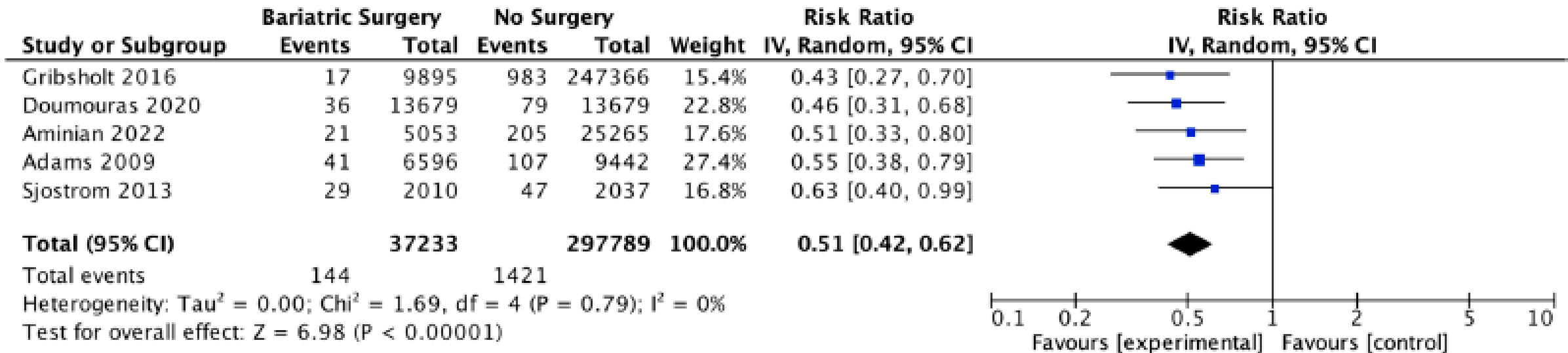
Chemaly R et al. *Obes Surg.* 2022;32(4):1300-11.

Basso L et al *J Clin Med.* 2022;11(6):1498.



# MBS & Cancer Related Mortality

- MBS was associated with a significant reduction in the incidence of cancer-related mortality (RR 0.51, 95% CI 0.42–0.62)





# GLP-1 and Breast Cancer

- Addressing obesity in breast cancer patients is critical for improving prognosis and quality of life.
- While current data do not suggest adverse safety signals with GLP-1 receptor agonists

| Study                 | Population                          | Intervention               | Duration                           | Risk of breast cancer  | References |
|-----------------------|-------------------------------------|----------------------------|------------------------------------|--|------------|
| Sun et al. (2024)     | Adults with and without cancer      | GLP-1 RA                   | Variable                           | Reduced risk of breast cancer (OR 0.92, 95% CI 0.88–0.96)                        | [94]       |
| Levy et al. (2024)    | Adults with obesity                 | GLP-1 RA                   | 5-year follow-up                   | Reduced risk of breast cancer (HR 0.72, 95% CI 0.64–0.82)                        | [95]       |
| Piccoli et al. (2021) | Adults with obesity and/or diabetes | GLP-1 RA                   | Variable, minimum 24 weeks         | No increased risk of breast cancer (RR 0.98, 95% CI 0.76–1.26)                   | [47]       |
| Hicks et al. (2016)   | Women with type 2 diabetes          | GLP-1 vs. DPP-4 inhibitors | Variable, mean follow-up 3.5 years | No increased risk of breast cancer compared to DPP-4 (HR 1.40, 95% CI 0.91–2.16) | [96]       |



# GLP-1 and Cancers

- Steepest weight regain after the cessation of semaglutide occurred in patients who had previously lost >20% of their TBW
- This reflects the persistence of neurohormonal and behavioural pathways in patients with obesity
- How pharmacological treatment translates to a long-term reduction in cancer incidence in obese patients remains to be shown



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# The Future state

- There is an opportunity for research to be conducted on the effect of MBS for cancers given the considerable variability in the existing data
- Additional research is required on the subtypes of various cancers and specific patient populations, such as pre- and postmenopausal breast cancer and ER-negative and ER-positive breast cancer, which would enable clarity on the molecular mechanisms involved and enable development of management strategies



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# In Conclusion

- Obesity is associated with elevated risk of cancers
- Level 1 evidence reports reduced overall incidence of cancer, obesity related cancer and cancer related mortality following MBS
- Procedure specific (MBS) concerns warrant continued research
- The tumor's biology, behavior, and aggressiveness depend not only on the gender but also on the patient's age and metabolic and biological conditions
- Whether pharmacological treatment translates to a long-term reduction in cancer incidence in obese patients remains to be shown



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