

JAMA | Original Investigation

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

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PRESENTATIE DOOR BEATA REIBER

6<sup>E</sup> JAARS DIFFERENTIANT GE – BARIATRIE

Rode Kruis Ziekenhuis

Medisch Specialistische Zorg

# ACHTERGROND

- Maligniteiten & obesitas
  - Renehan et. al. Lancet 2008<sup>1</sup>: systematic review + meta analyse 141 studies (282 137 patienten)
    - Associatie 5 punten BMI stijging met RR tot 1.59 maligniteit in mannen en vrouwen
- Meerdere cohort studies bariatric en incidentie (obesitas gerelateerde) maligniteiten
  - Geen LRYGB / LSG (SOS 2010<sup>2</sup>)
  - Matching obv weinig karakteristieken (Adams 2017<sup>3</sup>)
  - Korte follow-up (Schauer 2017<sup>4</sup>)
  - Geen analyse tav maligniteit geassocieerde mortaliteit

# OBSITAS GERELATEERDE MALIGNITEITEN

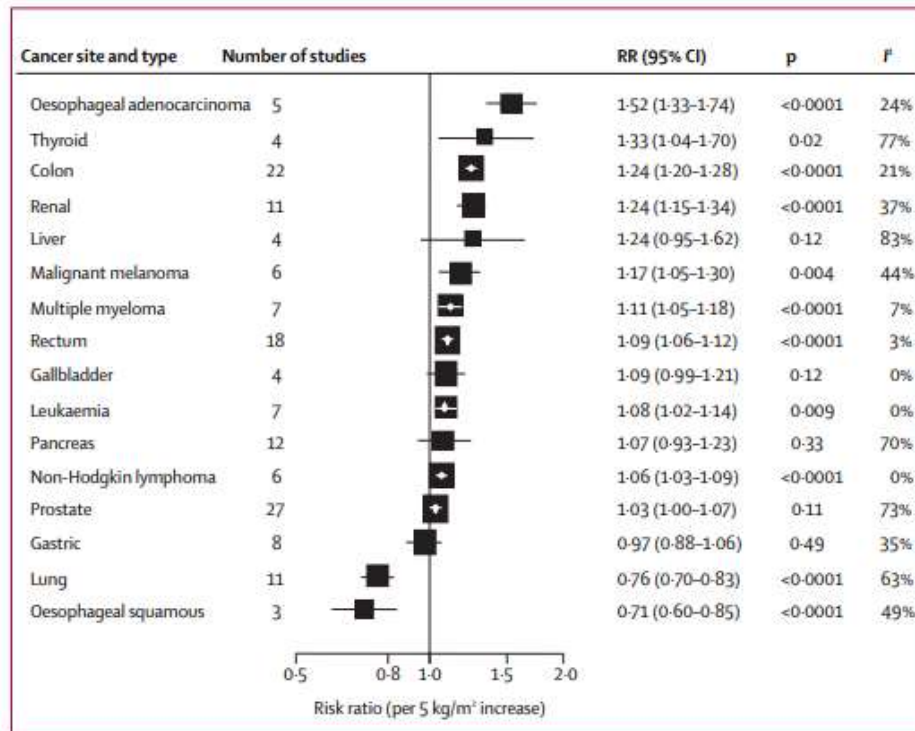


Figure 3: Summary risk estimates by cancer sites in men

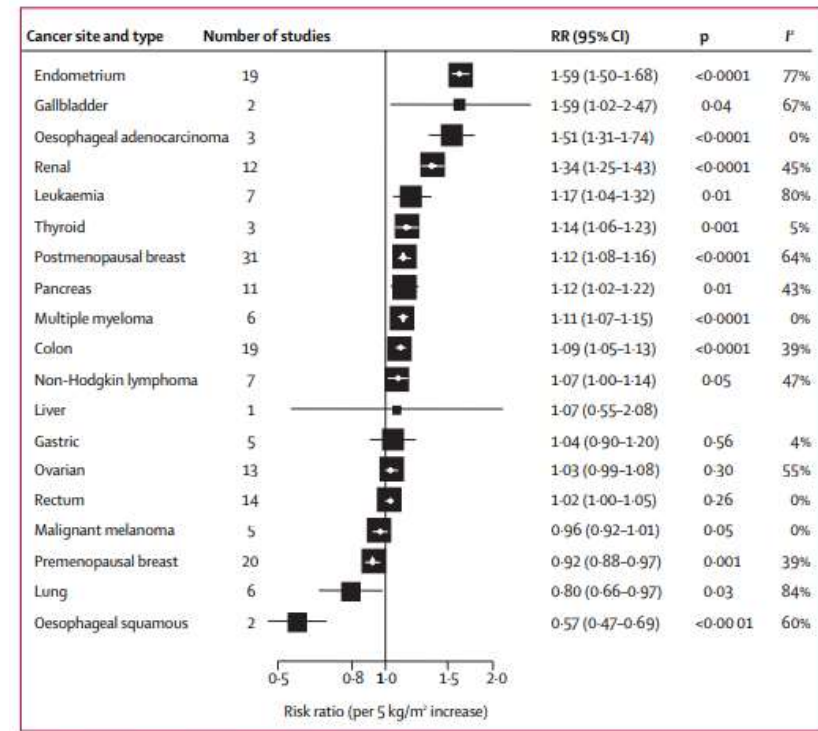


Figure 4: Summary risk estimates by cancer sites in women

# IN DEZE STUDIE

International Agency  
for Research on Cancer



Cancer Site or Type	Strength of the Evidence in Humans <sup>†</sup>	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI
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) <sup>§</sup>
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) <sup>§</sup>
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

## DOEL

Het onderzoeken van de associatie van de incidentie van (obesitas gerelateerde) maligniteit en maligniteit geassocieerde mortaliteit, met de huidige bariatrische procedures (LRYGB en LSG) tijdens lange follow-up.

# UITKOMSTEN

- Primaire uitkomst:
  - De incidentie van de 13 types obesitas gerelateerde maligniteit bariatrisch versus controle cohort
  - Subgroep analyse LRYGB vs LSG
- Secundaire uitkomsten:
  - Incidentie van alle maligniteiten en maligniteit gerelateerde mortaliteit
- Overig
  - Analyse minimale hoeveelheid gewichtsverlies nodig voor beschermend effect

# METHODE

- Retrospectief cohort Cleveland Clinic Health System 2004 - 2017
  - Surgical Procedures and Long-term Effectiveness in Neoplastic Disease Incidence and Death (SPLENDID)
- Bariatrische patiënten: LSG en LRYGB
  - Inclusie: leeftijd 18-80, BMI 35-80
  - Exclusie: oa (pre)maligniteit in VG, alcohol abus, ulcus lijden, HIV, ascites, dialyse, verminderde LVEF
- Controle patiënten:
  - In / exclusie obv bovenstaande en indien bariatrische ingreep in VG

## Slide 7

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**Ma1** The Elixhauser Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category is dichotomous -- it is either present or it is not. The Index can be used to predict hospital resource use and in-hospital mortality (Elixhauser et al., 1998).

Microsoft account; 6-4-2023

**Ma2** <https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci>

Microsoft account; 6-4-2023



# METHODE

- Propensity score matched nearest neighbor (1:5)
- Matching obv 10 potentiële confounders
  - leeftijd / geslacht / ethniciteit / BMI / roken / T2D / Elixhauser Comorbidity Index / Charlson Comorbidity index / state of residence
- Cox regressie aangepast op
  - jaarlijks inkomen obv postcode / Hb / Ca<sup>2+</sup> / eGFR / medicatie gebruik (oa hormonen / HT / T2D)
  - 10 potentiële confounders

NB maligniteiten < 3 jaar na index datum niet mee genomen.
- %TWL bepaald:
  - Tussen chirurgie en >12 mnd voorafgaand aan diagnose maligniteit // laatste FU

# RESULTATEN

## - BASELINE

- Totaal n = 30 318 patiënten
  - 46 jaar; BMI 45; 77% vrouw; 73% wit; FU 6.1 jaar
- Bariatrisch cohort n = 5053
  - 66% LRYGB, 34% LSG
- Baseline characteristics over het algemeen gelijk
  - Bariatrische groep:
    - Meer medicatie (antihypertensiva) en meer comorbiditeiten (obv comorbidity indexes)
    - Zowel voor – als na operatie datum significant vaker gescreend voor maligniteiten

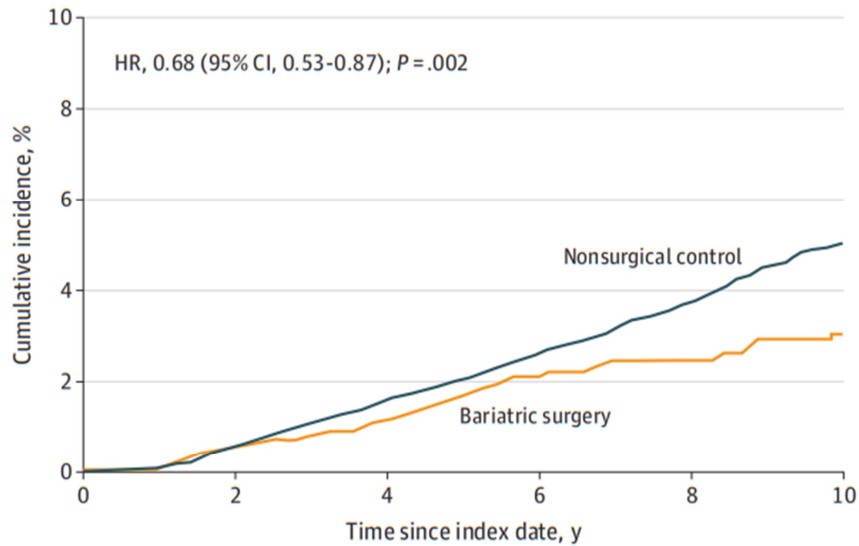
# RESULTATEN

	Bariatrisch cohort (n=5053)	Controle cohort (n=25 265)
1. Obesitas gerelateerd maligniteit; n	96	780
- Incidentie / 1000 persoon jaren	3.0	4.6
- Cumulatief na 10 jaar	2.9% (95% CI 2.2 – 3.6%)	4.9% (95% CI 4.5 – 5.3)
	Adjusted HR 0.68 (0.53 – 0.87)	
2. Totaal aantal maligniteiten; n	200	1331
- Incidentie / 1000 persoon jaren	6.3	8.0
- Cumulatief na 10 jaar	6.8% (95% CI 5.7-7.9%)	8.3% (95% CI 7.8%-8.8%)
	Adjusted HR 0.83 (0.69-0.99)	
3. Maligniteit gerelateerd mortaliteit; n	21	205
- Incidentie / 1000 persoon jaren	0.6	1.2
- Cumulatief na 10 jaar	0.8% (95% CI 0.4-1.2%)	1.4% (95% CI 1.1 – 1.6%)
	Adjusted HR 0.52 (0.31-0.88)	

# RESULTATEN

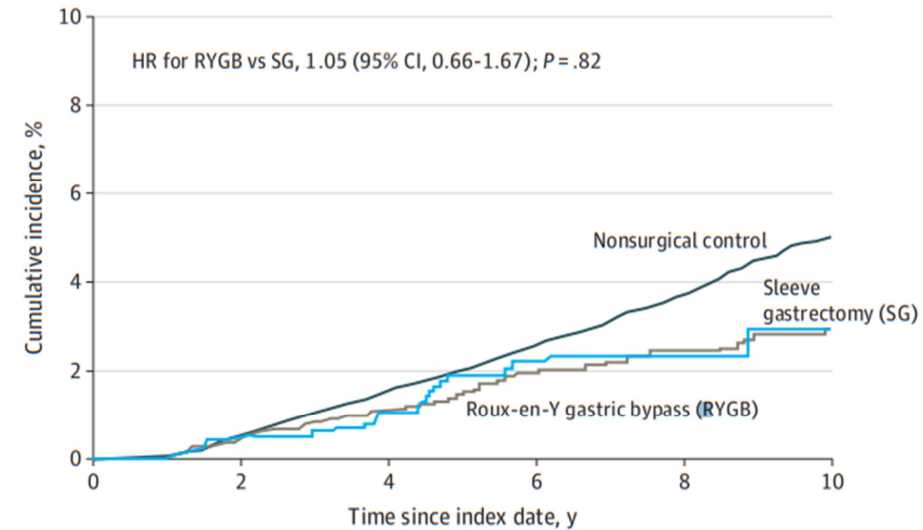
# - PRIMAIRE UITKOMST

**A** Obesity-associated cancer cases



No. at risk	0	2	4	6	8	10
Nonsurgical control	25 265	23 796	18 588	13 055	8 334	4 571
Bariatric surgery	5 053	4 487	3 409	2 453	1 588	939

**B** Obesity-associated cancer cases by surgery type

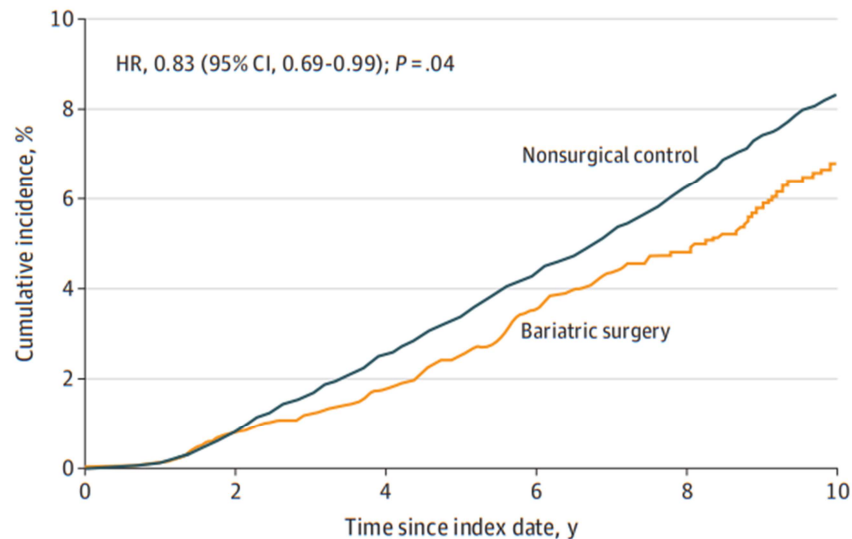


No. at risk	0	2	4	6	8	10
Nonsurgical control	25 265	23 796	18 588	13 055	8 334	4 571
RYGB	3 348	3 028	2 430	1 889	1 332	830
SG	1 705	1 459	979	564	256	109

# RESULTATEN

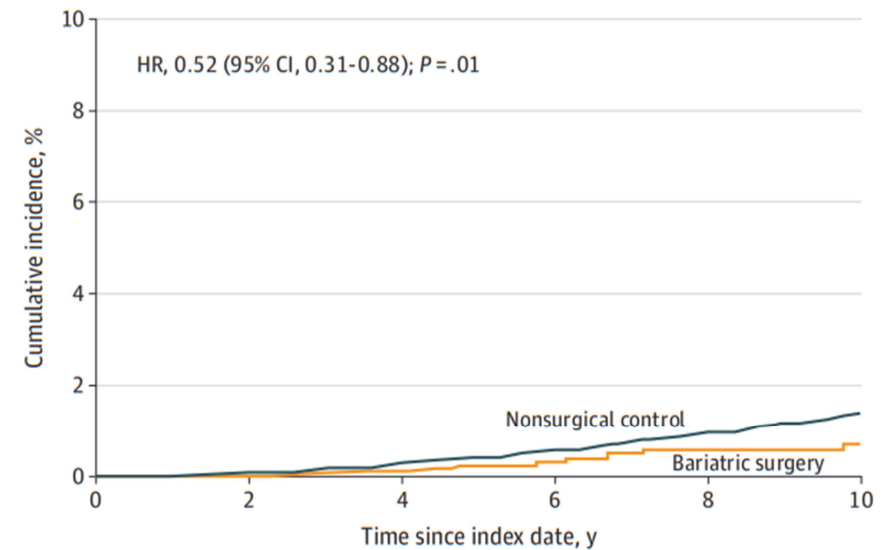
# - SECUNDAIRE UITKOMSTEN

**C** Total cancer cases



No. at risk	0	2	4	6	8	10
Nonsurgical control	25265	23724	18422	12881	8174	4475
Bariatric surgery	5053	4468	3381	2416	1548	902

**D** Cancer-related mortality



No. at risk	0	2	4	6	8	10
Nonsurgical control	25265	23898	18826	13345	8590	4778
Bariatric surgery	5053	4508	3440	2497	1622	963

Meest frequent voorkomende maligniteit: mamma – en endometrium carcinoom

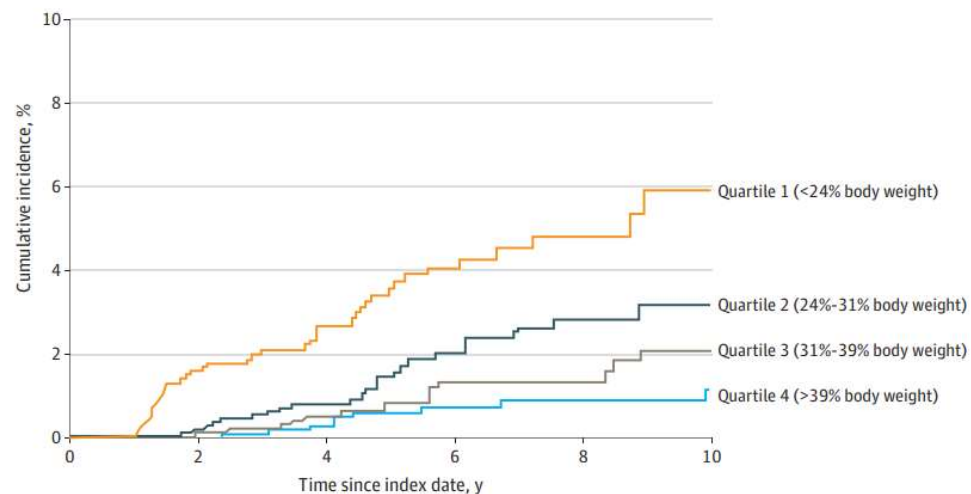
→ Associatie bariatric en individuele type maligniteit: alleen endometrium carcinoom (HR 0.47)

# RESULTATEN

# - OVERIG

- Gewichtsverlies in bariatric groep 27.5 kg versus 2.7 kg in controle groep ( $\Delta$  19.2 % bij 10 jaar FU)
- Hoogste incidentie obesitas gerelateerde maligniteit: in bariatrische groep bij < 24% gewichtsverlies
  - Meer gewichtsverlies leidt tot minder incidentie maligniteit dose-dependent

B Obesity-associated cancer cases by surgically induced maximum weight loss quartiles



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

# CONCLUSIE & DISCUSSIE

- Bariatrische chirurgie is geassocieerd met significante reductie van:
  - Obesitas gerelateerde maligniteiten
  - Alle invasieve maligniteiten
  - Maligniteit gerelateerde mortaliteit
- Gewichtsverlies zelf (i.t.t. anatomische verandering operatie) is van belang voor risico reductie
  - Deze studie >24%; Strout e.a. SOARD 2020 >20% TWL
- Limitaties:
  - Ongemeten confounders: omgevingsfactoren
  - Healthy user (selectie) bias
  - Surveillance bias
  - Patienten relatief jong en FU kort

Newcastle Ottawa scale: 8 uit 9 \*  
+ Veel potentiële confounders mee genomen  
- verschillende populaties

## TAKE HOME MESSAGE

- Bariatrische chirurgie reduceert het risico op (obesitas gerelateerde) maligniteiten en gerelateerde mortaliteit
  - Reductie 32%
- Het behalen van >20-25% totaal gewichtsverlies is relevant i.k.v. risico reductie



# REFERENTIES

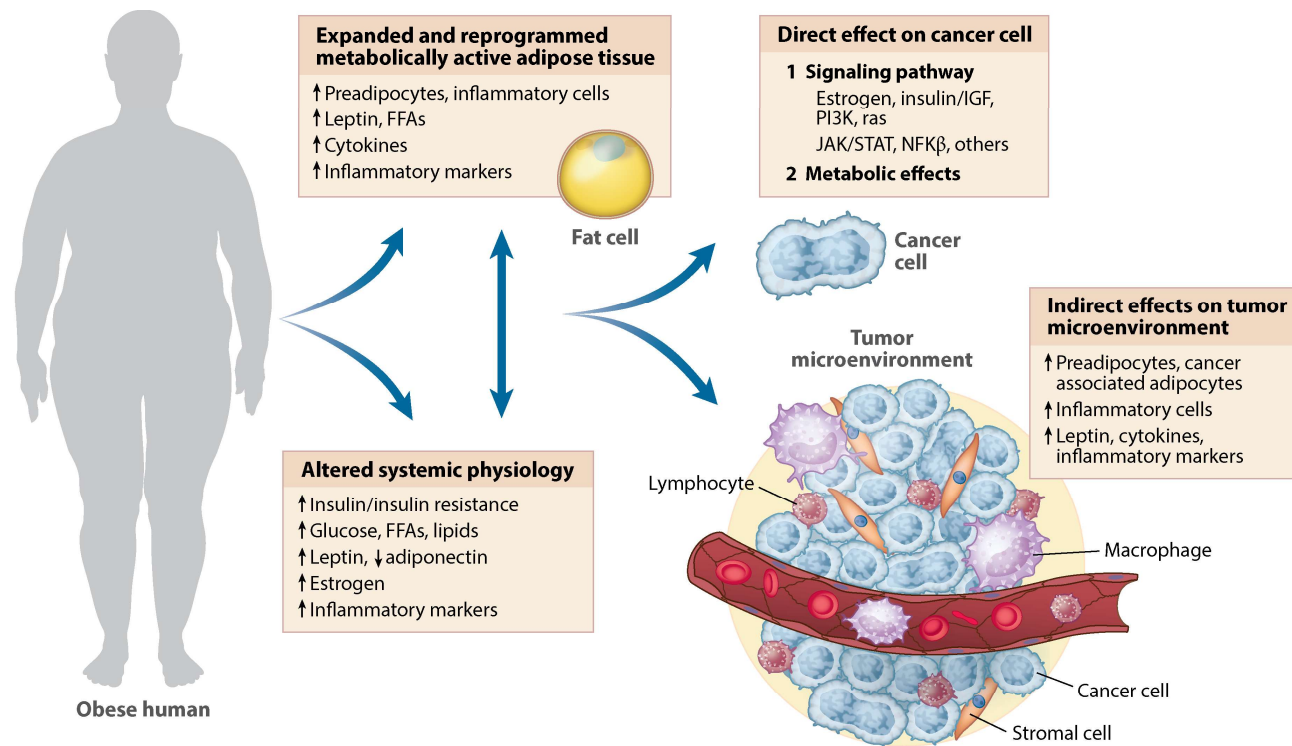
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EXTRA SLIDES VOOR EVENTUELE DISCUSSIE



# MECHANISME



# SENSITIVITEITSANALYSE

- Analyse zelf (15 data sets): mediane HR primaire uitkomst 0.67 (0.64 – 0.71)
- Exclusie obesitas gerelateerde maligniteiten 1<sup>e</sup> 3 jaar:
  - Bariatrie 33 en controle groep 227
    - HR 0.59 (0.43-0.79)
- E value:
  - Primaire uitkomst 1.94 (tov HR roken 1.02 en diabetes 0.96)
  - Maligniteit gerelateerde mortaliteit 2.52 (tov HR roken 1.68)

# RESULTATEN

# - BASELINE

	Bariatric surgery (n = 5053)	Nonsurgical control (n = 25 265)	Standardized mean difference, % <sup>a</sup>
Cancer screening before the index date, No. (%) <sup>k</sup>			
For breast cancer	891 (17.6)	1429 (5.7)	38.0
For colorectal cancer	322 (6.4)	277 (1.1)	28.1
For prostate cancer	128 (2.5)	168 (0.7)	14.9
Cancer screening after the index date, No. (%) <sup>l</sup>			
For breast cancer	1883 (37.3)	3482 (13.8)	55.9
For colorectal cancer	1340 (26.5)	1880 (7.4)	52.5
For prostate cancer	420 (8.3)	578 (2.3)	27.1

NB vooraf aan inclusie 13% exclusie obv (pre)maligne ziekte in bariatrische groep vs 8.5% in controle groep

**eTable 6.** Cancer-Specific Event Rates (%) per 1000 Person-Years of Follow-up for Each Cancer Type Stratified by Surgical and Nonsurgical Patients

	Number		Rate per 1000 person-years		Difference in event rate per 1000 person-years	
	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group	Estimate	95% CI <sup>a</sup>
Obesity-associated cancers	96	780	2.98	4.63	1.65	(0.97, 2.33)
All malignant cancers	200	1331	6.28	7.97	1.69	(0.72, 2.66)
Cancer-related mortality	21	205	0.64	1.20	0.56	(0.24, 0.88)
Breast cancers (in female)	39	252	1.20	1.48	0.28	(-0.14, 0.70)
Uterus corpus (endometrium) cancers <sup>b</sup>	16	215	0.49	1.26	0.77	(0.48, 1.06) <sup>b</sup>
Breast cancers (postmenopausal)	21	182	0.65	1.07	0.42	(0.10, 0.74)
Hematologic cancers	33	113	1.02	0.66	-0.36	(-0.73, 0.01)
Thyroid cancers	21	110	0.65	0.64	-0.01	(-0.31, 0.29)
Colorectal cancers	16	86	0.49	0.50	0.01	(-0.25, 0.27)
Prostate cancers	12	74	0.37	0.43	0.06	(-0.17, 0.29)
Renal cell carcinomas	10	75	0.31	0.44	0.13	(-0.09, 0.35)
Colon cancers	13	69	0.40	0.40	0	(-0.24, 0.24)
Lung and bronchial cancers	10	71	0.31	0.42	0.11	(-0.11, 0.33)
Meningioma	7	57	0.22	0.33	0.11	(-0.07, 0.29)
Melanoma	14	32	0.43	0.19	-0.24	(-0.48, -0.01)
Urinary bladder cancers	6	38	0.18	0.22	0.04	(-0.12, 0.20)
Ovarian cancers	1	33	0.03	0.19	0.16	(0.07, 0.25)
Pancreatic cancers	4	30	0.12	0.18	0.06	(-0.08, 0.20)
Hepatic cancers	3	26	0.09	0.15	0.06	(-0.06, 0.18)
Multiple myeloma	5	22	0.15	0.13	-0.02	(-0.16, 0.12)
Connective tissue cancers (sarcomas)	4	23	0.12	0.13	0.01	(-0.12, 0.14)
Cervix uteri cancers	3	18	0.09	0.11	0.02	(-0.09, 0.13)
Rectal cancers	3	18	0.09	0.11	0.02	(-0.09, 0.13)
Neuroendocrine tumors	1	19	0.03	0.11	0.08	(0.002, 0.16)
Pharynx, larynx, mouth, nose, salivary gland cancers	1	18	0.03	0.11	0.08	(0.002, 0.16)
Bile duct cancers	2	9	0.06	0.05	-0.01	(-0.10, 0.08)
Central nervous system cancers <sup>c</sup>	1	9	0.03	0.05	0.02	(-0.05, 0.09)
Gastric cancers	0	7	0	0.04	NA	NA
Esophageal adenocarcinoma	2	5	0.06	0.03	-0.03	(-0.12, 0.06)
Gallbladder cancers	0	5	0	0.03	NA	NA
Gastric cardia cancers	0	3	0	0.02	NA	NA

Individual cancer types with total number of events  $\geq 10$  in both groups and all obesity-associated cancers are shown in descending order of frequency.



# ELIXHAUSER COMORBIDITY INDEX OBV ICD 10 CODES (DICHOT)

Hypertension- uncomplicated

Diabetes- uncomplicated

Chronic pulmonary disease

Congestive heart failure

Depression

Solid tumors

Diabetes- complicated

Psychiatric

Cardiac arrhythmias

Fluid and electrolyte disorders

RA/collagen vascular disease

Renal failure

Valvular disease

Peripheral vascular disease

Metastatic cancer

Other neurological disorders

Coagulopathy

Hypertension- complicated

Pulmonary circulatory disorders

Liver disease

Obesity

Paraplegia

Deficiency anemia

Alcohol abuse

Hypothyroidism

Drug abuse

Peptic ulcer disease

Lymphoma

Weight loss

AIDS

Blood loss anemia

# CHARLSON COMORBIDITY INDEX

Condition	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease [1]	1
Connective tissue disease-rheumatic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without complications	1
Diabetes with complications	2
Paraplegia and Hemiplegia	2
Renal disease	2
Cancer	2
Moderate or severe liver disease	3
Metastatic carcinoma	6
AIDS/HIV	6



## DISCUSSIE DMSBS

- Matig generaliseerbaar naar mannen of andere ethniciteiten
- Best practice American Endocrinology / ASMBS<sup>6</sup>:
  - “Controleer preoperatief compleetheid screening maligniteiten door huisarts”
    - Potentiele kandidaten verwijderd uit selectie: overschatting bariatrisch effect?