Obesity, Bariatric Surgery and Cancer Telomere Effect

John Morton, MD, MPH, FACS, FASMBS

Professor & Vice-Chair, Quality

Division Chief, Bariatric & Min Invasive Surgery

Yale School of Medicine

Past-President, American Society of Metabolic and Bariatric Surgery

Inaugural Chair, Committee on Metabolic and Bariatric Surgery, American College of Surgeons

DISCLOSURES

Teleflex/Standard Bariatrics	Advisory Board	Honoraria
Novo Nordisk	Consultant	Honoraria
Olympus	Consultant	Honoraria
Ethicon	Consultant	Honoraria

Medical Implications of Obesity

American Society of Clinical Oncology Summit on Addressing Obesity Through Multidisciplinary Provider Collaboration: Key Findings and Recommendations for Action

Jennifer A. Ligibel[1], Catherine M. Alfano[2], Dawn L. Hershman[3], Janette K. Merrill[4], Karen Basen-Engquist[5], Zachary T. Bloomgarden[6], Wendy Demark-Wahnefried[7], Suzanne Dixon[8], Sandra G. Hassink[9], John M. Jakicic[10], John Magaña Morton[11], Tochi M. Okwuosa[12], Tiffany M. Powell-Wiley[13], Amy E. Rothberg[14], Mark Stephens[15], Sarah E. Streett[11], Robert A. Wild[16], Eric A. Westman[17], Ronald J. Williams[18], Dana S. Wollins[4], and Clifford A. Hudis[4]

Leading Cause of Preventable Risk Factor for Cancer by 2025

American Society of Clinical Oncology

BACKGROUND & WORK GROUP CHARGE

In 2014, the American Society of Clinical Oncology (ASCO) initiated a multi-pronged strategic effort to address obesity, identifying the following priorities: Promote education and awareness of the links between obesity and cancer; develop tools and resources to help oncology providers communicate with their patients about healthy lifestyle behaviors and encourage behavior change; support research to study the impact of weight loss/lifestyle change on cancer risk and outcomes; and advocate for policies to support healthy lifestyles for the general population and cancer survivors. This initiative has resulted in the development of several work products, including an ASCO position statement on obesity and cancer in 2014, an obesity research statement in 2015, as well as increased education, tools and resources for oncologists and patients regarding obesity prevention and treatment.

Results

Practice pattern studies demonstrate that up to 40% of obese patients receive limited chemotherapy doses that are not based on actual body weight. Concerns about toxicity or overdosing in obese patients with cancer, based on the use of actual body weight, are unfounded.

J Clin Oncol 30:1553-1561.

OBESITY AND CANCER

- INSULIN IS A GROWTH FACTOR
- SURVEILLANCE EFFECT
- CANCER THERAPY IS WEIGHED DOWN
- OBESITY PREVENTS PREVENTION

Obesity (2011) doi:10.1038/oby.2011.268

Obesity Disparities in Preventive Care: Findings From the National Ambulatory Medical Care Survey, 2005–2007

Tina Hernandez-Boussard[1], Shushmita M. Ahmed[1] and John M. Morton[1]

- **National Ambulatory Medical Care Survey (NAMCS) (N=866,415,856) 2005-7**
- **Obese patients were significantly less likely to receive:**
  - **breast examination (OR) 0.8**
  - **mammogram 0.7,**
  - **Pap smear 0.7, pelvic exam 0.8**
  - **rectal exam 0.7**
  - **tobacco education, 0.7**
  - **injury prevention education, 0.7**
- **Obese less likely to see physician at the index clinic visit (OR, 0.8) or receive psychotherapy referral (0.6).**

Original article

Mammography before and after bariatric surgery

Tara E. Mokhtari, B.S.[a], Ulysses S. Rosas, B.A.[a], John R. Downey, M.D., M.P.H.[b], Kanae K. Miyake, M.D., Ph.D.[b], Debra M. Ikeda, M.D.[b], John M. Morton, M.D., M.P.H.[a,*]

DIAGNOSIS IS BETTER AFTER WEIGHT LOSS

Table 4
Mammogram image quality and BI-RADS scores

	Preoperative (n)	Postoperative (n)	*P* value
Image quality			
Poor	0	0	.12
Acceptable	1	1	
Good	3	0	
Excellent	6	9	
BI-RADS density			
Fatty	8	0	.002
Scattered	12	20	
Dense	0	0	
Right BI-RADS final assessment			
BI-RADS 1	8	9	
BI-RADS 2	2	1	
Left BI-RADS final assessment			
BI-RADS 1	8	9	
BI-RADS 2	2	1	

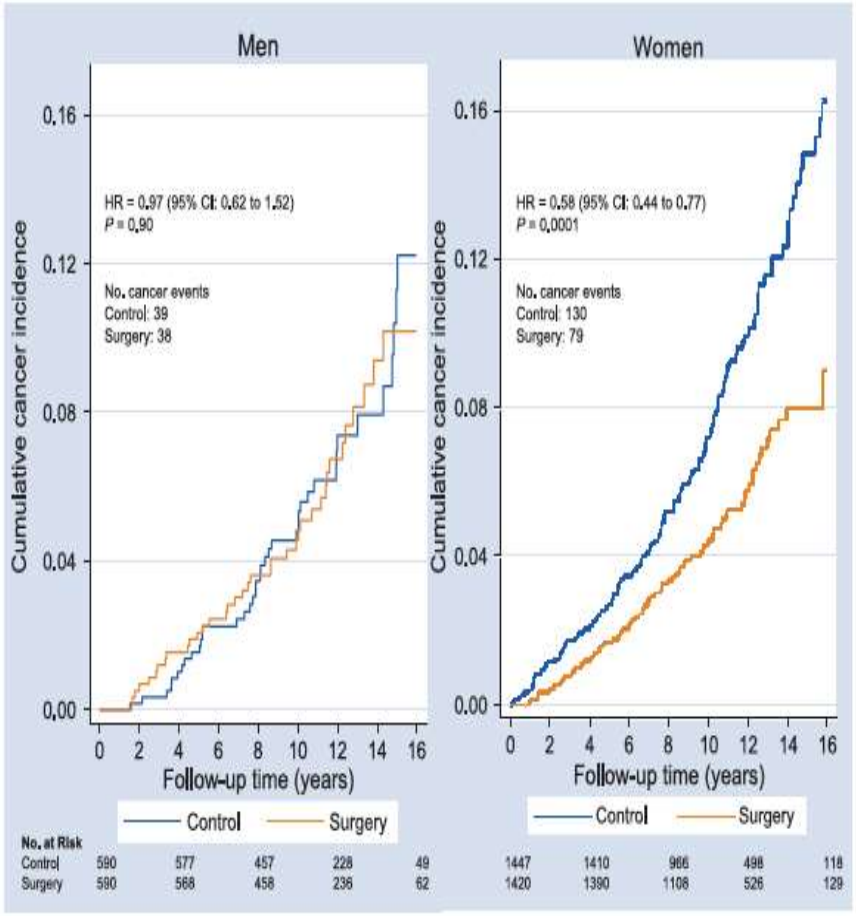
BI-RADS = Breast Imaging Reporting and Data System

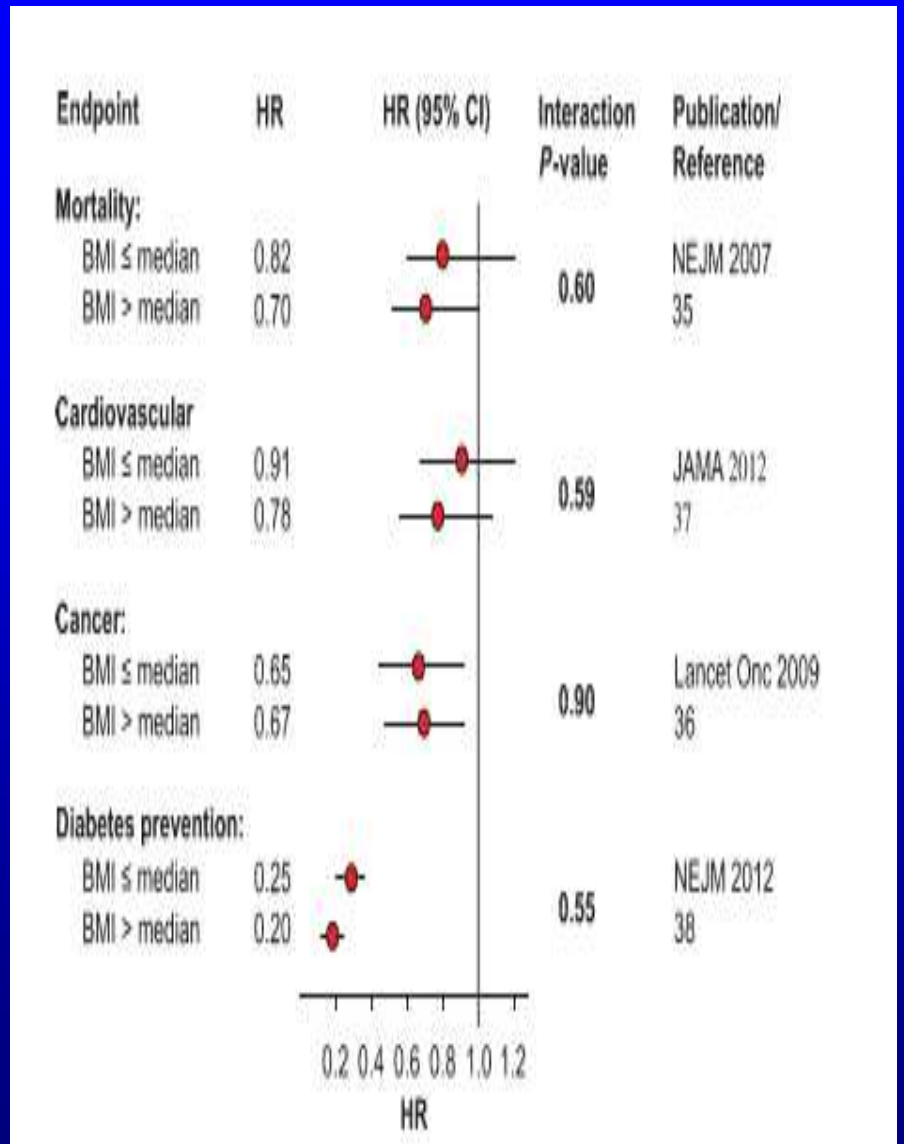
Surgery for Obesity and Related Diseases 13 (2017) 451–456

BARIATRIC SURGERY AND CANCER: WHATS THE EVIDENCE?

SOS AND CANCER

Fig. 6 *Unadjusted cumulative fatal plus nonfatal cancer incidence by gender during 16 years of follow-up in surgically treated obese individuals and in obese control individuals in the Swedish Obese Subjects study. Calculations are based on data available on 31 December 2005. From Sjöström L et al., Lancet Oncol 2009 with permission [36].*





Obesity (Silver Spring). 2009 April ; 17(4): 796–802. doi:10.1038/oby.2008.610.

Cancer Incidence and Mortality After Gastric Bypass Surgery

Ted D. Adams[1,2], **Antoinette M. Stroup**[3], **Richard E. Gress**[1], **Kenneth F. Adams**[4], **Eugenia E. Calle**[5], **Sherman C. Smith**[6], **R. Chad Halverson**[6], **Steven C. Simper**[6], **Paul N. Hopkins**[1], and **Steven C. Hunt**[1]

Table 5

Hazard ratios for mortality according to cancer groups

	Deaths		Hazard ratios for cancer deaths[a]	
	Surgery group *N* = 6,596	Control group *N* = 9,442	Surgery vs. control groups	
Cancer site	*N* (rates/1,000 person years)	*N* (rates/1,000 person years)	Hazard ratio (95% CI)	*P* value*
All cancers: males and females combined	41 (0.50)	107 (0.94)	0.54 (0.37–0.78)	0.001
All cancers: males only	10 (0.12)	24 (0.21)	0.70 (0.34–1.48)	0.35
All cancers: females only	31 (0.38)	83 (0.73)	0.38 (0.23–0.64)	0.0003
Obesity-related cancers[b]	20 (0.24)	55 (0.48)	0.54 (0.32–0.90)	0.02
Nonobesity-related cancers[c]	21 (0.25)	52 (0.46)	0.53 (0.31–0.91)	0.02

Research

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

IMPORTANCE Obesity increases the incidence and mortality from some types of cancer, but it remains uncertain whether intentional weight loss can decrease this risk.

OBJECTIVE To investigate whether bariatric surgery is associated with lower cancer risk and mortality in patients with obesity.

DESIGN, SETTING, AND PARTICIPANTS In the SPLENDID (Surgical Procedures and Long-term Effectiveness in Neoplastic Disease Incidence and Death) matched cohort study, adult patients with a body mass index of 35 or greater who underwent bariatric surgery at a US health system between 2004 and 2017 were included. Patients who underwent bariatric surgery were matched 1:5 to patients who did not undergo surgery for their obesity, resulting in a total of 30 318 patients. Follow-up ended in February 2021.

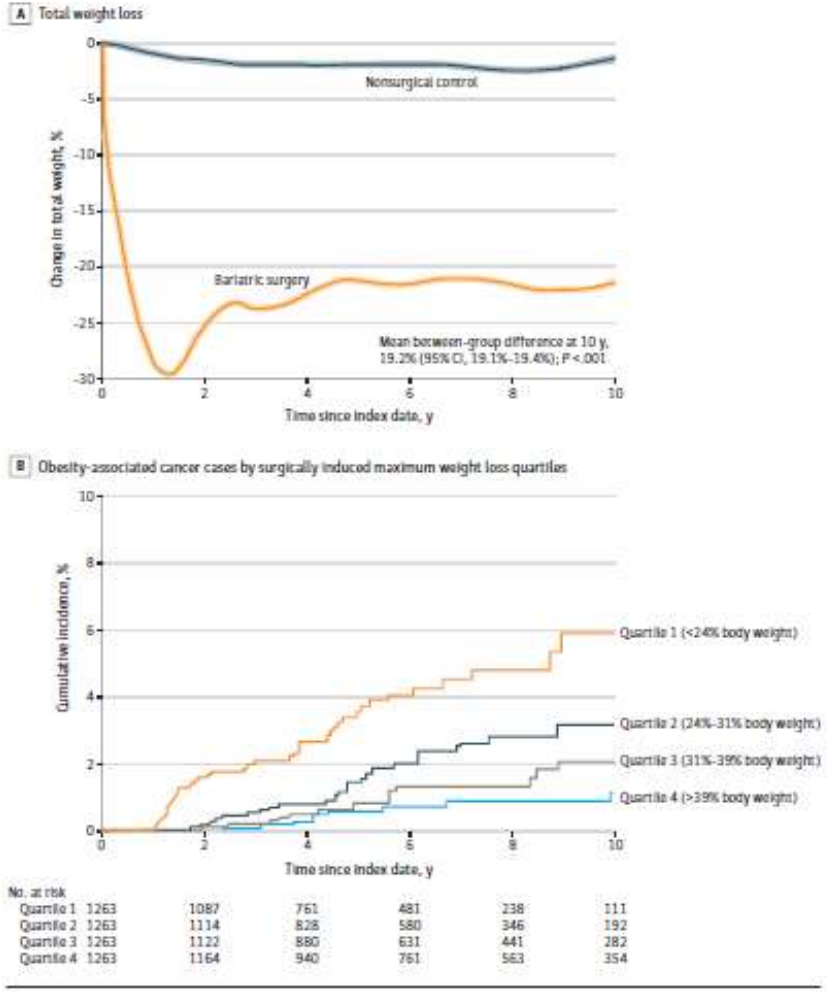
EXPOSURES Bariatric surgery (n = 5053), including Roux-en-Y gastric bypass and sleeve gastrectomy, vs nonsurgical care (n = 25 265).

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

Figure 4. Weight Loss and Cumulative Incidence of Primary End Point Stratified by Maximum Weight Loss Quartile



A, The data were smoothed and are mean trends for the percentage change in body weight from baseline in patients in the bariatric surgery group and the nonsurgical control group during follow-up. The shaded areas indicate 95% CIs. The mean between-group difference at 10 years from baseline was estimated from a flexible regression model with a 4-knot restricted cubic spline for the time × treatment interaction. The median observation time was 5.9 years (IQR, 3.4-9.0 years) for patients in the bariatric surgery group and was 6.3 years (IQR, 4.0-9.2 years) for patients in the nonsurgical control group. B, The data are Kaplan-Meier estimates for incidence of obesity-associated cancer types by the quartile of maximum (the largest) weight loss in the bariatric surgery group ($P < .001$ from log-rank test). The findings suggest that weight loss in the bariatric surgery group was associated with lower risk of incident cancer cases in a dose-dependent response.

25% TBW is Threshold

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

Colon and rectal cancer risk after bariatric surgery in a multicountry Nordic cohort study

Wenjing Tao [1], Miia Artama [2], My von Euler-Chelpin [3], Mark Hull [4], Rickard Ljung [5], Elsebeth Lynge [3], Guðríður H. Ólafsdóttir [6], Eero Pukkala [2,7], Pål Romundstad [8], Mats Talbäck [5], Laufey Tryggvadottir [6,9] and Jesper Lagergren [1,10]

Table 3. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) of colon and rectal cancer in individuals with obesity who have and have not undergone bariatric surgery compared to the general population, stratified by country

		Bariatric surgery			No bariatric surgery		
Cancer site	Country	Observed cases (*n*)	Expected cases (*n*)[1]	SIR (95% CI)	Observed cases (*n*)	Expected cases (*n*)[1]	SIR (95% CI)
Colon	Total	109	69.8	1.56 (1.28–1.88)	2,232	1,703.3	1.31 (1.25–1.37)
	Denmark	1	2.1	0.47 (0.01–2.63)	1,074	805.7	1.33 (1.25–1.42)
	Finland	4	3.1	1.27 (0.35–3.26)	316	272.5	1.16 (1.04–1.29)
	Iceland	1	0.7	1.39 (0.04–7.77)	37	37.6	0.98 (0.69–1.36)
	Norway	3	1.8	1.71 (0.35–4.98)	44	29.6	1.49 (1.08–2.00)
	Sweden	100	62.0	1.61 (1.31–1.96)	761	557.9	1.36 (1.27–1.46)
Rectum	Total	46	40.4	1.14 (0.83–1.52)	926	888.3	1.04 (0.98–1.11)
	Denmark	0	1.2	0.00 (0.00–3.04)	439	389.0	1.13 (1.03–1.24)
	Finland	2	2.2	0.91 (0.11–3.28)	156	173.5	0.90 (0.76–1.05)
	Iceland	1	0.3	2.96 (0.07–16.0)	13	14.2	0.92 (0.49–1.56)
	Norway	1	1.3	0.80 (0.02–4.43)	22	17.4	1.27 (0.79–1.92)
	Sweden	42	35.4	1.19 (0.85–1.60)	296	294.2	1.01 (0.89–1.13)

[1]Based on country-, sex-, age- and calendar-specific colorectal cancer incidence rates.

Int. J. Cancer: 00, 00–00 (2019) © 2019 UICC

? Fiber, Bile Acid Shift

Breast Cancer

Inflammation of mammary adipose tissue occurs in overweight and obese patients exhibiting early-stage breast cancer

Charlotte Vaysse[1,2], Jon Lømo[3], Øystein Garred[3], Frøydis Fjeldheim[1,4], Trygve Lofteroed[1,4], Ellen Schlichting[5], Anne McTiernan[6], Hanne Frydenberg[1], Anders Husøy[1], Steinar Lundgren[7], Morten W. Fagerland[8,9], Elin Richardsen[10], Erik A. Wist[1], Catherine Muller[2] and Inger Thune[1,9,11]

Excess adiposity, even in overweight patients, is associated with mammary adipose tissue inflammation, an event that could contribute to breast cancer development and progression.

npj | Breast Cancer

Breast Cancer

Weight change in postmenopausal women and breast Cancer risk in the women's health initiative observational study. *Chlebowski RT et al.*

SAN ANTONIO BREAST CANCER SYMPOSIUM®

61,335 Postmenopausal women, no prior breast cancer, normal mammogram, between ages 50-79 years.

Evaluated the relationship between weight change and breast cancer incidence.

Concluded: Weight loss in postmenopausal women is associated with lower breast cancer risk.

Breast Cancer

CLINICAL TRIAL

Randomized controlled trial of weight loss versus usual care on telomere length in women with breast cancer: the lifestyle, exercise, and nutrition (LEAN) study

Tara Sanft[1] · Ilana Usiskin[1] · Maura Harrigan[2] · Brenda Cartmel[1,2] · Lingeng Lu[2] · Fang-Yong Li[2] · Yang Zhou[1] · Anees Chagpar[1] · Leah M. Ferrucci[2] · Lajos Pusztai[1] · Melinda L. Irwin[1,2]

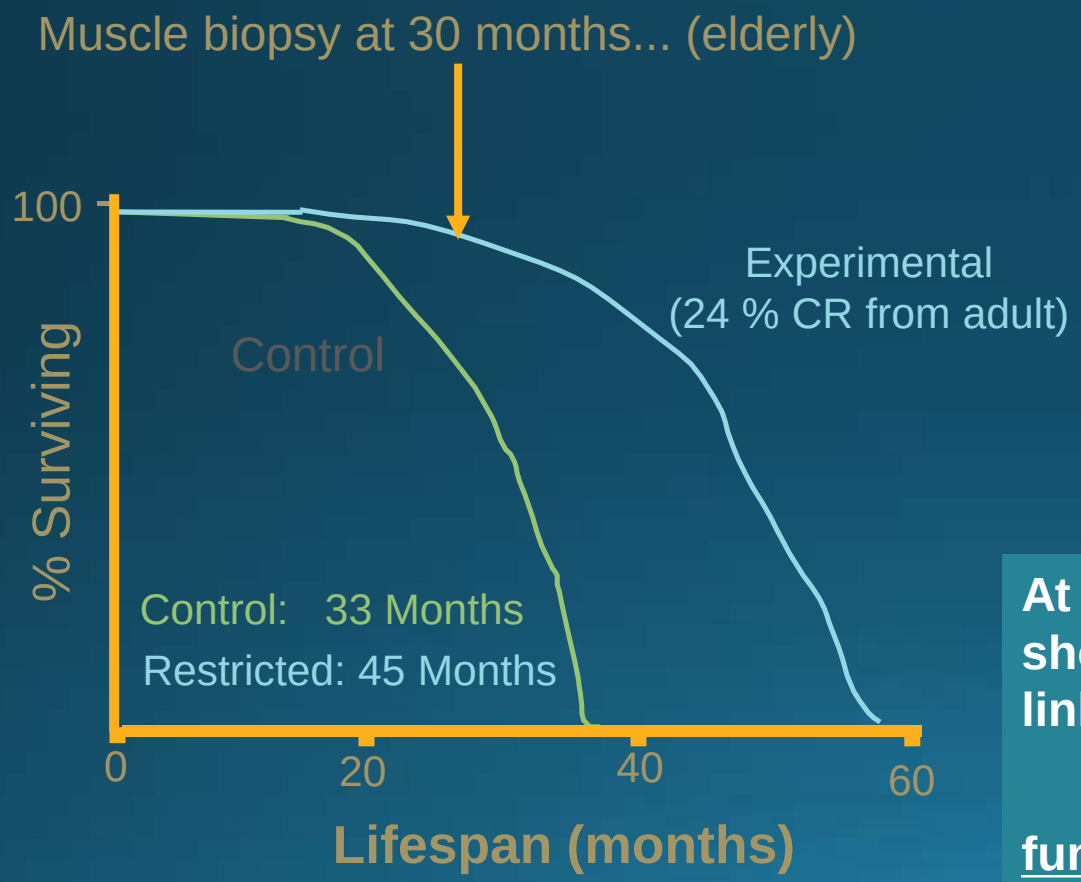
Springer science+business media

Accepted: 15 July 2018

Effect of a 6-month diet and exercise-induced weight loss intervention vs usual care on telomere length in breast cancer survivors.

Findings suggest a weight loss intervention in stage 0 and 1 breast cancer survivors may lead to telomere lengthening, compared to shortening in their usual care counterparts.

Low Calorie Intake Turns on Genes that Leads to Slower Aging—A Gene Environment Interaction (Lee *et al*., Science 285, 1390 (1999)



At 30 months muscle biopsy showed that with over 6,000 genes linked to aging →

84% of genes had altered function in the low calorie group with many linked to insulin signaling

Obesity and Aging

- Experiments in mice suggest that obesity increases the formation of reactive oxygen species in fat cells, shortens telomeres—and ultimately results in activation of the p53 tumor suppressor, inflammation and the promotion of insulin resistance

Ahima, R. *Nat Med.* **15**, 996 - 997 (2009)
Minamino, T. *et al*. *Nat Med.* **15**, 1082–1087 (2009).

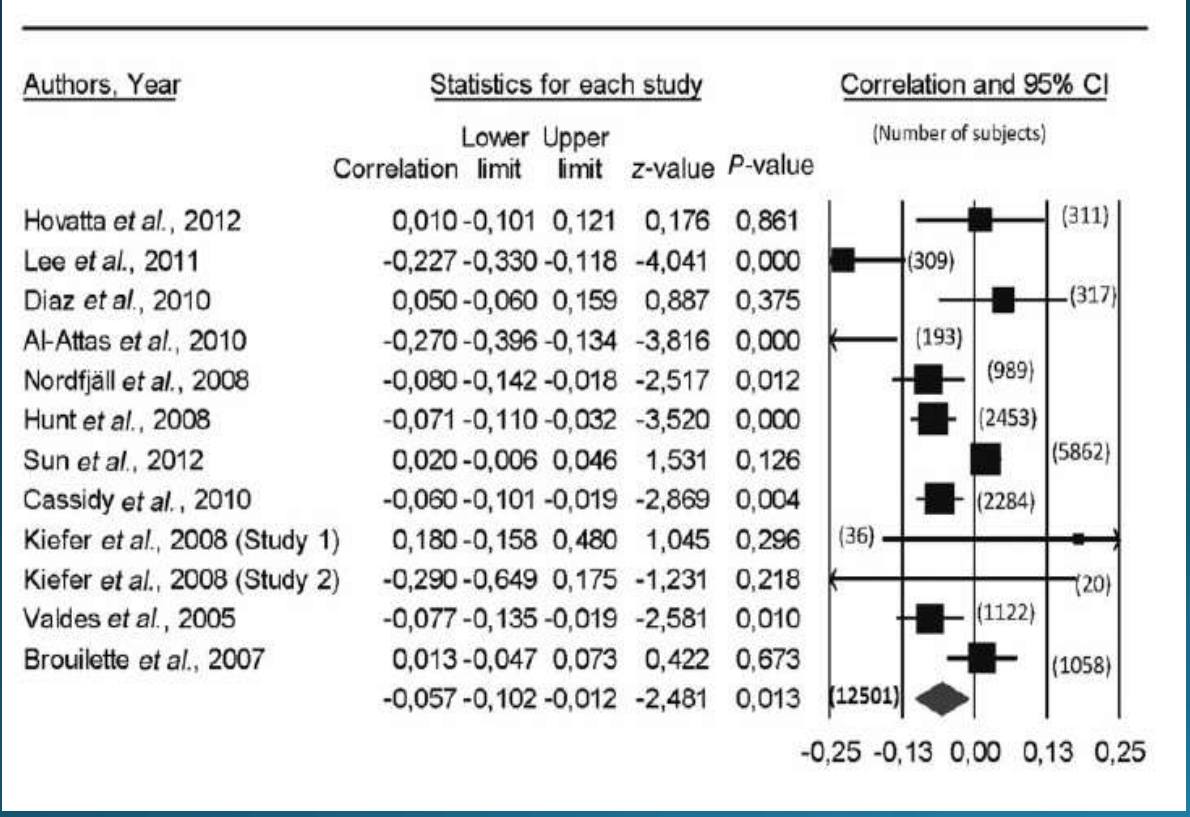
Telomeres and Aging

Deng, Y. *et al*. *Nat. Rev. Cancer* **8**, 450–458

Etiology and Pathophysiology

Body mass index and leukocyte telomere length in adults: a systematic review and meta-analysis

A. Müezzinler[1,2], A. K. Zaineddin[1] and H. Brenner[2]



29 Studies

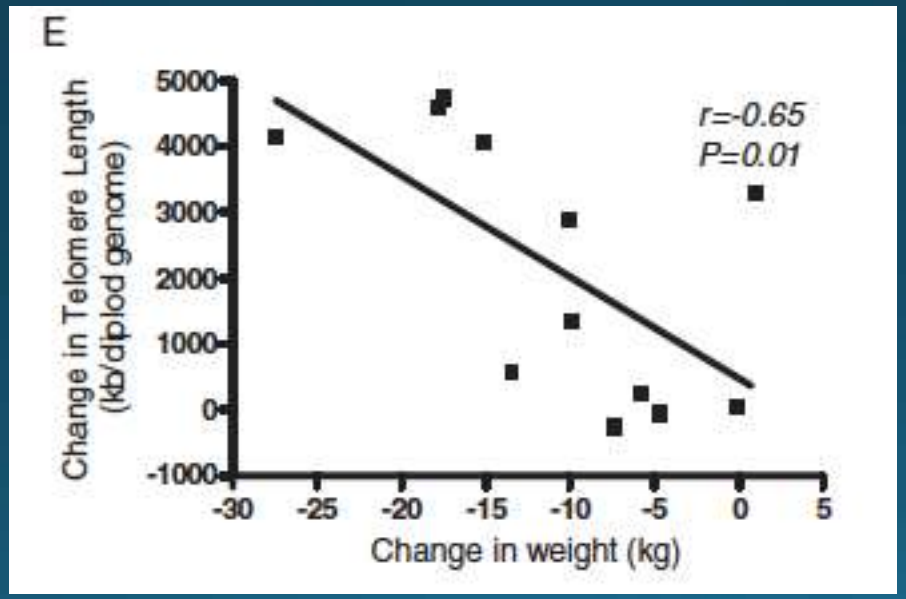
16 eligible meta-analysis

Only 2 Longitudinal Studies

BMI and Telomere Length Inversely Correlated

Weight Loss in Obese Men Is Associated with Increased Telomere Length and Decreased Abasic Sites in Rectal Mucosa

Telomere shortening may cause genome instability and is an initiating event in colorectal cancer (CRC).



REJUVENATION RESEARCH
Volume 12, Number 3, 2009

Independent and Combined Effects of Dietary Weight Loss and Exercise on Leukocyte Telomere Length in Postmenopausal Women

Results: Baseline telomere length was inversely associated with age ($r = -0.12$ $P < 0.01$) and positively associated with maximal oxygen uptake ($r = 0.11$, $P = 0.03$), but not with BMI or %body fat. Change in telomere length was inversely correlated with baseline telomere length ($r = -0.47$, $P < 0.0001$). No significant difference in leukocyte telomere length was detected in any intervention group compared to controls, nor was the magnitude of weight loss associated with telomere length at 12 months.

Conclusions: Twelve months of dietary weight loss and exercise did not change telomere length in postmenopausal women.

Obesity (2013) **00**, 00–00. doi:10.1002/oby.20509

ORIGINAL ARTICLE

Longitudinal association of telomere length and obesity indices in an intervention study with a Mediterranean diet: the PREDIMED-NAVARRA trial

Table 2. Pearson's correlations coefficients of baseline and follow-up TL with changes in adiposity parameters after 5 years of the nutritional intervention in participants of the PREDIMED-NAVARRA trial

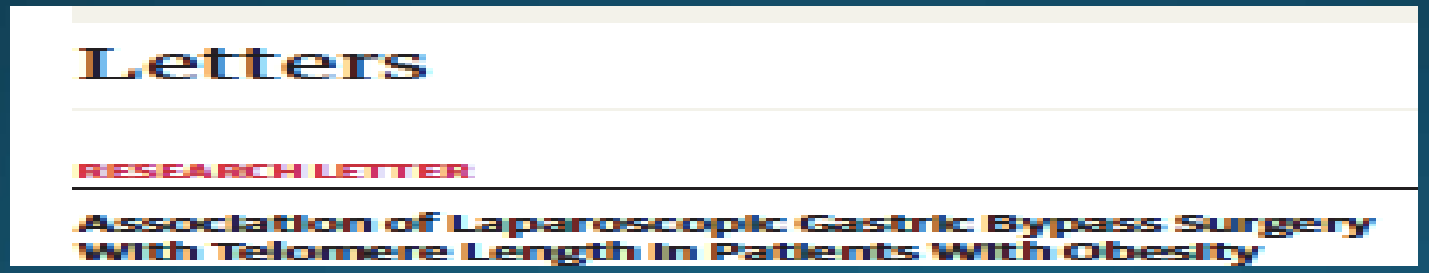
	Baseline TL[a]	*ΔTL*[b]
ΔBody weight (kg)	r = −0.110 (−0.194 to −0.024)	r = −0.088 (−0.172 to −0.002)
ΔBMI (kg m^{-2})	r = −0.119 (−0.205 to −0.034)	r = −0.089 (−0.174 to −0.003)
ΔWC (cm)	r = −0.141 (−0.224 to −0.055)	r = −0.052 (−0.138 to 0.035)
ΔWHtR	r = −0.144 (−0.227 to −0.058)	r = −0.053 (−0.138 to 0.034)

CONCLUSIONS: Our research suggests that TL is inversely associated with changes in obesity parameters. The assessment of TL can provide further insights for biological pathways leading to adiposity. We show for the first time an improvement of obesity indices when an increase in TL is observed after a 5-year Mediterranean diet intervention.

International Journal of Obesity (2013), 1–6

Study Aim

To study the relationship between telomere length and surgical weight loss



Letters

RESEARCH LETTER

Association of Laparoscopic Gastric Bypass Surgery With Telomere Length in Patients With Obesity

JAMA Surgery Dec 2018

Results: patient demographics

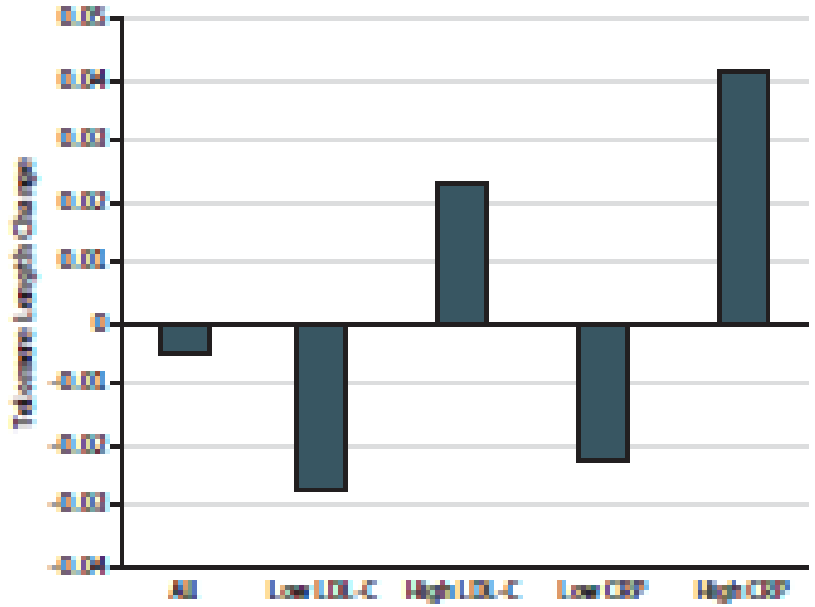
N	55
Age (yrs)	48.5
BMI (kg/m2)	44.3
Weight (lbs)	274
Waist Circumference (in)	51.7
Female (%)	76.5
White (%)	52.9
Private Insurance (%)	78.6

Results: all patients

	Pre-op	12 months	*p* -value
% EWL	-	70.4	-
Telomere length	0.987	0.982	0.764
C reactive protein	6.7	3.6	0.118
Fasting insulin	20.5	6.1	0.003
LDL cholesterol	96.8	102	0.581
HDL cholesterol	45.3	56.3	0.004

- High LDL (>140) had significant telomere lengthening in comparison to low LDL patients (-0.0271 (low LDL) vs. +0.0227 (high LDL), p=0.0387.
- High CRP (>7) had significant telomere lengthening in comparison to low CRP patients (-0.02294 (low CRP) vs. +0.04125 (high CRP), p=0.005.

Figure. One-Year Change in Telomere Length



Quantitative polymerase chain reaction was used to create a relative telomere to single copy gene ratio, which is proportional to mean telomere length. CRP indicates high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Summary

This is the first study to demonstrate surgical weight loss leading to decreased aging by increasing telomere length. Patients with high preoperative CRP and LDL sustained the greatest increases in telomere length. In addition to weight loss, HDL increase was significantly and positively correlated with telomere length increase.

Thank You

John. Morton@ Yale.Edu

Twitter X @jmortonmd