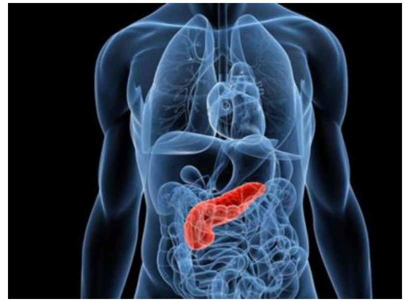


Obesity and Cancer

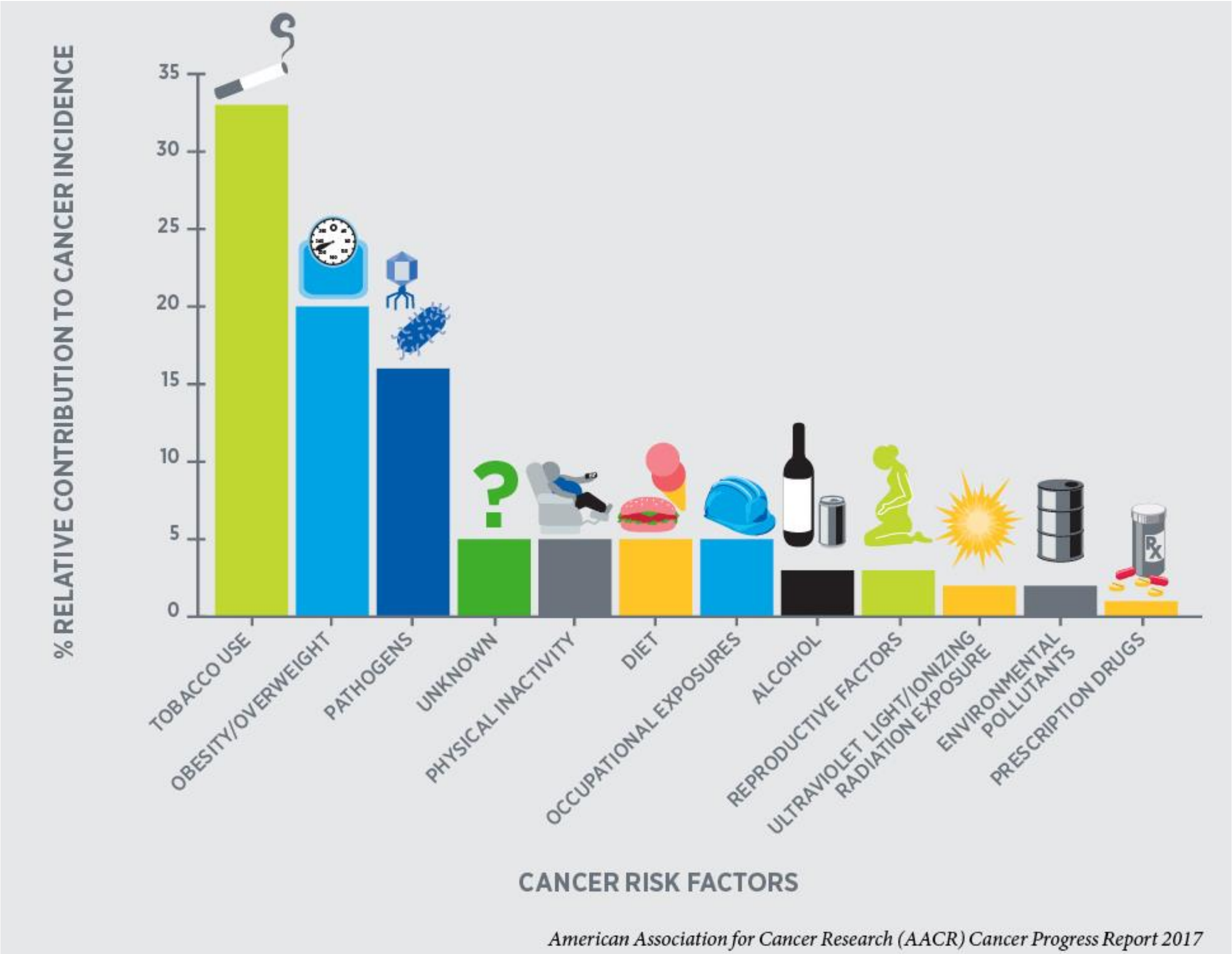
Zobeida Cruz-Monserrate Ph.D.

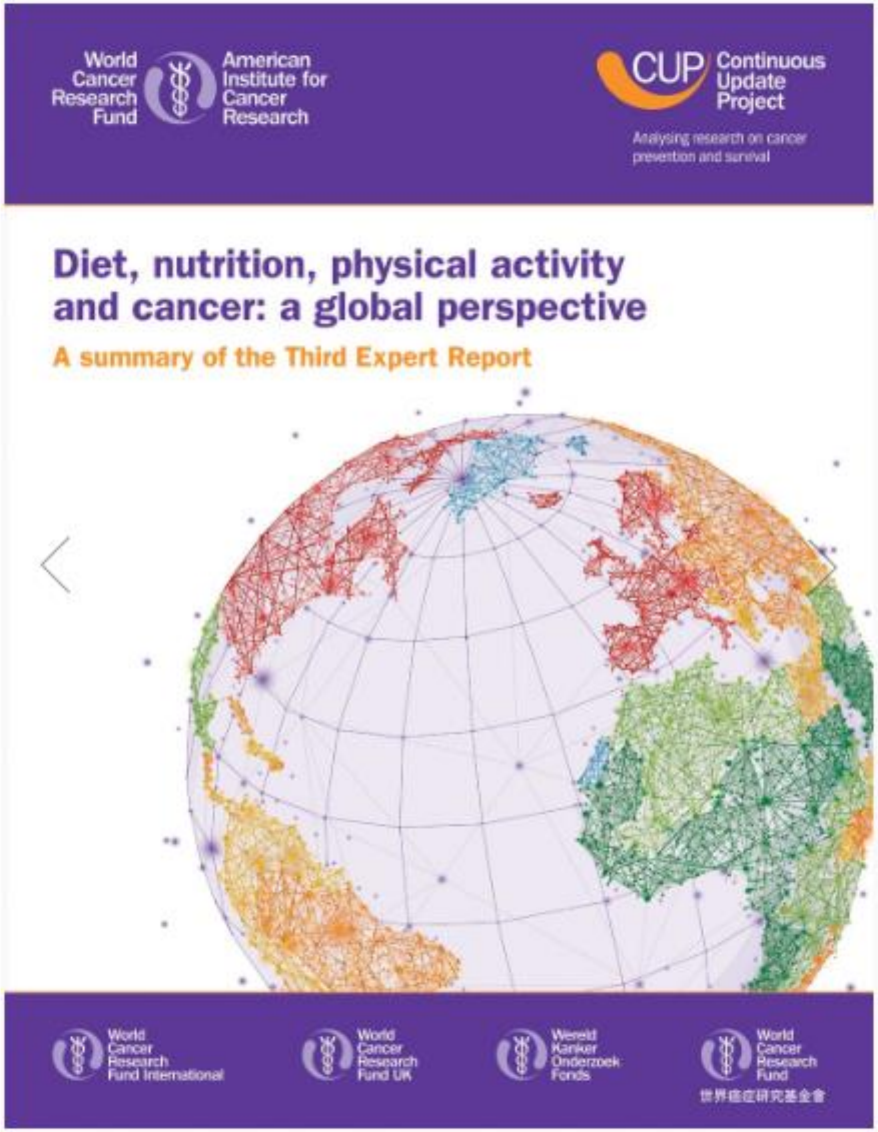
PancreasFest

July 2019

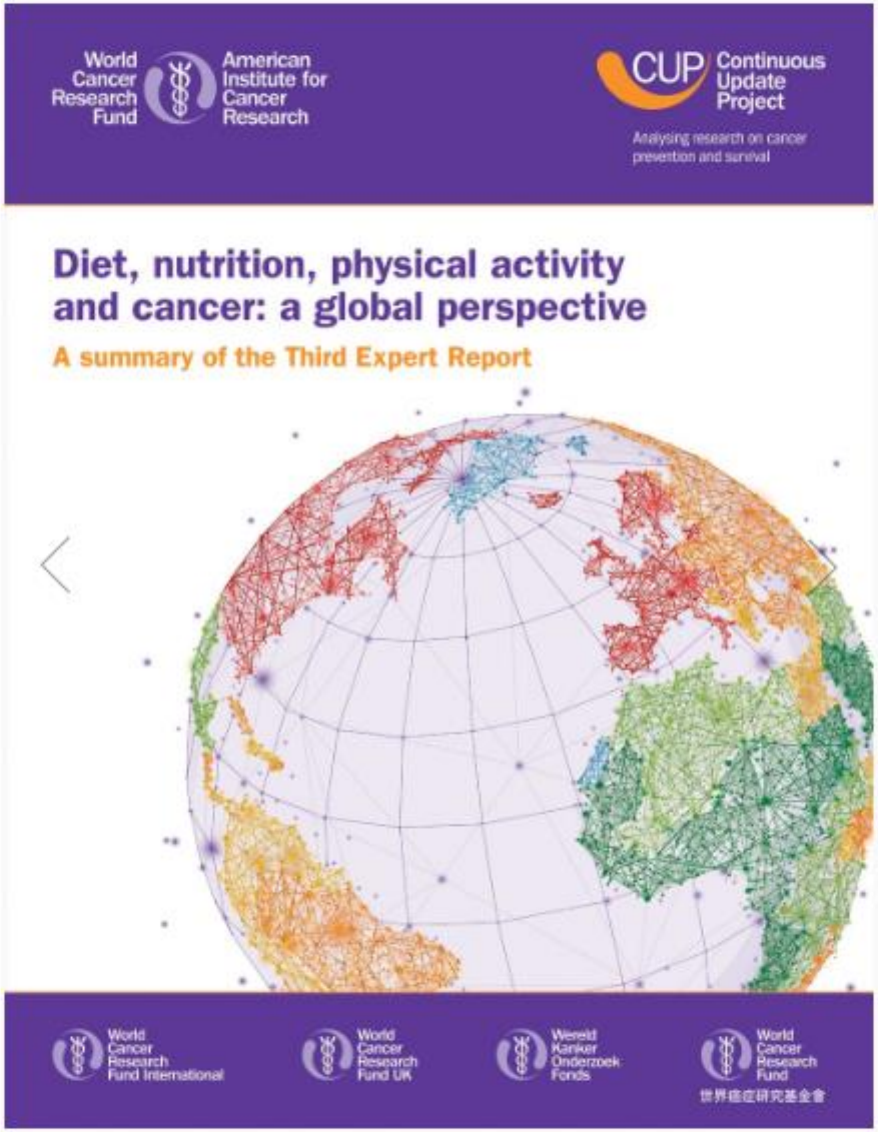
The Ohio State University
WEXNER MEDICAL CENTER

What are some environmental factors that increase the risk of developing cancer?



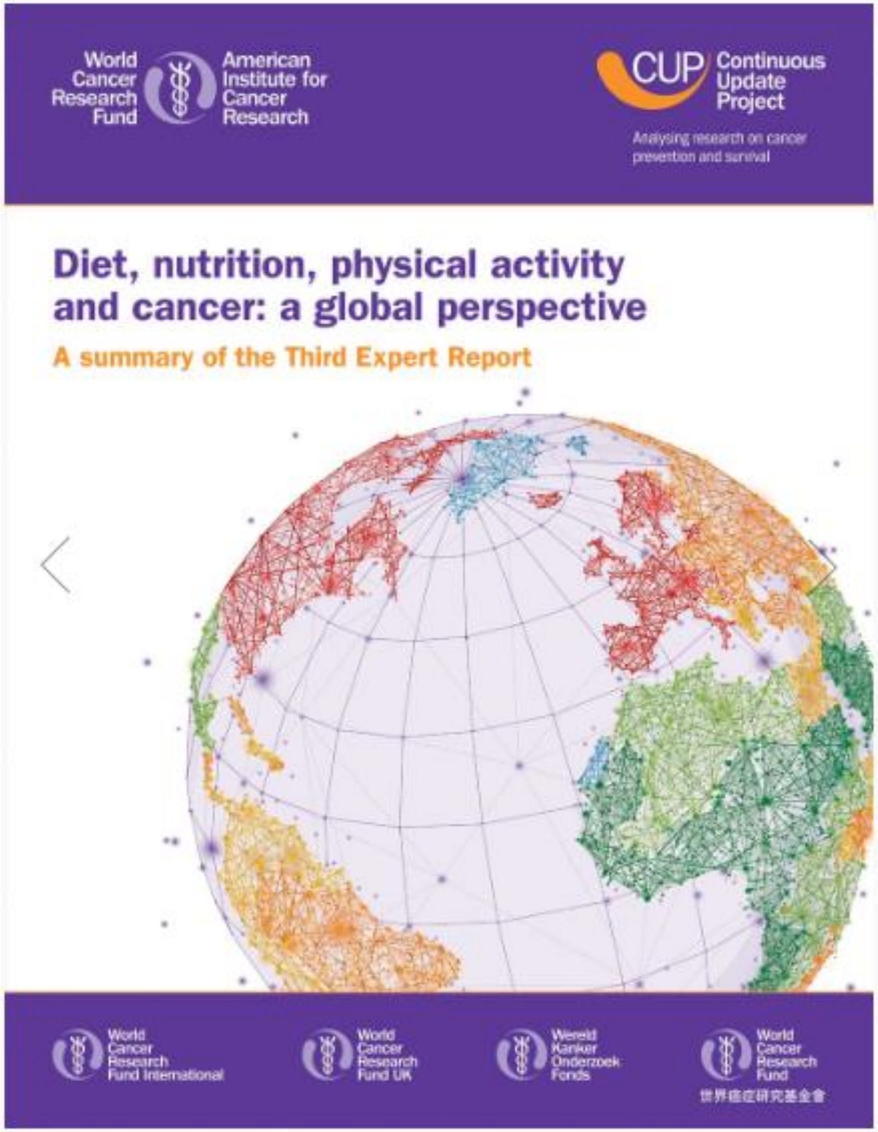


https://www.wcrf.org/sites/default/files/Pancreatic-cancer-report.pdf



2012	DIET, NUTRITION, PHYSICAL ACTIVITY AND PANCREATIC CANCER		
		DECREASES RISK	**INCREASES RISK**
STRONG EVIDENCE	**Convincing**		**Body fatness**[1]
	Probable		**Adult attained height**[2]
LIMITED EVIDENCE	**Limited – suggestive**		Red meat[3] Processed meat[4] Alcoholic drinks (heavier drinking)[5] Foods and beverages containing fructose[6] Foods containing saturated fatty acids
	Limited – no conclusion	Physical activity; fruits; vegetables; folate; fish; eggs; tea; soft drinks; coffee; carbohydrates; sucrose; glycaemic index; glycaemic load; total fat; monounsaturated fat; polyunsaturated fats; dietary cholesterol; vitamin C; and multivitamin/mineral supplements	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

https://www.wcrf.org/sites/default/files/Pancreatic-cancer-report.pdf



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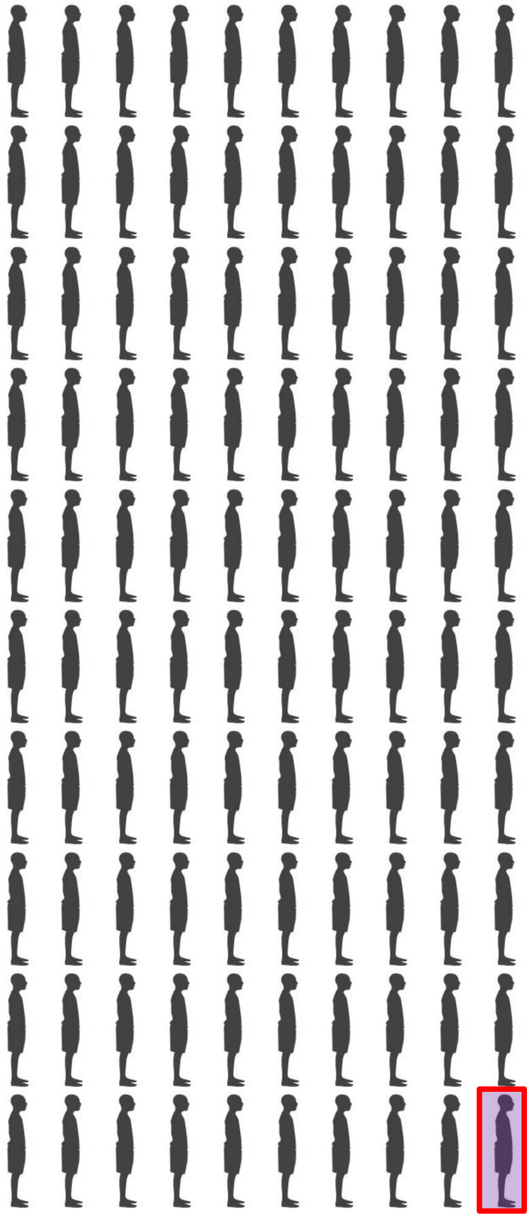
Convincing evidence

Body fatness: Greater body fatness is a convincing cause of pancreatic cancer.

https://www.wcrf.org/sites/default/files/Pancreatic-cancer-report.pdf

Absolute risk in for a rare disease



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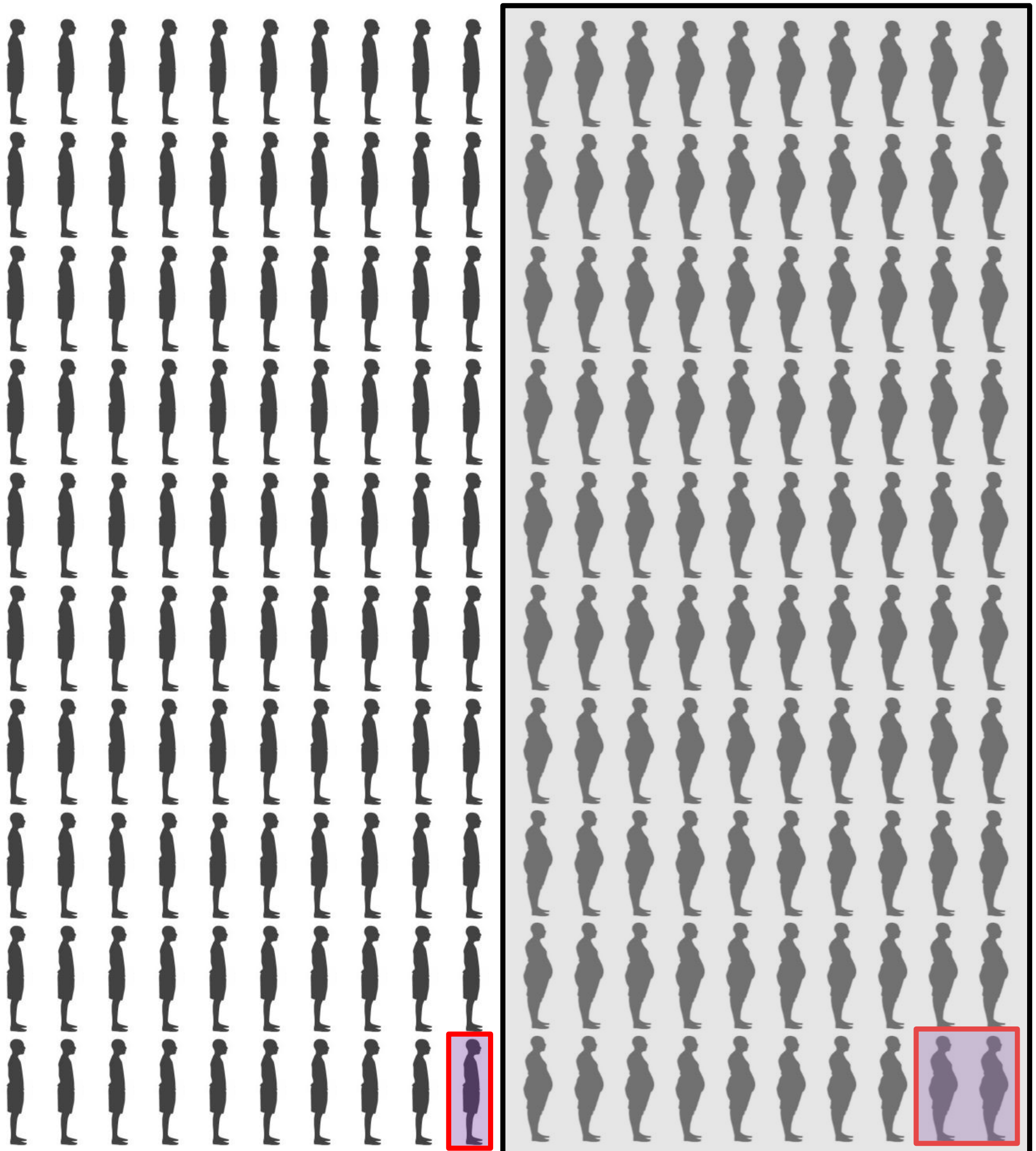


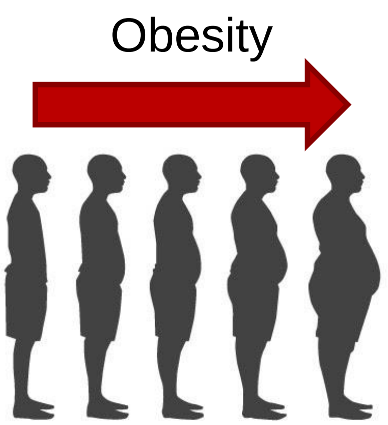
What is the relative risk of obesity that influence pancreatic cancer?

Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

Variable	Approximate Risk
Risk factor	
Smoking[3]	2–3
Long-standing diabetes mellitus[4]	2
Nonhereditary and chronic pancreatitis[5]	2–6
Obesity, inactivity, or both[6]	2
Non–O blood group[7]	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (*PRSS1, SPINK1*)[8]	50
Familial atypical multiple mole and melanoma syndrome (*p16*)[9]	10–20
Hereditary breast and ovarian cancer syndromes (*BRCA1, BRCA2, PALB2*)[10,11]	1–2
Peutz–Jeghers syndrome (*STK11* [*LKB1*])[12]	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (*MLH1, MSH2, MSH6*)[13]	4
Ataxia–telangiectasia (*ATM*)[14]	Unknown
Li–Fraumeni syndrome (P53)[15]	Unknown

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

N Engl J Med 2014; 371:1039-1049



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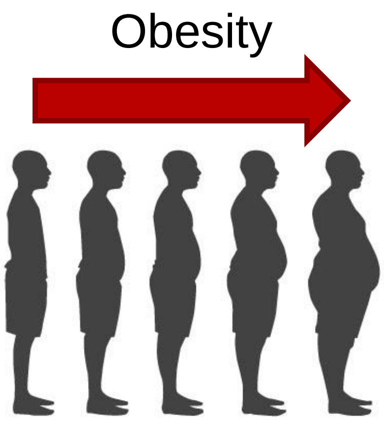

Obesity is a **Modifiable** PDAC Risk Factor

	Risk factor	Increased PDAC risk
Smoking	Current cigarette use	1.7-2.2
	Current pipe or cigar use	1.5
Alcohol	> 3 alcoholic drinks per day	1.2-1.4
	Chronic pancreatitis	13.3
Obesity	BMI > 40 kg/m^2, male	1.5
	BMI > 40 kg/m^2, female	2.8
Diabetes	Diabetes mellitus, type 1	2.0
	Diabetes mellitus, type 2	1.8
	Cholecystectomy	1.2
	Gastrectomy	1.5
	Helicobacter pylori infection	1.4

PDAC: Pancreatic ductal adenocarcinomas; BMI: Body mass index.

Becker, A.E, et. al., World J Gastroenterology, 2014

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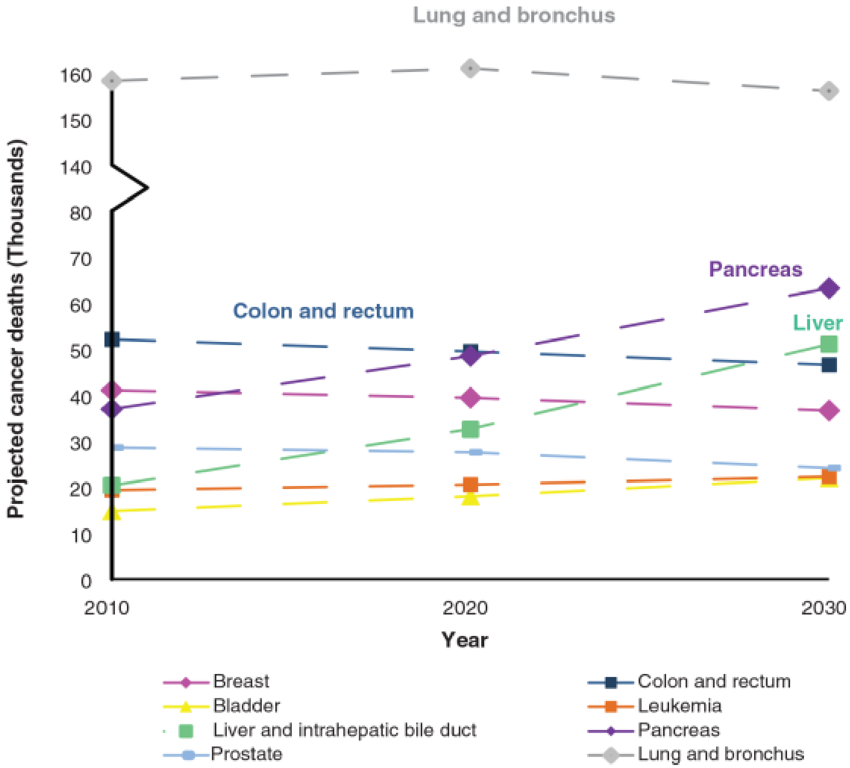
Can we prevent?

Becker, A.E, et. al., World J Gastroenterology, 2014

Projected Increase in Pancreatic Cancer Deaths by 2030 Thought to Correlate with Obesity Trends

Cancer Incidence in the United States



Perspective

Cancer Research

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib[1], Benjamin D. Smith[2], Rhonda Aizenberg[1], Allison B. Rosenzweig[1], Julie M. Fleshman[1], and Lynn M. Matrisian[1]

Cancer Res; 74(11) June 1, 2014

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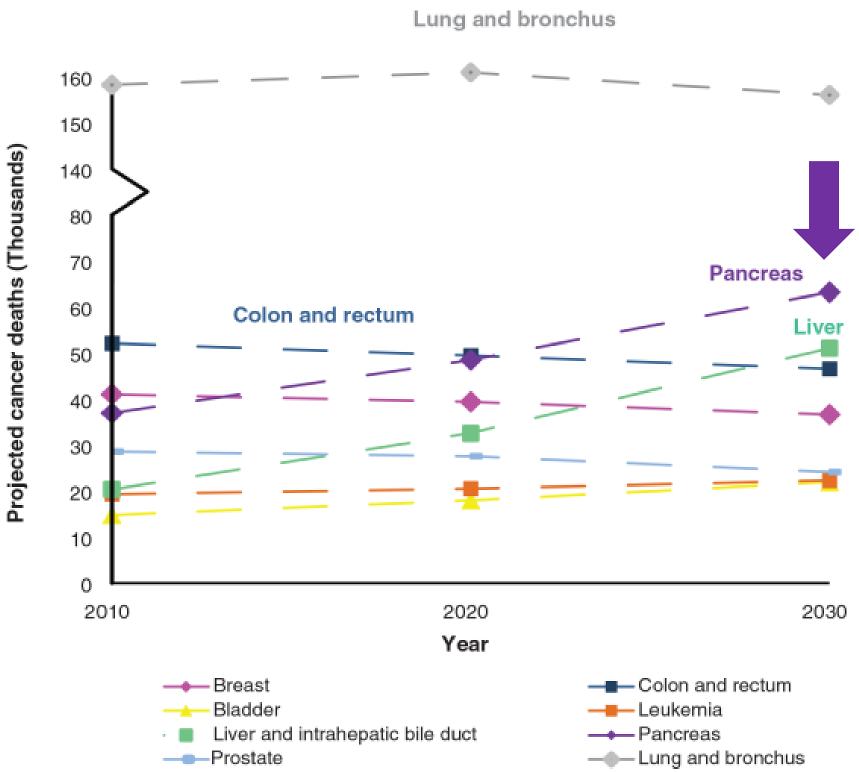

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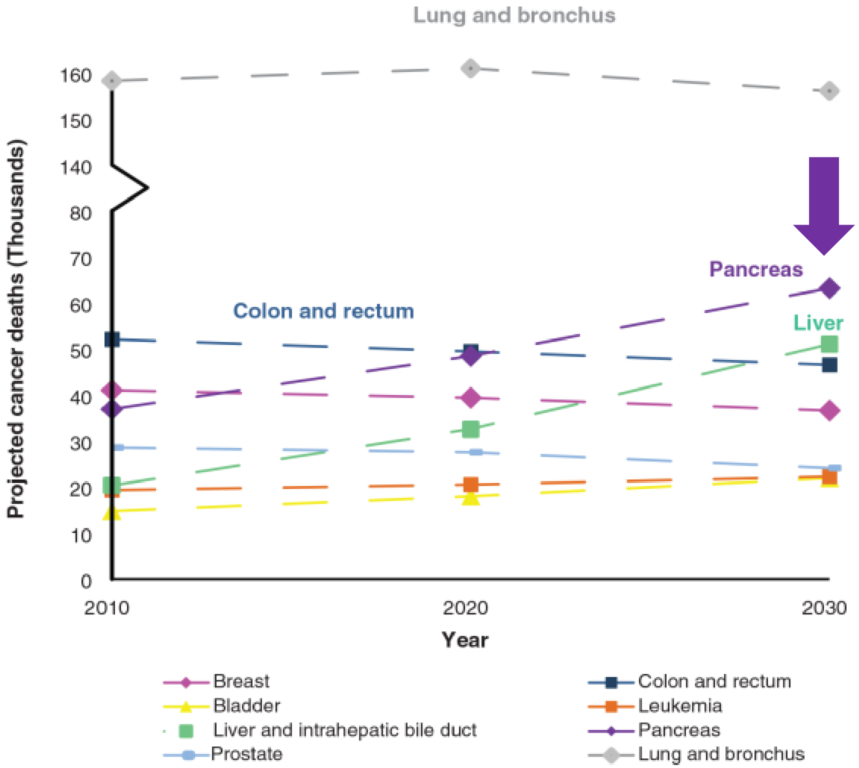
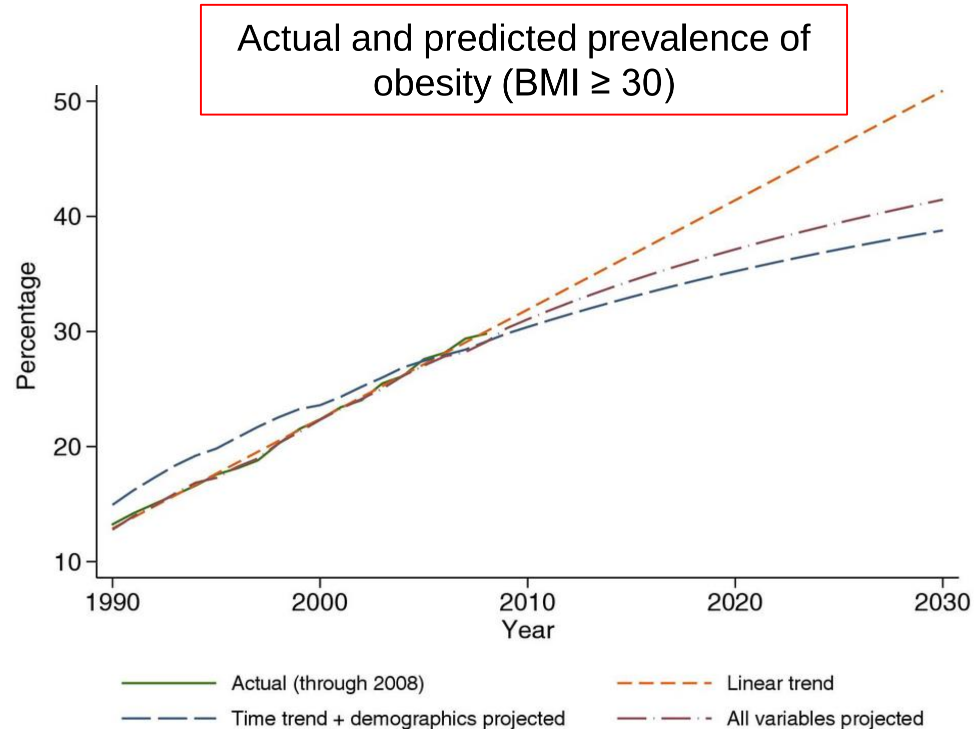


Obesity Trend in the United States



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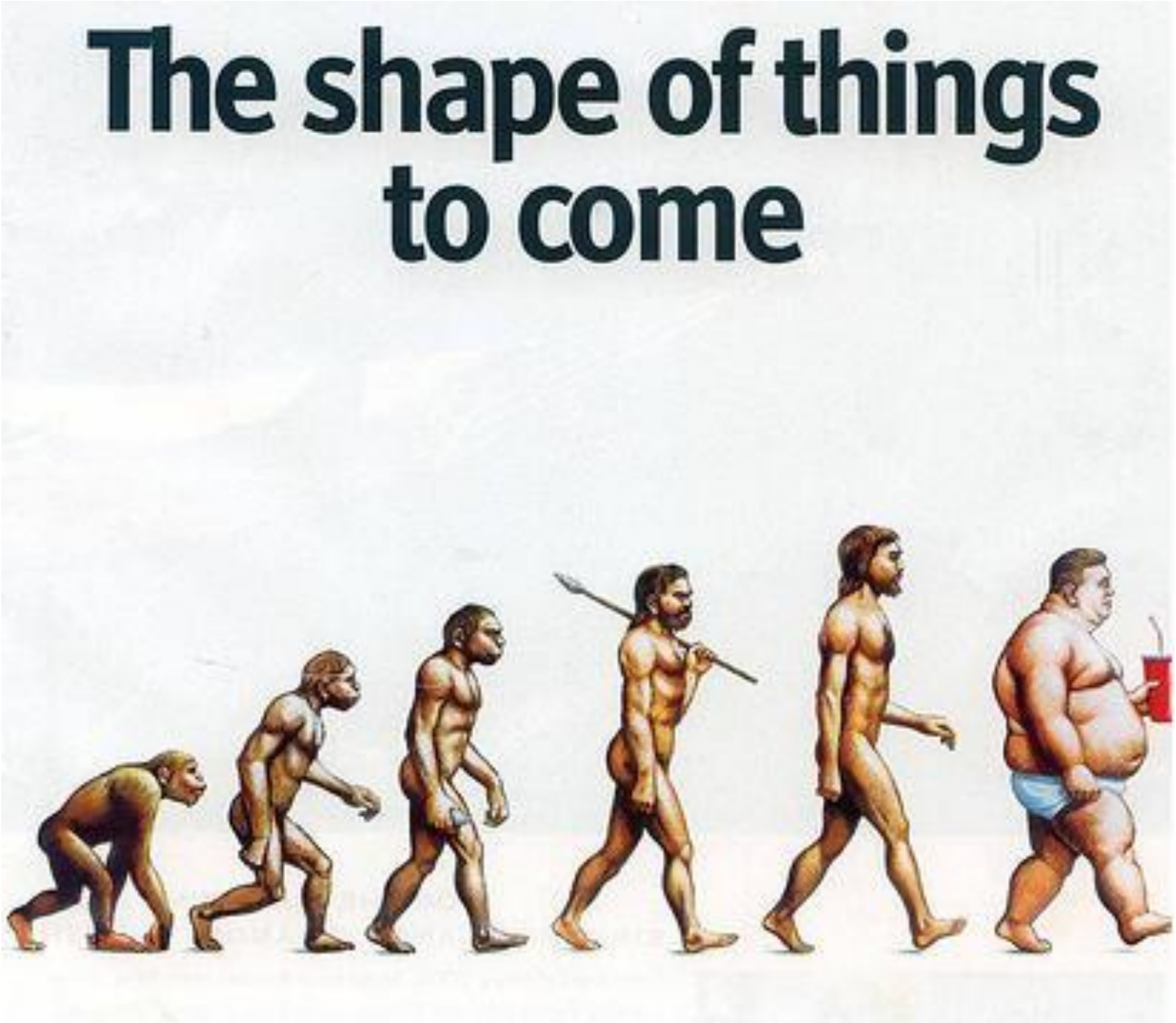
Obesity and Severe Obesity Forecasts Through 2030

Eric A. Finkelstein, PhD, MHA, Olga A. Khavjou, MA, Hope Thompson, BA, Justin G. Trogdon, PhD, Liping Pan, MD, MPH, Bettylou Sherry, PhD, RD, William Dietz, MD, PhD

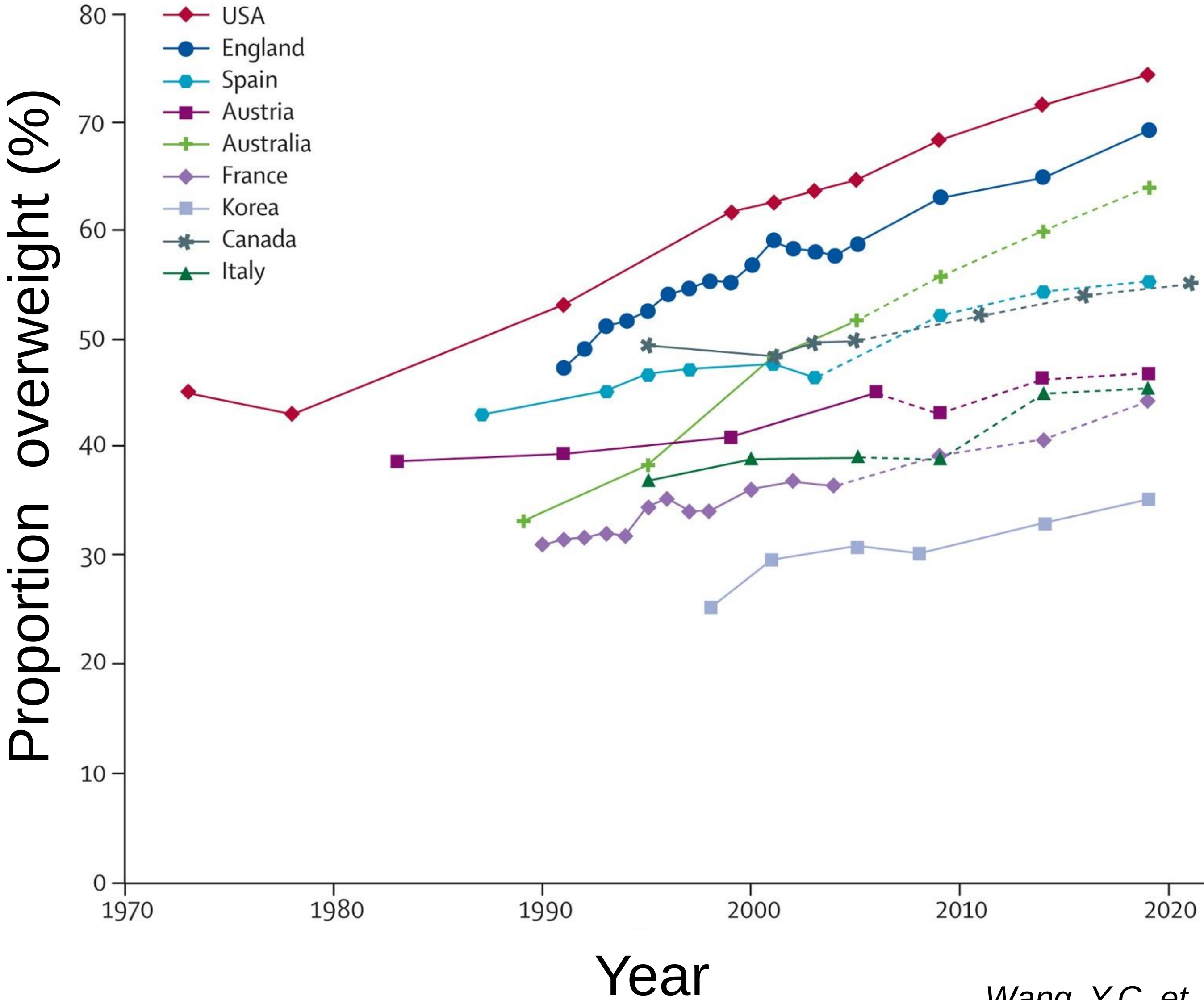
Am J Prev Med 2012;42(6):563–570



12/11/2013

The Economist

Obesity is a Worldwide Epidemic in Adults and Children



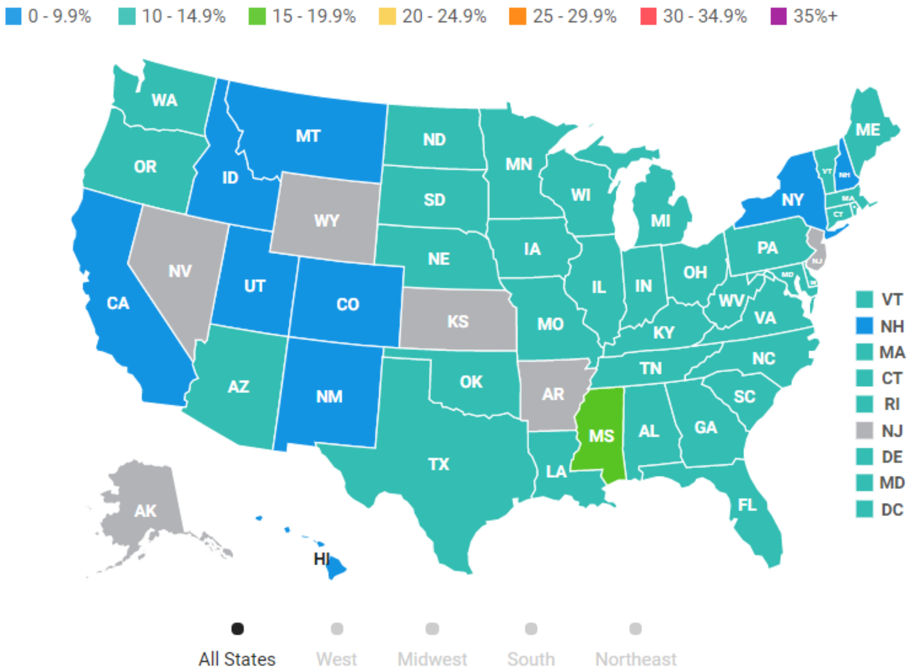
Wang, Y.C. et. al., The Lancet, 2011

Obesity Trends Increasing in the United States

Adult Obesity Rate by State, 1990

Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)



http://stateofobesity.org/adult-obesity/

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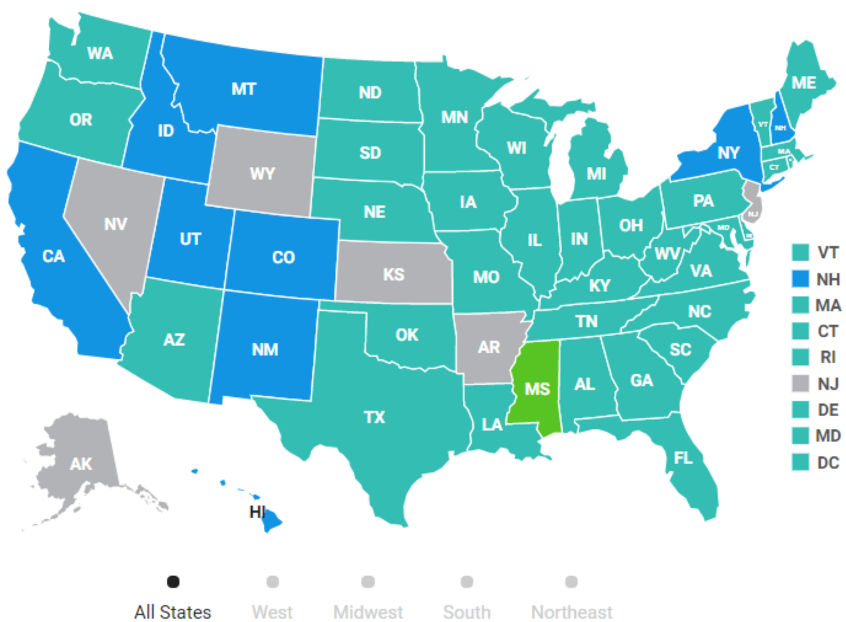
0 - 9.9% 10 - 14.9% 15 - 19.9% 20 - 24.9% 25 - 29.9% 30 - 34.9% 35%+



Adult Obesity Rate by State, 2017

Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)

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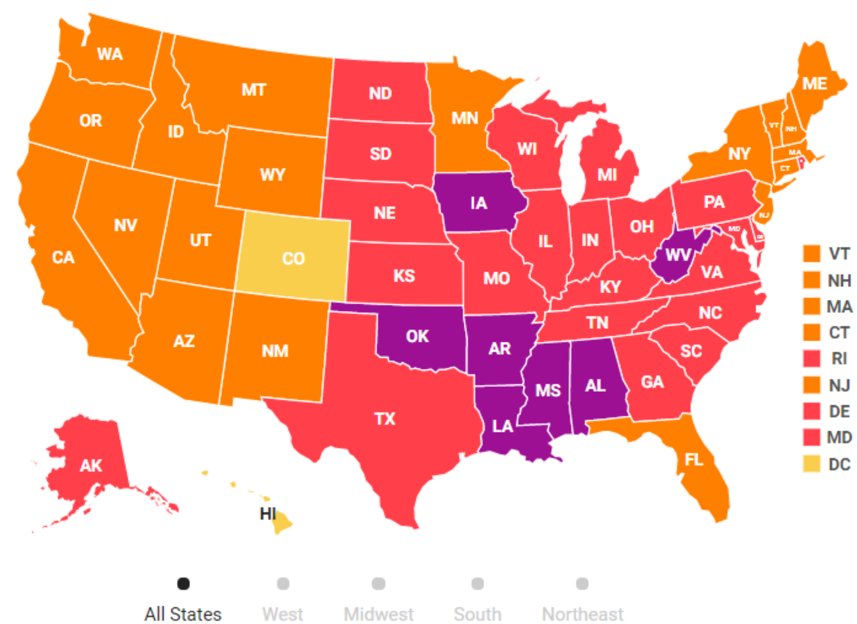

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Obesity Trends Increasing in the United States

Rank	State	Adult Obesity Rate 2017	95% Confidence Interval	Trend 1990 - 2017
1	West Virginia	38.1%	+/- 1.7%	
2	Mississippi	37.3%	+/- 2.0%	
3	Oklahoma	36.5%	+/- 1.6%	
4	Iowa	36.4%	+/- 1.3%	
5	Alabama	36.3%	+/- 1.6%	
6	Louisiana	36.2%	+/- 1.8%	
7	Arkansas	35.0%	+/- 2.4%	
8	Kentucky	34.3%	+/- 1.7%	
9	Alaska	34.2%	+/- 2.9%	
10	South Carolina	34.1%	+/- 1.3%	
11	Ohio	33.8%	+/- 1.3%	
12	Indiana	33.6%	+/- 1.1%	
13	North Dakota	33.2%	+/- 1.6%	
14	Texas	33.0%	+/- 1.8%	
15	Nebraska	32.8%	+/- 1.2%	
15	Tennessee	32.8%	+/- 1.8%	
17	Missouri	32.5%	+/- 1.5%	
18	Kansas	32.4%	+/- 0.8%	
19	Michigan	32.3%	+/- 1.2%	
20	North Carolina	32.1%	+/- 1.8%	

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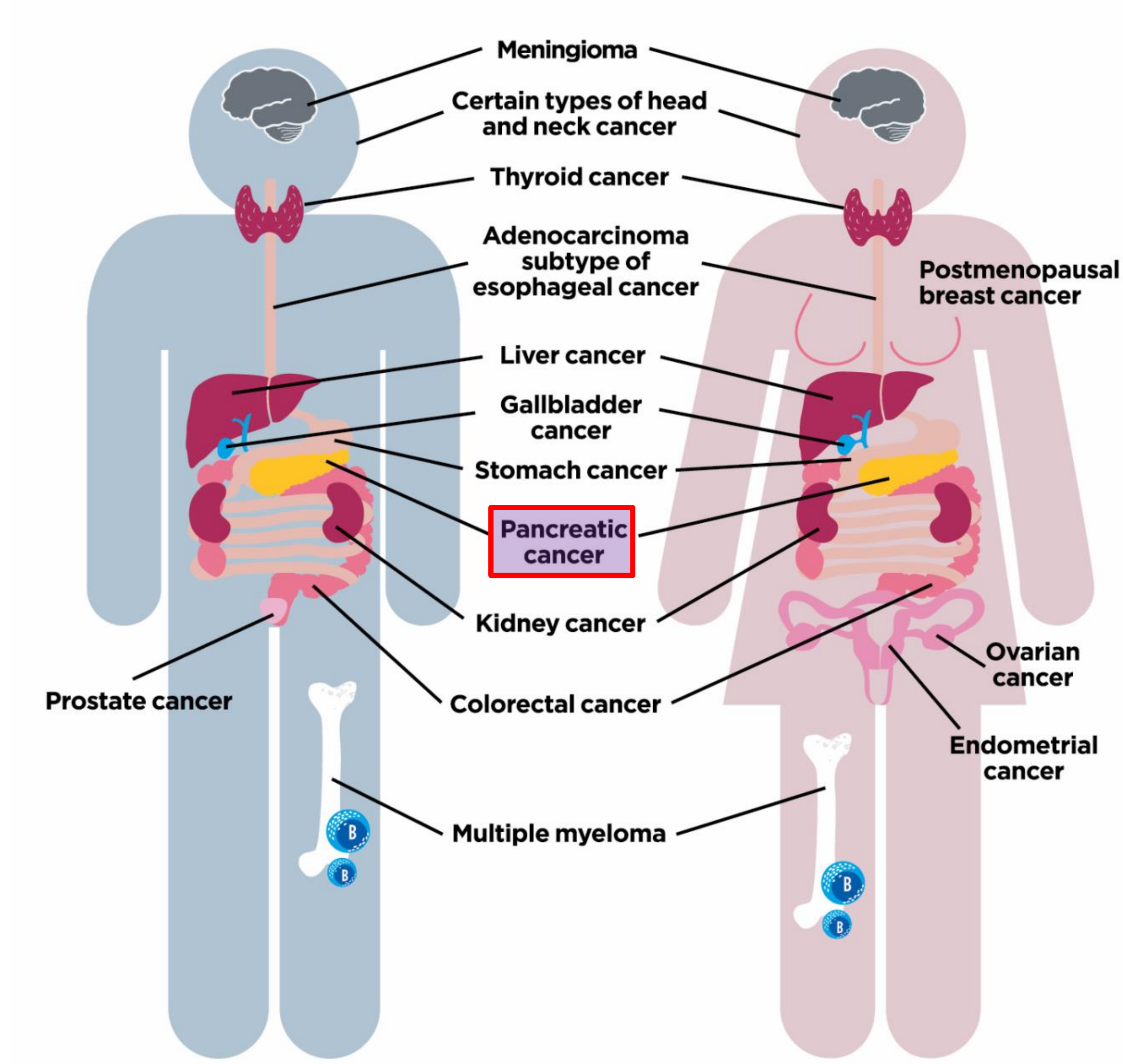
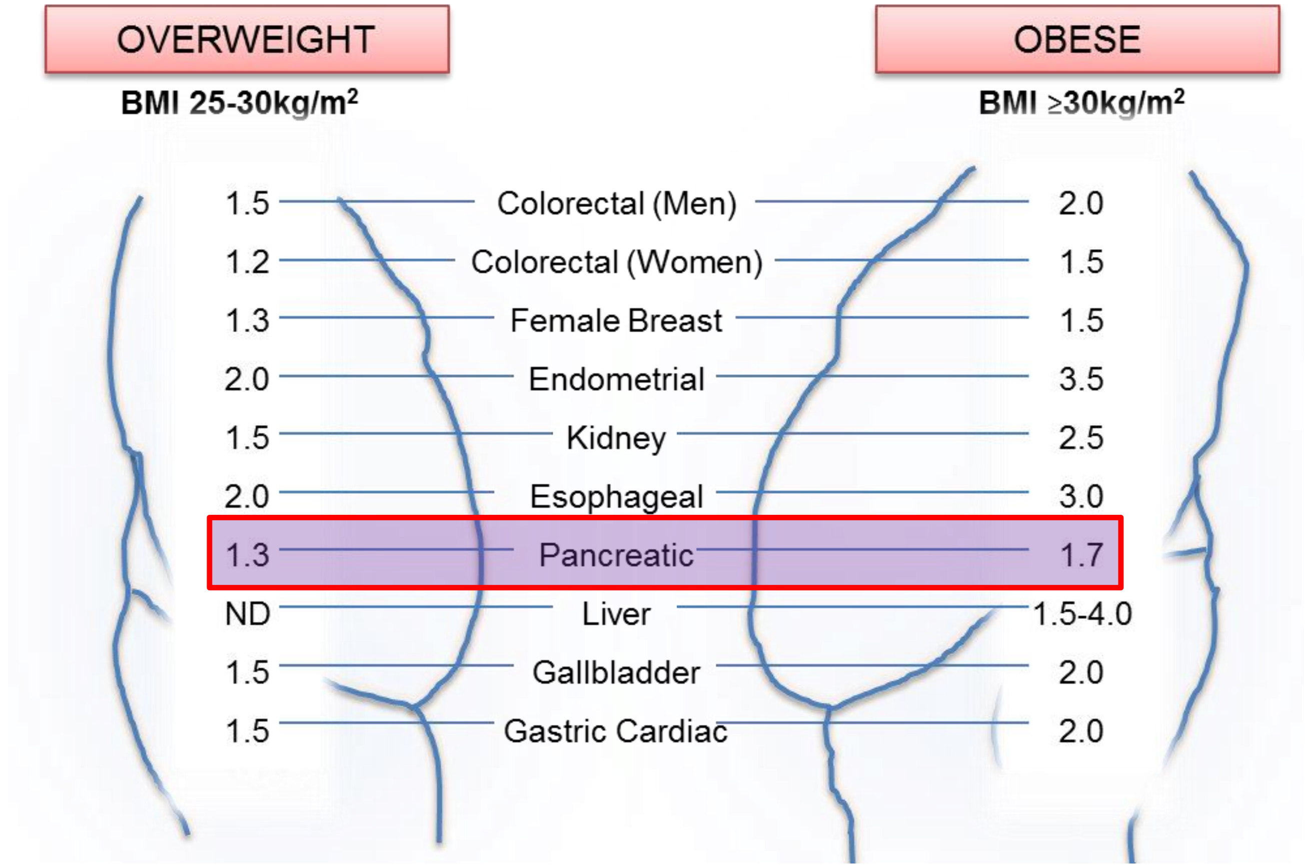
15 Types of Cancer have being directly linked to being overweight or obese.

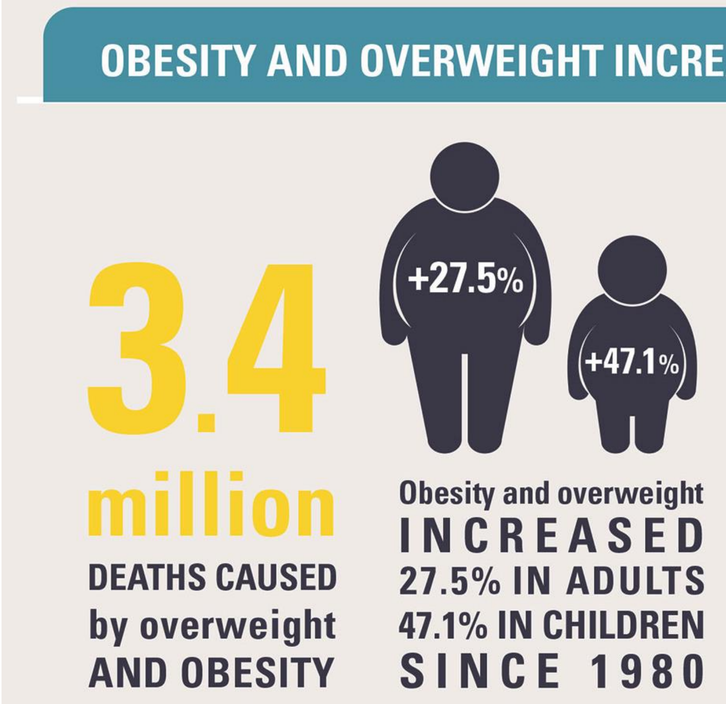


American Association for Cancer Research (AACR) Cancer Progress Report 2018 https://seer.cancer.gov/csr/1975_2015/

Obesity is a Risk Factor for Many Cancers



Eugenia E. Calle* and Rudolf Kaaks 2004:4:579-591


OBESITY AND OVERWEIGHT INCREASING WORLDWIDE
+27.5%
+47.1%
3.4 million
DEATHS CAUSED by overweight AND OBESITY
Obesity and overweight INCREASED 27.5% IN ADULTS 47.1% IN CHILDREN SINCE 1980

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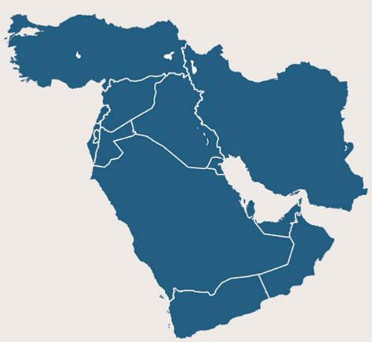
Middle Eastern countries experiencing some of the largest increases in obesity globally:

SAUDI ARABIA, BAHRAIN, EGYPT, KUWAIT, AND PALESTINE



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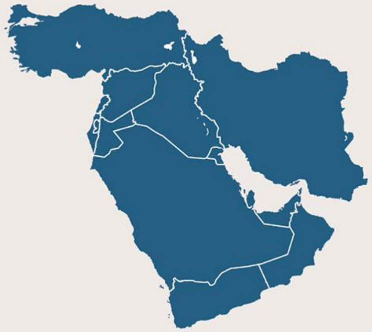


37
Percentage of the world's adult population that is overweight or obese

0
Number of countries succeeding in decreasing obesity in last 33 years

14
Percentage of overweight or obese children and adolescents worldwide

62
Percentage of the world's obese living in developing countries

THE US ACCOUNTS FOR 13% OF THE NUMBER OF OBESE PEOPLE GLOBALLY BUT JUST 5% OF THE WORLD'S POPULATION

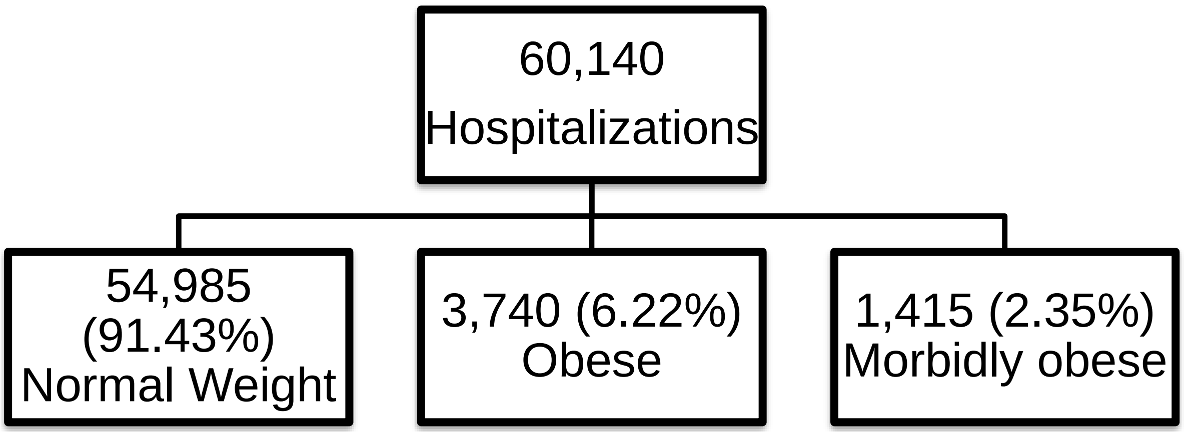
OBESITY AND OVERWEIGHT CONTRIBUTE TO:

- CARDIOVASCULAR DISEASE
- DIABETES
- CANCER
- JOINT PAIN

Based on findings published in *The Lancet* in 2014. Learn more at: www.healthdata.org/gbd

IHME UNIVERSITY *of* WASHINGTON

Obesity is Associated with Increased Healthcare Utilization in Hospitalized Patients with Pancreatic Cancer



Patient group:
Inclusion criteria:
A **secondary diagnosis of pancreatic cancer**
(ICD-9 codes: 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9)

Exclusion criteria:
Age less than 18 years
Admission in the month of December

Exposure of interest:
- Obesity: 278.00, 278.01,V853, V85.30-V85.39,V85.4, V854.1-V854.5.
- Subgroup analysis: Morbid obesity: V85.4, V854.1-V854.5, 278.01

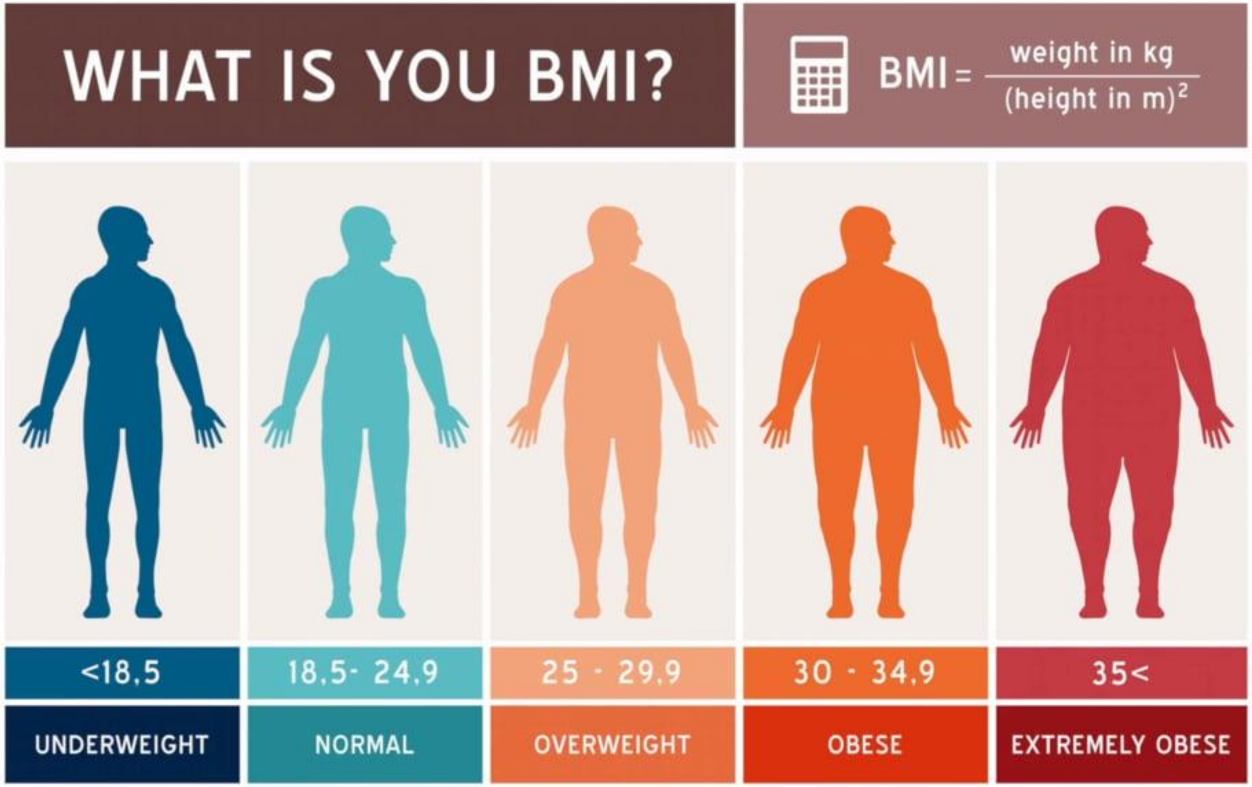
Normal Weight vs Obese Pancreatic Cancer-Related Hospitalizations

	Normal weight	Obese	P-value	Adjusted mean difference *
Mortality rate	7.7% (7.2-8.3)	7.5% (5.8-9.6)	0.7878	1.00 (0.75-1.34) P=0.98 Adjusted odds
Mean length of stay	5.6 days (5.5-5.74)	6.8 days (6.4-7.3)	**< 0.01**	1.19 days (0.72-1.66) P<0.01
Mean hospitalization charges	$48,337 ($46,300-$50,373)	$61,056 ($55,411-$66,700)	**< 0.01**	$13,432 ($7,848-$19,016) P<0.01
Mean hospitalization costs	$12,489 ($12,091-$12,889)	$15,652 ($14,386-$16,919)	**< 0.01**	$3,311 ($2,022 - $4,599) P<0.01
Palliative care consult for metastatic pancreatic cancer	19.3% (18.2%-20.4%)	20.8% (17.2%-24.9%)	0.44	0.89 (0.72-1.11) P=0.32

<u>Obese vs Morbidly Obese</u> Pancreatic Cancer-Related Hospitalizations

	Obese	Morbidly Obese	P-value	Adjusted mean difference *
Mortality rate	7.7% (7.2-8.2)	8.8 % (6.0-12.8)	0.4867	1.16 (0.75-1.79) P=0.496 Adjusted odds
Mean length of stay	5.6 days (5.8-5.7)	7.4 days (6.6-8.2)	**< 0.01**	1.79 (1.02-2.57) P<0.01
Mean hospitalization charges	$48,672 ($46,660-$50,684)	$67,726 ($57,824 - $77,627)	**< 0.01**	$20,528 ($10,735-$30,321) P<0.01
Mean hospitalization costs	$12,599 ($12,200-$12,997)	$16,215 ($14,470-$17,961)	**< 0.01**	$3,986 ($2,197 - $5,774) P<0.01
Palliative care consult for metastatic pancreatic cancer	19.3% (18.2%-20.4%)	25.3% (19.1%-32.8%)	P =0.0575	1.11 (0.82-1.52) P=0.49

How to measure obesity?



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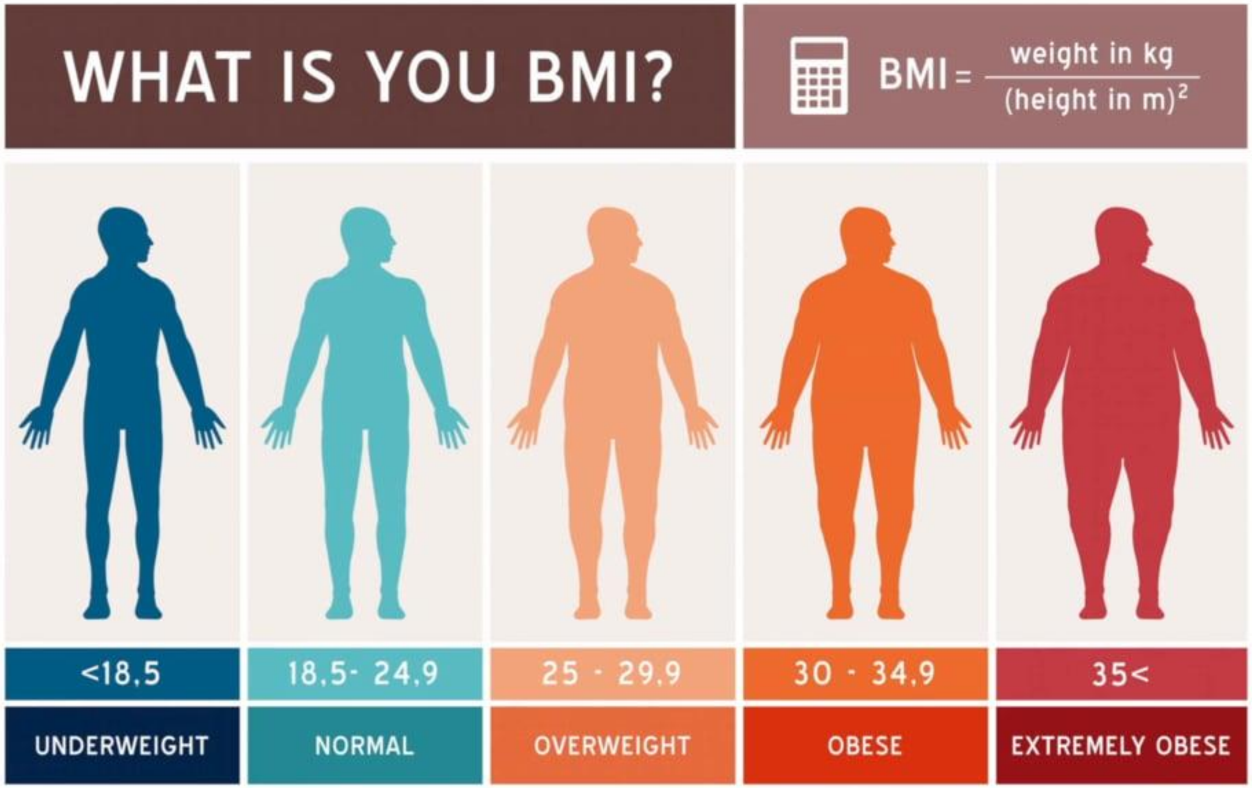
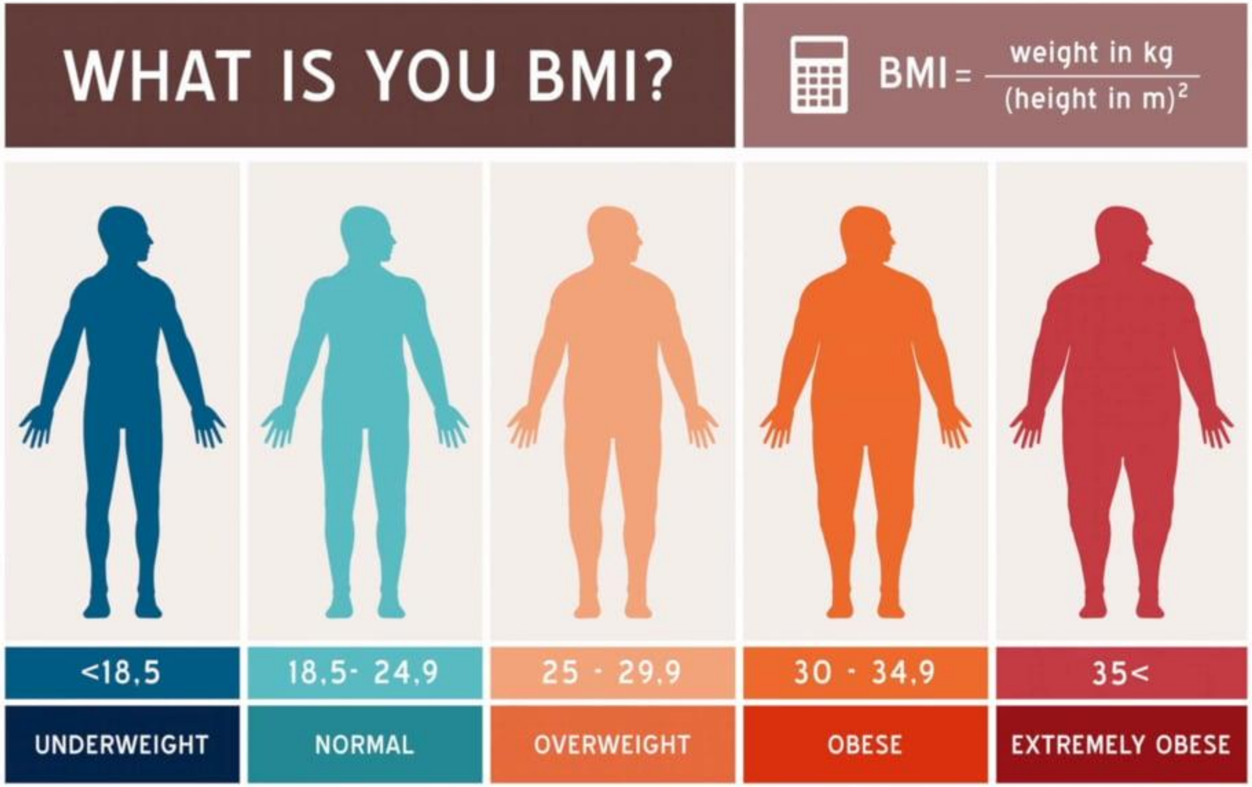


Skinfold Thickness

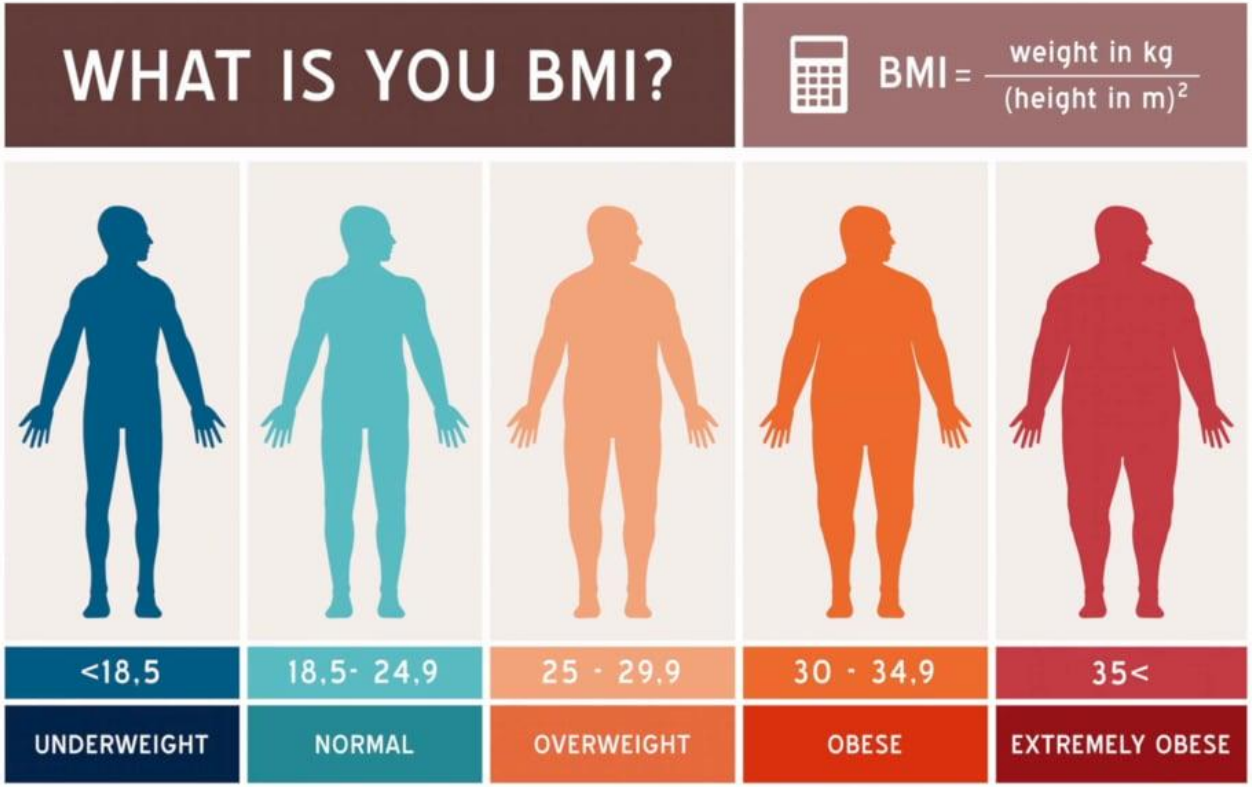
How to measure obesity?



Skinfold Thickness

Waist Circumference

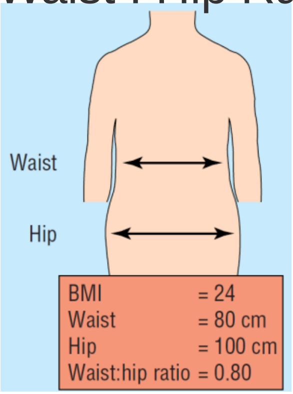
How to measure obesity?



Skinfold Thickness

Waist Circumference

Waist : Hip Ratio



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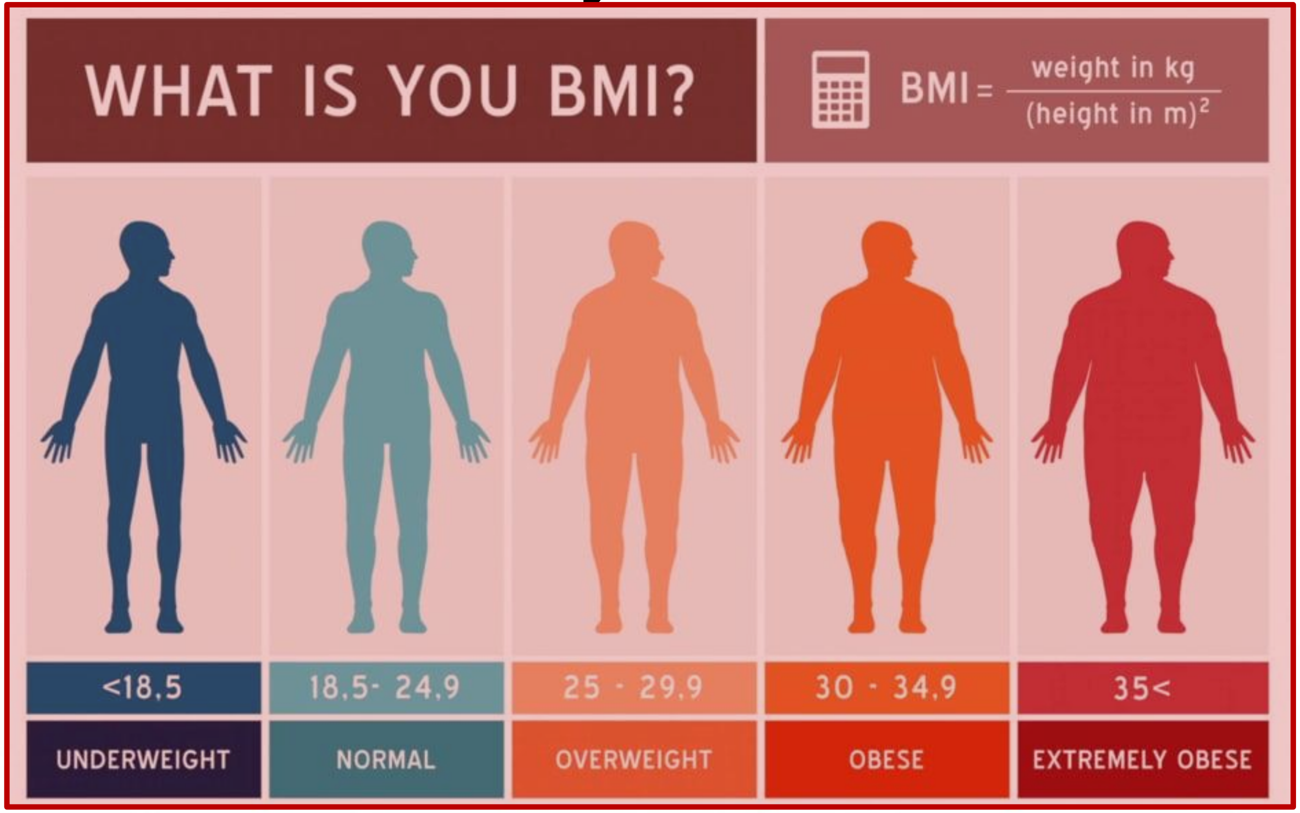
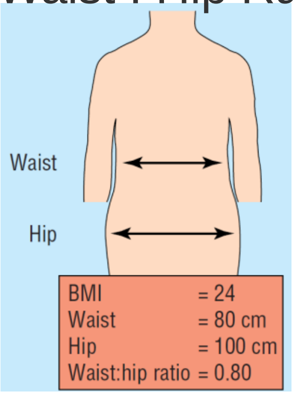


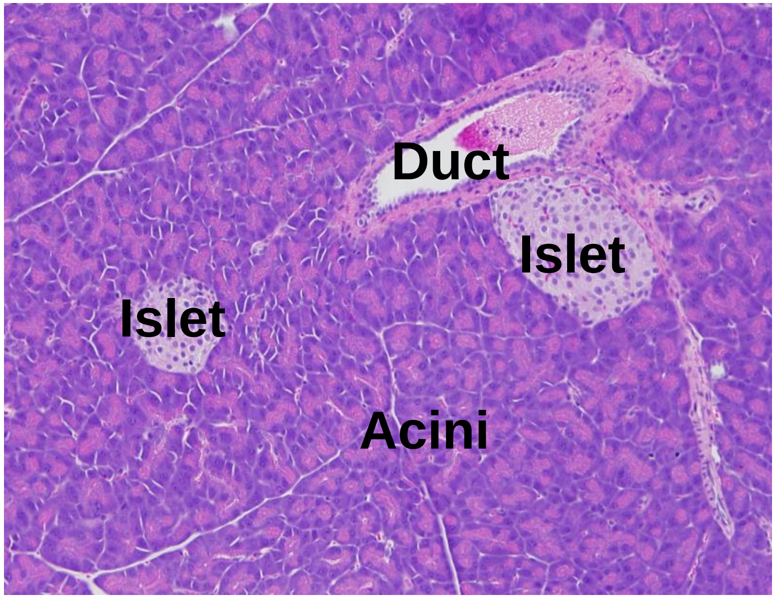
Skinfold Thickness

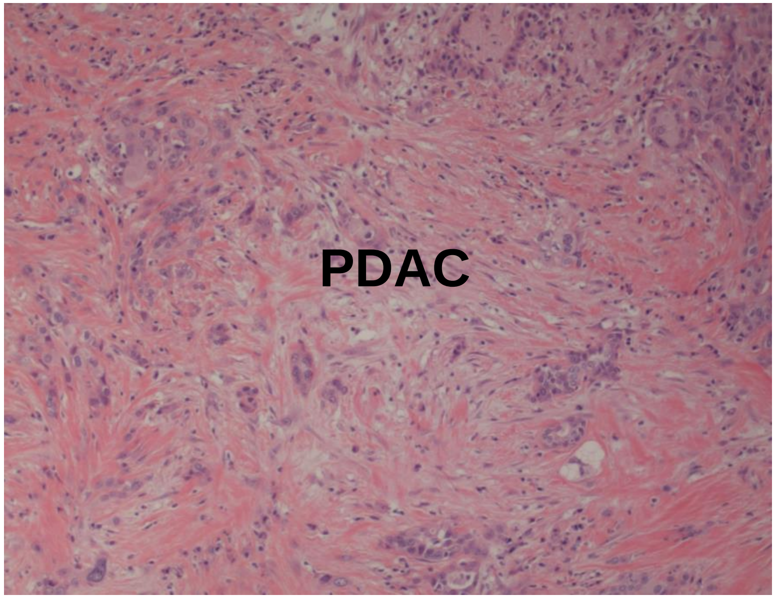
Waist Circumference

Waist : Hip Ratio



What are the Molecular Mechanisms that Increase the Risk of PDAC Development in Obese Individuals?





Stroma is about
90% of tumor volume

What are the Molecular Mechanisms that Increase the Risk of PDAC Development in Obese Individuals?

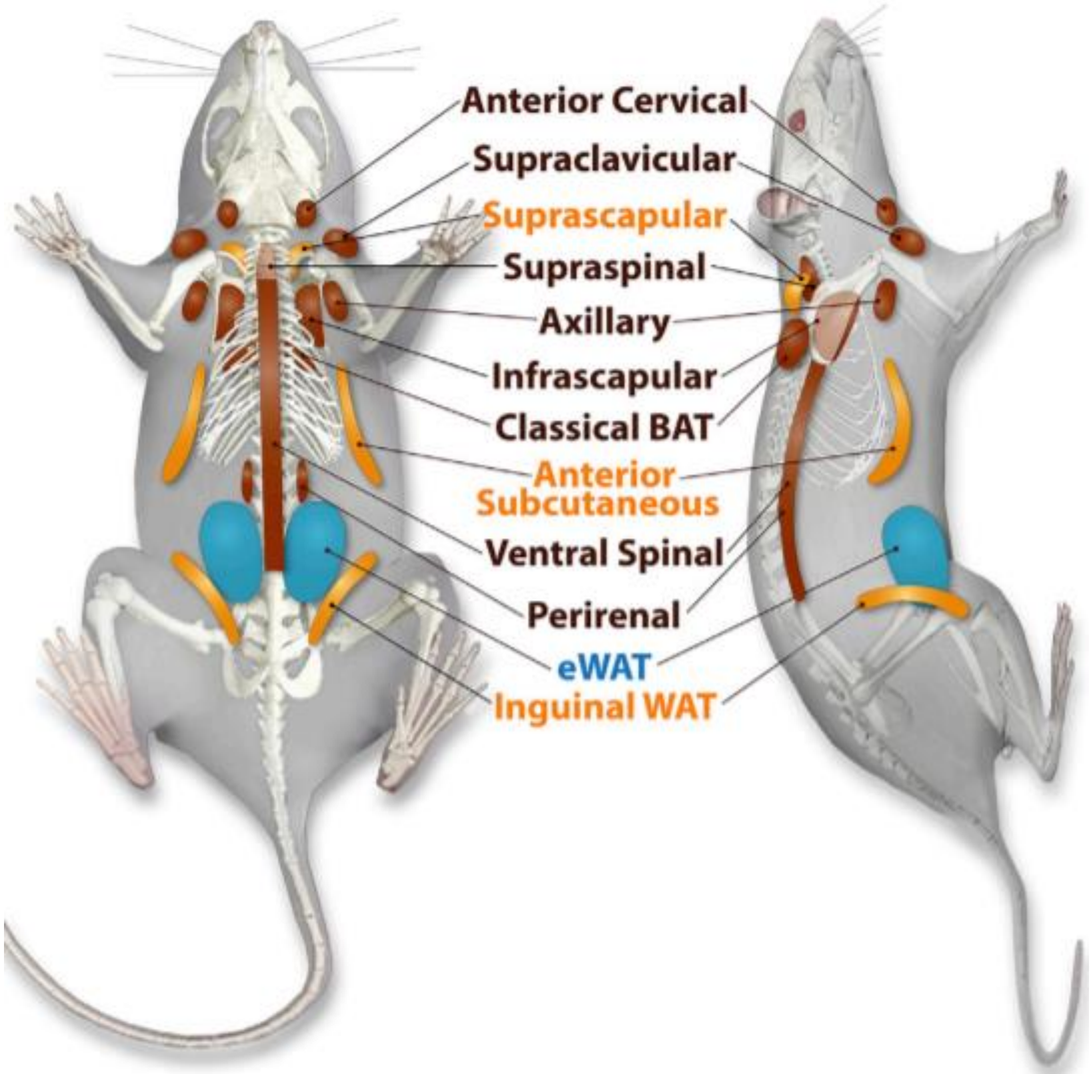
Obesity-Associated Cancer In Mice

Obesity-Associated Cancer In Humans

What are the Molecular Mechanisms that Increase the Risk of PDAC Development in Obese Individuals?

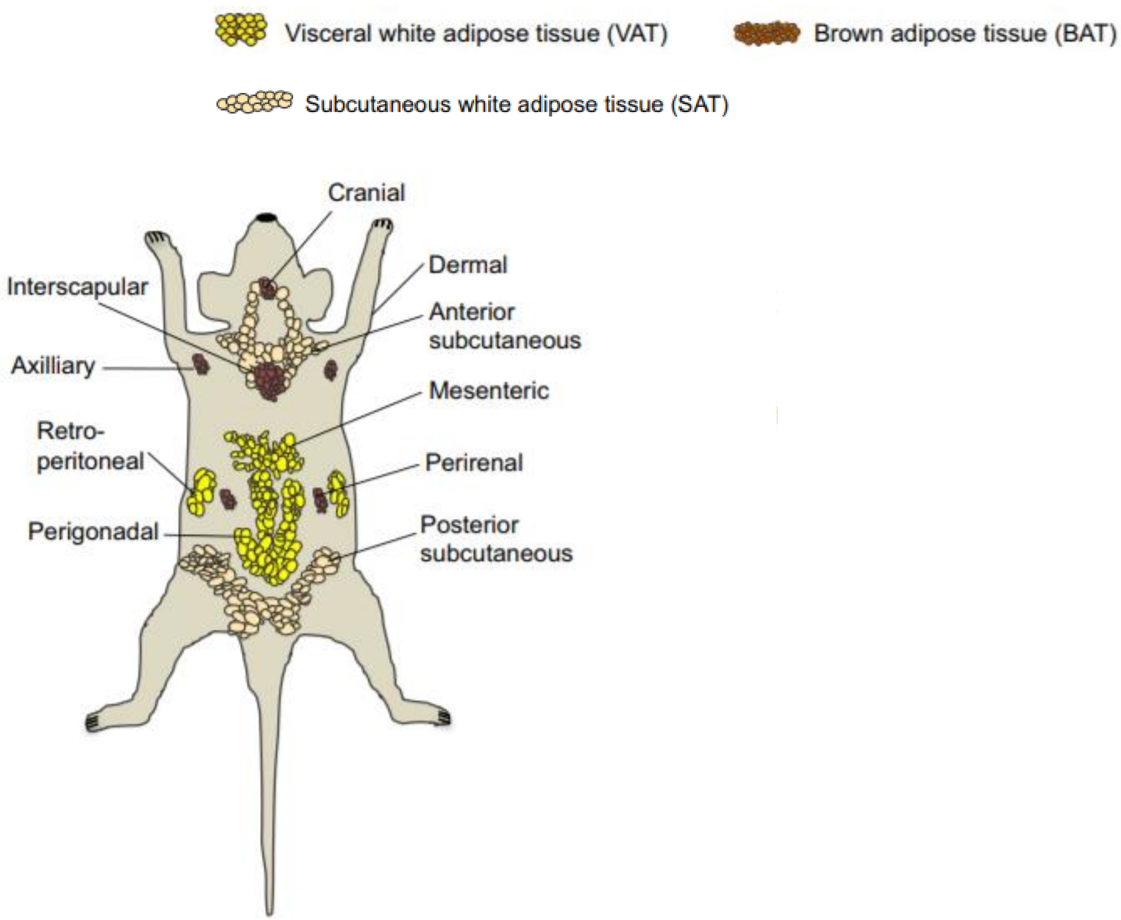
Obesity-Associated Cancer In Mice

Obesity-Associated Cancer In Humans



252 Cell Metabolism 27, 252–262, January 9, 2018

Adipose tissue depots in mice vs humans



Journal of Experimental Biology (2018) 221, jeb162958. doi:10.1242/jeb.162958

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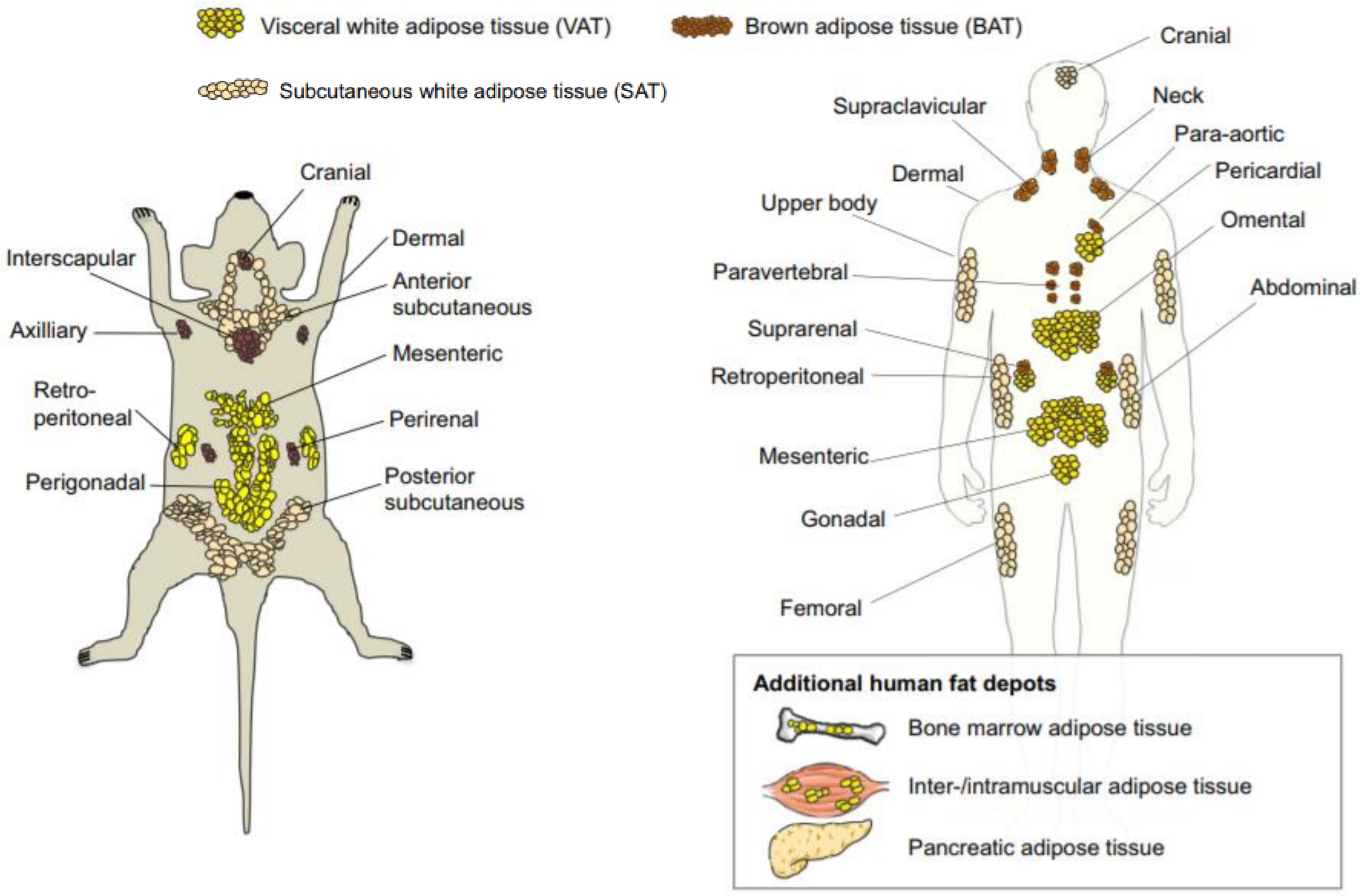

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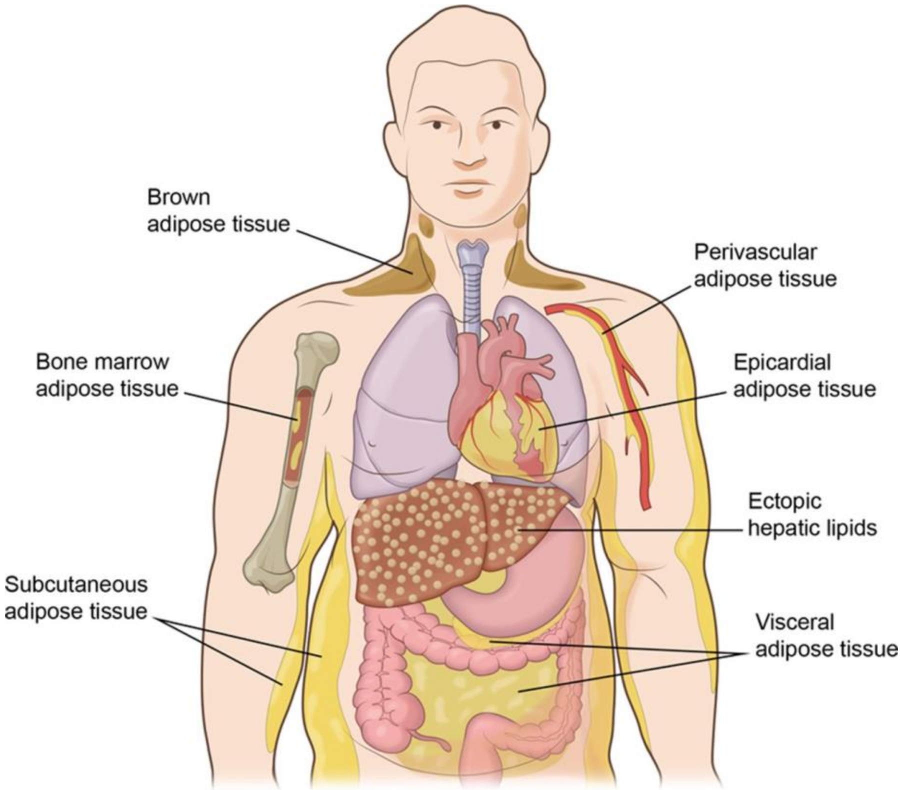
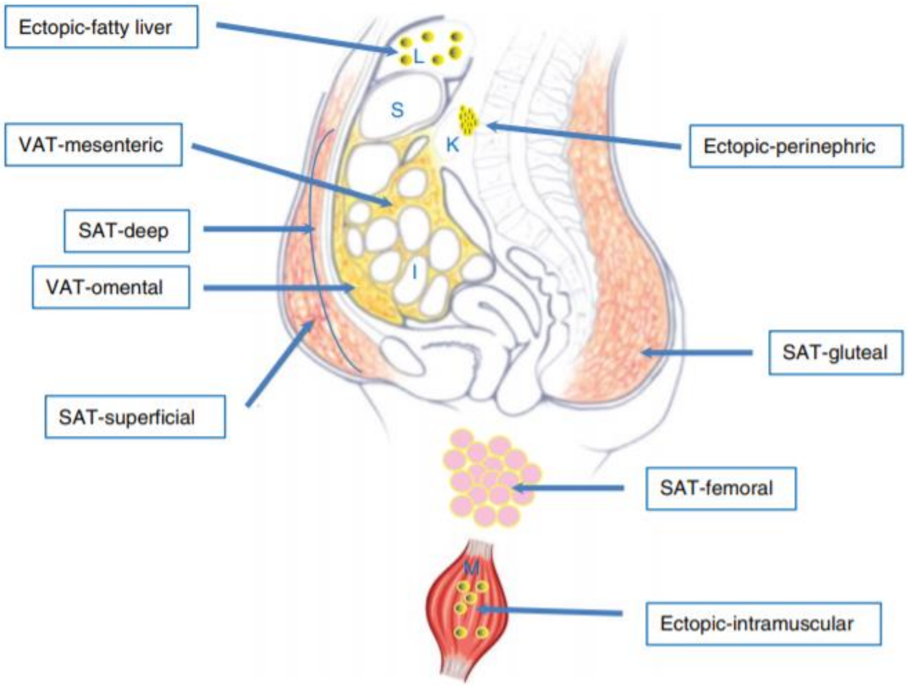
Adipose tissue depots occur throughout the body

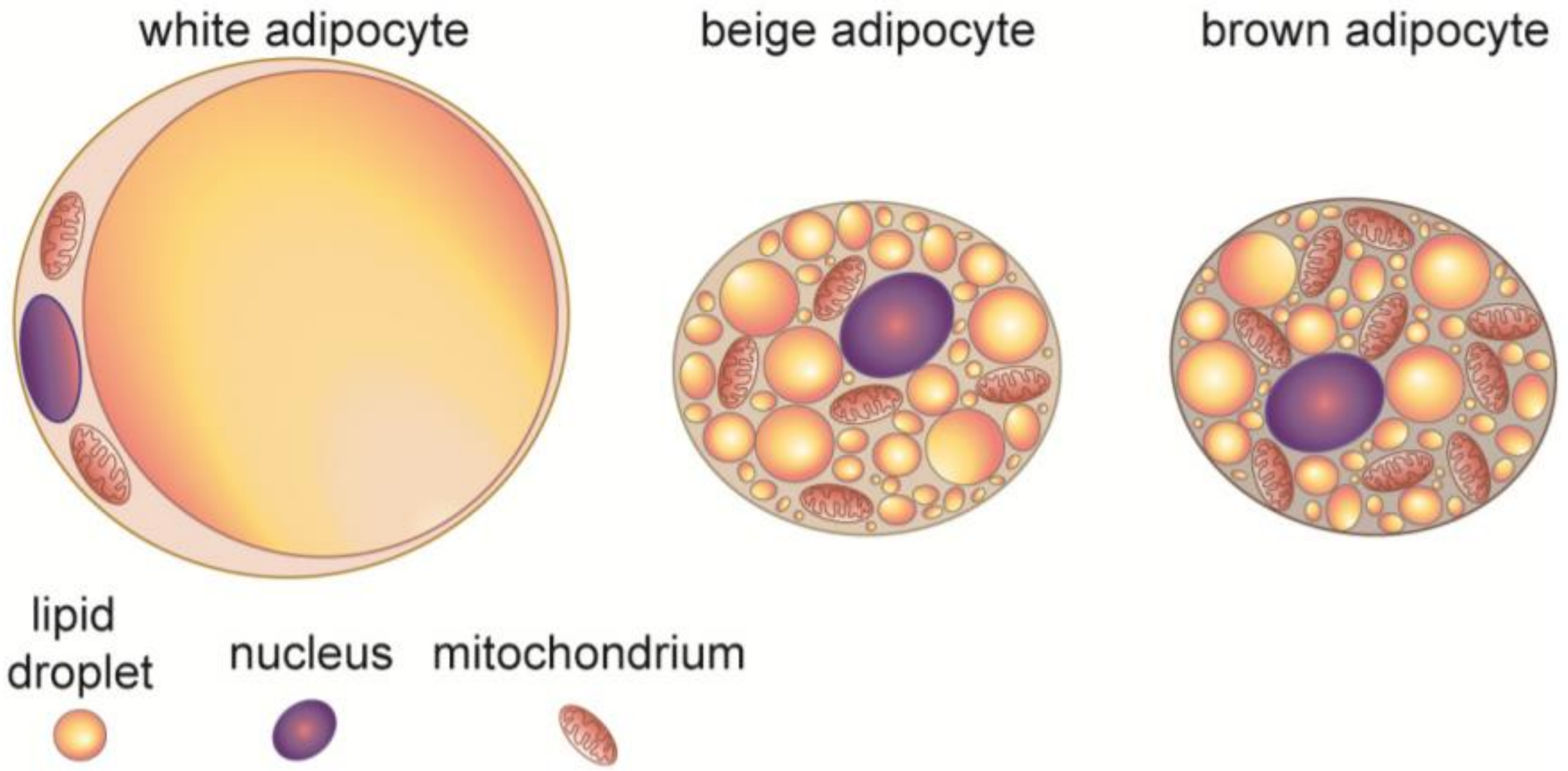


Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease, Volume: 118, Issue: 11, Pages: 1786-1807, DOI: (10.1161/CIRCRESAHA.115.306885)



Horm Mol Biol Clin Invest 2014; 19(1): 57–74

Three types of adipocyte: brown, white and beige (brite)



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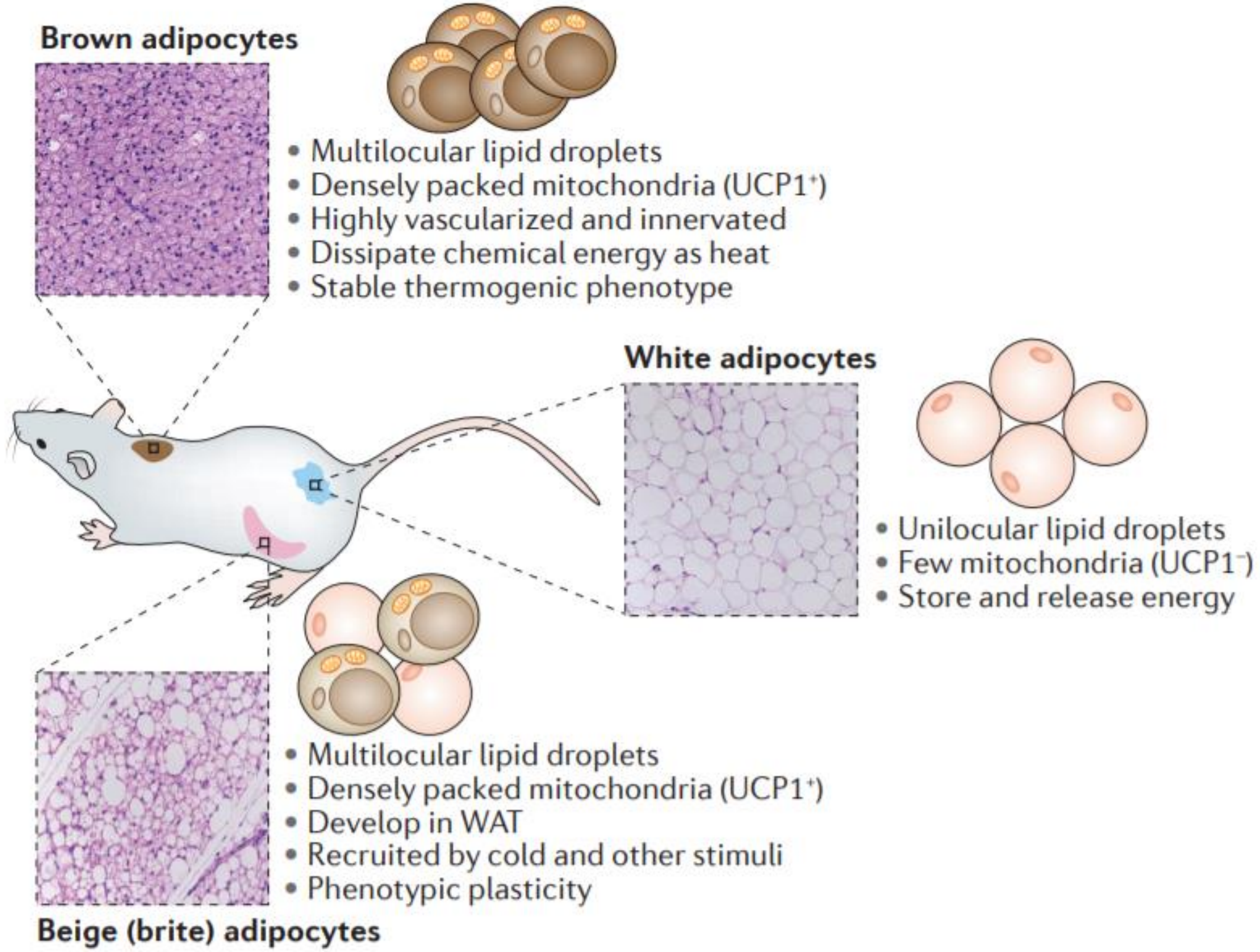
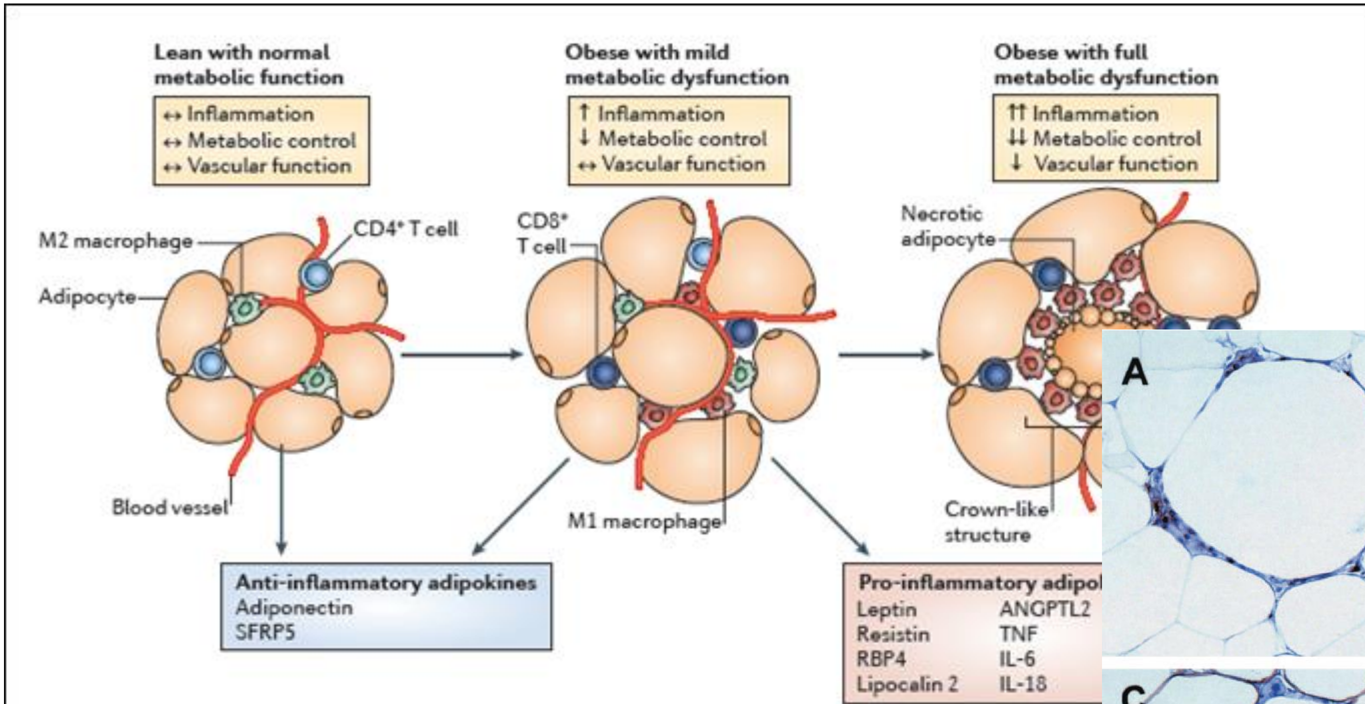


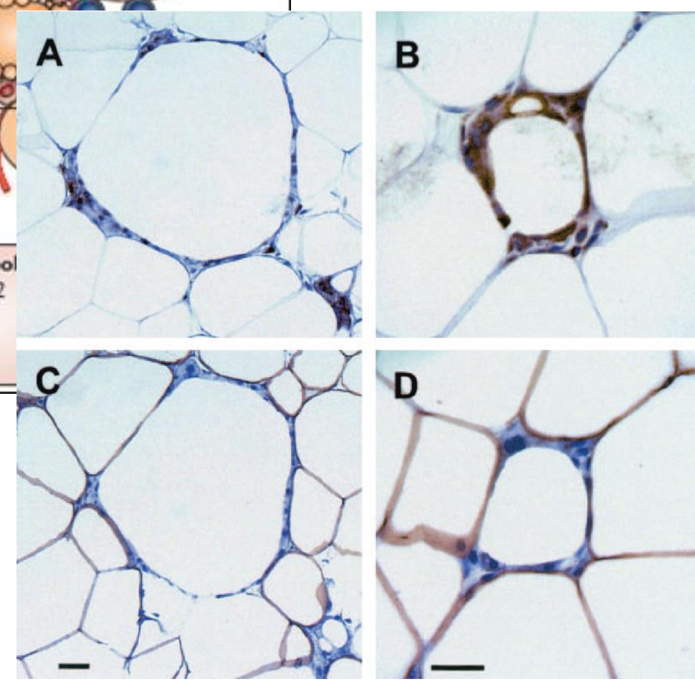
Control of brown and beige fat development

Wenshan Wang and Patrick Seale

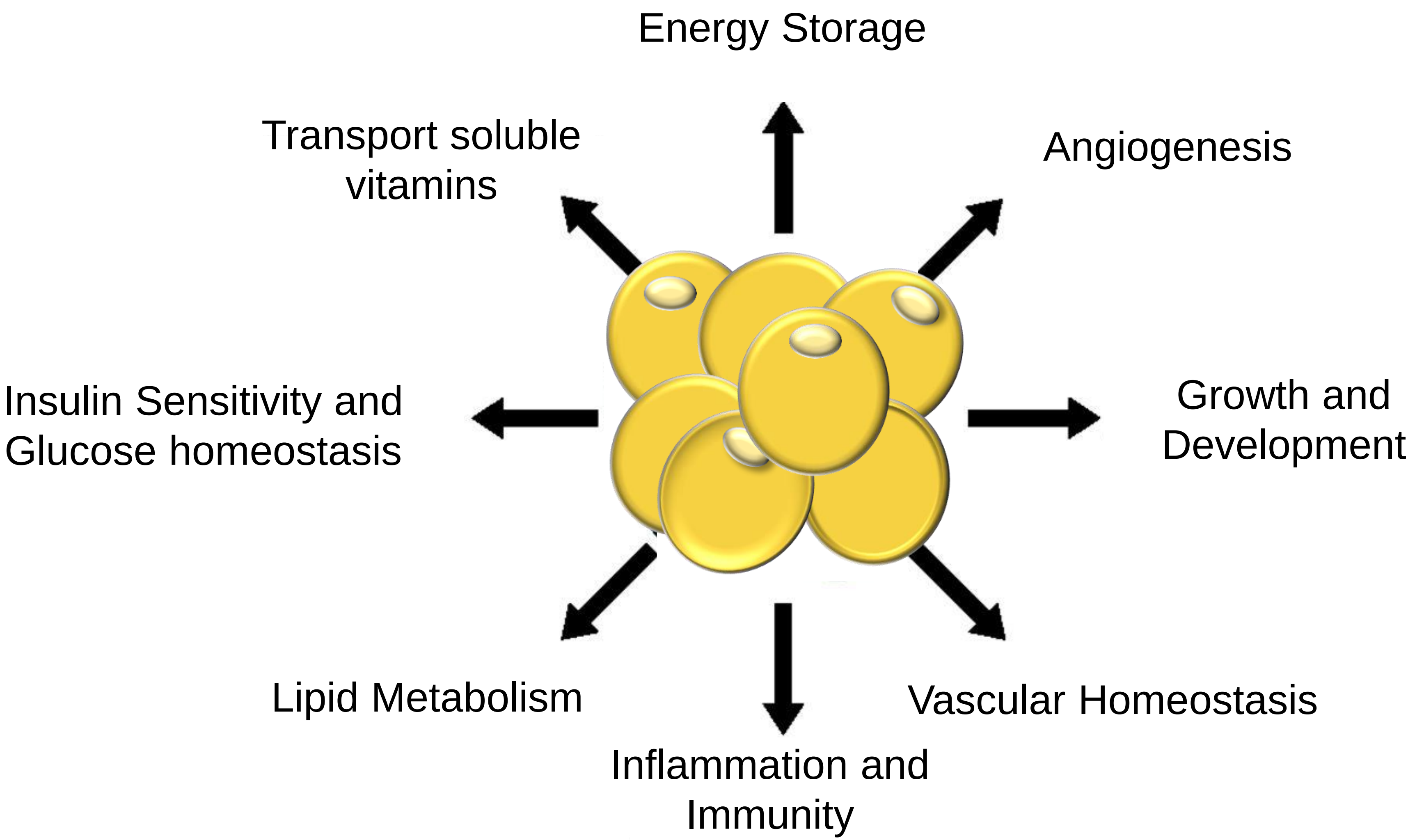
NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 17 | NOVEMBER 2016 | 691

“Crown-like” structures of immune cells defined adipose tissue inflammation

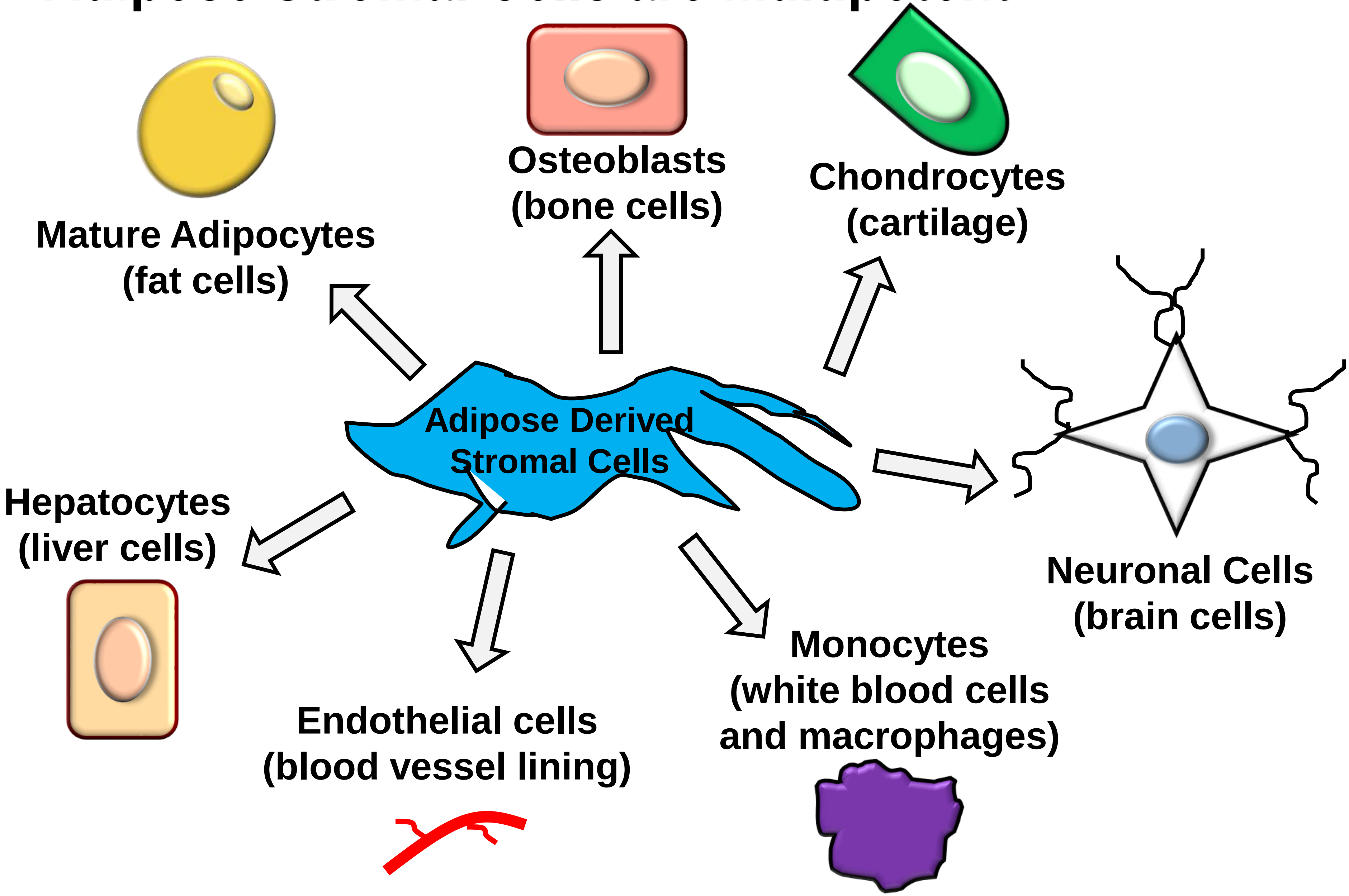




White adipose tissue is essential for survival



Adipose Stromal Cells are Multipotent



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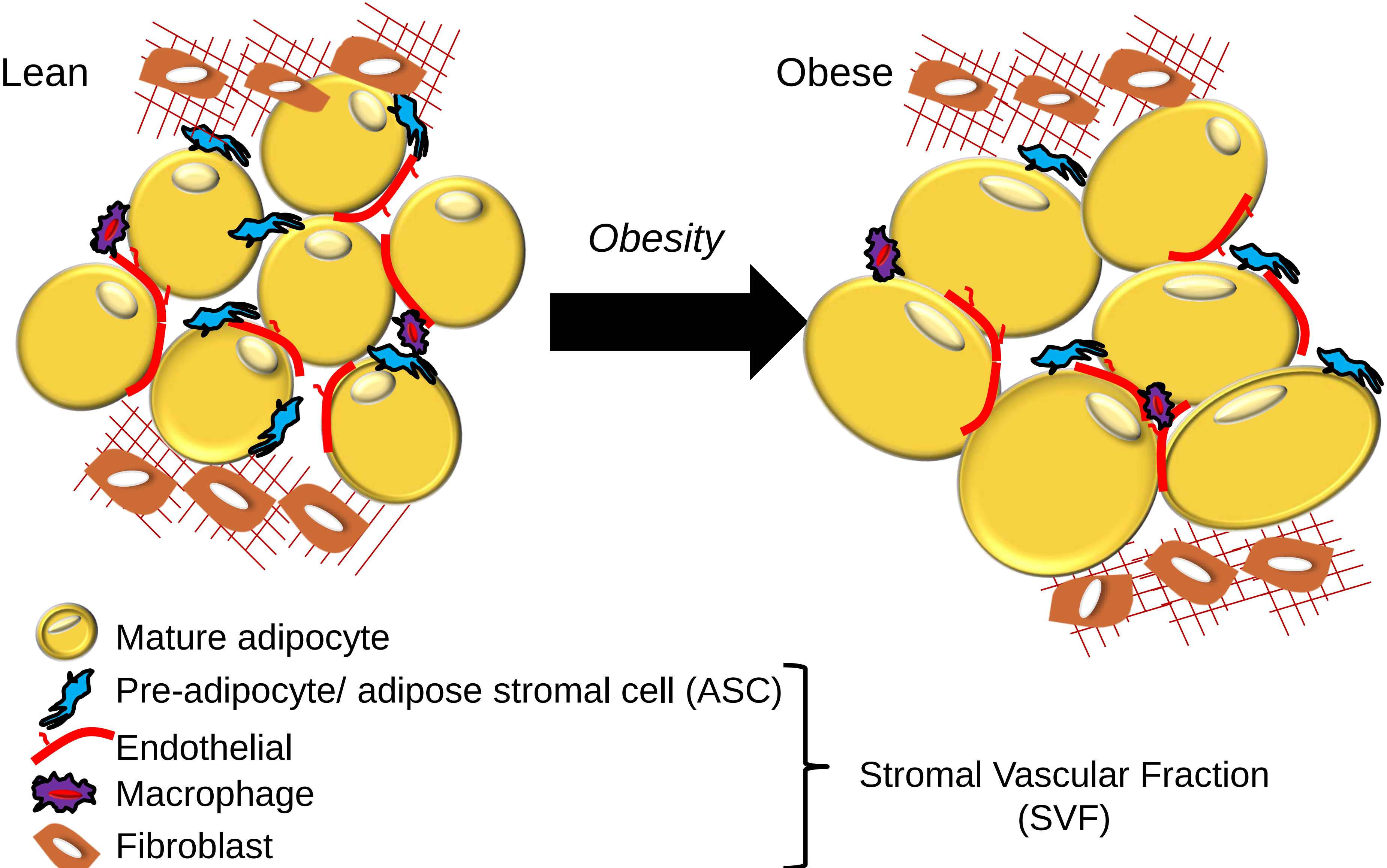

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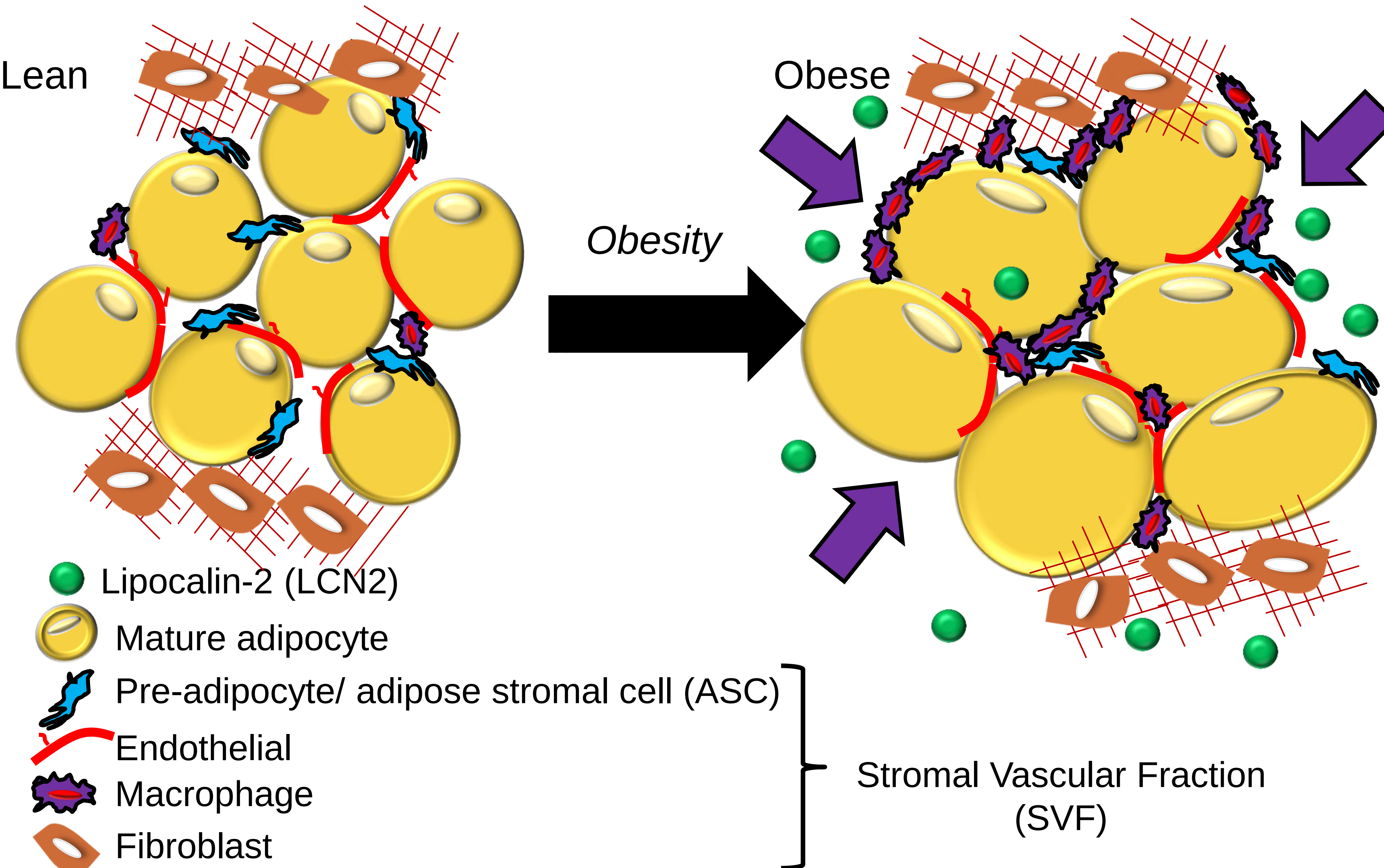
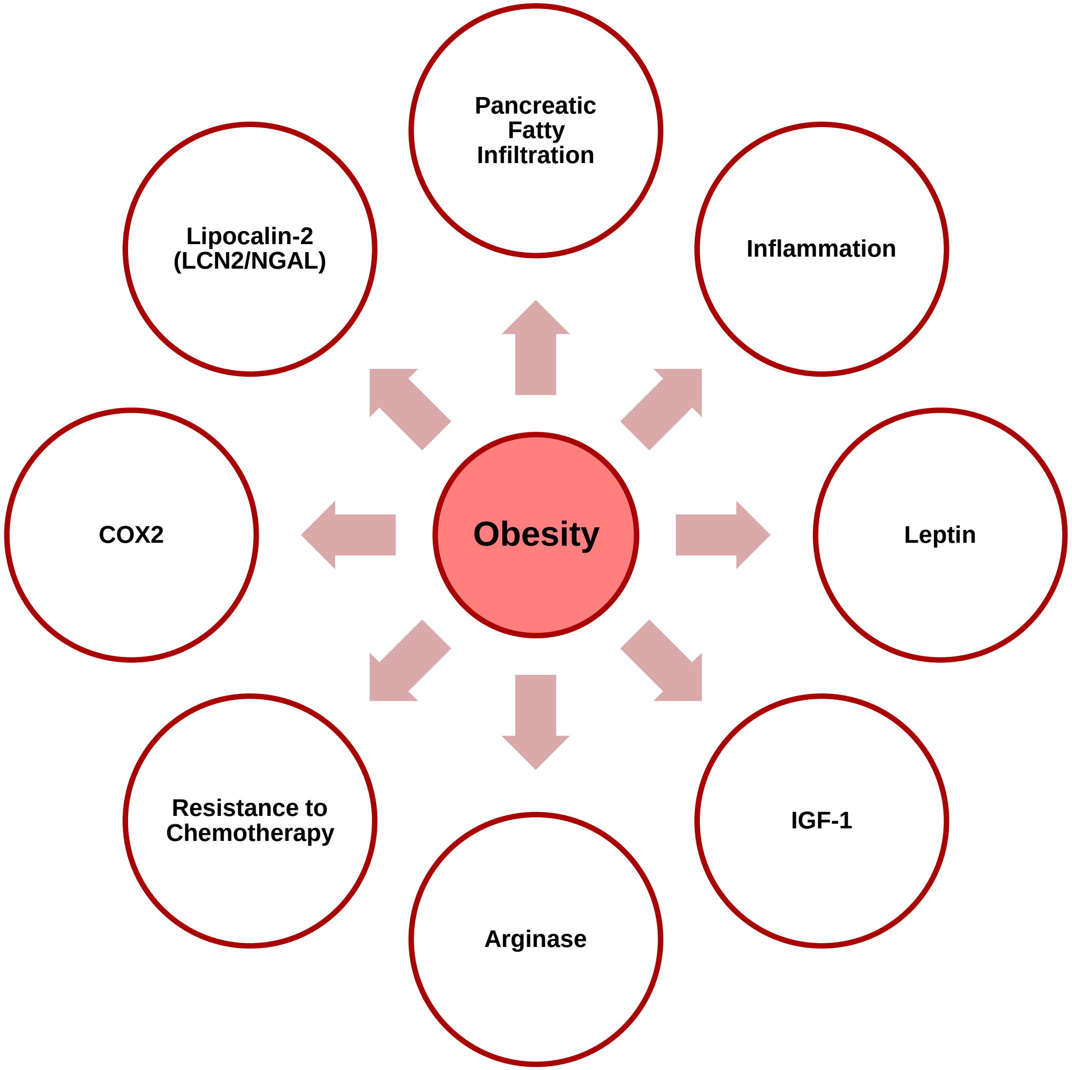


Factors Related to Obesity Affecting PDAC



Factors Related to Obesity Affecting PDAC

Association of Pancreatic Fatty Infiltration With Pancreatic Ductal Adenocarcinoma

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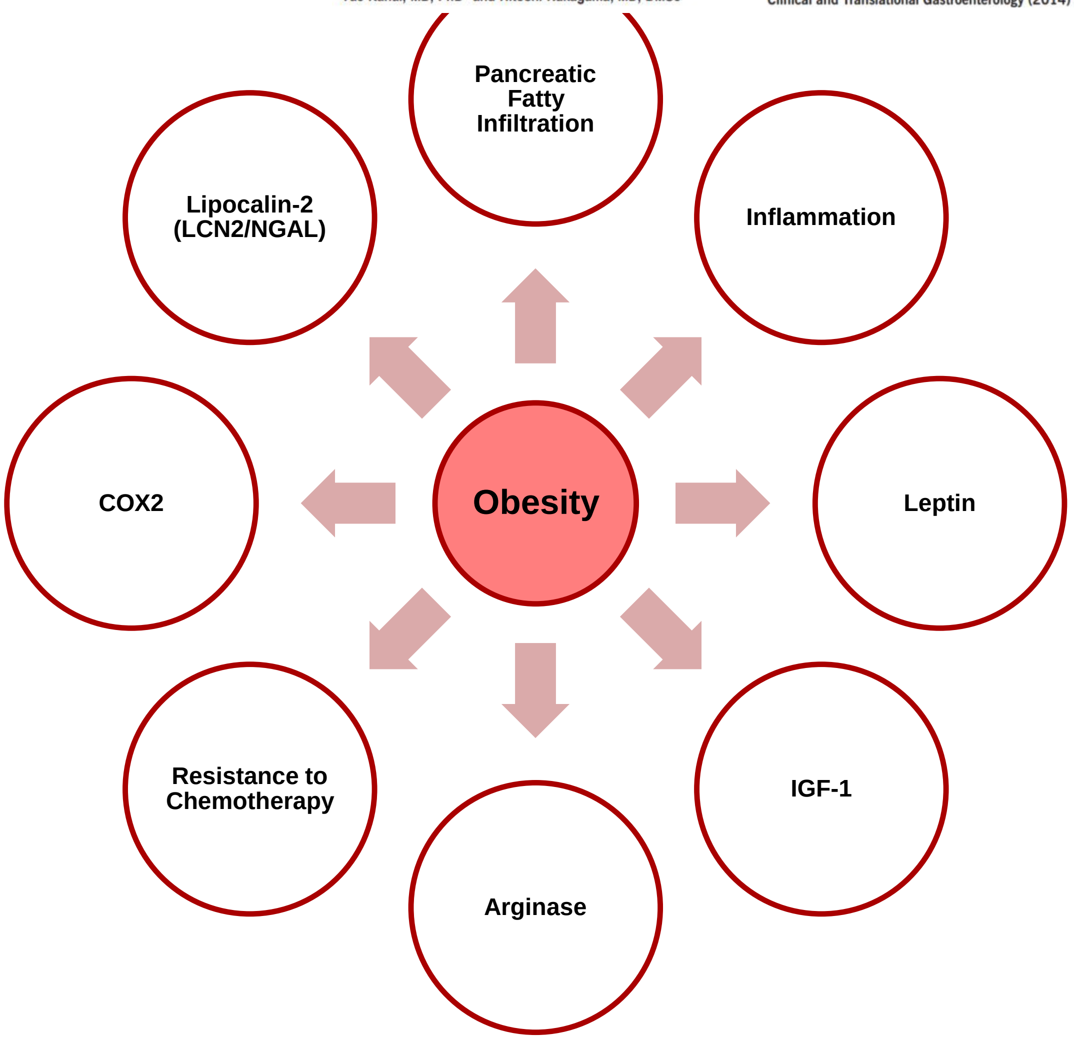
Clinical and Translational Gastroenterology (2014) 5, e53



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PNAS | March 3, 2009 | vol. 106 | no. 9

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[1]Department of Cancer Biology, [2]Surgical Oncology, [3]Pathology, [4]GI Medical Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas; [5]Department of Gastroenterology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; and [6]Mayo Clinic, Rochester, Minnesota

GASTROENTEROLOGY 2013;145:1449–1458

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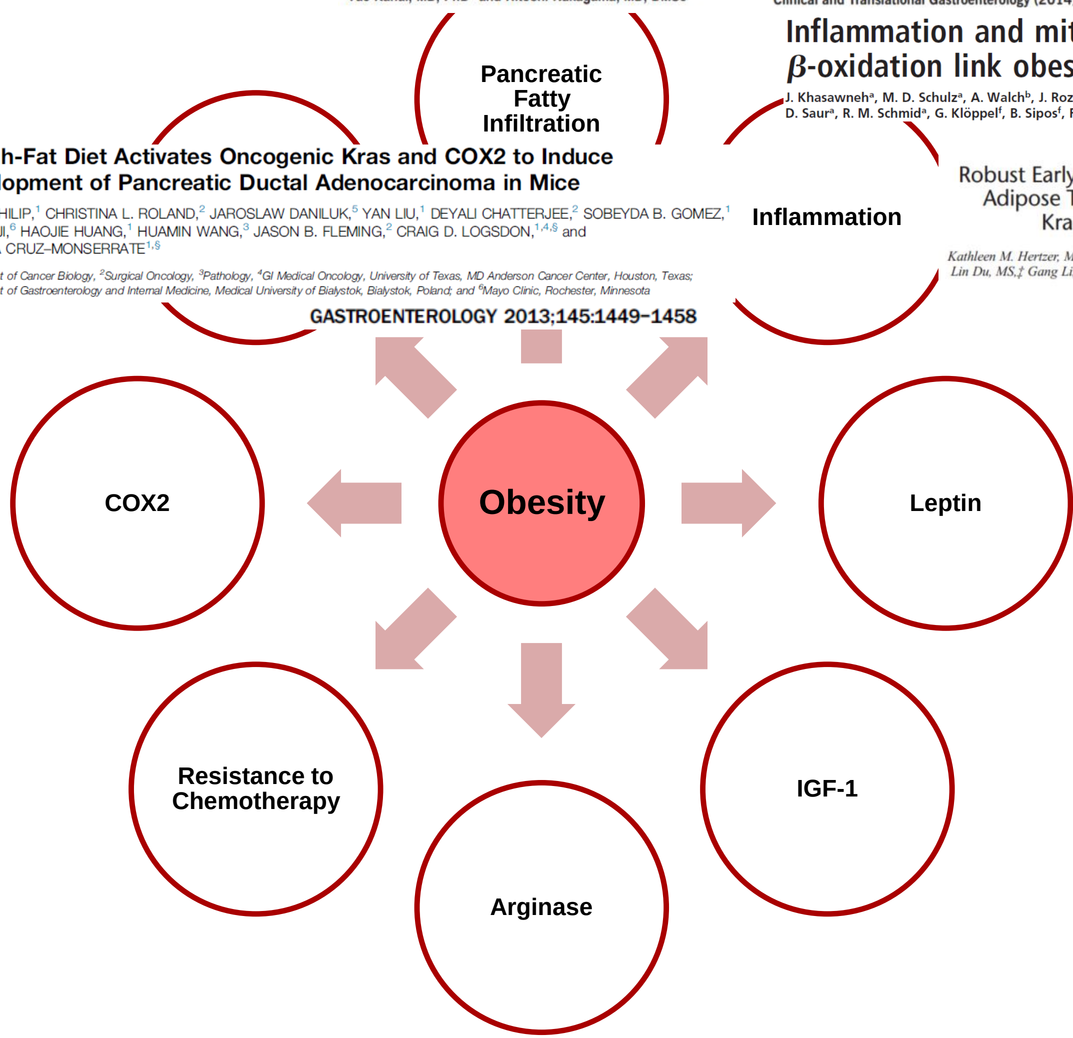
Pancreas • Volume 45, Number 3, March 2016



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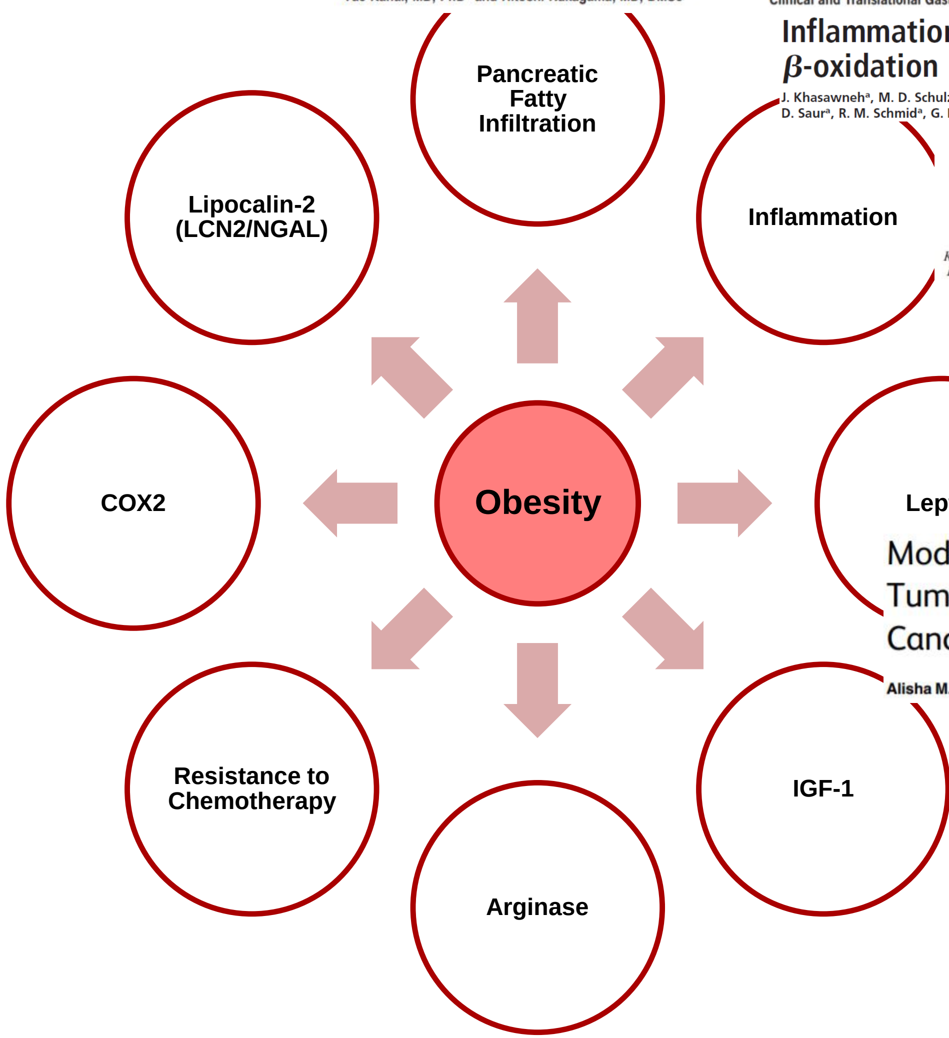

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PLOS ONE | DOI:10.1371/journal.pone.0126686 April 28, 2015

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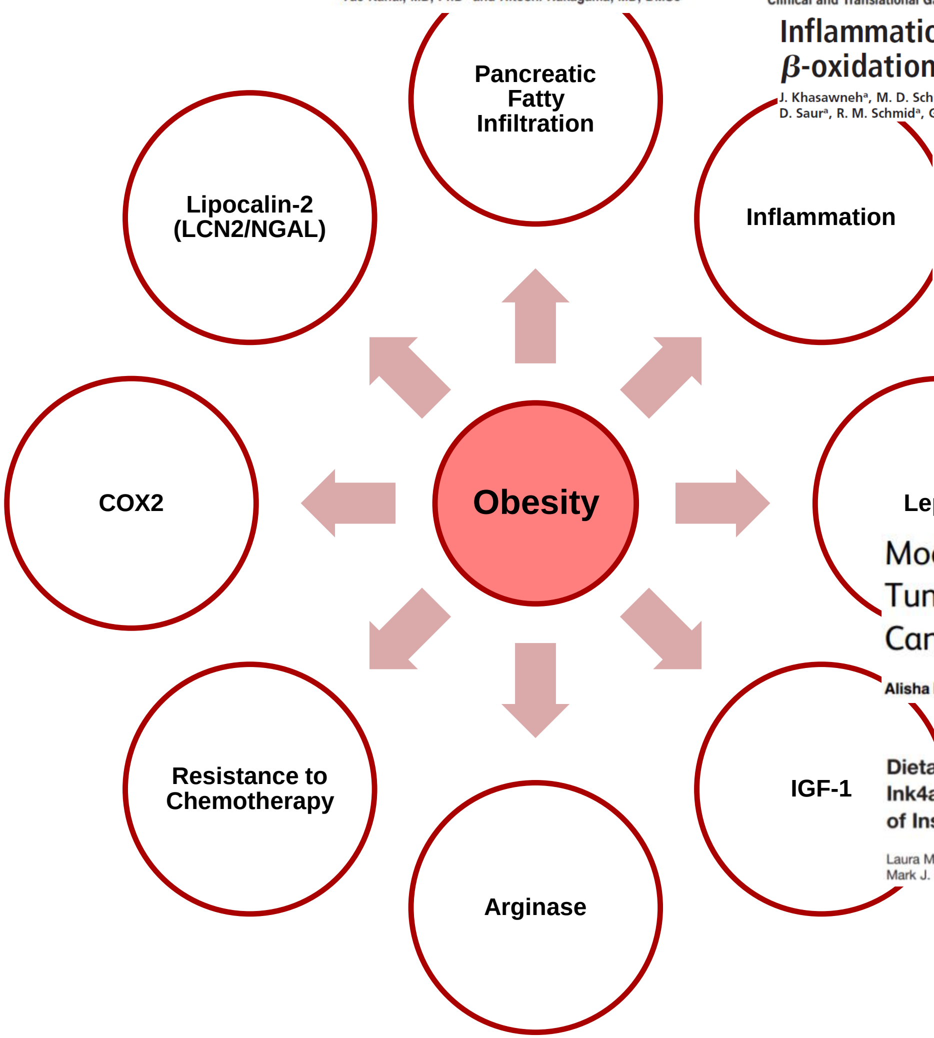

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Cancer Prev Res; 6(10) October 2013

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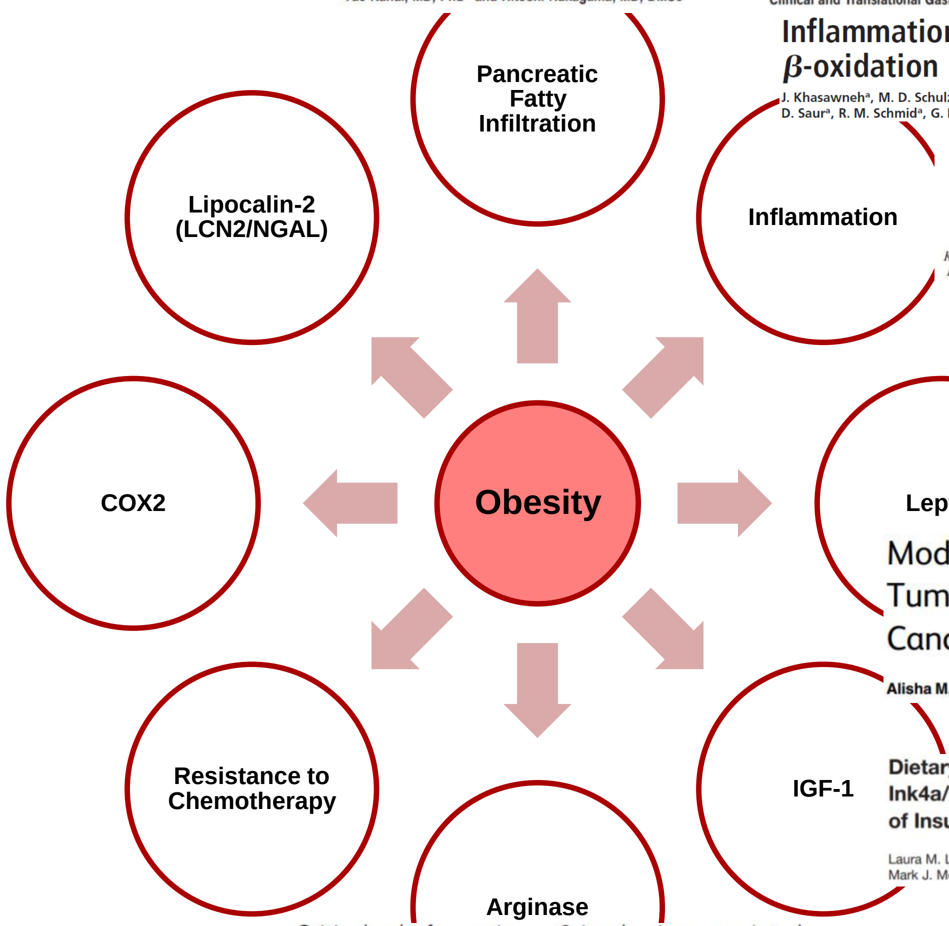

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NATURE COMMUNICATIONS | 8: 242

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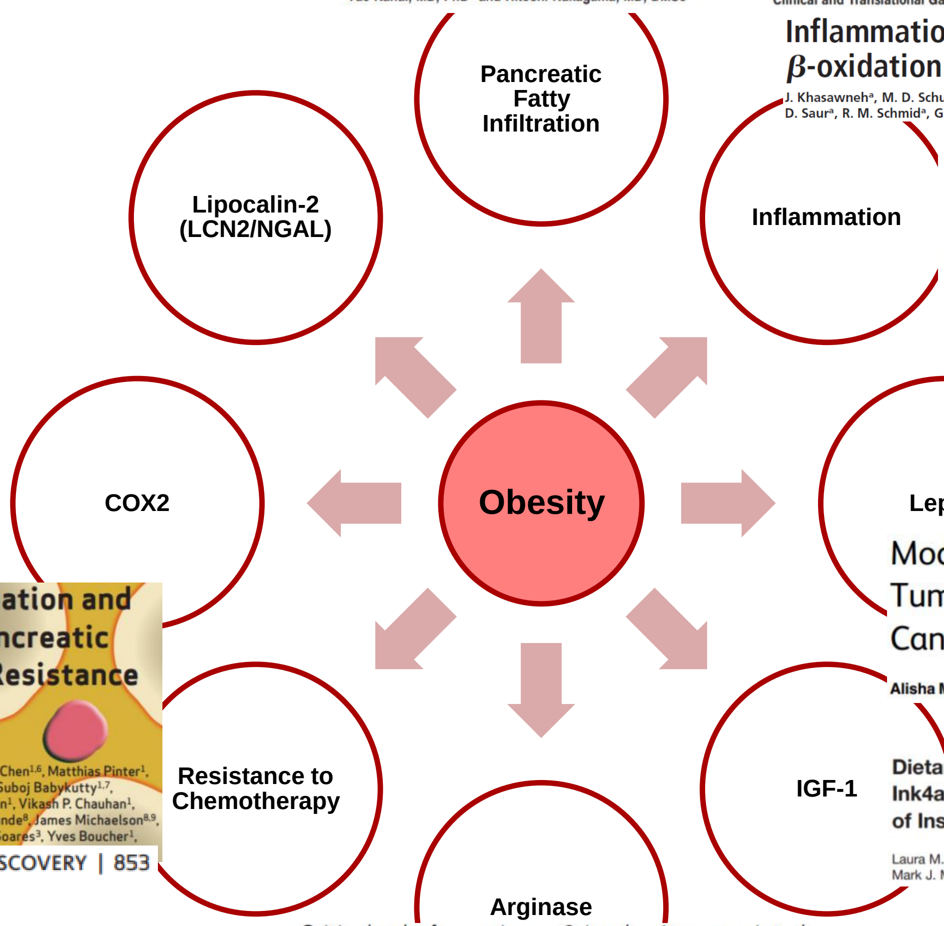

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CANCER DISCOVERY | 853

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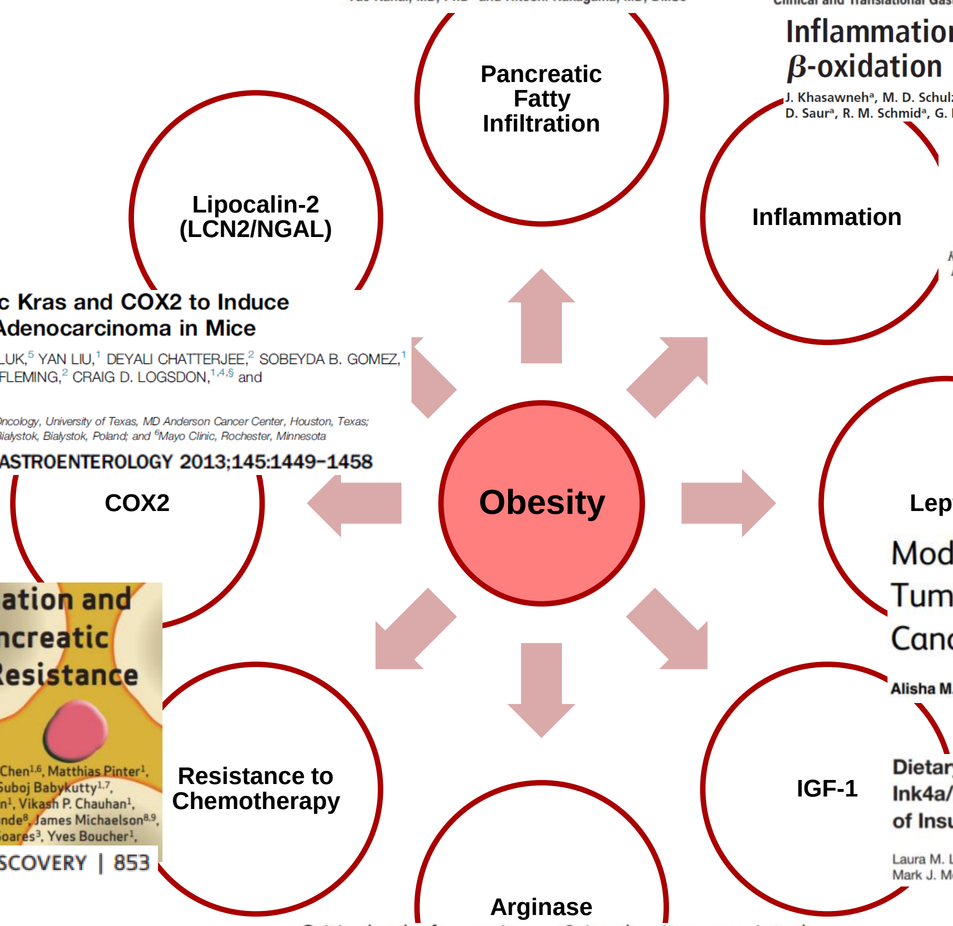

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PNAS | March 3, 2009 | vol. 106 | no. 9

Robust Early Inflammation of the Peripancreatic Visceral Adipose Tissue During Diet-Induced Obesity in the KrasG12D Model of Pancreatic Cancer

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Pancreas • Volume 45, Number 3, March 2016

Pancreatic Cancer Risk Associated with Prediagnostic Plasma Levels of Leptin and Leptin Receptor Genetic Polymorphisms

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Cancer Res; 76(24) December 15, 2016

Modulation of the Leptin Receptor Mediates Tumor Growth and Migration of Pancreatic Cancer Cells

Alisha M. Mendonsa[1], Madeleine C. Chalfant[1], Lee D. Gorden[1,2], Michael N. VanSaun[3]*

PLOS ONE | DOI:10.1371/journal.pone.0126686 April 28, 2015

Dietary Energy Balance Modulation of Kras- and Ink4a/Arf$^{+/-}$-Driven Pancreatic Cancer: The Role of Insulin-like Growth Factor-I

Laura M. Lashinger[1], Lauren M. Harrison[1], Audrey J. Rasmussen[1], Craig D. Logsdon[2], Susan M. Fischer[3], Mark J. McArthur[3,4], and Stephen D. Hursting[1,3]

Cancer Prev Res; 6(10) October 2013

Critical role for arginase 2 in obesity-associated pancreatic cancer

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NATURE COMMUNICATIONS | 8: 242

Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy

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CANCER DISCOVERY | 853

A High-Fat Diet Activates Oncogenic Kras and COX2 to Induce Development of Pancreatic Ductal Adenocarcinoma in Mice

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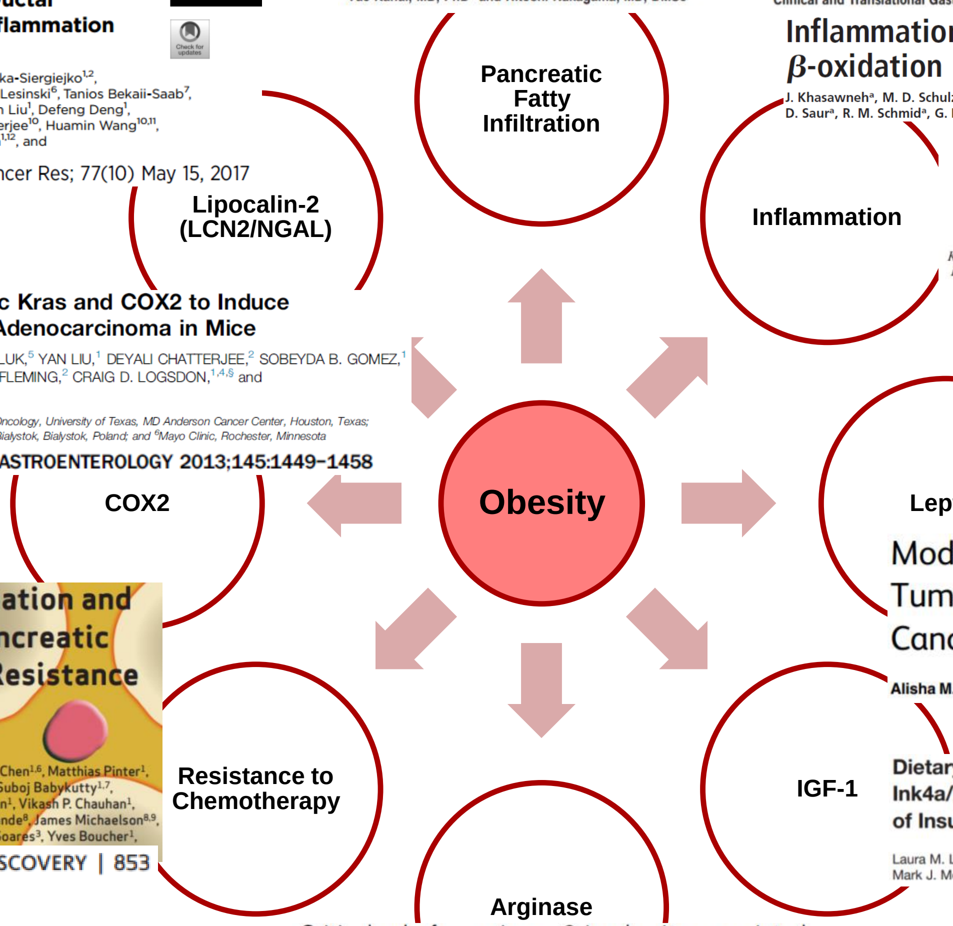
GASTROENTEROLOGY 2013;145:1449–1458

Factors Related to Obesity Affecting PDAC



Molecular and Cellular Pathobiology

Cancer Research

Lipocalin-2 Promotes Pancreatic Ductal Adenocarcinoma by Regulating Inflammation in the Tumor Microenvironment

Sobeyda B. Gomez-Chou[1], Agnieszka Katarzyna Swidnicka-Siergiejko[1,2], Niharika Badi[3,4,5], Myrriah Chavez-Tomar[3,4,5], Gregory B. Lesinski[6], Tanios Bekaii-Saab[7], Matthew R. Farren[6], Thomas A. Mace[3], Carl Schmidt[8], Yan Liu[1], Defeng Deng[1], Rosa F. Hwang[9], Liran Zhou[9], Todd Moore[9], Deyali Chatterjee[10], Huamin Wang[10,11], Xiaohong Leng[11], Ralph B. Arlinghaus[11], Craig D. Logsdon[1,12], and Zobeida Cruz-Monserrate[3,4,5]

Cancer Res; 77(10) May 15, 2017

Association of Pancreatic Fatty Infiltration With Pancreatic Ductal Adenocarcinoma

Mika Hori, PhD[1], Mami Takahashi, PhD[2], Nobuyoshi Hiraoka, MD, PhD[3], Taiki Yamaji, MD, PhD, MPH[4], Michihiro Mutoh, MD, PhD[5], Rikako Ishigamori, PhD[5], Koh Furuta, MD, PhD[6], Takuji Okusaka, MD, PhD[7], Kazuaki Shimada, MD, PhD[8], Tomoo Kosuge, MD, PhD[8], Yae Kanai, MD, PhD[3] and Hitoshi Nakagama, MD, DMSc[1,5]

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Obesity-Induced PDAC in Genetically Engineered Mouse Models (GEMM)

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PNAS | March 3, 2009 | vol. 106 | no. 9

Chow vs HFD Research Diets lard

High-Fat, High-Calorie Diet Promotes Early Pancreatic Neoplasia in the Conditional Kras^{G12D} Mouse Model

David W. Dawson[1,5], Kathleen Hertzer[2], Aune Moro[2], Graham Donald[2], Hui-Hua Chang[2], Vay Liang Go[3], Steven J. Pandol[3,6,7], Aurelia Lugea[3,6], Anna S. Gukovskaya[3,6], Gang Li[4,5], Oscar J. Hines[2,5], Enrique Rozengurt[3,5], and Guido Eibl[2,5]

Cancer Prev Res; 6(10) October 2013

12% or a 40% fat diet AIN-76A, HFCD Corn oil

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GASTROENTEROLOGY 2013;145:1449–1458

10% or a 60% fat diet Test Diet DIO 58Y2 and DIO 58Y1; Lab Supply lard

AUGUST 2016 CANCER DISCOVERY | 853

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10% or a 60% fat diet (D12450J and D12492; Research Diets) lard

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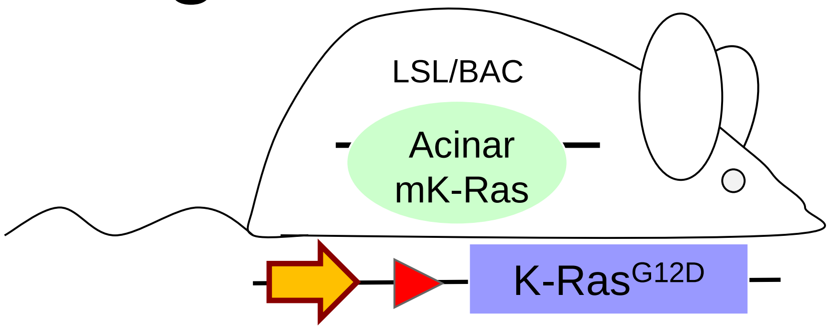
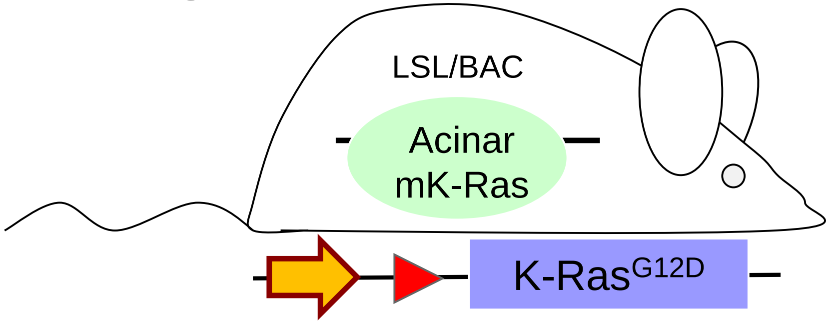


Endogenous
mutant K-Ras expression in acinar cells

Caloric Breakdown	% kcal of each nutrient	
	Control Diet	High Fat Diet
Protein	18.3	18.1
Fat	10.2	61.6
Carbohydrate	71.5	20.3

Isocaloric

Obesity-Induced PDAC in Genetically Engineered Mouse Models (GEMM)



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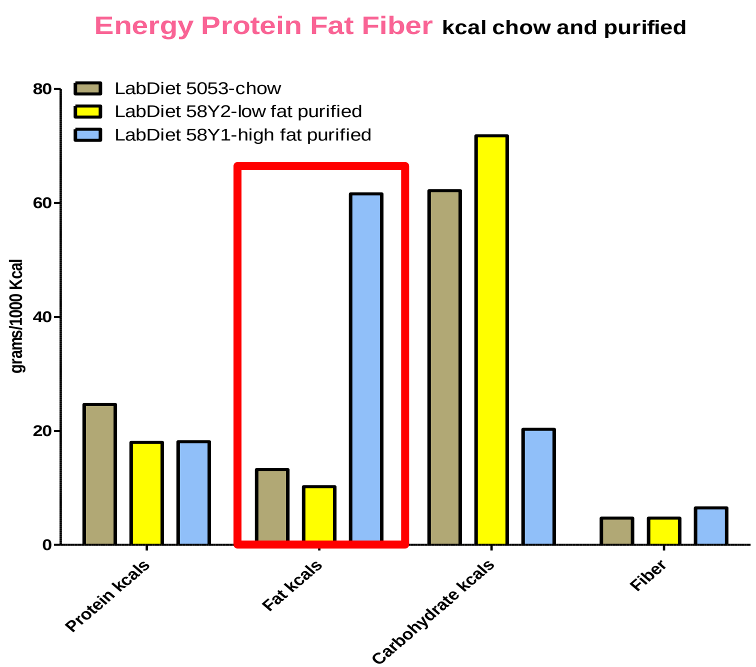

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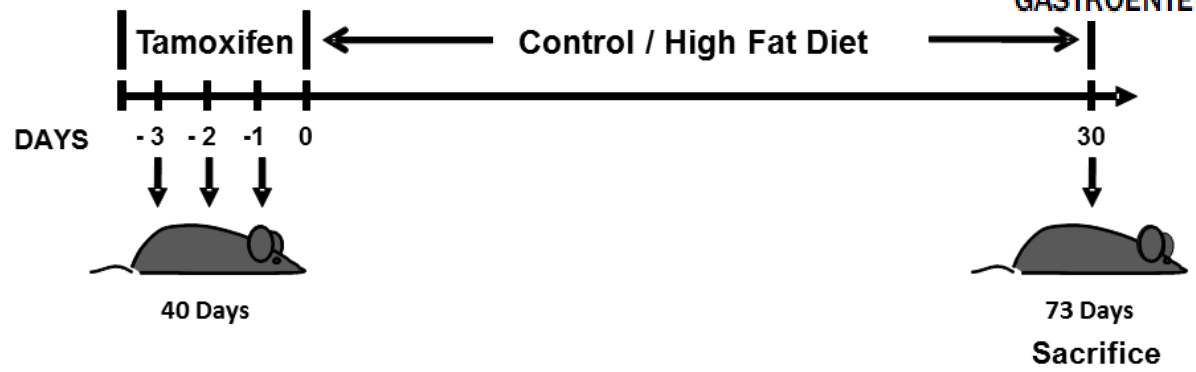

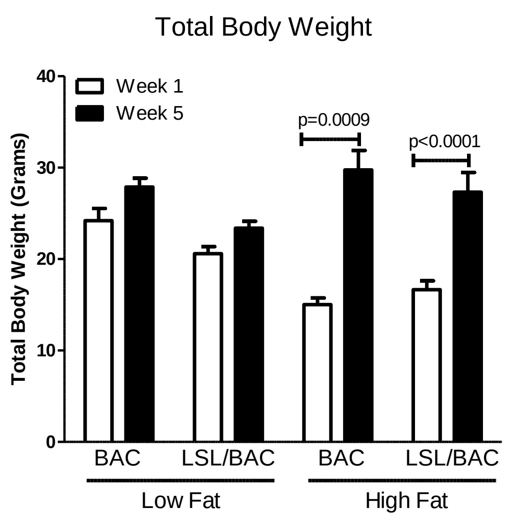

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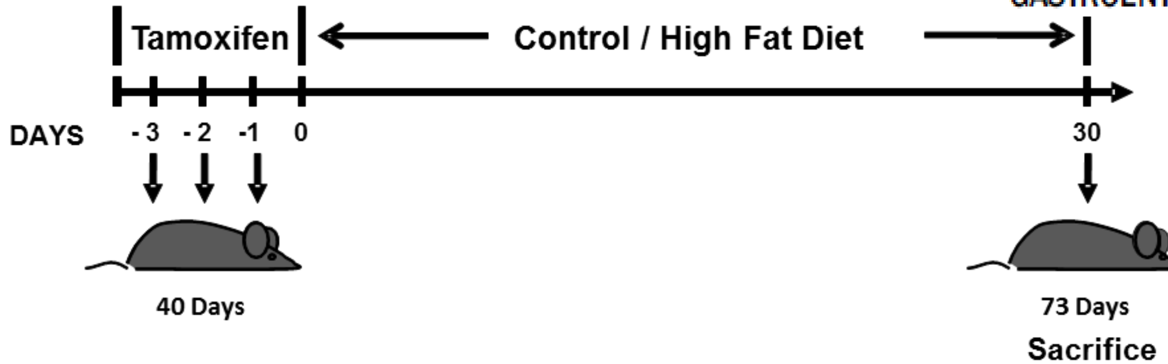

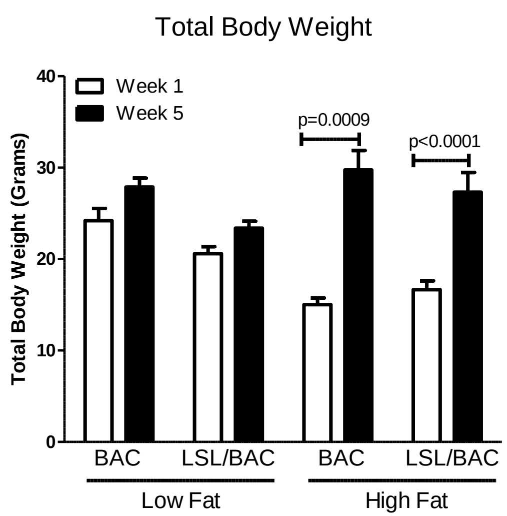

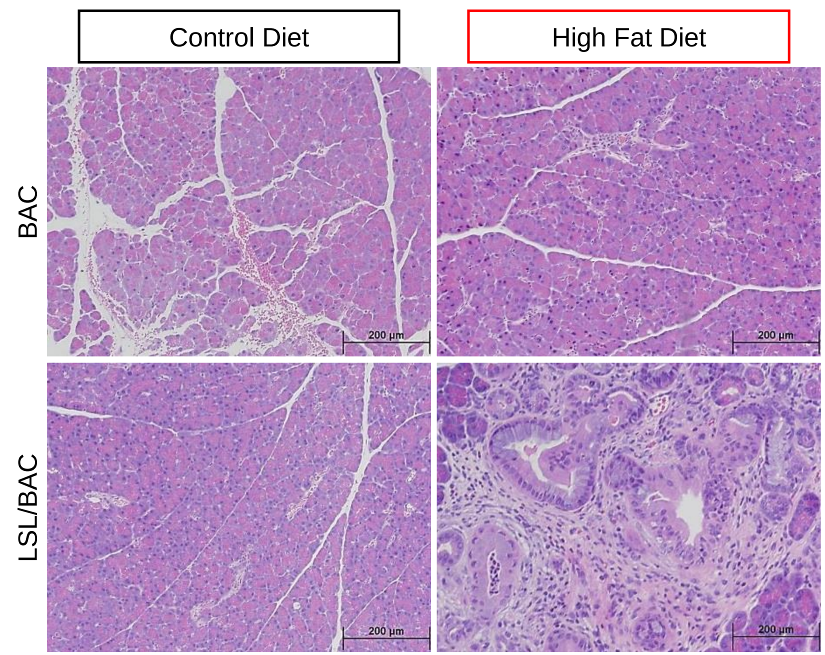

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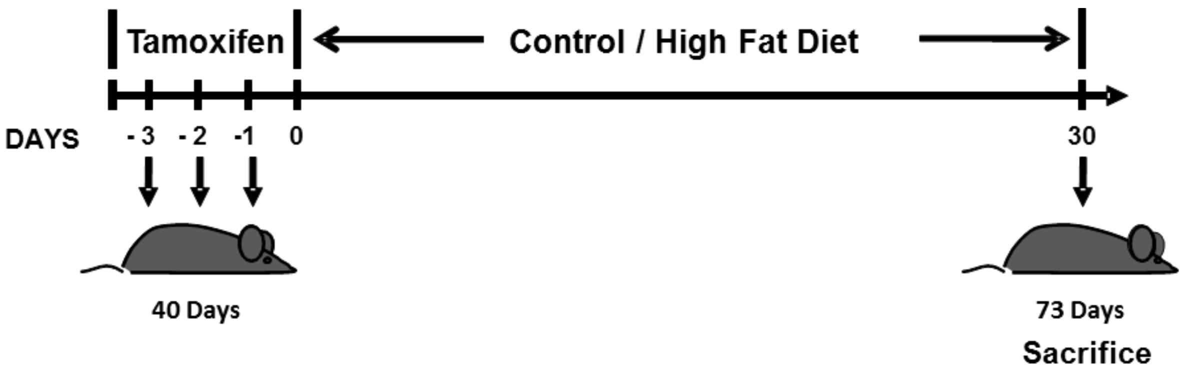

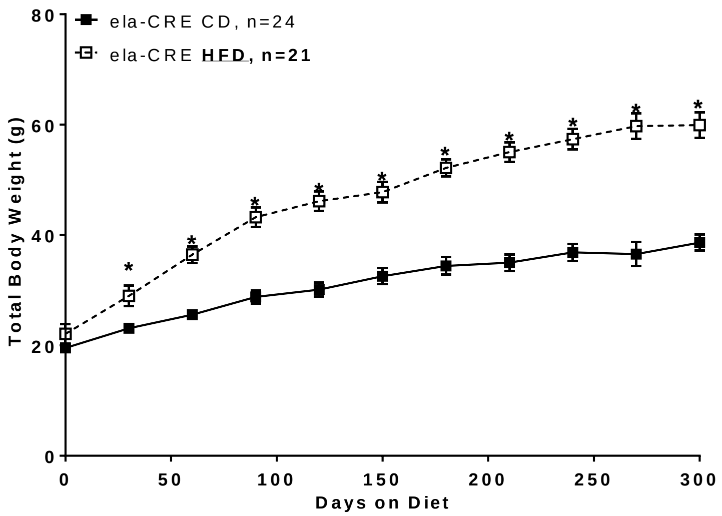

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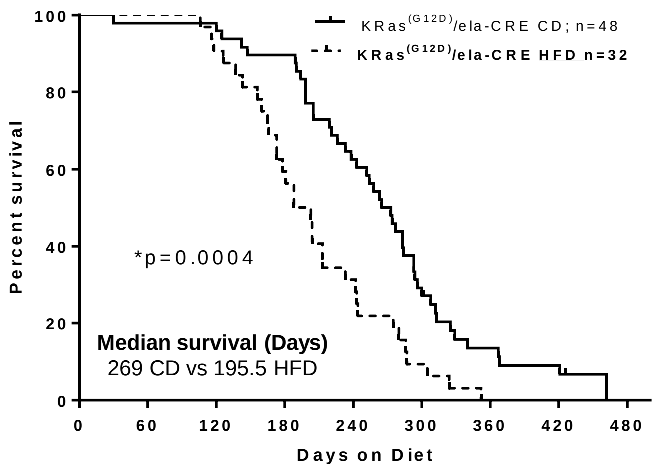

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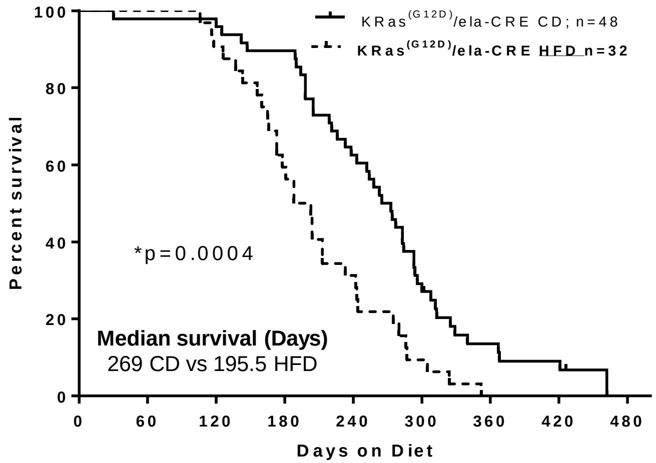
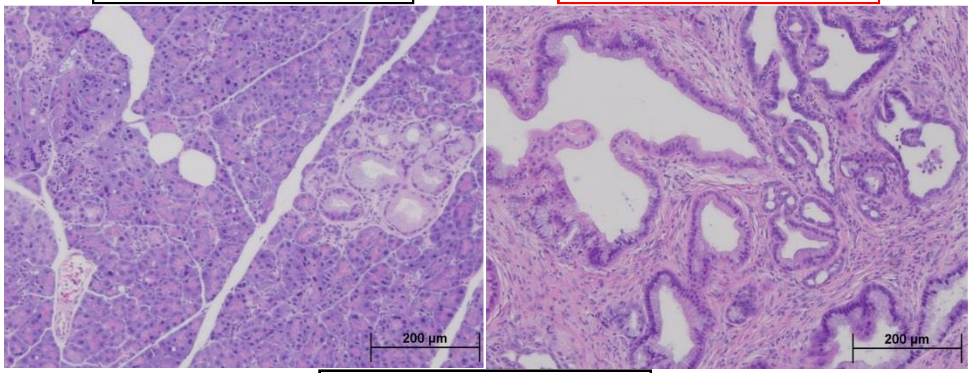


Control Diet

High Fat Diet



5.3 months / 160 days

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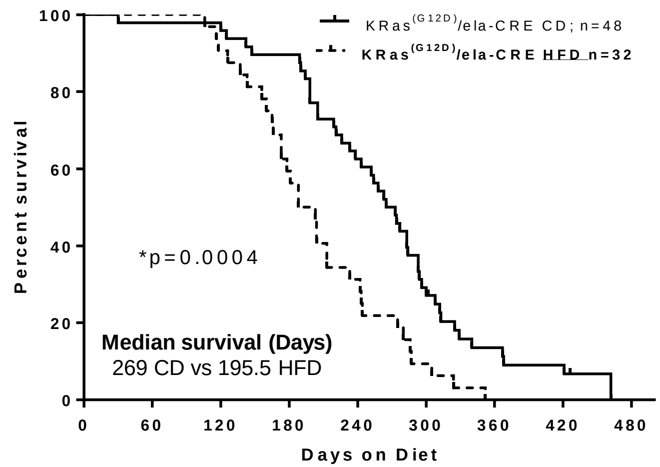

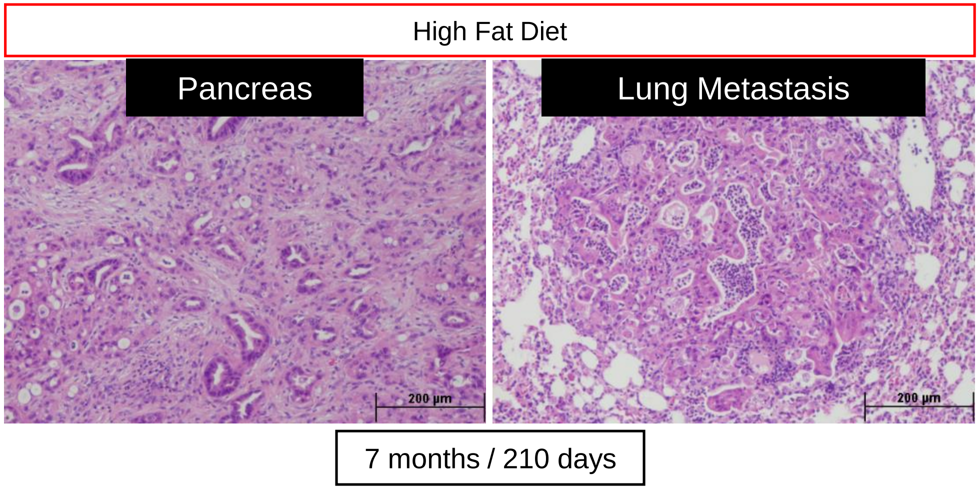

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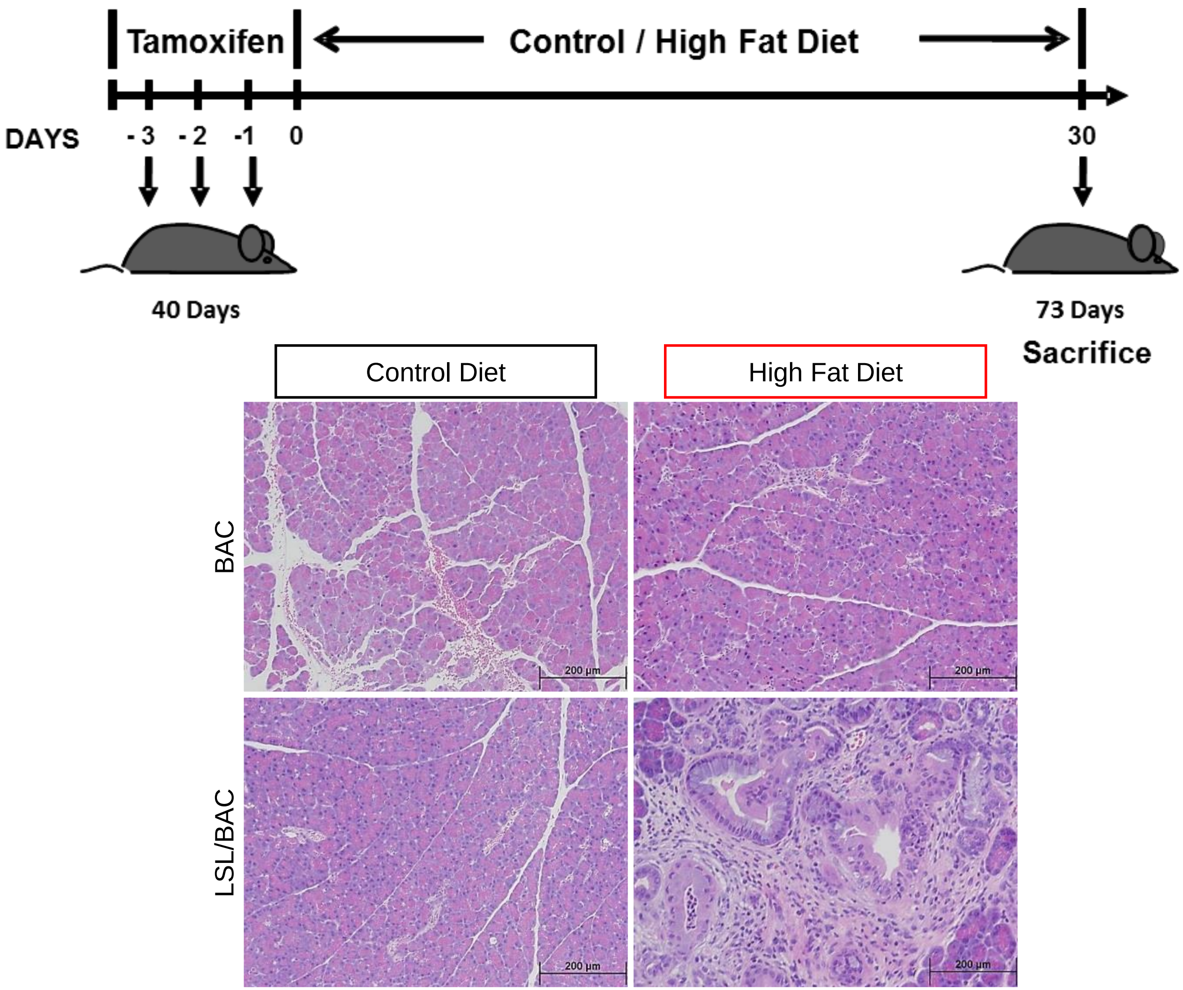
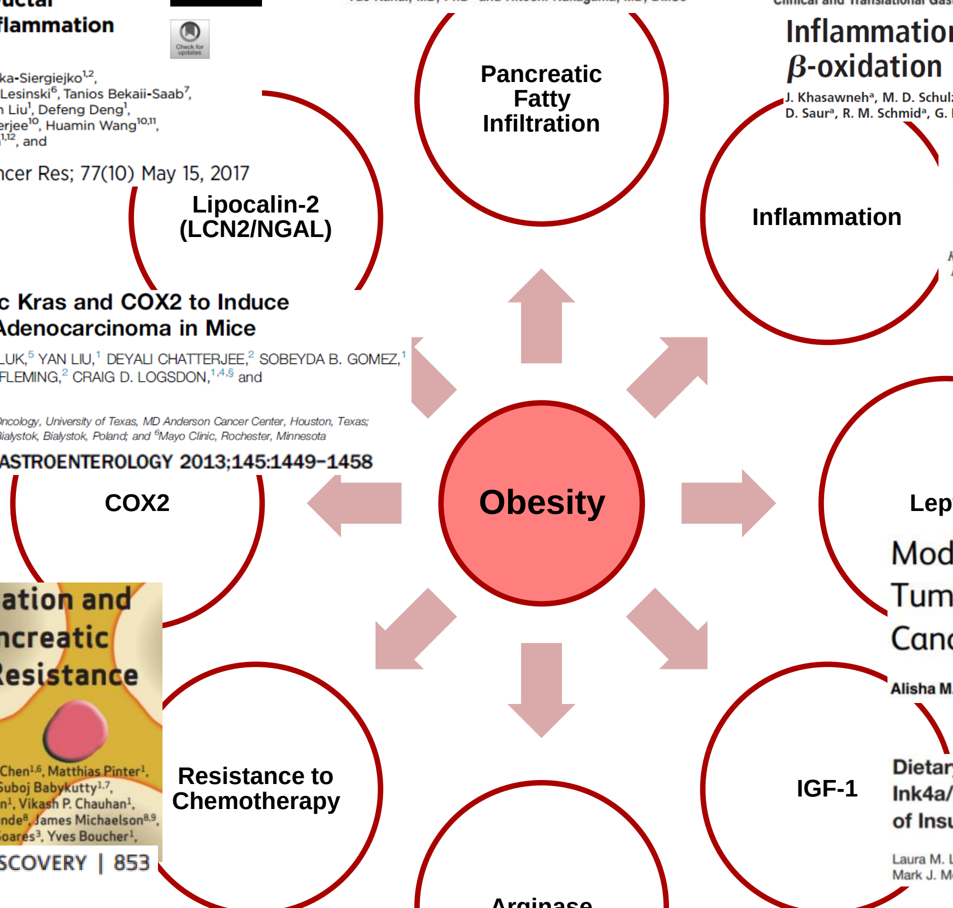


Factors Related to Obesity Affecting PDAC



Association of Pancreatic Fatty Infiltration With Pancreatic Ductal Adenocarcinoma

Mika Hori, PhD[1], Mami Takahashi, PhD[2], Nobuyoshi Hiraoka, MD, PhD[3], Taiki Yamaji, MD, PhD, MPH[4], Michihiro Mutoh, MD, PhD[5], Rikako Ishigamori, PhD[5], Koh Furuta, MD, PhD[6], Takuji Okusaka, MD, PhD[7], Kazuaki Shimada, MD, PhD[8], Tomoo Kosuge, MD, PhD[8], Yae Kanai, MD, PhD[3] and Hitoshi Nakagama, MD, DMSc[1,5]

Clinical and Translational Gastroenterology (2014) 5, e53

Inflammation and mitochondrial fatty acid β-oxidation link obesity to early tumor promotion

J. Khasawneh[a], M. D. Schulz[a], A. Walch[b], J. Rozman[c], M. Hrabe de Angelis[c], M. Klingenspor[d], A. Buck[e], M. Schwaiger[e], D. Saur[a], R. M. Schmid[a], G. Klöppel[f], B. Sipos[f], F. R. Greten[a], and M. C. Arkan[a,1]

PNAS | March 3, 2009 | vol. 106 | no. 9

Robust Early Inflammation of the Peripancreatic Visceral Adipose Tissue During Diet-Induced Obesity in the KrasG12D Model of Pancreatic Cancer

Kathleen M. Hertzer, MD, PhD, Mu Xu, MD, PhD,* Aune Moro, MSc,* David W. Dawson, MD, PhD,† Lin Du, MS,‡ Gang Li, PhD,‡ Hui-Hua Chang, PhD,* Alexander P. Stark, MD,* Xiaoman Jung, MD,* Oscar Joe Hines, MD,* and Guido Eibl, MD**

Pancreas • Volume 45, Number 3, March 2016

Pancreatic Cancer Risk Associated with Prediagnostic Plasma Levels of Leptin and Leptin Receptor Genetic Polymorphisms

Ana Babic[1], Ying Bao[2], Zhi Rong Qian[1], Chen Yuan[1], Edward L. Giovannucci[2,3,4], Hugues Aschard[3], Peter Kraft[3,5], Laufey T. Amundadottir[6], Rachael Stolzenberg-Solomon[7], Vicente Morales-Oyarvide[1], Kimmie Ng[1], Meir J. Stampfer[2,3,4], Shuji Ogino[1,8], Julie E. Buring[9,10], Howard D. Sesso[3,9], John Michael Gaziano[9,11], Nader Rifai[12], Michael N. Pollak[13], Matthew L. Anderson[14], Barbara B. Cochrane[15], Juhua Luo[16], JoAnn E. Manson[2,3,13], Charles S. Fuchs[1,2], and Brian M. Wolpin[1]

Cancer Res; 76(24) December 15, 2016

Modulation of the Leptin Receptor Mediates Tumor Growth and Migration of Pancreatic Cancer Cells

Alisha M. Mendonsa[1], Madeleine C. Chalfant[1], Lee D. Gorden[1,2], Michael N. VanSaun[3]*

PLOS ONE | DOI:10.1371/journal.pone.0126686 April 28, 2015

Dietary Energy Balance Modulation of Kras- and Ink4a/Arf$^{+/-}$-Driven Pancreatic Cancer: The Role of Insulin-like Growth Factor-I

Laura M. Lashinger[1], Lauren M. Harrison[1], Audrey J. Rasmussen[1], Craig D. Logsdon[2], Susan M. Fischer[3], Mark J. McArthur[3,4], and Stephen D. Hursting[1,3]

Cancer Prev Res; 6(10) October 2013

Critical role for arginase 2 in obesity-associated pancreatic cancer

Tamara Zaytouni[1,2,3], Pei-Yun Tsai[1,2], Daniel S. Hitchcock[3], Cory D. DuBois[1,3], Elizaveta Freinkman[4,8], Lin Lin[2], Vicente Morales-Oyarvide[5], Patrick J. Lenehan[1,2], Brian M. Wolpin[5], Mari Mino-Kenudson[6], Eduardo M. Torres[7], Nicholas Stylo...

NATURE COMMUNICATIONS | 8: 242

Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy

Joao Incio[1,2,3], Hao Liu[1,4], Priya Suboj[1,5], Shan M. Chin[1], Ivy X. Chen[1,6], Matthias Pinter[1], Mei R. Ng[1], Hadi T. Nia[1], Jelena Grahovac[1], Shannon Kao[1], Suboj Babykutty[1,7], Yuhui Huang[1], Keehoon Jung[1], Nuh N. Rahbari[1], Xiaoxing Han[1], Vikash P. Chauhan[1], John D. Martin[1], Julia Kahn[1], Peigen Huang[1], Vikram Desphande[8], James Michaelson[8,9], Theodoros P. Michelakos[10], Cristina R. Ferrone[8,10], Raquel Soares[3], Yves Boucher[1], Dai Fukumura[1], and Rakesh K. Jain[1]

CANCER DISCOVERY | 853

A High-Fat Diet Activates Oncogenic Kras and COX2 to Induce Development of Pancreatic Ductal Adenocarcinoma in Mice

BINCY PHILIP,[1] CHRISTINA L. ROLAND,[2] JAROSLAW DANILUK,[5] YAN LIU,[1] DEYALI CHATTERJEE,[2] SOBEYDA B. GOMEZ,[1] BAOAN JI,[6] HAOJIE HUANG,[1] HUAMIN WANG,[3] JASON B. FLEMING,[2] CRAIG D. LOGSDON,[1,4,§] and ZOBEIDA CRUZ-MONSERRATE[1,§]

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GASTROENTEROLOGY 2013;145:1449–1458

Molecular and Cellular Pathobiology

Cancer Research

Lipocalin-2 Promotes Pancreatic Ductal Adenocarcinoma by Regulating Inflammation in the Tumor Microenvironment

Sobeyda B. Gomez-Chou[1], Agnieszka Katarzyna Swidnicka-Siergiejko[1,2], Niharika Badi[3,4,5], Myrriah Chavez-Tomar[3,4,5], Gregory B. Lesinski[6], Tanios Bekaii-Saab[7], Matthew R. Farren[6], Thomas A. Mace[3], Carl Schmidt[8], Yan Liu[1], Defeng Deng[1], Rosa F. Hwang[9], Liran Zhou[9], Todd Moore[9], Deyali Chatterjee[10], Huamin Wang[10,11], Xiaohong Leng[11], Ralph B. Arlinghaus[11], Craig D. Logsdon[1,12], and Zobeida Cruz-Monserrate[3,4,5]

Cancer Res; 77(10) May 15, 2017

Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort

Daniel P. Schauer, MD, MSc, Heather Spencer Feigelson, PhD, MPH,† Corinna Koebnick, MSc, PhD,‡ Bette Caan, DrPH,§ Sheila Weinmann, PhD, MPH,¶ Anthony C. Leonard, PhD,|| J. David Powers, MS,† Panduranga R. Yenumula, MD,§ and David E. Arterburn, MD, MPH***

Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort

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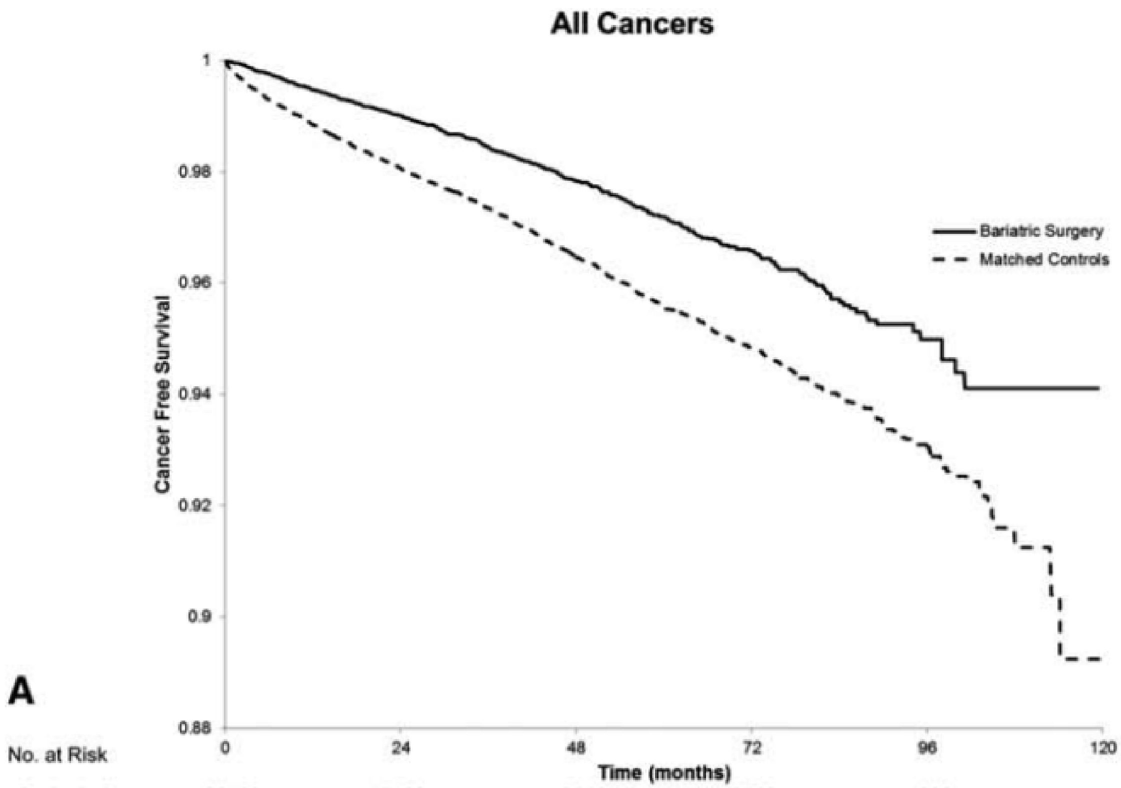
Objective: To determine whether bariatric surgery is associated with a lower risk of cancer.

Background: Obesity is strongly associated with many types of cancer. Few studies have examined the relationship between bariatric surgery and cancer risk.

Methods: We conducted a retrospective cohort study of patients undergoing bariatric surgery between 2005 and 2012 with follow-up through 2014 using data from a large integrated health insurance and care delivery systems with 5 study sites. The study included 22,198 subjects who had bariatric surgery and 66,427 nonsurgical subjects matched on sex, age, study site, body mass index, and Elixhauser comorbidity index. Multivariable Cox proportional-hazards models were used to examine incident cancer up to 10 years after bariatric surgery compared to the matched nonsurgical patients.

Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort

Daniel P. Schauer, MD, MSc, * *Heather Spencer Feigelson, PhD, MPH,*† *Corinna Koebnick, MSc, PhD,*‡ *Bette Caan, DrPH,*§ *Sheila Weinmann, PhD, MPH,*¶ *Anthony C. Leonard, PhD,*|| *J. David Powers, MS,*† *Panduranga R. Yenumula, MD,*§ *and David E. Arterburn, MD, MPH***



No. at Risk					
Bariatric Surgery	22198	19126	9048	3566	628
Matched Controls	66427	49131	20844	8284	1764

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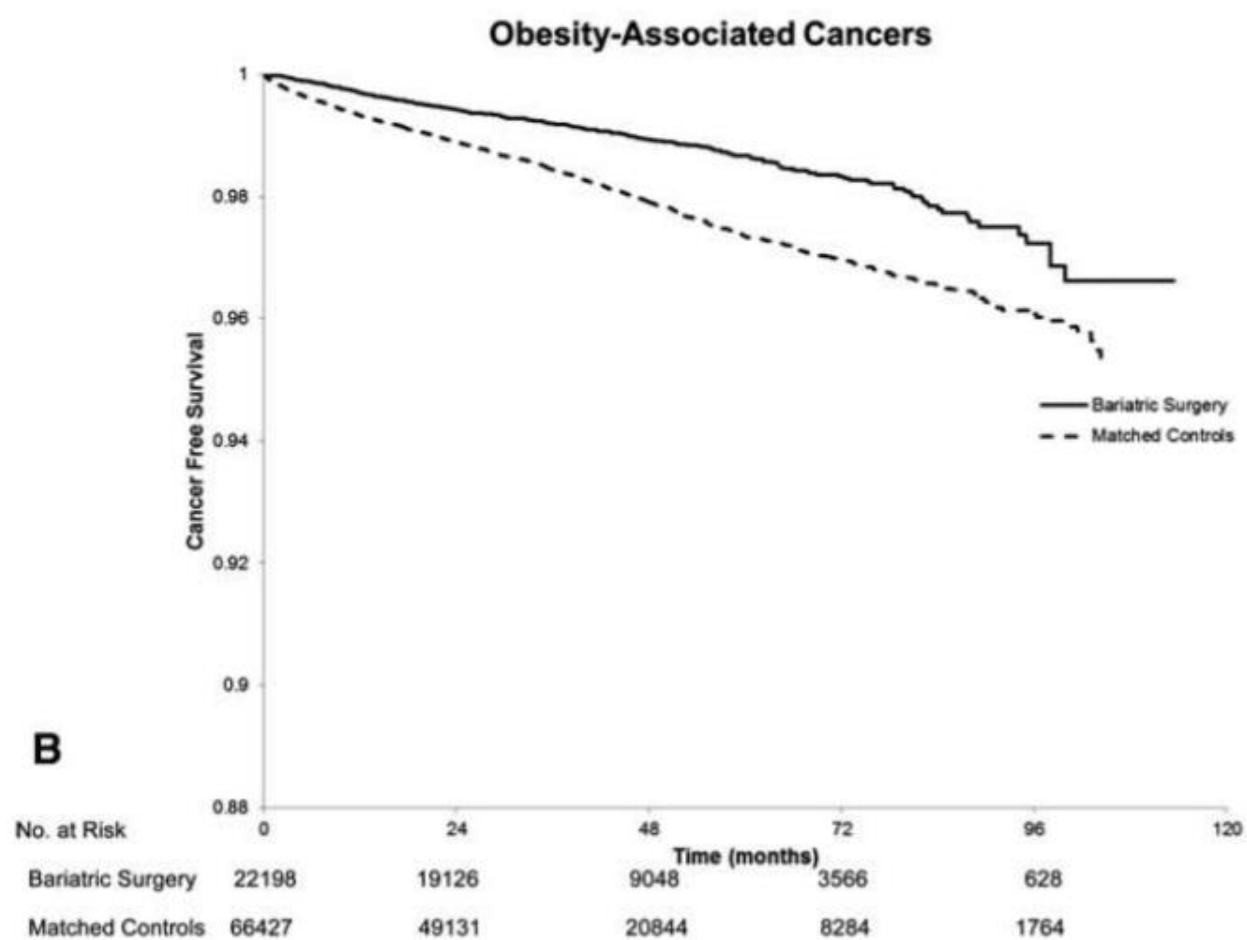

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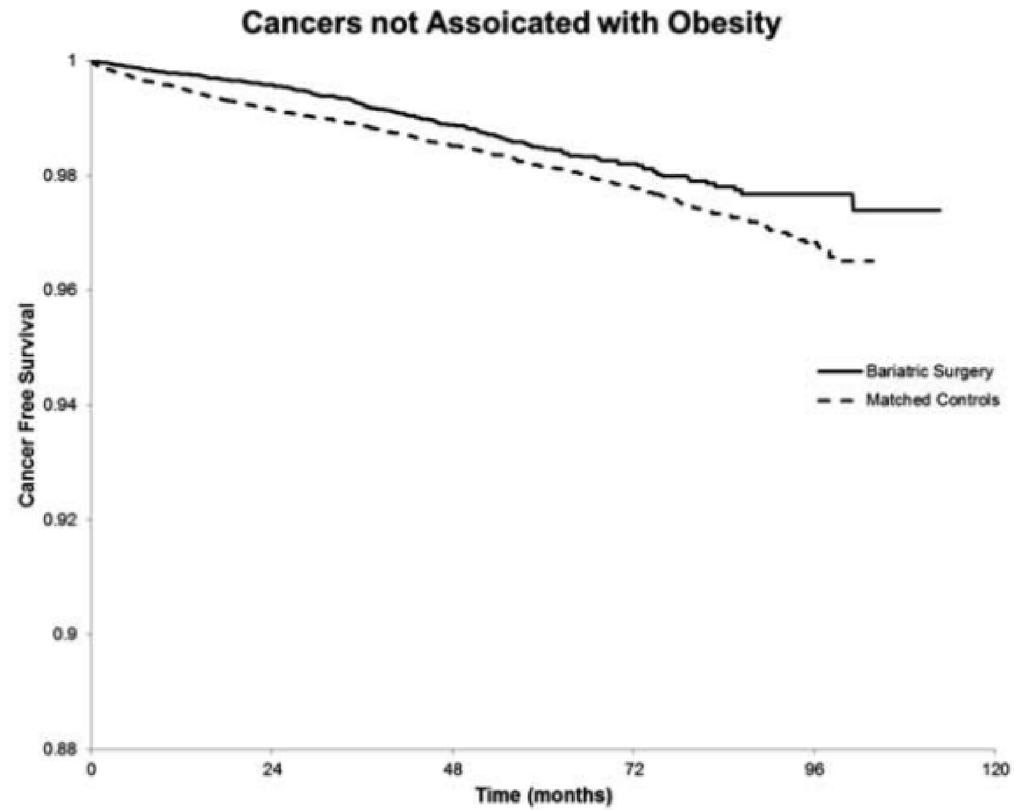

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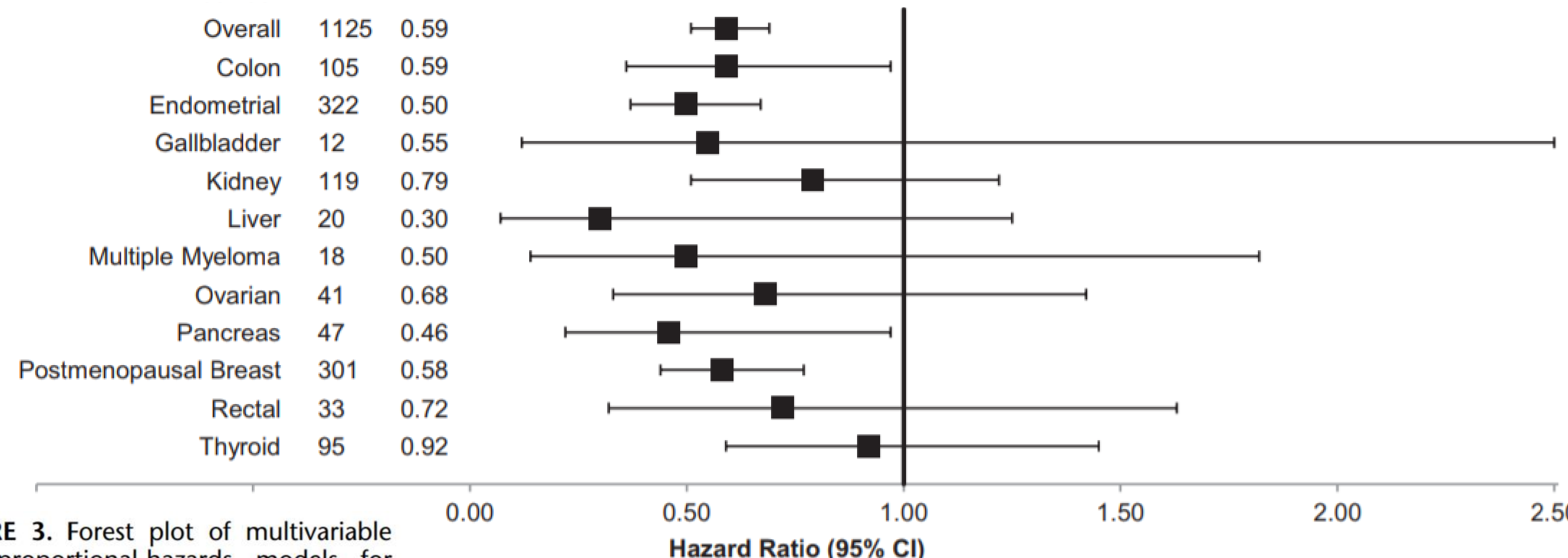

FIGURE 3. Forest plot of multivariable Cox proportional-hazards models for obesity-associated cancers. The box represents the hazard ratio and the error bars depict the 95% confidence interval. Matching occurred on age, sex, BMI, Elixhauser comorbidity index score, and study site. The models are adjusted for race, diabetes, hyperlipidemia, hypertension, coronary artery disease, peripheral vascular disease, nonalcoholic steatohepatitis, a history of smoking, alcohol use, and use of hormone replacement therapy.

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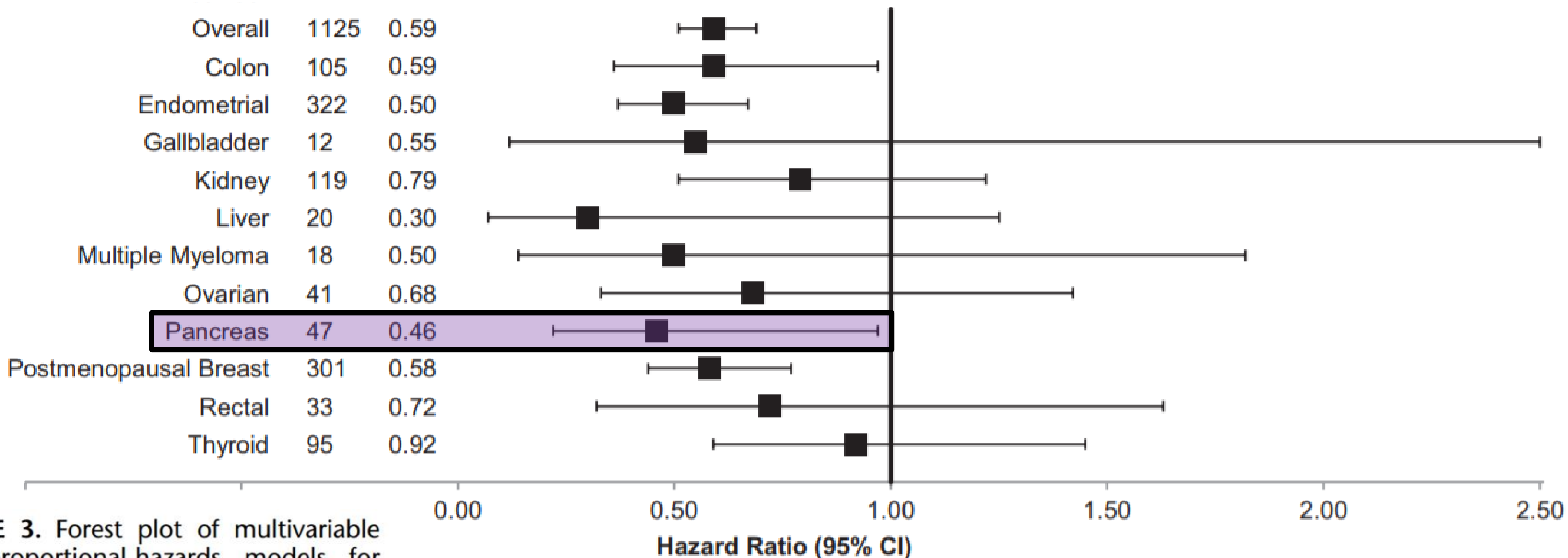

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Results: After a mean follow-up of 3.5 years, we identified 2543 incident cancers. Patients undergoing bariatric surgery had a 33% lower hazard of developing any cancer during follow-up [hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.60, 0.74, $P < 0.001$) compared with matched patients with severe obesity who did not undergo bariatric surgery, and results were even stronger when the outcome was restricted to obesity-associated cancers (HR 0.59, 95% CI 0.51, 0.69, $P < 0.001$). Among the obesity-associated cancers, the risk of postmenopausal breast cancer (HR 0.58, 95% CI 0.44, 0.77, $P < 0.001$), colon cancer (HR 0.59, 95% CI 0.36, 0.97, $P =$ 0.04), endometrial cancer (HR 0.50, 95% CI 0.37, 0.67, $P < 0.001$), and pancreatic cancer (HR 0.46, 95% CI 0.22, 0.97, $P = 0.04$) was each statistically significantly lower among those who had undergone bariatric surgery compared with matched nonsurgical patients.

Conclusions: In this large, multisite cohort of patients with severe obesity, bariatric surgery was associated with a lower risk of incident cancer, particularly obesity-associated cancers, such as postmenopausal breast cancer, endometrial cancer, and colon cancer. More research is needed to clarify the specific mechanisms through which bariatric surgery lowers cancer risk.

Knowledge Gaps

- How are factors secreted from adipose tissue affecting the tumor microenvironment of PDAC?
- Are these factors affecting cancer cells only or other cells in the tumor microenvironment?
- How is the adipose cellular microenvironment contributing to PDAC?
- Are the characteristics of an obesity-associated PDAC the same as non-obese PDAC?
- Best preclinical model that mimics human obesity-associated PDAC.
- Identify specific patient populations
  - Who are at greatest risk of developing obesity-related cancer
  - Who will benefit most from weight loss or enhanced screening
- Identify markers, metabolic intermediates or predictors of obesity-related cancer

Paradoxical impact of obesity on cancer immunotherapy

nature medicine

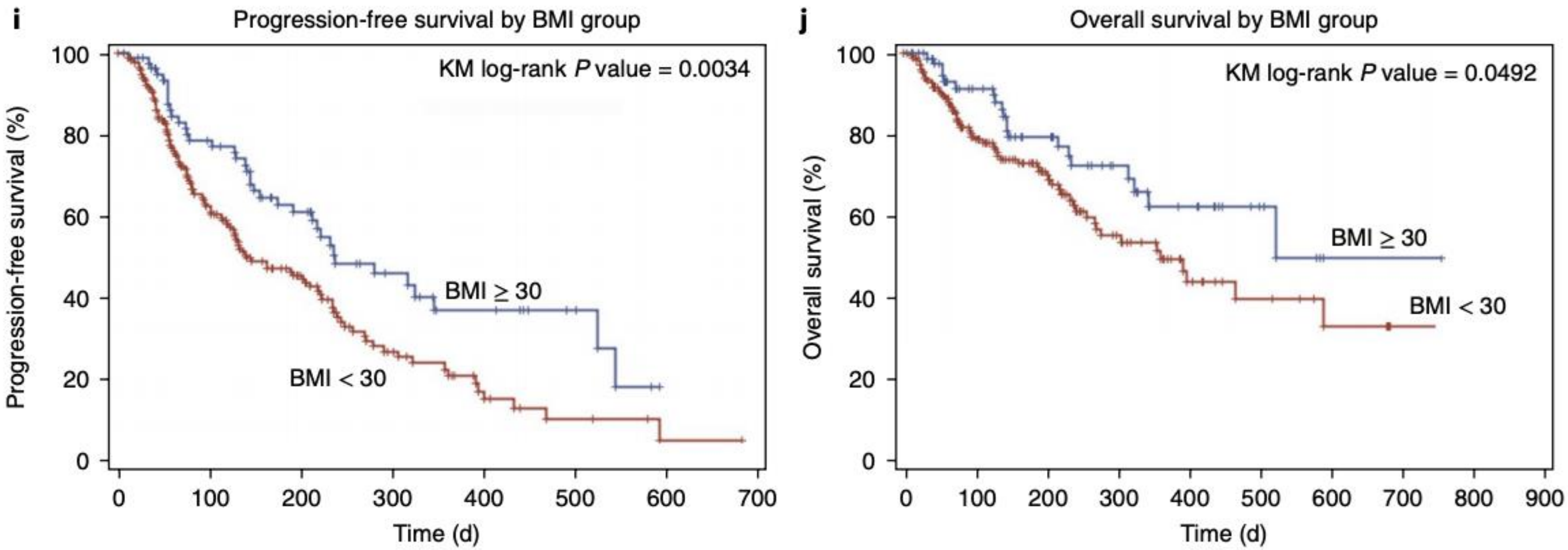
ARTICLES

https://doi.org/10.1038/s41591-018-0221-5

Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade

"There is heightened immune dysfunction and tumor progression but also **greater anti-tumor efficacy and survival after checkpoint blockade** which directly targets some of the pathways activated in obesity."

Paradoxical impact of obesity on cancer immunotherapy



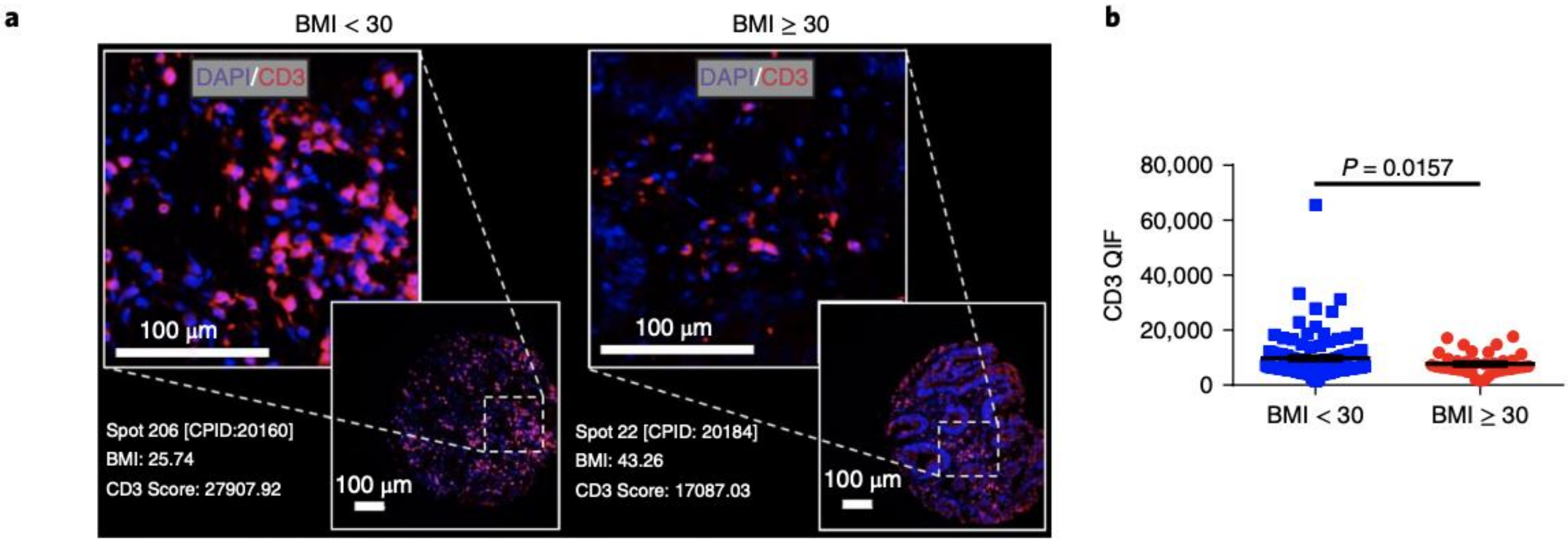
There is a statistically significant improvement in progression-free survival and overall survival in obese patients

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0221-5

Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade

Impact of obesity on exhaustion and PD-1 checkpoint blockade in patients with cancer

CD3+ infiltrates in the TME of human colorectal cancers



There are significantly fewer tumor-infiltrating cells in obese patients

Paradoxical impact of obesity on cancer immunotherapy

nature medicine
ARTICLES
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Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade

"There is heightened immune dysfunction and tumor progression but also **greater anti-tumor efficacy and survival after checkpoint blockade** which directly targets some of the pathways activated in obesity."

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POSTDOCTORAL POSITION AVAILABLE!!!!

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ZCM-Lab Summer 2019

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