



# Diet, Nutrition and Cancer Prevention



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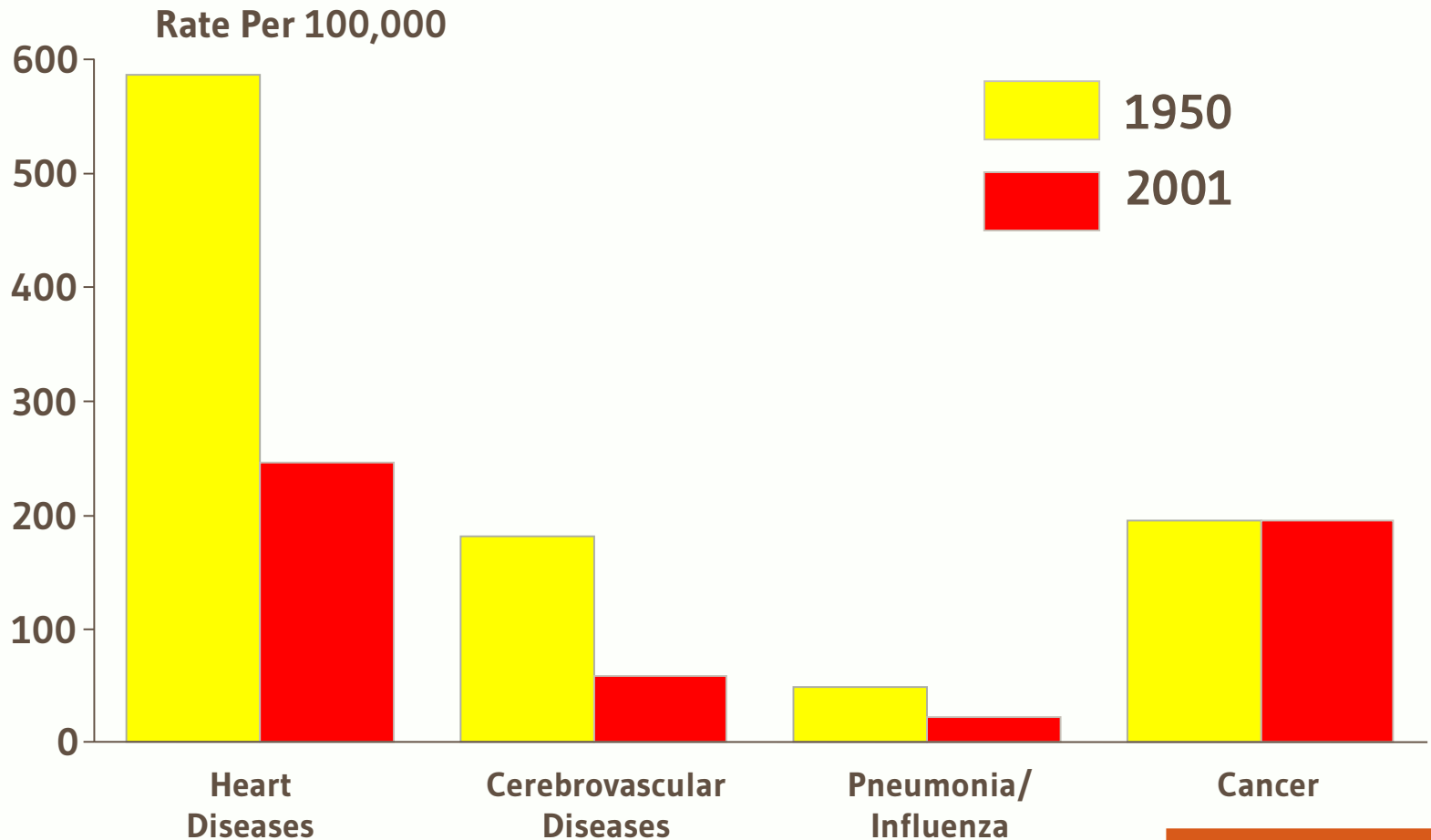


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and Human Sciences**

# Change in the US Death Rates\* by Cause, 1950 & 2001

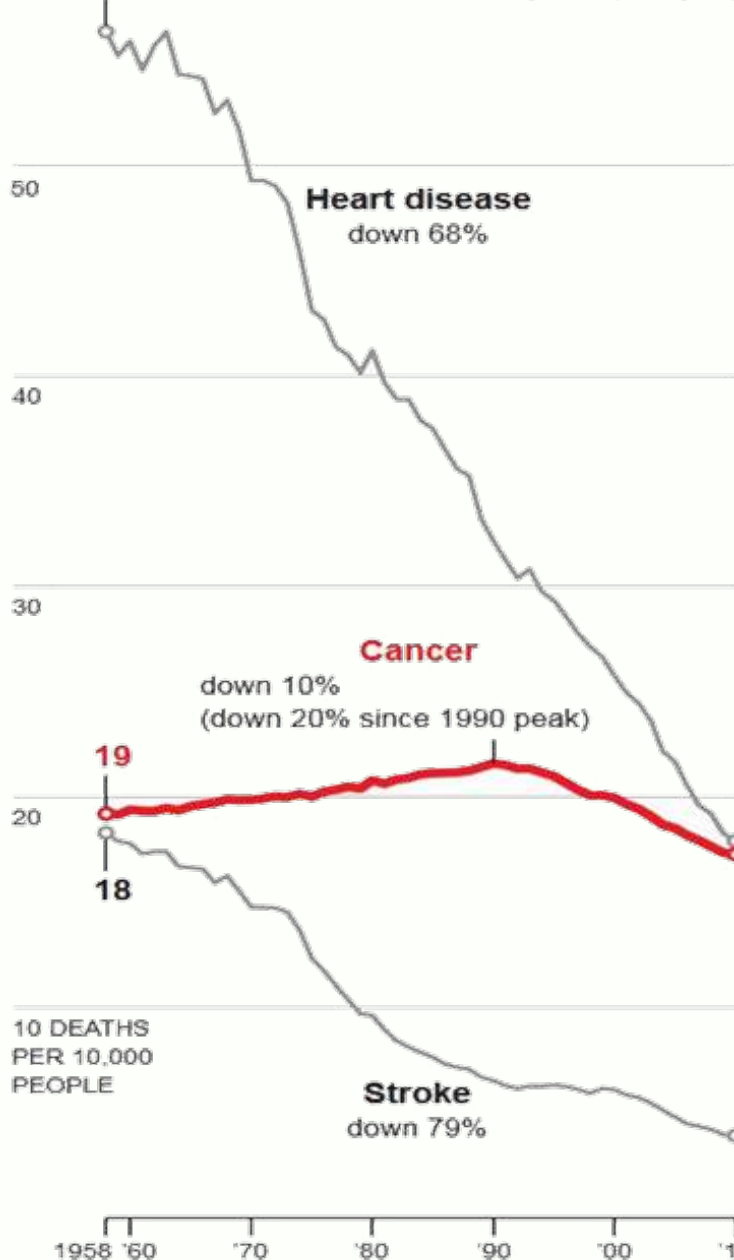


\* Age-adjusted to 2000 US standard population.

Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised. 2001 Mortality Data—NVSR-Death Final Data 2001—Volume 52, No. 3. [http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52\\_03.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf)

Heart disease death rate for 1958: **56** per 10,000 people.

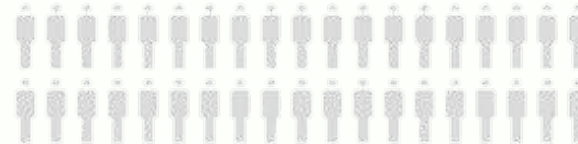
2010 death rate: **18** per 10,000 people.



**Heart disease**  
down 68%

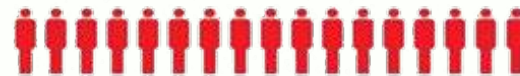
**Cancer**  
down 10%  
(down 20% since 1990 peak)

**Stroke**  
down 79%



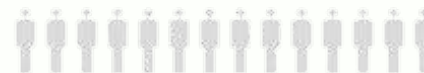
Compared with 1958, this is a reduction of **38** deaths per 10,000.

2010 cancer death rate: **17** per 10,000.



Compared with 1958, a reduction of **2**.

2010 stroke death rate: **4** per 10,000.



Compared with 1958, a reduction of **14**.

10 DEATHS  
PER 10,000  
PEOPLE

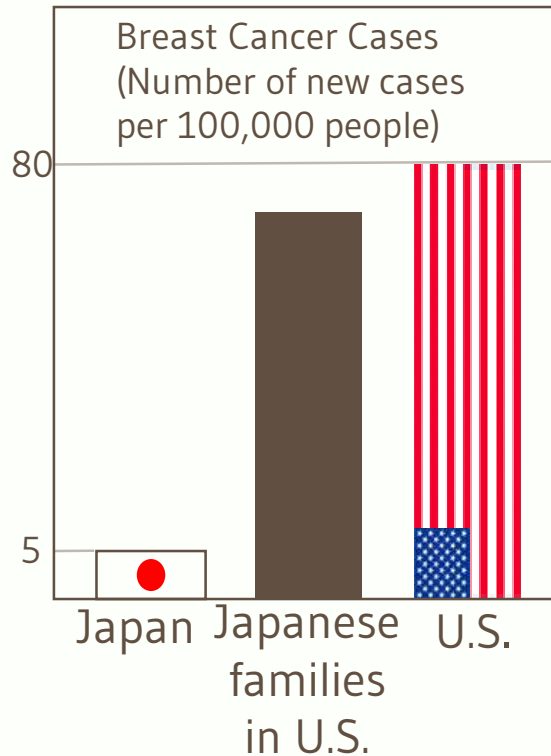
# Causes of Cancer

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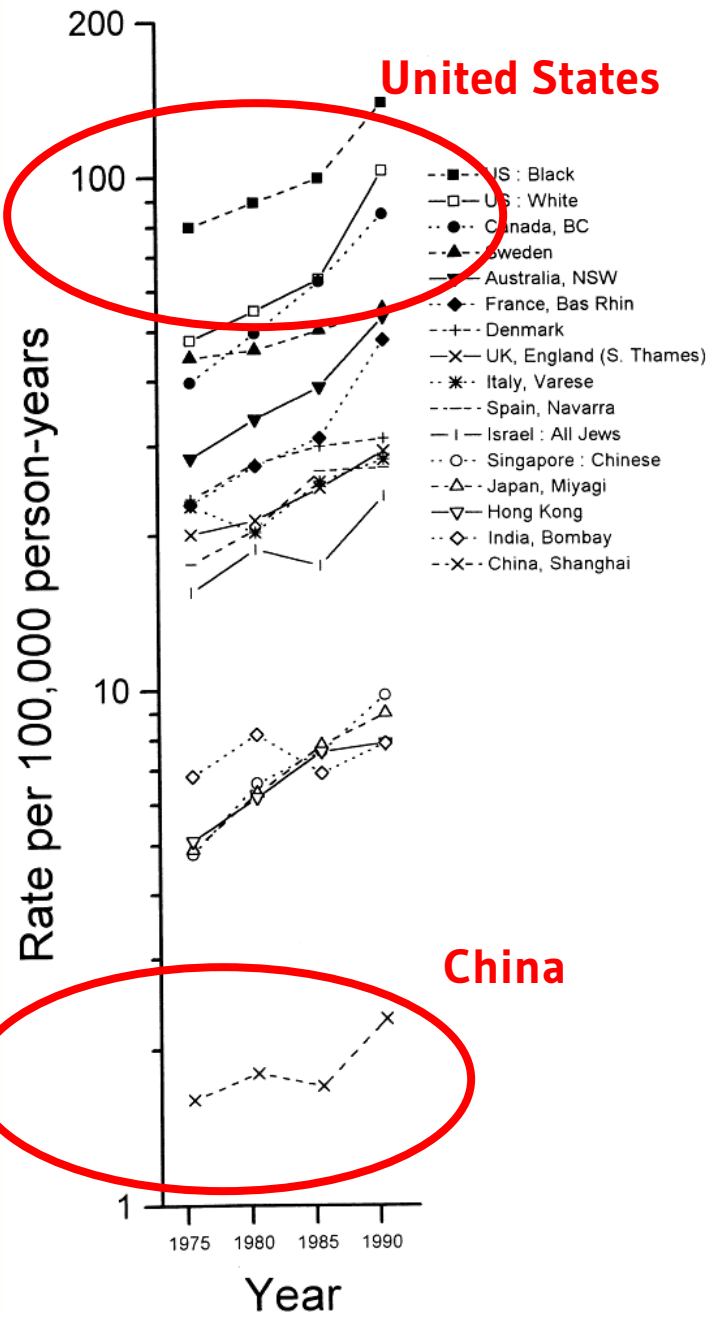
Smoking	~ 30%
<b>Diet</b>	<b>~35%</b>
Infection	~20%
Occupation	~2%
Pollution	~1%

# Genetics vs Lifestyle ?

- Rates of breast cancer are much lower in other parts of the world such as Japan.



- Migrant studies suggest breast cancer risk is modifiable and that differences in population rates may be due to lifestyle or environmental factors.

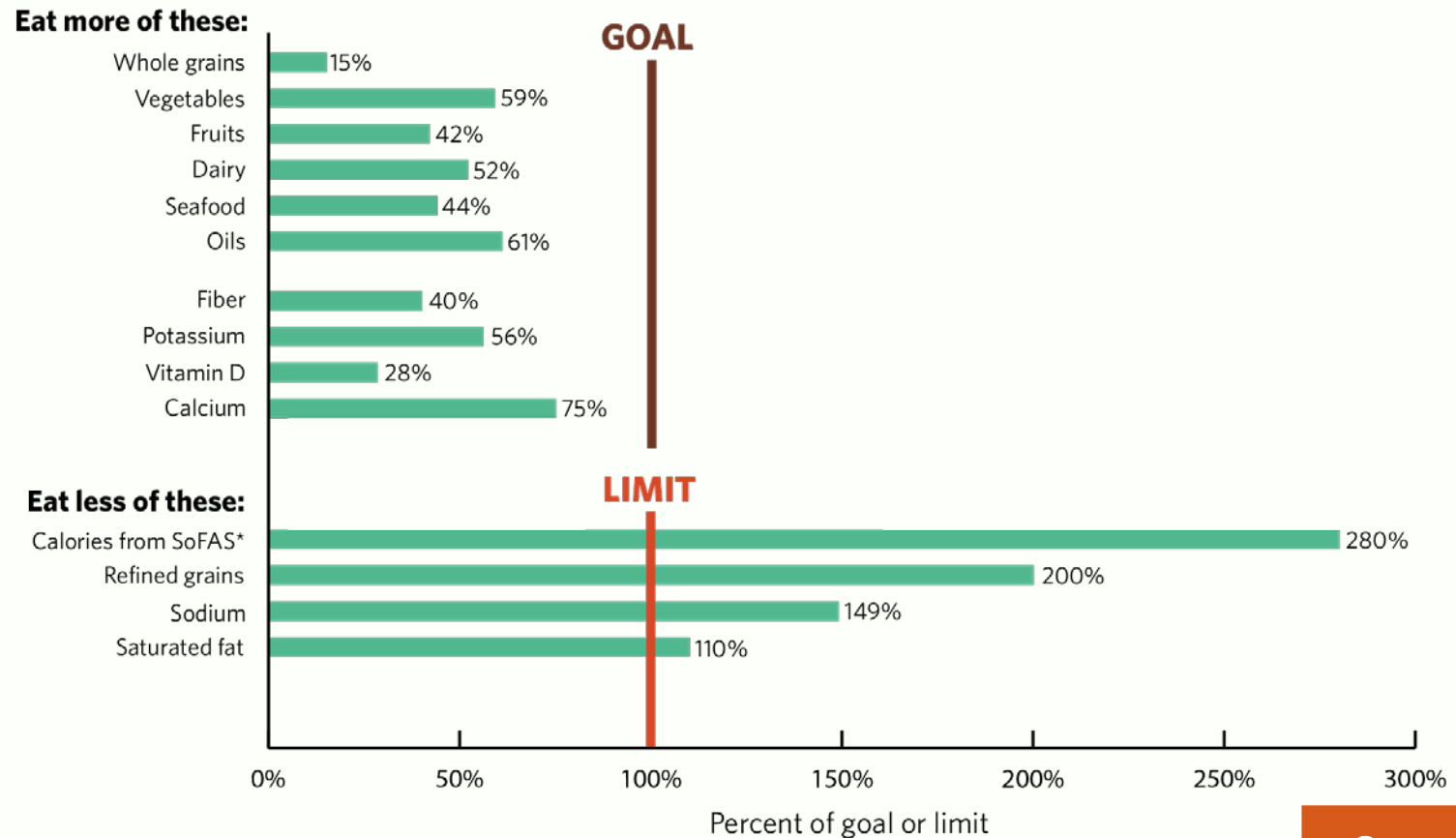


	Prostate Cancer Rate
Shanghai born Chinese	1.8
China born Chinese (live U.S. 5-10yr)	23
U.S. born Chinese	37
U.S. born Caucasian	58

Int.J. Cancer (2000) 85:60-7

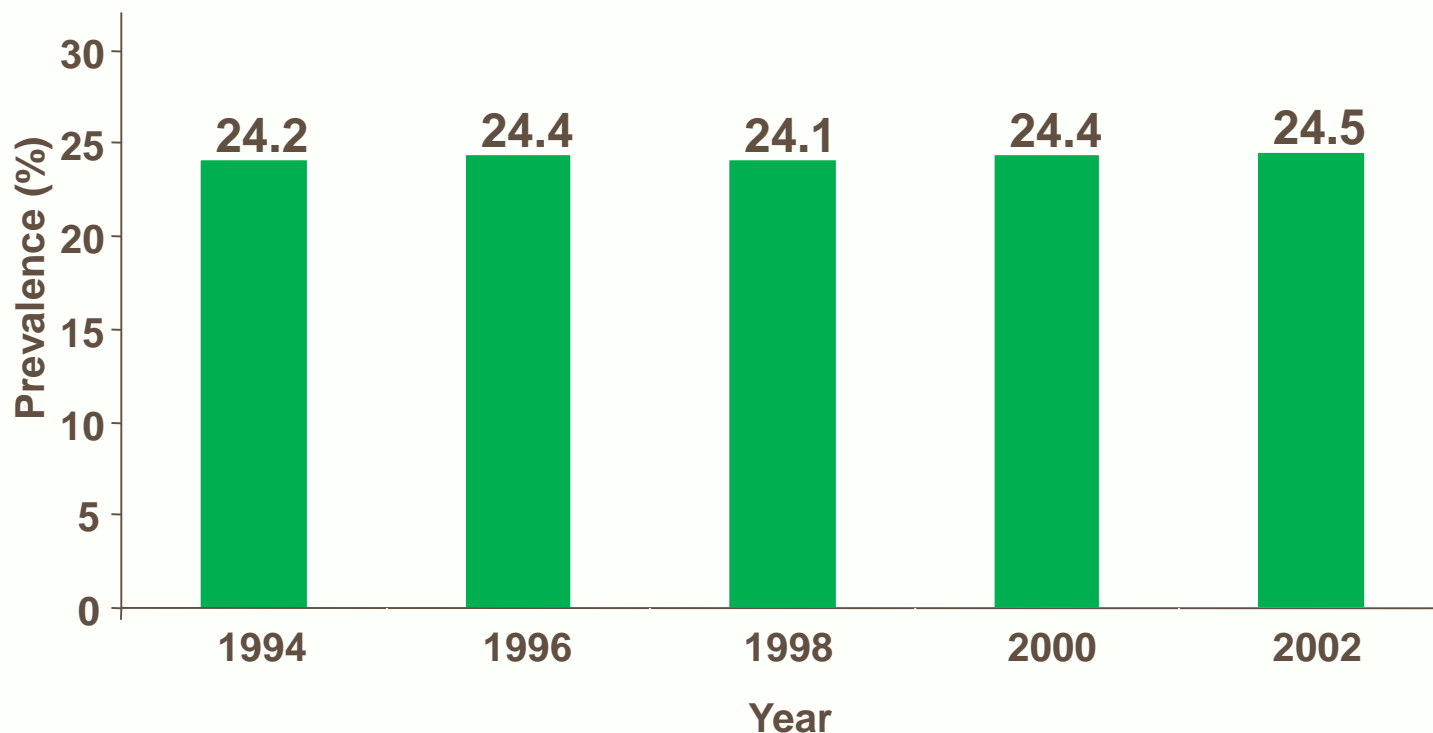
# How do Typical American Diets Compare to Recommended Intake Levels or Limits?

Usual intake as a percent of goal or limit



Source: Dietary Guidelines for Americans 2010 (Health.gov)

# How often do Americans eat the Recommended amount of Fruits and Vegetables per day?



Source: Behavioral Risk Factor Surveillance System CD-ROM (1984-1995, 1996, 1998) and Public Use Data Tape (2000), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1997, 1999, 2000, 2001.



**INITIATION**

DNA DAMAGE



Repair is incomplete

DNA replication



RAPID DIVISION OF CELLS  
"CLONAL EXPANSION"  
OF INITIATED CELLS

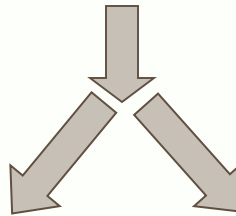
**PROMOTION**

Still reversible  
Rapid division,  
more mutations



**PROGRESSION**

TUMOR FORMATION



irreversible

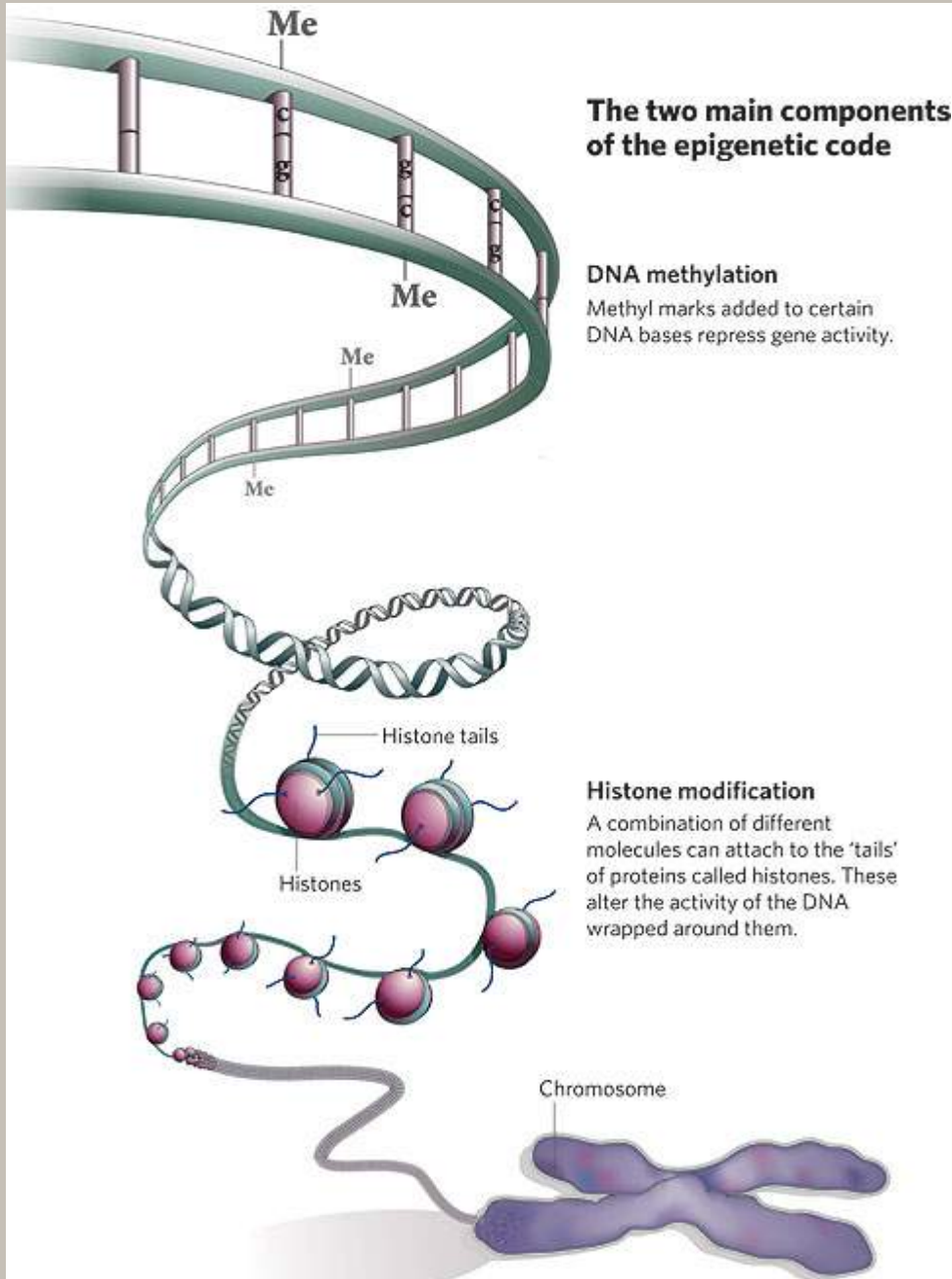
BENIGN  
TUMOR

MALIGNANT  
TUMOR

**METASTASIS**

# The Epigenetic Revolution



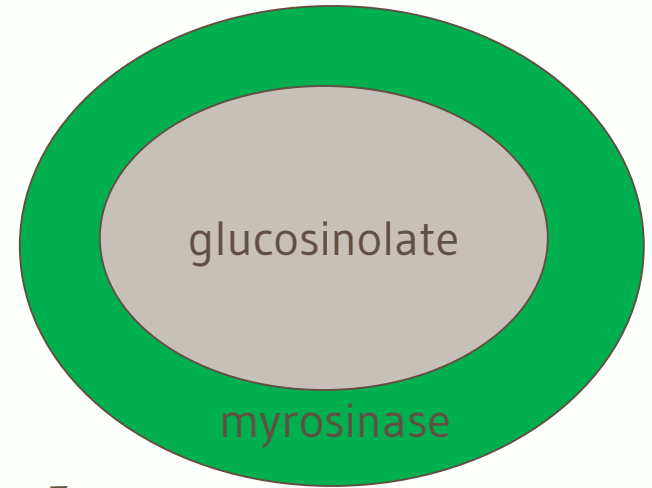


- Non coding RNA
- Methylation of CpG islands
- Changes in chromatin – “histone code”
  - Methylation of histones
  - Phosphorylation of histones
  - Ubiquitination of histones
  - Biotinylation of histones
  - Acetylation of histones...

Catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs)



BRASSICA



SULFORAPHANE

# What about people?

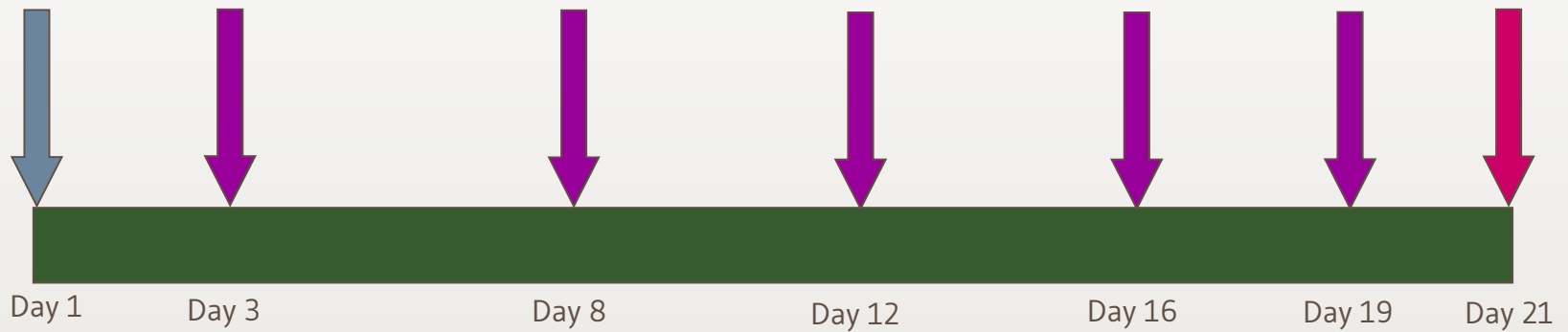
Broccoli  
Sprouts



50 times higher glucosinolates  
Than mature plant

# Sulforaphane slows tumor growth

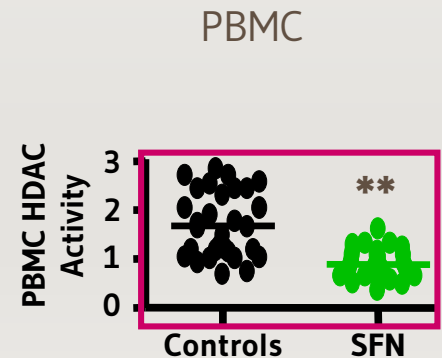
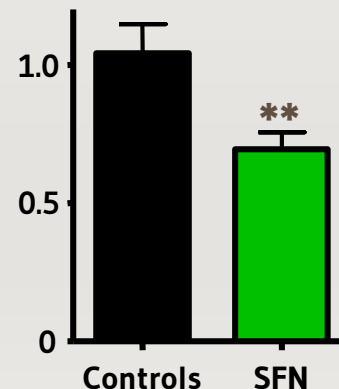
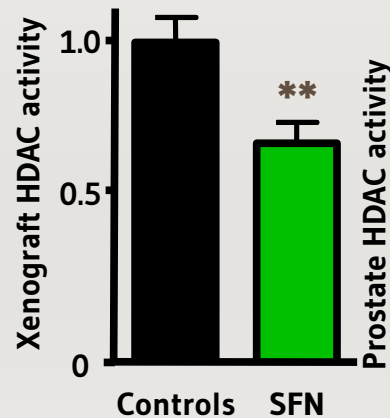
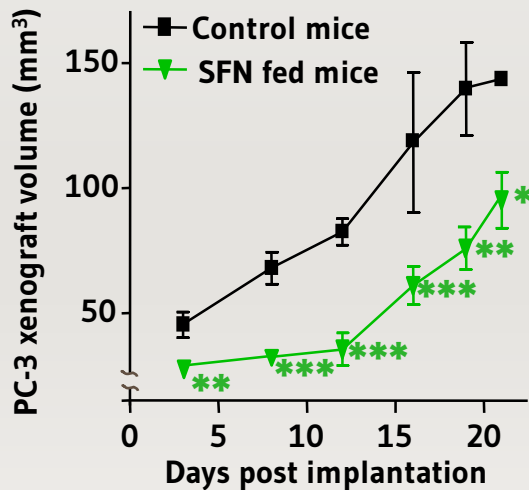
Xenograft measurements



Implant PC-3 cells  
Begin SFN diet

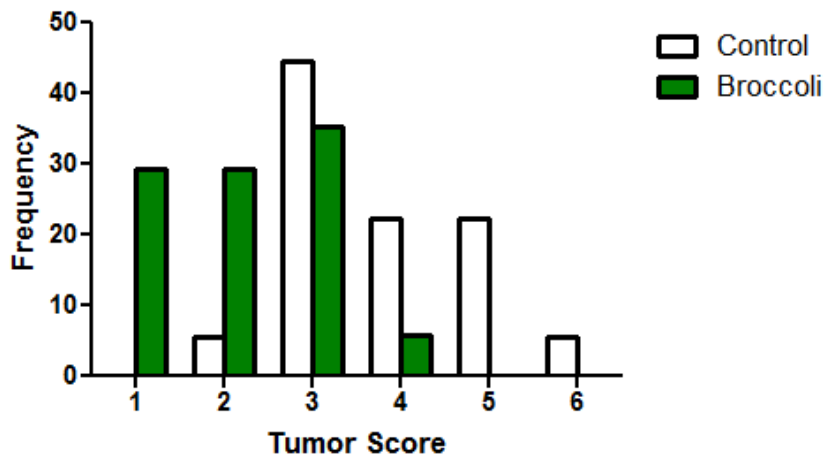
Mice consumed ~ 7.5  $\mu\text{mol}$  SFN per day

Terminate study

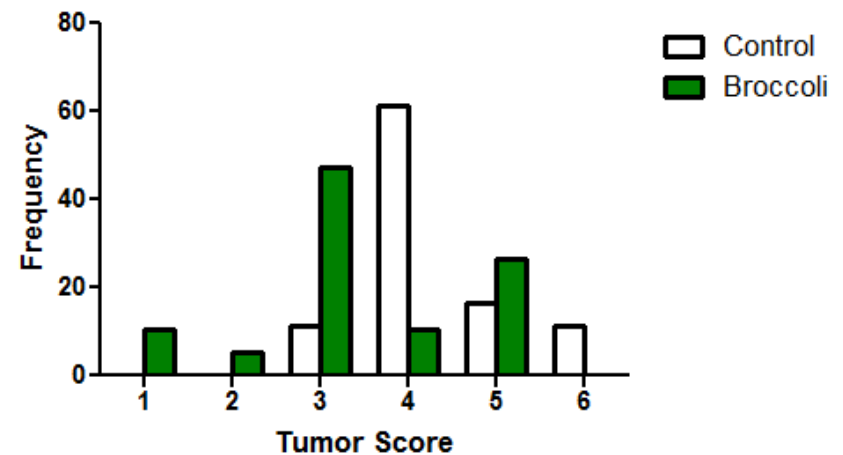


# Broccoli sprout diets delay prostate tumor progression

12 Week Old Tumor Score Distribution by Treatment Group



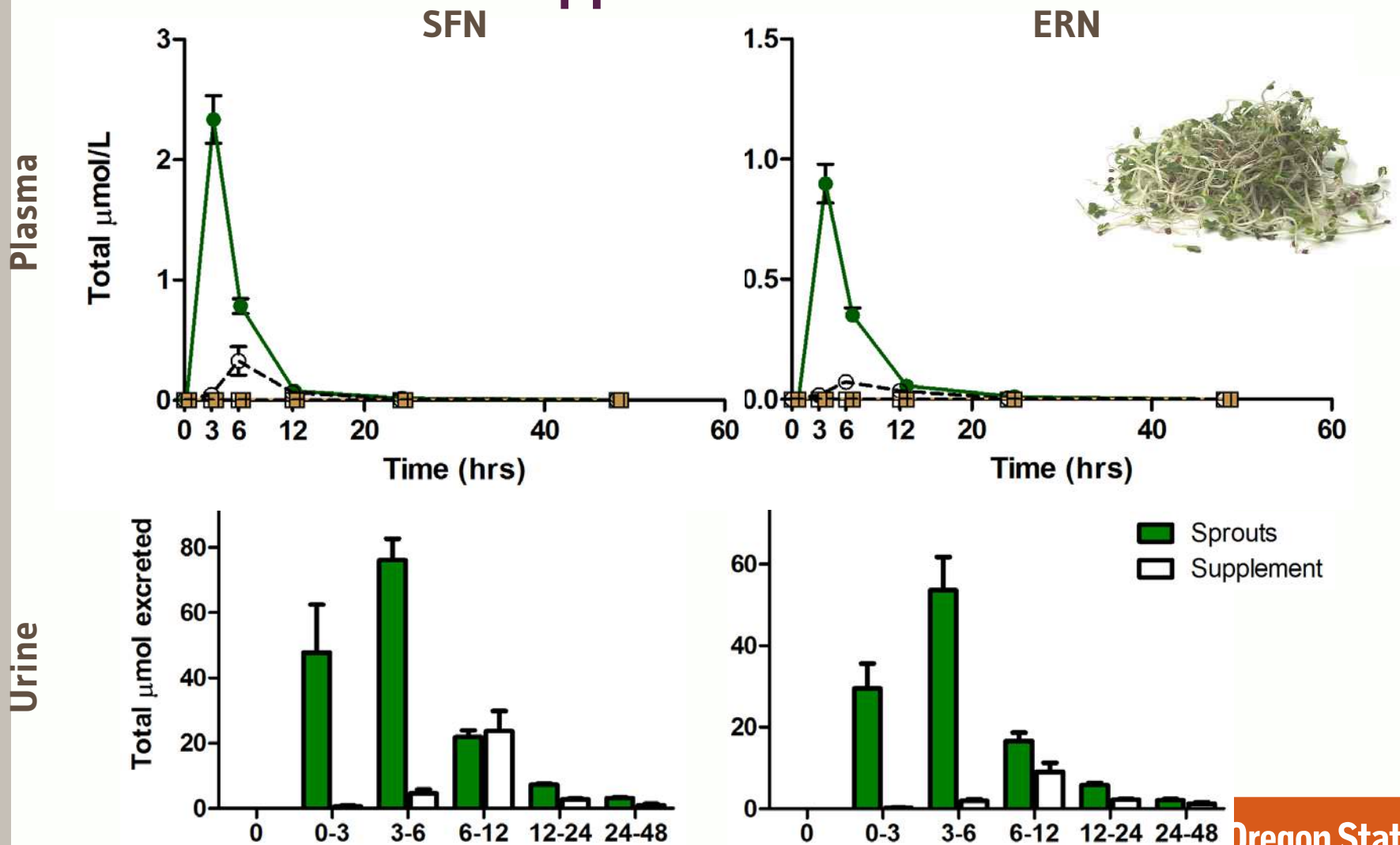
29 Week Old Tumor Score Distribution by Treatment Group



1. normal
2. PIN
3. cribriform
4. early adenocarcinoma
5. moderate adenocarcinoma
6. poorly differentiated adenocarcinoma

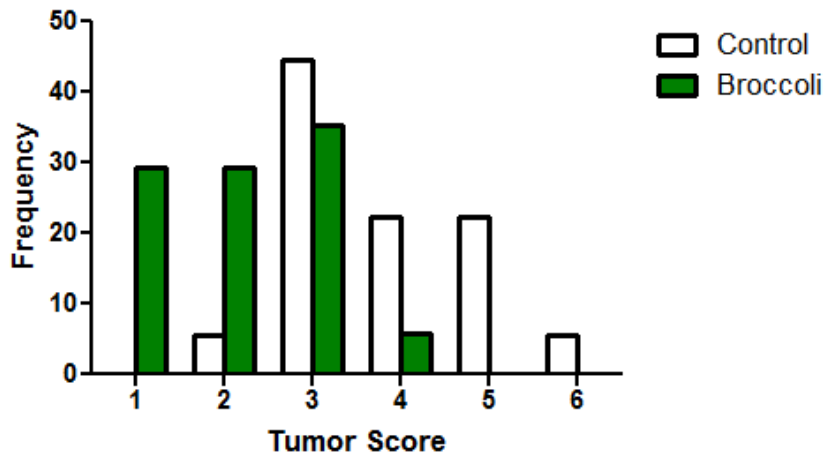


# Food sources does better job than a supplement source

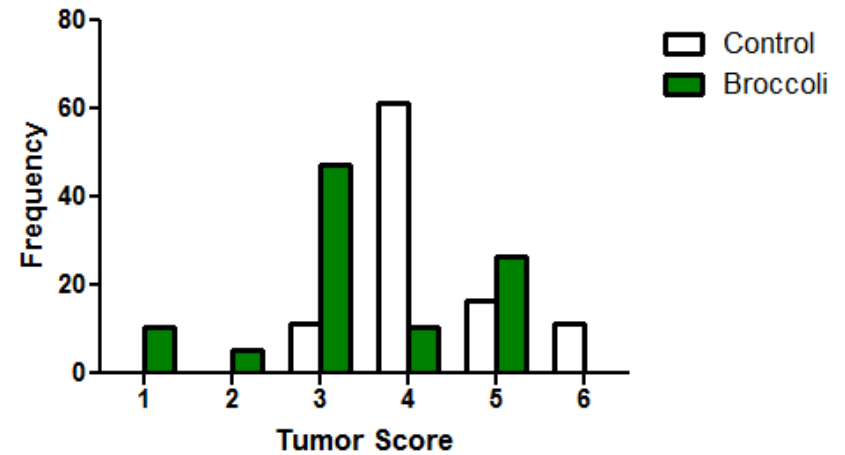


# Broccoli sprout diet delays progression

12 Week Old Tumor Score Distribution by Treatment Group



29 Week Old Tumor Score Distribution by Treatment Group



Significant decrease in median tumor score in sprout-fed young mice ( $p < 0.001$ ).

Significant decrease in median tumor score in sprout-fed old mice ( $p < 0.05$ ).

Mann-Whitney Rank Sum test.

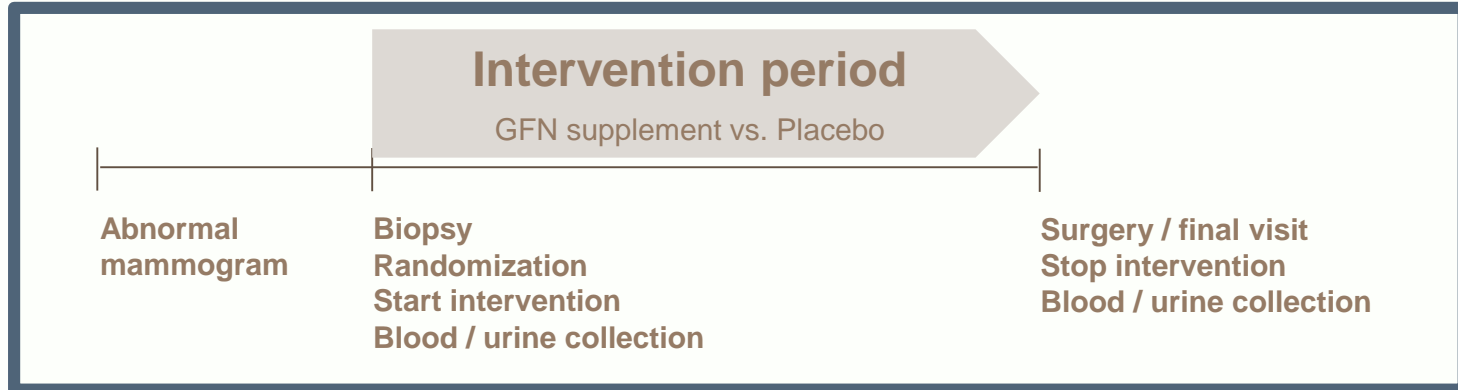
1. normal
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# Breast Cancer Clinical Trial Study – Broccoli Sprout Extract Supplementation

Double-blind, randomized, placebo-controlled clinical trial

N=54, adult women (21+ years)

4-8 week intervention period



\*Cruciferous vegetable intake similar between treatment groups

GFN, glucoraphanin

# HDAC activity in PMBCs decreases following glucoraphanin supplementation

Pre- and post-intervention levels within groups

	Pre-intervention	Post-intervention	Changes <sup>1</sup>
BSE	<i>n</i> = 23 447.51 (48.80)	<i>n</i> = 24 371.14 (44.78)	<i>n</i> = 23 <b>-80.39</b> <b>(48.53)</b>
Placebo	<i>n</i> = 25 432.76 (42.00)	<i>n</i> = 24 476.57 (43.83)	<i>n</i> = 24 <b>27.52</b> <b>(32.58)</b>
<i>p</i> -value (supplement vs. placebo, all)			0.07
<i>p</i> -value (supplement vs. placebo, NSAIDs non-users only)			<b>0.02</b>
Values shown are not separated by NSAIDs use. <sup>1</sup> Only includes matched pre/post samples; pmol/min/mg protein.			

# (Ki-67) decreases following glucoraphanin supplementation

Changes from pre- to post-intervention levels within groups

	Benign <i>n</i> = 48/62 <sup>4</sup>	DCIS <sup>2</sup> <i>n</i> = 19/28	IDC <sup>3</sup> <i>n</i> = 13/16
<b>Ki-67</b>			
Supplement <i>p</i> -value <sup>1</sup>	<b>-1.39 (-2.23, -0.55)</b> <b>0.0035</b>	0.42 (-1.18, 2.02) 0.55	0.98 (-3.89, 5.85) 0.24
Placebo <i>p</i> -value <sup>1</sup>	0.23 (-0.61, 1.07) 0.57	-0.48 (-1.69, 0.72) 0.32	0.28 (-3.22, 3.78) 0.37

Supplement vs. placebo, *p* = 0.01

<sup>1</sup> Pre- vs. post-intervention levels; <sup>2</sup> DCIS alone + DCIS/ADH; <sup>3</sup> IDC w/component of DCIS; <sup>4</sup> 1<sup>st</sup> number is number of subjects; 2<sup>nd</sup> number is number of observations when multiple tissue sections were observed from same person. Values represent change in H-score.

Evidence that SFN may reduce proliferative activity in human breast tissue

# HDAC 3 expression decreases following glucoraphanin supplementation

Changes from pre- to post-intervention levels within groups

	Benign	DCIS <sup>c</sup>	IDC <sup>d</sup>
<b>HDAC 3</b>	<i>n</i> = 33/37 <sup>a</sup>	<i>n</i> = 10/12 <sup>b</sup>	<i>n</i> = 4/5
Supplement	<b>-1.32 (-2.60, -0.04)<sup>1</sup></b>	n/a	n/a
Placebo	-0.38 (-1.73, 0.97)	n/a	n/a
<b>H3K9ac</b>	<i>n</i> = 41/51	<i>n</i> = 18/29	<i>n</i> = 15/18
Supplement	-0.95 (-2.21, 0.31)	-0.49 (-2.18, 1.20)	0.93 (-4.99, 6.86)
Placebo	-1.12 (-2.26, 0.02)	<b>-1.39 (-2.48, -0.30)<sup>2</sup></b>	-1.62 (-6.22, 2.98)

<sup>1</sup> *p* = 0.047    <sup>2</sup> *p* = 0.02    <sup>a</sup> 1<sup>st</sup> number is number of subjects; 2<sup>nd</sup> number is number of observations when multiple tissue sections were observed from same person.    <sup>b</sup> HDAC 3 added late to analysis when several blocks had no more tissue.    <sup>c</sup> DCIS alone + DCIS/ADH;    <sup>d</sup> DCIS+IDC

## Evidence that SFN may alter epigenetic mechanisms in human breast tissue

HDAC, histone deacetylase; H3K9ac, histone 3 lysine 9 acetylation; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma

Many dietary compounds show promise as cancer chemoprevention agents

Many exert action via multiple mechanisms

These studies will be significant because of the potential to qualify or change recommendations for patients at high-risk for breast cancer and thereby increase the likelihood of survival through simple dietary choices incorporating easily accessible foods into a patient's diet.

# Randomized Controlled Clinical Trial of Broccoli Sprout Extract supplementation in men at risk of prostate cancer

Chemoprevention of Prostate Cancer, HDAC Inhibition and DNA Methylation

## Instructions:

- Take one broccoli sprout/placebo pill 2 times a day (morning & evening).
- Important - Store capsules in freezer to preserve supplement stability.

**Study Coordinator:**  
Wesley Stoller  
503-220-8262 x54931



**Volunteers Needed For a Nutritional Supplement Study (Broccoli Sprout Extract) on Prostate Health**

**A Research Study**  
No cost to you. Study supplements are provided at no cost to you. You may or may not benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit future patients.

**Who May Participate?**  
**You may be eligible if...**  
You are a male over the age of 21 and your doctor has recommended a prostate biopsy.

**How Do I Learn More About The Study?**  
Contact the Study Coordinator:  
**Wesley Stoller**  
503-220-8262 X-54931  
[wesley.stoller@va.gov](mailto:wesley.stoller@va.gov)  
[stoller@ohsu.edu](mailto:stoller@ohsu.edu)

**What is Involved?**

- Take a broccoli sprout extract supplement for four to eight weeks
- Two (2) blood samples
- Two (2) urine samples
- Diet History Questionnaire
- Cruciferous Vegetable (ie: broccoli, Brussels sprouts) Questionnaire
- Four (4) prostate biopsy cores (taken at the same time as your scheduled biopsy)
- Total four (4) visits (2 in person and 2 over the phone)

**Principal Investigator:** Jackilen Shannon, PhD  
**VA Clinician:** Mark Garzotto, MD  
Portland VA Medical Center, 3710 SW Veterans Hospital Rd.  
Portland, OR 97239  
VA IRB# 2096  
To check the validity of the above information, call (503) 273-5122

**APPROVED**  
APR -7 2011  
2096  
PVAMC IRB



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