1-2

Terry Mason MD, FACC, reports no relationship with industry to disclose relative to this CME activity.

Public Health (Population) Approach to Cancer via Diet

Terry Mason MD

COO Cook County Department of Public Health

I have no Conflicts of Interest

3

What is Public health? American Public Health Association

- **"Public health** promotes and protects the health of people and the communities where they live, learn, work and play."

4

- How Public Health works ..

5

Just to set the record straight!

6

Imhotep – The Father of Medicine

7

Primary Prevention

- "Primary prevention denotes action taken to prevent the development of a disease in a person who is **well and does not have the disease in question"**

- Gordis L. *Epidemiology: Second Edition.* New York, NY: W.B. Saunders Co. 2000.

8

All "early" detection, not primary **prevention** activities.

Mammography
PSA Testing
EKG
Urine For Cytology
Pap Smear
Fecal Occult Blood Test

9

Cancers

- **"All cancers are genetic but *very few* are familial."**
  - Rick Kittles PhD., Director, Center for Population Genetics
  - Professor, Surgery and Professor, Public Health University of Arizona – College of Medicine
- **Could dietary patterns be 'familial'?**

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This is Cancer

11

So how does the cancer spread?

- What is the difference in the cancer cells and the regular cells?
- What do the cancer cells need to grow?
  - Food
  - Water
  - In the blood

12

Let's take a look at this interesting history!

13

Some interesting Epidemiology

- **Incidence of 'Western Diseases' in South Africa**
  - **In South Africa there are 4 ethnic populations:**
    Blacks (30 Million), Coloreds (Euro-African-Malay) 3 million, Indians 1 million, and Whites 5 million

Temple, N. J., & Burkitt, D. P. (1994). ***Western diseases: their dietary prevention and reversibility.*** Totowa, NJ: Humana Press.

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Dietary Patterns

- **..Rural Blacks – low intake of energy, of total protein, of total fat (animal fat) and high fiber**
- **..Diet of whites… - high energy, total protein and fat (animal origin) dietary fiber intake low**

Temple, N. J., & Burkitt, D. P. (1994). *Western diseases: their dietary prevention and reversibility*. Totowa, NJ: Humana Press.

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Table 2
Cancer Patterns in South African Populations

	Rural blacks	Urban blacks	Coloreds	Indians	Whites
Lung	–[a]	++	+++	++	++++
Breast	–[a]	++	+++	+++	+++++
Colon	–	+	++	++	+++++
Stomach	–	+	+++	++	++
Pancreas	–	+	++	+	+++
Liver	++[b]	++	++	+	+
Esophagus	++++[b]	+++	++	+	+
Cervix	++	++++	+++	+	+
Prostate	–	+	++	++	++++

[a]Implies that occurrence is rare.
[b]Frequency of occurrence related to some regional but not nationwide

Temple, N. J., & Burkitt, D. P. (1994). *Western diseases: their dietary prevention and reversibility*. Totowa, NJ: Humana Press.

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What does this mean for us?

17

International Agency for Research on Cancer Classifications (IARC)

- **Group 1 – <u>The agent is carcinogenic to humans</u>.**
- **Group 2 – Includes agents with a range of carcinogenicity.**
  - **2A – Probably carcinogenetic to humans**
    - **Limited evidence in humans and sufficient evidence in experimental animals**
  - **2B – Possibly carcinogenic to humans**
    - **Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals**

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International Agency for Research on Cancer Classifications

- **Group 3**
  - **The agent is not classifiable as to its carcinogenicity to humans**
- **Group 4**
  - **The agent is probably not carcinogenic to humans**

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IARC Definitions

- **Red Meat – all mammalian muscle meat, including beef, veal, pork, lamb, mutton, horse and goat.**
- **Processed meat – meat that has been transformed though salting, curing, fermentation, smoking or other processes that enhance flavor or improve preservation**

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IARC Classifications

- **Red meat was classified as Group 2A**
  - **Colorectal Cancer**
  - **There is also links with pancreatic and prostate cancer (for every 100 grams increased risk 17%)**
- **Processed meat was classified as Group 1**
  - **Colorectal cancer – per every 50 grams consumed daily increases colorectal cancer risk by 18%, (4 strips of bacon or 1 hotdog)**

21

Prostate Cancer - Eggs

- **Men who consumed 2.5 or more eggs per week had an 81% increased risk of lethal prostate cancer compared to men who consumed 0.5 eggs per week**
- **Predominately Caucasian study participants**

– Richman, E. L., Kenfield, S. A., Stampfer, M. J., Giovannucci, E. L., & Chan, J. M. (2011). Egg, Red Meat, and Poultry Intake and Risk of Lethal Prostate Cancer in the Prostate-Specific Antigen-Era: Incidence and Survival. *Cancer Prevention Research,4*(12), 2110-2121. doi:10.1158/1940-6207.capr-11-0354

22

Prostate Cancer - Eggs

- **Eggs are rich in Choline and Cholesterol both concentrated in prostate cancer cells**
  - **Nested case control study reported men in highest quartile of plasma choline had 48% increased risk of prostate cancer**

- Richman, E. L., Kenfield, S. A., Stampfer, M. J., Giovannucci, E. L., & Chan, J. M. (2011). Egg, Red Meat, and Poultry Intake and Risk of Lethal Prostate Cancer in the Prostate-Specific Antigen-Era: Incidence and Survival. *Cancer Prevention Research,4*(12), 2110-2121. doi:10.1158/1940-6207.capr-11-0354

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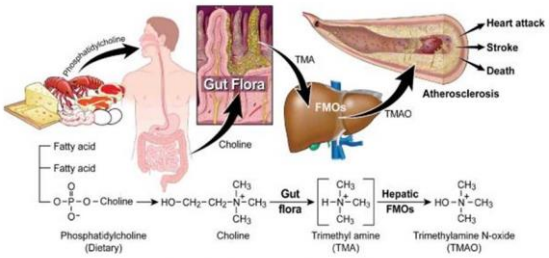
Role of Choline, L-carnitine and Inflammation, CVD and Cancer



Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., & Sheehy, B. T. et al (2013). Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19(5), 576-585. doi:10.1038/nm.3145

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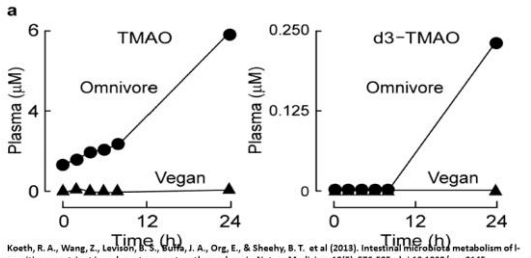
Male and female steak and d3 Carnitine challenge



Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., & Sheehy, B. T. et al (2013). Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19(5), 576-585. doi:10.1038/nm.3145

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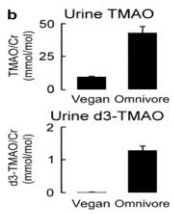
Urine concentrations of TMAO



Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., & Sheehy, B. T. et al (2013). Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19(5), 576-585. doi:10.1038/nm.3145

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TMAO

- **Eggs, Milk, Liver, Red Meat , Shellfish and Fish major dietary source of Carnitine and Choline**
- **Gut bacteria metabolize both to TMAO**
- **Resultant inflammation – mechanism for cancer promotion/blunting reverse cholesterol transport.**
- **Effect is blunted in vegans/vegetarians**
  - **Gut bacteria because of the shift from animal product digesting bacteria**

Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., & Sheehy, B. T. et al (2013). Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19(5), 576-585. doi:10.1038/nm.3145

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Role of Choline and Prostate cancer Cells

- **Detection of Increased Choline Compounds with Proton Nuclear Magnetic Resonance Spectroscopy Subsequent to Malignant Transformation of Human Prostatic Epithelial Cells**
  - **Ellen Ackerstaff, Beth R. Pflug et al**
  - **Cancer Research61, 3599-3603, May 1, 2001**

28

Role of Choline and Prostate cancer Cells

- **"..we have shown that HPCs derived from metastases exhibit significantly higher phosphocholine as well as glycerophosphocholine levels compared to normal prostate epithelial and stromal cells."**

Ellen Ackerstaff, Beth R. Pflug et al Cancer Research61, 3599-3603, May 1, 2001

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Difference in LNCap Growth

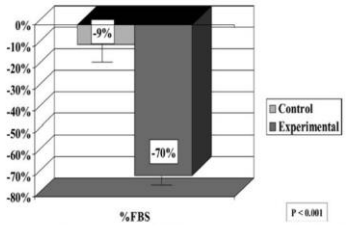

FIG. 2. Mean changes ± SEM in percent serum stimulated LNCaP cell growth from baseline to 1 year in experimental and control groups.

Ornish, D., Weidner, G., & Fair, W. R. et al (2005). Intensive Lifestyle Changes May Affect The Progression Of Prostate Cancer. *The Journal of Urology,174*(3), 1065-1070. doi:10.1097/01.ju.0000169487.49018.73

30

Limitations

A limitation of the current study is that it cannot provide definitive conclusions concerning the effect of our intervention on disease specific survival. Any intervention, including diet and lifestyle, may affect the progression of prostate cancer without necessarily affecting survival. Because patients in this study had early, less aggressive tumors, they would be unlikely to show changes in clinical progression in only 1 year.

Ornish, D., Weidner, G., & Fair, W. R. et al (2005). Intensive Lifestyle Changes May Affect The Progression Of Prostate Cancer. *The Journal of Urology*,174(3), 1065-1070. doi:10.1097/01.ju.0000169487.49018.73

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Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention

Dean Ornish*†‡, Mark Jesus M. Magbanua§, Gerdi Weidner*, Vivian Weinberg¶, Colleen Kemp*, Christopher Green§, Michael D. Mattie§, Ruth Marlin*, Jeff Simko‖, Katsuto Shinohara§, Christopher M. Haqq§ and Peter R. Carroll§

‡Department of Urology, The Helen Diller Family Comprehensive Cancer Center, and ‖Department of Pathology, University of California, 2340 Sutter Street, San Francisco, CA 94115; *Preventive Medicine Research Institute, 900 Bridgeway, Sausalito, CA 94965; †Department of Medicine, School of Medicine, University of California, 505 Parnassus Avenue, San Francisco, CA 94143; and ¶Biostatistics Core, The Helen Diller Family Comprehensive Cancer Center, University of California, 513 Parnassus Avenue, Box 0127, San Francisco, CA 94143

Communicated by J. Craig Venter, The J. Craig Venter Institute, Rockville, MD, April 2, 2008 (received for review February 13, 2008)

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Changes in Gene Expression

- Each man had baseline and 3 months post intervention
- Each man was his own control
- Plant Based diet
- Stress management 60min/day
- Supported by professionals
- 'a set of RAS family oncogenes were down regulated
- Need studies with control group or > 3 month intervention

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Changes in Gene expression

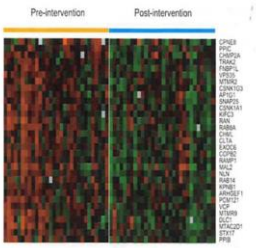

Fig. 4. Heat map of the gene ontology group "Intracellular Protein Traffic" illustrating the down-regulation of these 31 transcripts. Pre- and postcomprehensive diet and lifestyle intervention samples are indicated.

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Down-regulated Genes

Table 3. Overrepresented ontology categories in molecular functions and biological processes ($P < 0.05$) among genes down-regulated after a diet/lifestyle intervention

	NCBI: *Homo sapiens* genes, number of genes	GEMINAL down-regulated genes, number of genes	Expected	*P*
Molecular function				
Ligase	468	19	5.72	0.007
Ubiquitin-protein ligase	523	12	3.09	0.014
Membrane traffic protein	359	13	4.39	0.017
Select regulatory molecule	1,190	27	14.55	0.049
Biological process				
Protein metabolism and modification	3,040	69	37.8	<0.001
Intracellular protein traffic	1,008	31	12.33	<0.001
Protein modification	1,157	32	14.15	0.003
Protein phosphorylation	660	20	8.07	0.044

8372 | www.pnas.org/cgi/doi/10.1073/pnas.0803080105 Ornish et al.

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Something for your wives, sisters etc.

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Something else to think about

- **1481 White women studied**
  - **Inverse relationship between frequency of Bowel movements and epithelial dysplasia in nipple aspirates of breast fluid (risk ratio 4.5) 2 or fewer bowel movements per week**
  - **Not seen with those with daily or every other day bowel movements**

- **Cytological abnormalities in nipple aspirates of breast fluid from women with severe constipation.**
- Lancet. 1981 Nov 28;2(8257):1203-4.
- Petrakis NL, King EB

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TABLE II—BOWEL MOVEMENT FREQUENCY AND CYTOLOGICAL DYSPLASIA IN NIPPLE ASPIRATES OF BREAST FLUID FROM 1481 WOMEN

Frequency of bowel movements		Breast fluid cytology: Dysplasia n/total	Adjusted risk ratio*	95% confidence interval
>1/day	(10·7%)	8/158	1·0	..
1 daily	(69·6%)	112/921	1·8	(0·9–4·2)
1 every other day	(14·9%)	22/199	1·6	(0·9–5·2)
2 or fewer/week	(4·7%)	16/53	4·5	(1·9–11·9)

*Mantel and Haenszel[12] estimates of risk ratios, adjusted over categories of age in decades. In all comparisons the referent category was women who had more than 1 bowel movement per day.
χ^2_1 for trend = 10·7; p<0·001.

Cytological abnormalities in nipple aspirates of breast fluid from women with severe constipation.
Lancet. 1981 Nov 28;2(8257):1203-4.
Petrakis NL, King EB

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Bile Acids and Cancer

- **Proven in the past bile acids, including known co-carcinogen lithocolic acid are present in breast cyst fluid and concentrations can be more than 100 times greater than those in the plasma.**
- **Needed to show the intestinal derived bile acids rather than being derived from steroid precursors metabolized by breast tissue**

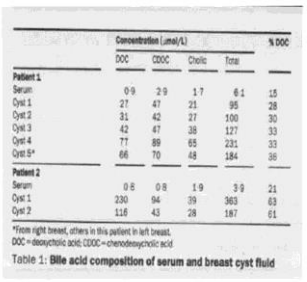
Javitt N, Budai K et al: Breast Gut Connection: Origin of chenodeoxycholic acid in breast tissue. Lancet 1994;343:633-35

39

How was gut origin proved

- **Gave 2 patients deuterium-labeled Chenodeoxycholic acid (3 – 200mg doses P.O) 9, 6, and 3 days before aspiration of breast cysts.**
- **Chenodeoxcholic used to dissolve radiolucent gallstones.**

40



	Concentration (μmol/L)				% DOC
	DOC	CDOC	Cholic	Total	
Patient 1					
Serum	0·9	2·9	1·7	6·1	15
Cyst 1	27	47	21	95	28
Cyst 2	31	42	27	100	30
Cyst 3	42	47	38	127	33
Cyst 4	77	89	65	231	33
Cyst 5*	66	70	48	184	36
Patient 2					
Serum	0·8	0·8	1·9	3·9	21
Cyst 1	230	94	39	363	63
Cyst 2	116	43	28	187	61

*From right breast, others in this patient in left breast.
DOC = deoxycholic acid; CDOC = chenodeoxycholic acid

Table 1: **Bile acid composition of serum and breast cyst fluid**

Javitt N, Budai K et al: Breast Gut Connection: Origin of chenodeoxycholic acid in breast tissue. Lancet 1994;343:633-35

41

Bile acids

- **Non-lactating breast takes up substances from the blood**
- **Proven to be mutagenic**
- **Part of the entero-hepatic circulation**

- Mutat Res. 2005 Jan;589(1):47-65.
- **Bile acids as carcinogens in human gastrointestinal cancers.**
- Bernstein H1, Bernstein C, Payne CM, Dvorakova K, Garewal H. Department of Microbiology and Immunology, College of Medicine, University of Arizona, Tucson

42

Bile acids

- **Lithocolic bile acids from the colon – in breast tissue 100 times the concentration in the blood**
- **Radio- pharmaceutically tagged bile acids proved colonic origin**

- N B Javitt, K Budai, D G Miller, A C Cahan, U Raju, M Levitz. Breast-gut connection: origin of chenodeoxycholic acid in breast cyst fluid. Lancet. 1994 Mar 12;343(8898):633-5.

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Bile acids - Estrogen Effect

- **Bile acids in breast exert and estrogen-like cancer promoting effect on breast tumor cells[1]**
- **50% higher higher bile acid levels in the blood stream of newly diagnosed cancer victims[2]**

- P R Baker, J C Wilton, C E Jones, D J Stenzel, N Watson, G J Smith. Bile acids influence the growth, oestrogen receptor and oestrogen-regulated proteins of MCF-7 human breast cancer cells. Br J Cancer. 1992 Apr;65(4):566-72.[1]
- Costarelli V, Sanders TA. Plasma deoxycholic acid concentration is elevated in postmenopausal women with newly diagnosed breast cancer. Eur J Clin Nutr. 2002 Sep;56(9):925-7.[2]

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The Enterohepatic Circulation

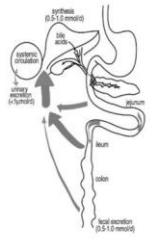

Fig. 2. The enterohepatic circulation of bile acids.

H. Bernstein, C. Bernstein, et al. Bile acids as carcinogens in human gastrointestinal cancers, Mutation Research 589 (2005) 47-65

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How did this happen?

- ***Slow oral-anal transit time***
- **Constipation is a marker for the increased contact time with colonic mucosa allowing for increased reabsorption of the bile acids.**
- **Bile acids are used to help to get rid of excess cholesterol**

- Am J Gastroenterol. 1999 Aug;94(8):2010-6.
- **The metabolic consequences of slow colonic transit.**
- Lewis SJ1, Heaton KW.University Department of Medicine, University Hospital of Wales, Cardiff.

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What would speed up oral-anal transport time?

What do you think?

- **Laxatives?**
- **Colonics**
- **Drinking Alkaline water**
- **Having hands laid**

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There are usually **no early "signs or symptoms"** of any cancer in its earliest stage.

Most symptoms related to a cancer happen in the later stages.

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So What do we do???
I have cancer

- **What is the Stage (how far is the spread?)**
- **What is the differentiation? (How different is the cancer from the normal cell of the organ of origin?)**
- **How to treat – In or Out or Combination**

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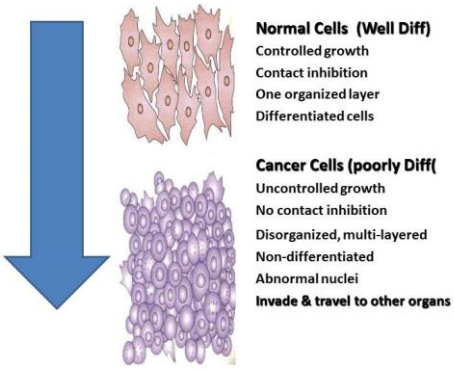
General Description of Cancer



Normal Cells (Well Diff)
Controlled growth
Contact inhibition
One organized layer
Differentiated cells

Cancer Cells (poorly Diff(
Uncontrolled growth
No contact inhibition
Disorganized, multi-layered
Non-differentiated
Abnormal nuclei
Invade & travel to other organs

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The real 'Farmacy'

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What is the Public health Message?

- The WHY of eating more fruits and vegetables
  - Decreasing oral-anal transit time
  - Increases the binding of cholesterol, and Bile acids
  - Decreasing Bile acid levels in the blood
  - Decreasing the concentration in the breast tissue
  - Decreasing the opportunity for mutagenic changes in the glands of the breast
  - Decreasing potential for breast cancer/Colon and other cancers
  - WITHOUT DRUGS OR EXPENSIVE TESTS

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What is more important

- It WORKS
- It is TRUE Prevention.

Thank You

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