



Cancer Research Center of Hawai'i  
UNIVERSITY OF HAWAII

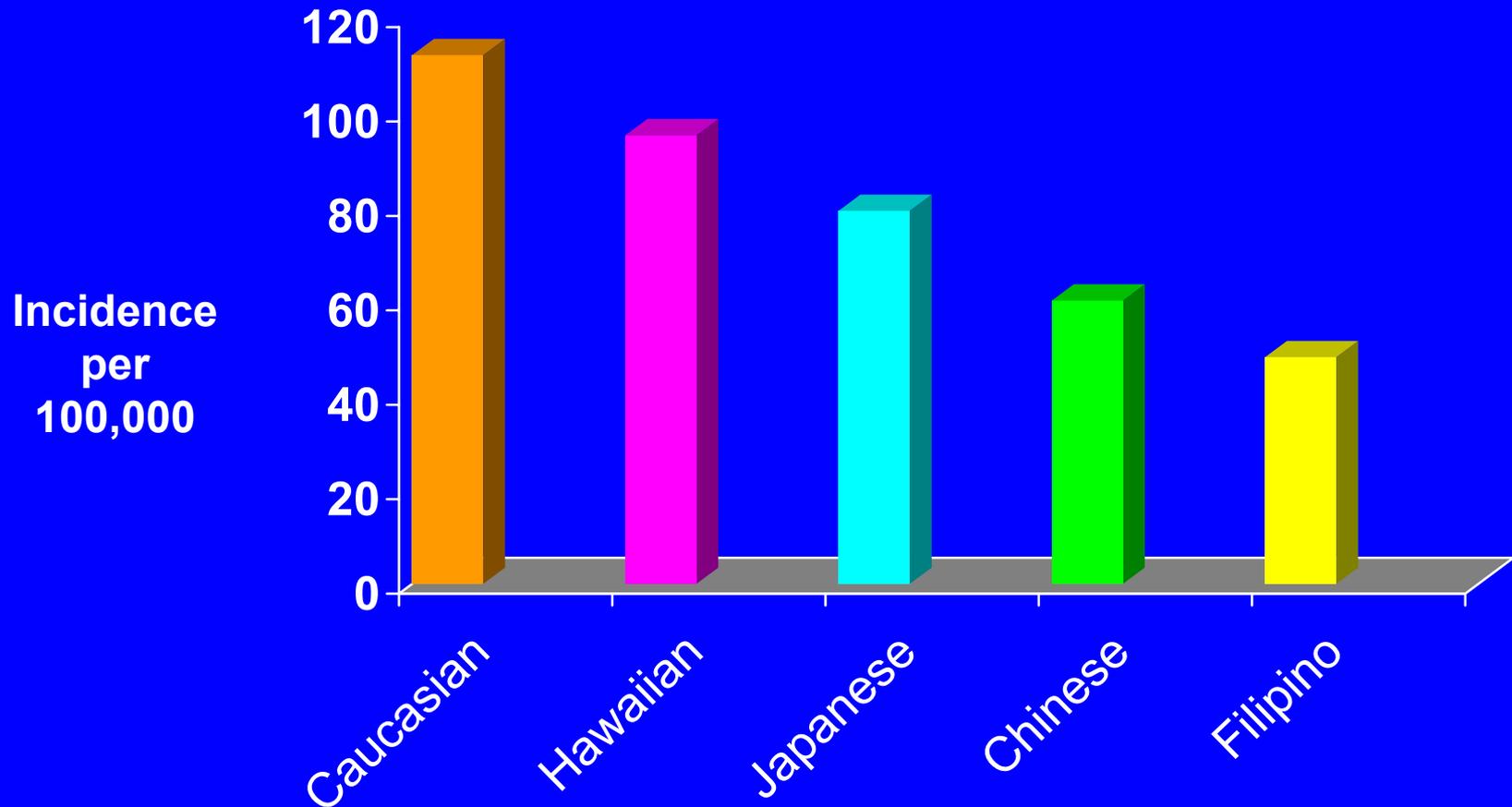
# Perspectives on Diet, Genes and Cancer

Laurence N. Kolonel

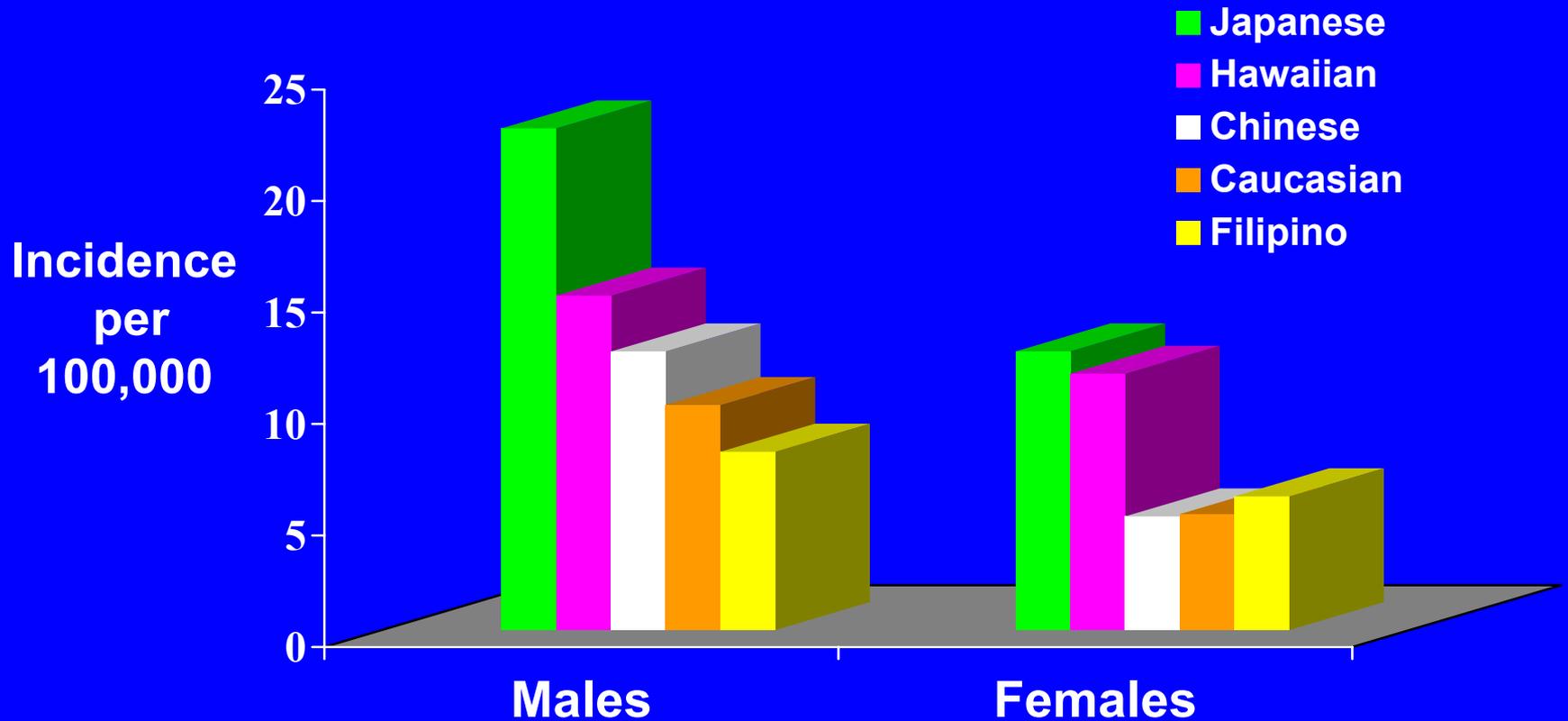
# Historical View

- Ethnic differences in cancer incidence in Hawaii in the 1970's.

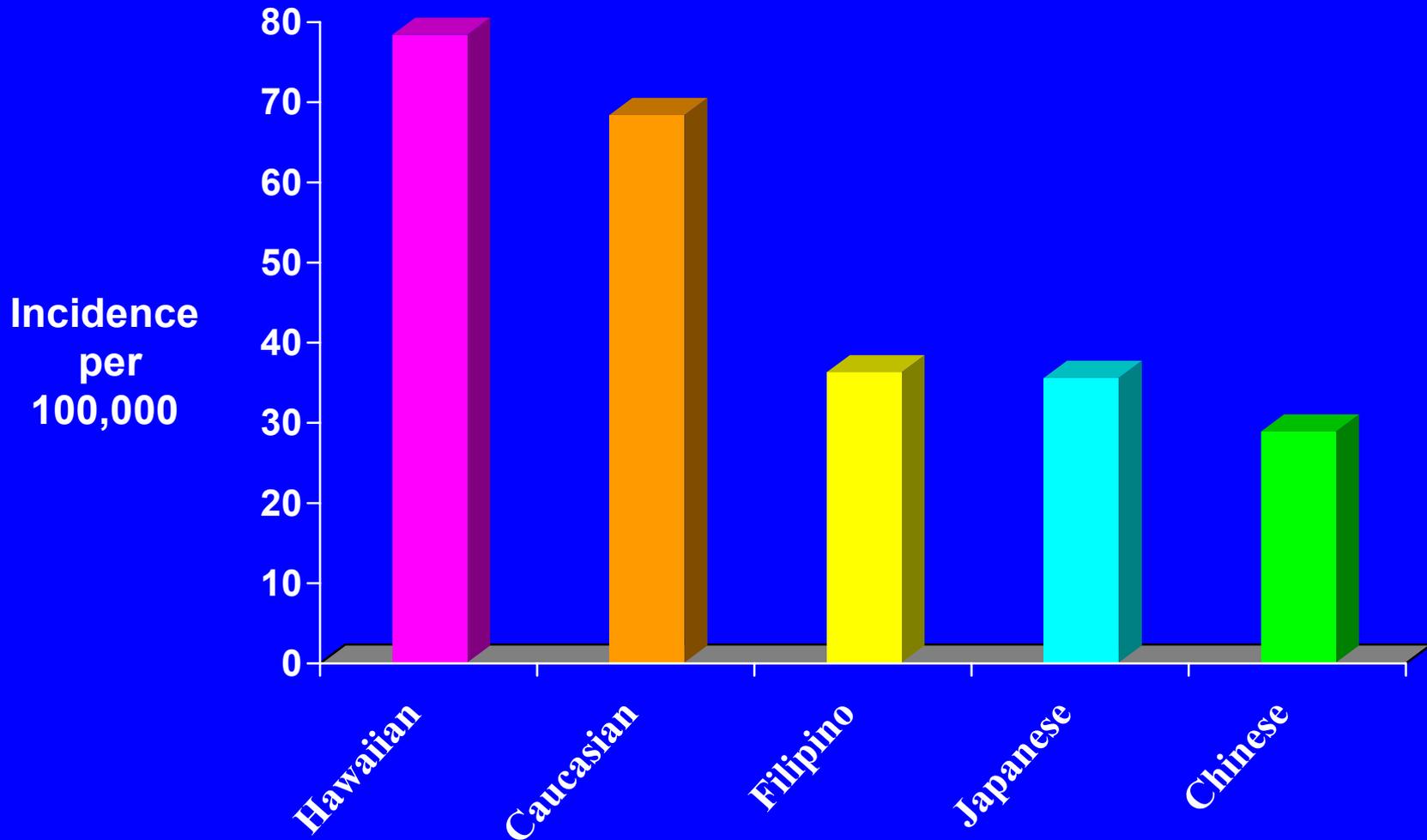
# Breast Cancer Incidence in Hawaii



# Stomach Cancer Incidence in Hawaii



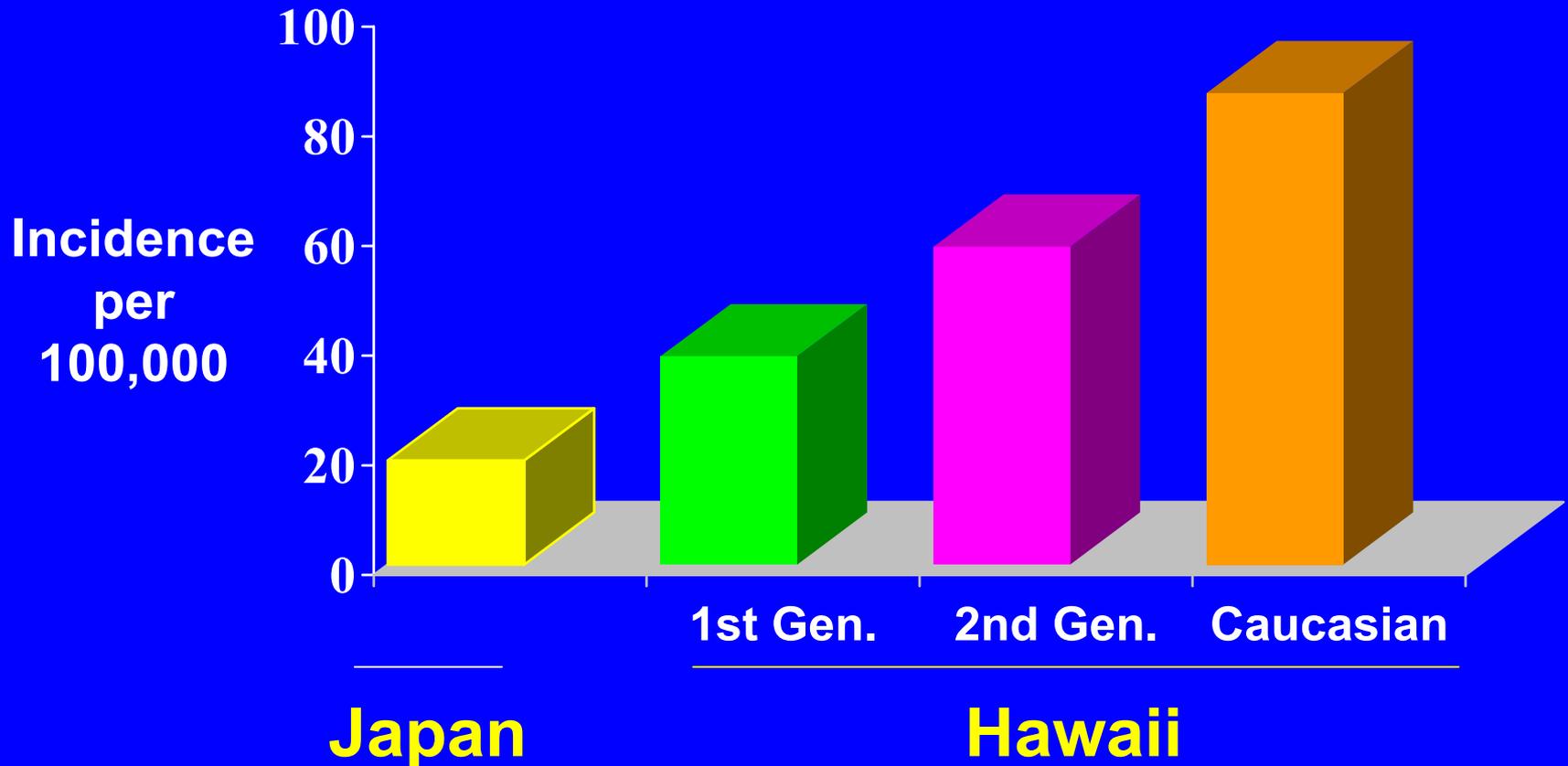
# Lung Cancer Incidence in Hawaii



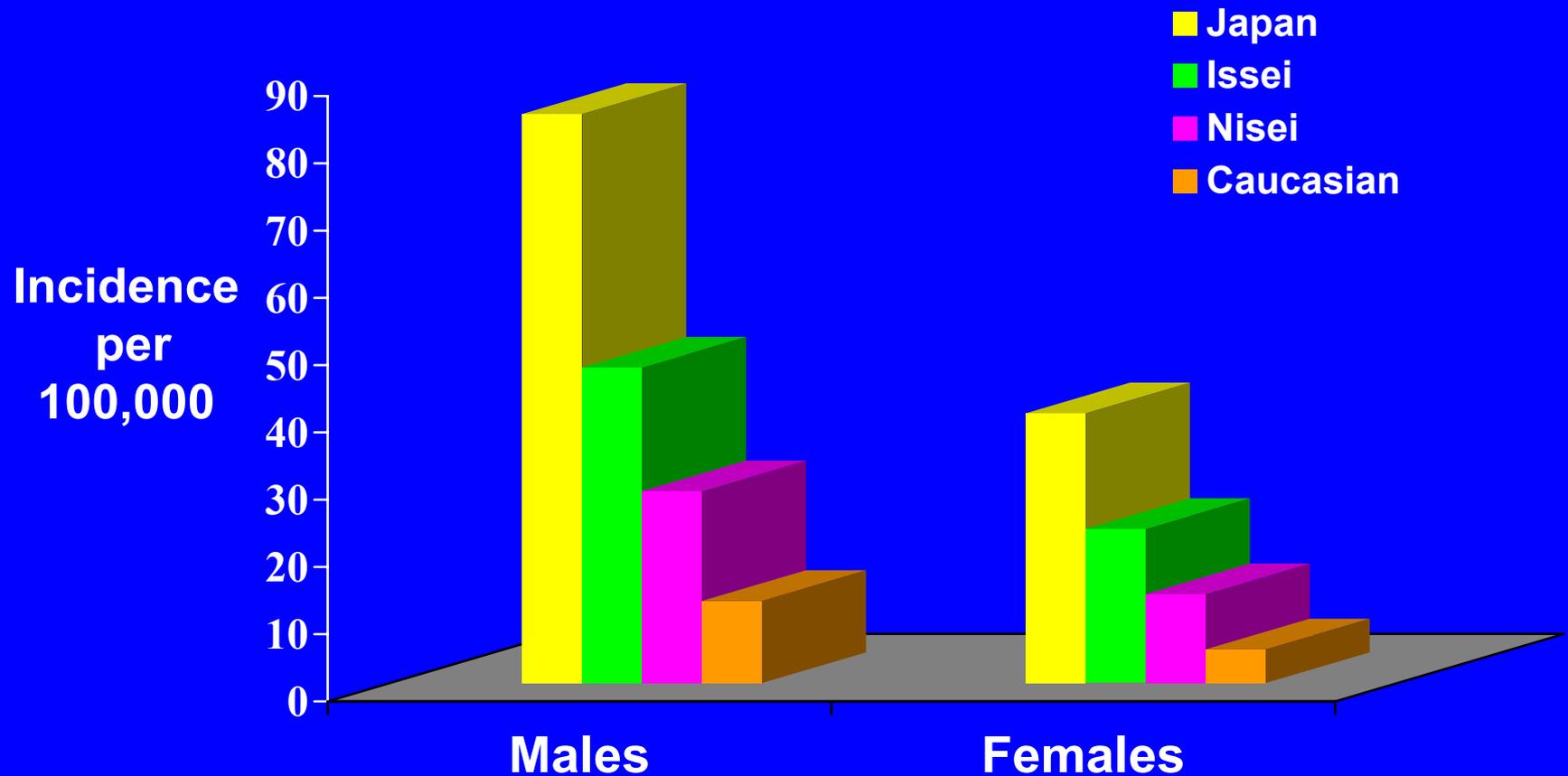
# Historical View

- Patterns of cancer incidence among Japanese migrants to Hawaii in the 1970's.

# Breast Cancer Incidence in Japanese Immigrants & Comparison Populations



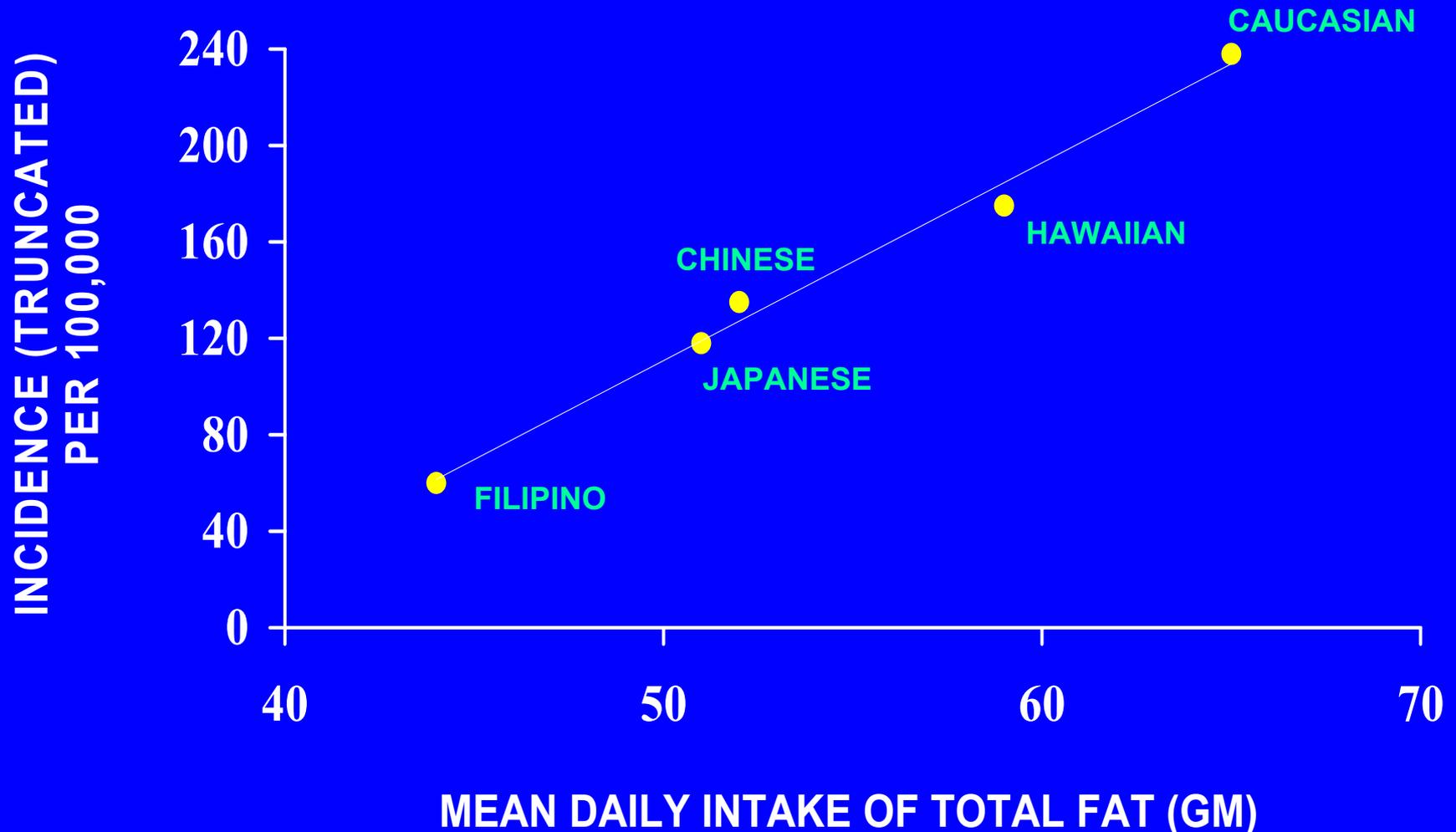
# Stomach Cancer Incidence in Japanese Immigrants & Comparison Populations



# Historical View

- **Conclusion:** Environment (lifestyle) factors are the major determinants of risk for the common cancer sites.

# DIETARY FAT AND BREAST CANCER INCIDENCE (FEMALE)



How have epidemiologists approached the study of nutrition and cancer?

Example: dietary fat

# Reductionist Approach to Research on Fat



# Prediagnostic Serum FAs and Prostate Cancer Risk

<u>Fat Variable</u>	<u>Odds Ratio</u>
<b>Saturated fat</b>	1.6 (ns)
Myristic	1.8 (ns)
Palmitic	2.3 ( $p=.02$ )
Stearic	1.3 (ns)
Arichidic	0.7 (ns)
Docosanoic	0.7 (ns)
Tetracosanoic	0.5 (.01)
<b>Monounsaturated fat</b>	1.3 (ns)
Palmitoleic	2.8 ( $p=.01$ )
Oleic	1.8 ( $p=.05$ )
Eicosenoic	1.2 (ns)
Tetracosenoic	0.7 (ns)
<b>Polyunsaturated fat</b>	1.1 (ns)
$\omega$ -6 PUFAs	0.7 (ns)
Linoleic	0.9 (ns)
Eicosadienoic	1.0 (ns)
Dihomo- $\gamma$ -linoleic	1.1 (ns)
Arachidonic	0.8 (ns)
$\omega$ -3 PUFAs	1.1 (ns)
$\alpha$ -linolenic	2.0 ( $p=.03$ )
Eicosapentaenoic	1.2 (ns)
Docosapentaenoic	0.7 (ns)
Docosahexaenoic	1.0 (ns)

(Int J Cancer, 1997)

# Major feature of findings from 30 years of dietary research

Inconsistency

# Proposed Reasons for Inconsistent Findings

1. Measurement error

systematic vs. random

differential vs. non-differential

2. Multifactorial (“web of causation”)

3. Individual variation in susceptibility

4. *Reductionist approach*

Too many findings!

# Odds Ratios\* for the Association of Food Groups with Endometrial Cancer

<u>Food Group</u>	<u>Q1</u>	<u>Q2</u>	<u>Q3</u>	<u>Q4</u>	<i>p</i> for trend
Vegetables	1.00	0.53	0.56	0.51	0.03
Fruits	1.00	0.62	0.57	0.48	0.004
Wh. Grain Foods	1.00	1.10	0.92	0.57	0.09
Wh. Grain Cereals	1.00	1.20	0.71	0.48	0.009
Legumes	1.00	0.63	0.61	0.51	0.009
Soy Products	1.00	0.55	0.53	0.46	0.01

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\* Adjusted for age, ethnicity, pregnancy history, use of BCPs, estrogen use, history of diabetes, BMI, and total calories.

# Possible Dietary Risk Factors for Prostate Cancer

## Foods

- Animal Products
- Dairy Products

- Vegetables
- Fruits
- Legumes
  - Soy
- Green Tea
- Fish

## Constituents

### *Increasing Risk*

- Fat
  - Various
- Calcium
- Cadmium

### *Decreasing Risk*

- Carotenoids
  - Lycopene
- Vitamin D
- Vitamin E
- Selenium
- Phytoestrogens
- Zinc

# The Issue

Perhaps the influence of diet on carcinogenesis is less specific (with regard to constituents) than we are assuming.

# Evolutionary Perspective

- Humans evolved in a particular environmental context (Paleolithic Age). Deviation from the diet to which we are adapted is detrimental to the organism.
- All cells share common metabolic processes, to which are added specialized functions in different tissues.
- The human body has evolved highly sophisticated defense mechanisms to preserve the species.

# Robustness of the Organism

**Proposition:** Given the fact that we have evolved (i.e., are adapted) to consume certain types of natural (wild) foods in order to sustain the organism, it is unlikely that ingesting too much of one particular fatty acid (out of 28) or too little of one particular carotenoid (out of >90) is the “cause” of prostate (or other site-specific) cancer.

Common metabolic processes suggest common mechanisms leading to carcinogenesis

Example: Oxidative Stress

Reactive oxygen species (ROS) are an inevitable by-product of aerobic metabolism in all tissues.

## **Adverse effects** of ROS include:

DNA: strand breaks, adduct formation, mutations, oncogene activation, tumor suppressor gene inactivation

RNA: alkylation

Protein: inactivation of DNA repair enzymes

Lipids: peroxidation leading to cell proliferation

## **Beneficial effects** of ROS include:

Mediation of apoptosis

Antimicrobial phagocytosis (inflammatory response)

Functioning of P450 enzymes (detoxification mechanism)

# Common Metabolic Process: Oxidative Stress

↑ROS  
Aerobic Metabolism  
Chronic Inflammation  
*Intake of Pro-oxidants*

Minimal Cancer Risk

↓ROS  
Antioxidant Enzymes  
Endogenous Antioxidants  
*Intake of Antioxidants*

↑ROS  
Aerobic Metabolism  
Chronic Inflammation  
*Intake of Pro-oxidants*

Increased Cancer Risk

↓ROS  
Antioxidant Enzymes  
Endogenous Antioxidants  
*Intake of Antioxidants*

↑ROS  
Aerobic Metabolism  
Chronic Inflammation  
*Intake of Pro-oxidants*

Increased Cancer Risk

↓ROS  
Antioxidant Enzymes  
Endogenous Antioxidants  
*Intake of Antioxidants*

Bottom line: Cancer reflects a dietary imbalance at a more macro-level.

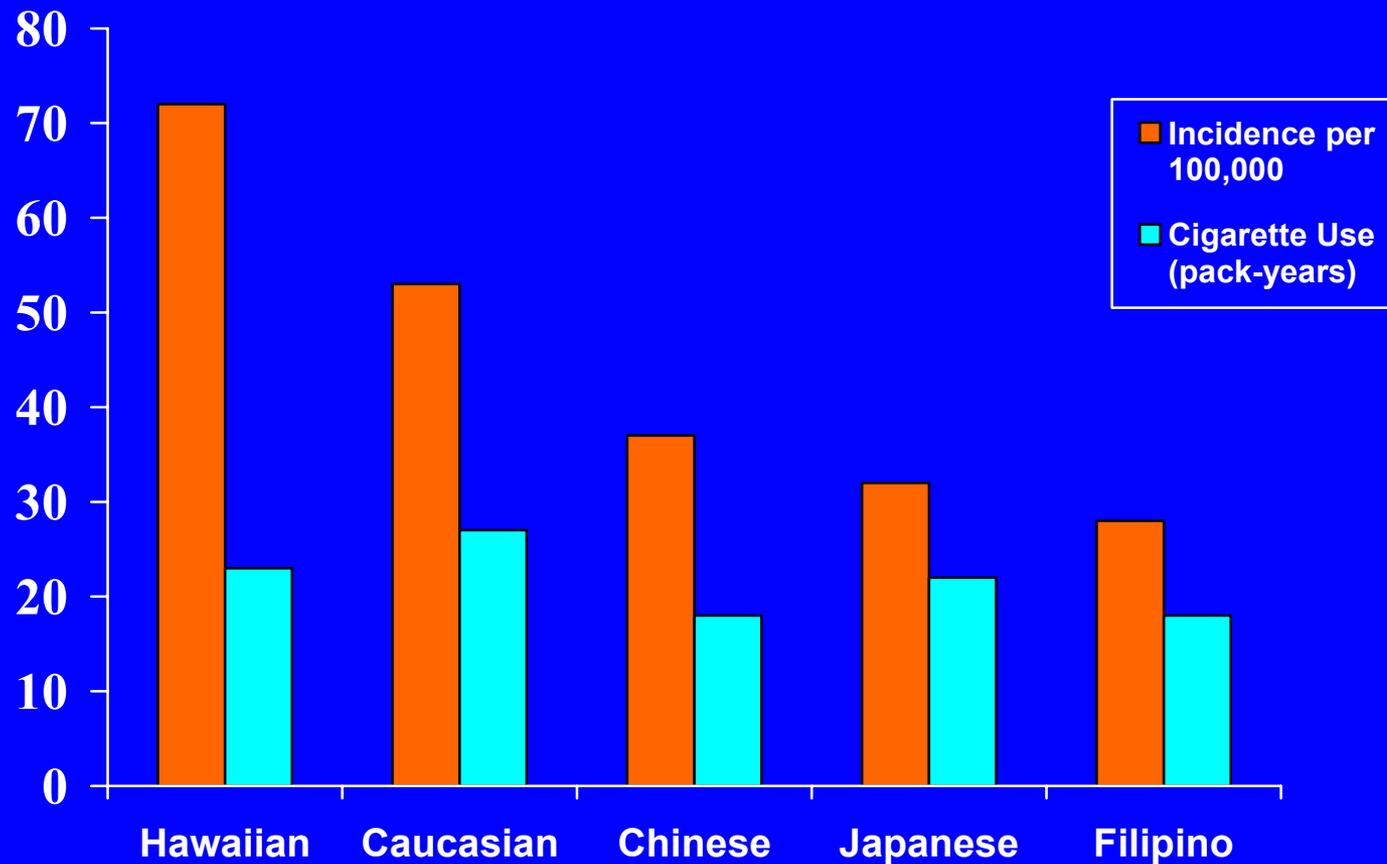
How can we best capture that?

# The Role of Genetics

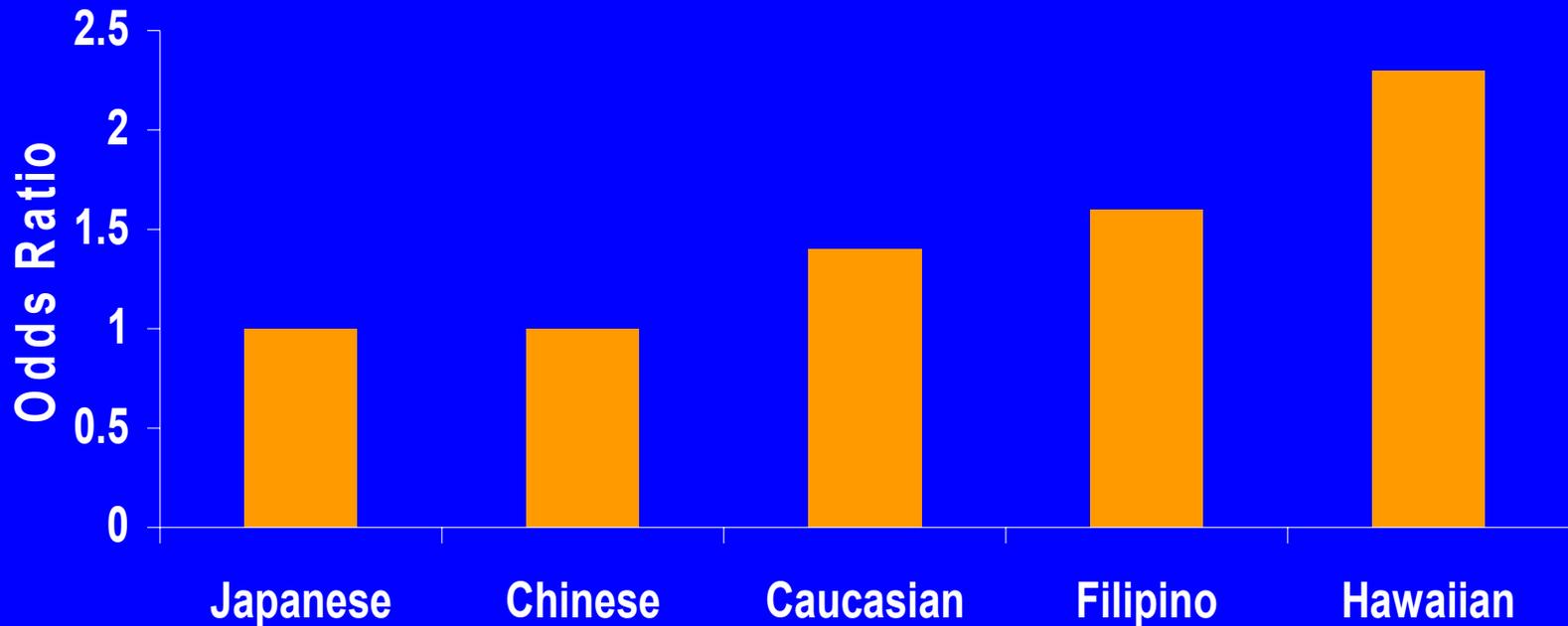
# Historical Review

- Unexpected research findings

# Correlation between Lung Cancer and Smoking among Five Ethnic Groups



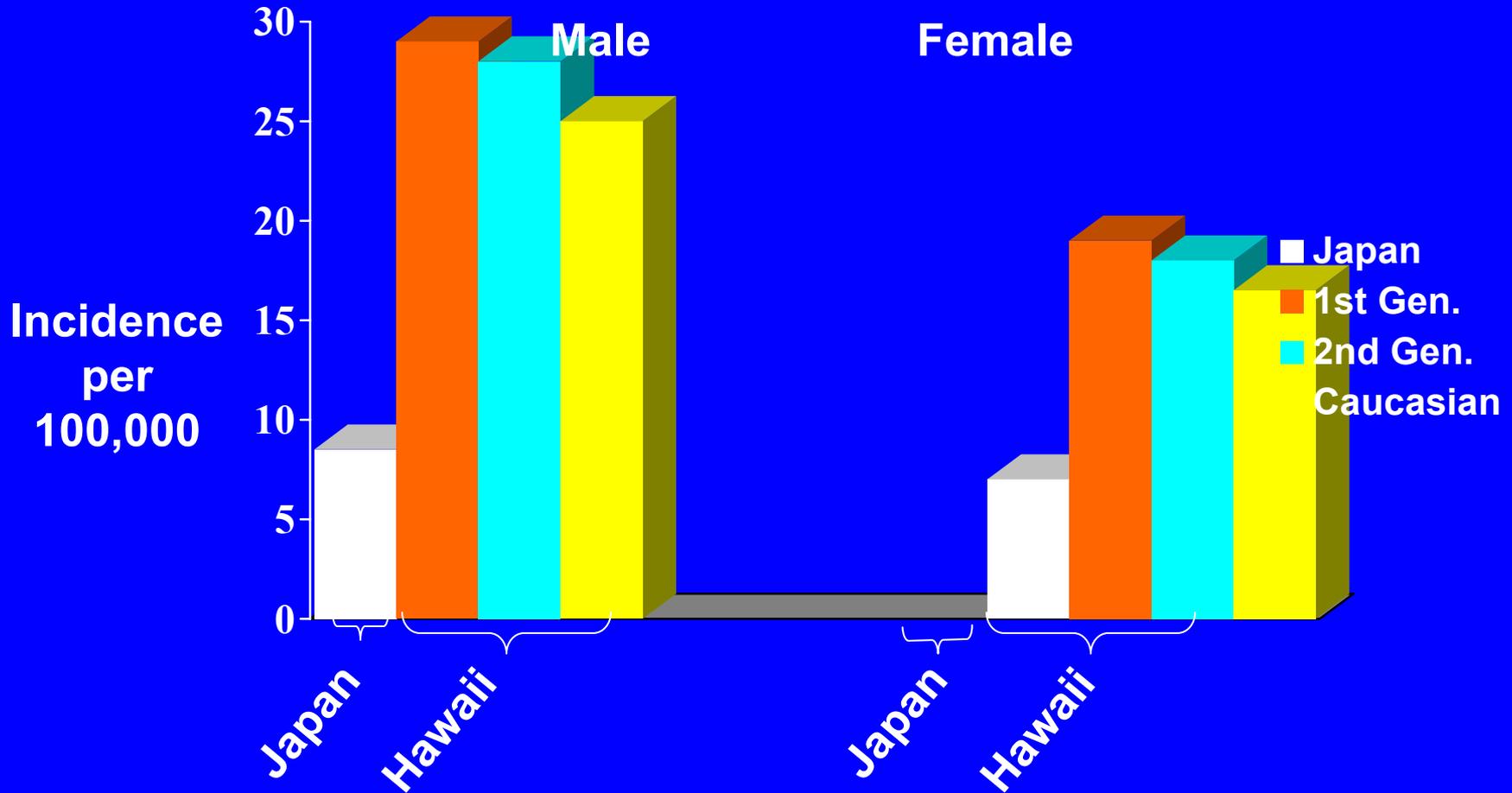
# Comparative Risk\* of Lung Cancer in Male Smokers Relative to Japanese



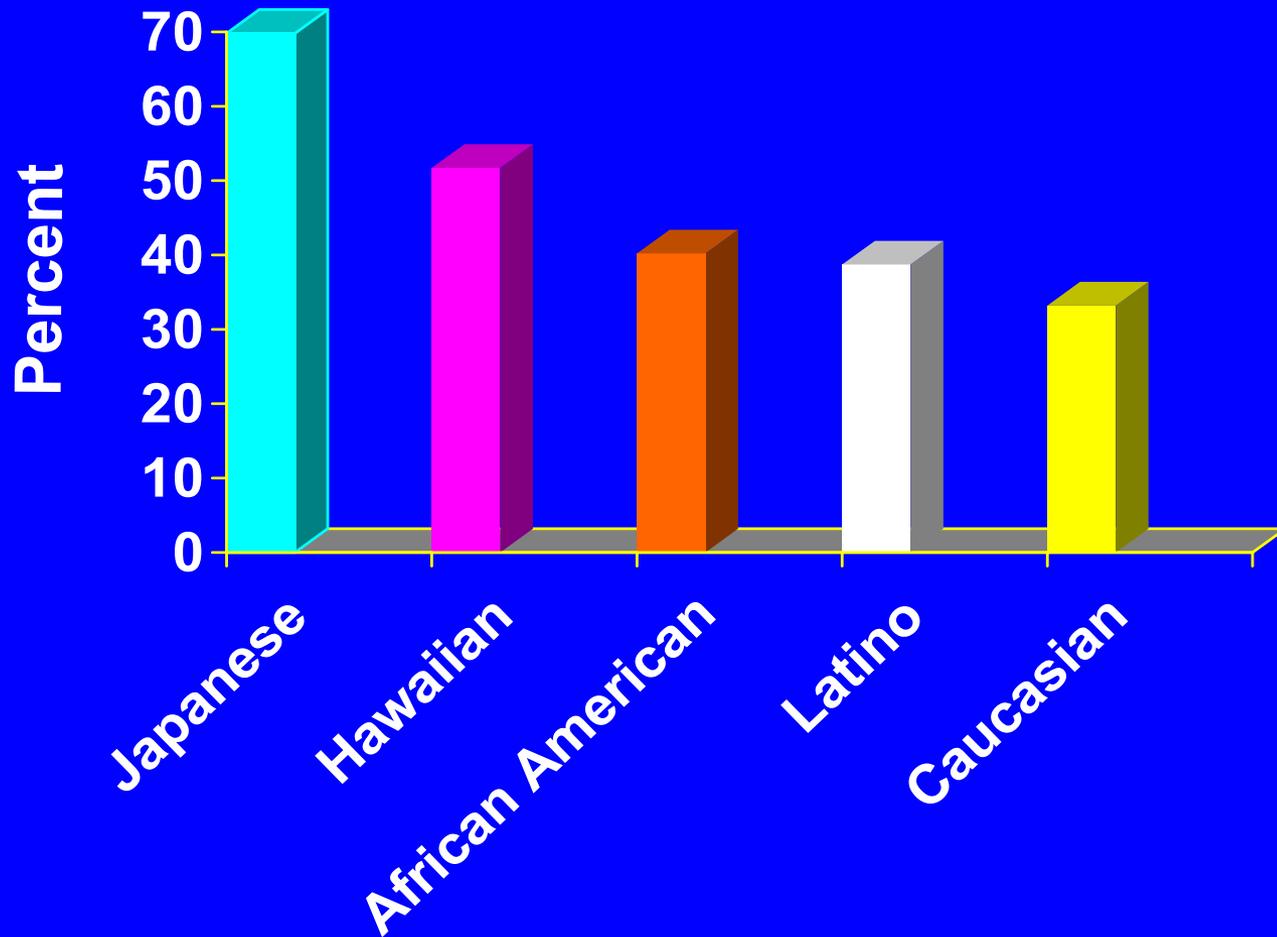
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\*Adjusted for age, education, extent of smoking, occupation,  $\beta$ -carotene, and cholesterol intake.

# Colon Cancer Incidence in Japanese Immigrants and Comparison Populations



# Distribution of the *NAT2* “Rapid” Allele in the Multiethnic Cohort Study



# Odds Ratios for Colorectal Cancer by Genotype and Meat Preference

<u><i>NAT2/CYP1A2</i></u> <u>Genotype</u>	<u>Meat Preference</u>	
	<u>Well-done</u>	<u>Rare/medium</u>
Non-rapid (both)	1.0	1.0
Rapid/rapid	3.6	1.4

# Historical View

- **Conclusion:** Genetic susceptibility factors account for at least a component of individual and group (ethnic) differences in risk for specific cancers.

Major feature of findings from ~~30~~ 10  
years of ~~dietary~~ genotyping research

Inconsistency

(Déjà vu)

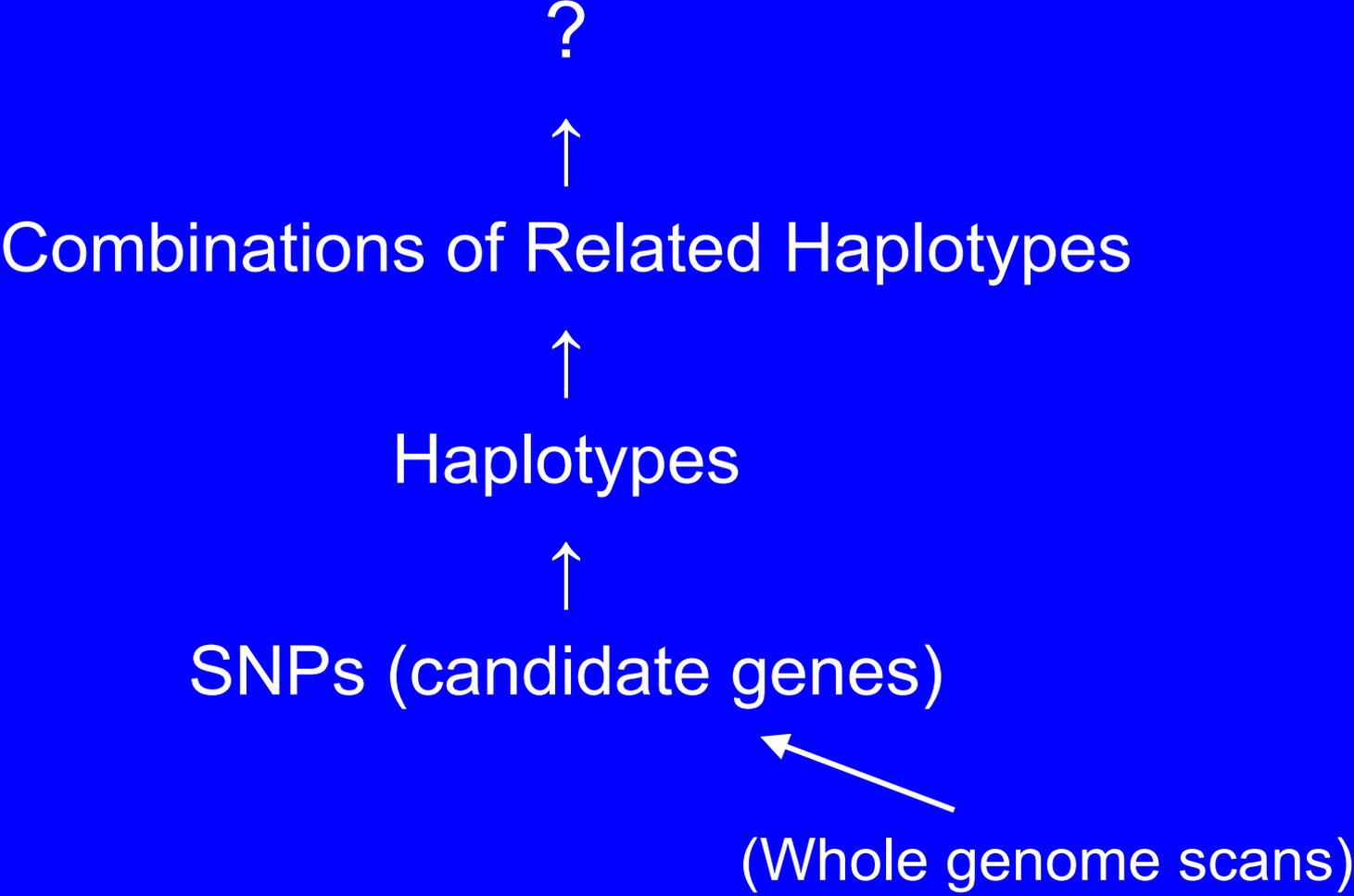
# Reasons for inconsistent findings

1. Can't blame measurement error
2. Low power to examine interactions
3. Markers vs. true causal variants
4. Population stratification and ethnic admixture
5. Complex metabolic pathways

# Reductionist Approach to Research on Fat



# Reductionist Approach to Research on Genomics



# Some questions

1. For complex (multigenic) pathways with many polymorphic loci, can the study of individual SNPs (even when limited to ones that are functional) ever lead to clear answers?
2. Will the move to haplotyping solve everything?
3. How do we incorporate epigenetic phenomena?  
(DNA methylation, gene expression, proteomics)
4. How can we best combine genotyping with phenotyping?
5. Are we being carried away by the technology?

# Characteristics of the “Natural” (Paleolithic Age) Human Diet?

## Two basic components

### 1. Plant foods

(Requirement for fiber, folate, carbohydrate)

### 2. Animal foods

(Requirement for Vitamin B<sub>12</sub>)

## Balance

1. Between plant food and animal food

2. Between intake and expenditure

# Dietary Guidelines to Reduce Cancer Risk (WCRF/AICR, 1997)

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- Emphasize plant-based foods, including whole grains and legumes
- Increase consumption of vegetables and fruits
- Reduce intake of fat, especially from animal products
- Drink alcohol in moderation, if at all
- Prepare and store food safely
- Limit salt intake
- Maintain proper weight
- Engage in regular physical activity

We've probably got it right

(We just haven't quite figured out why!)