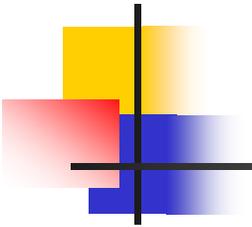


The Hormonal Epidemiology of Breast Cancer: 1842-2002

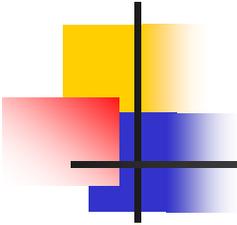


Proportionate Mortality for Breast Cancer in Verona, Italy, 1760-1839

	<u>All Women</u>	<u>Nuns</u>
Proportion	0.0043	0.0267
#	319	36
	Ratio = 6.2	

Adapted from:

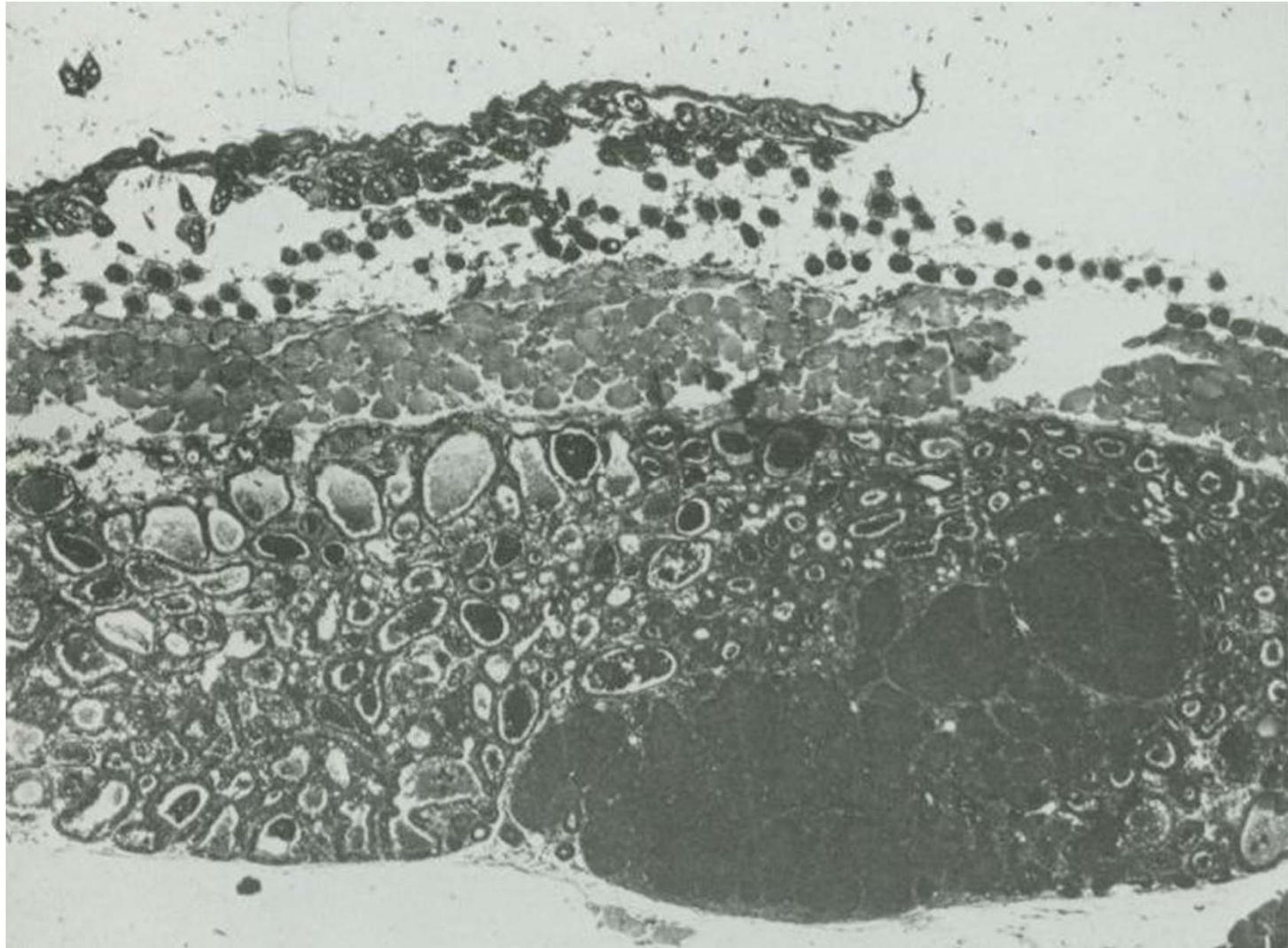
Rigoni-Stern. *Giornale par servire al Progressi della Patologin e della Tarapeutica* 2(2):507-517 (1842).

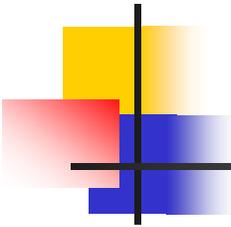


“Is cancer of the mamma due to some ovarian irritation, as from some defective steps in the cycle of ovarian changes; and, if so, would the cell proliferation be brought to a standstill; were the ovaries to be removed.”

Beatson GT Lancet 2:104-107, 162-165, 1896.

Mammary Tumor in Male Mouse Induced By Estrogens (from Lacassagne, 1932)





“Hormonal” Risk Factors

Hormone Replacement Therapy

Serum Estrogens (Post Menopausal)

Oophorectomy (**Protective**)

Late Age at menopause

Early Age at menarche

Lactation (**Protective**)

Late Age at first birth

Heavier at birth

Parity (**Protective**)

Obesity (Post Menopausal)

Mammographic density

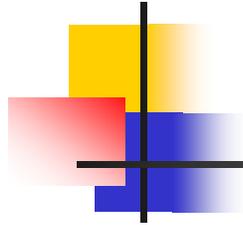
Alcohol Consumption

Proliferative benign breast disease

Westernization

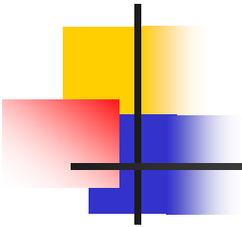
Exercise (Post Menopausal) (**Protective**)

Maternal Pre-Eclampsia (**Protective**)



Is Estrogen Action the Unifying Hypothesis?

- particularly lifetime accumulated dose**



Time and Hormonal Risk Factors

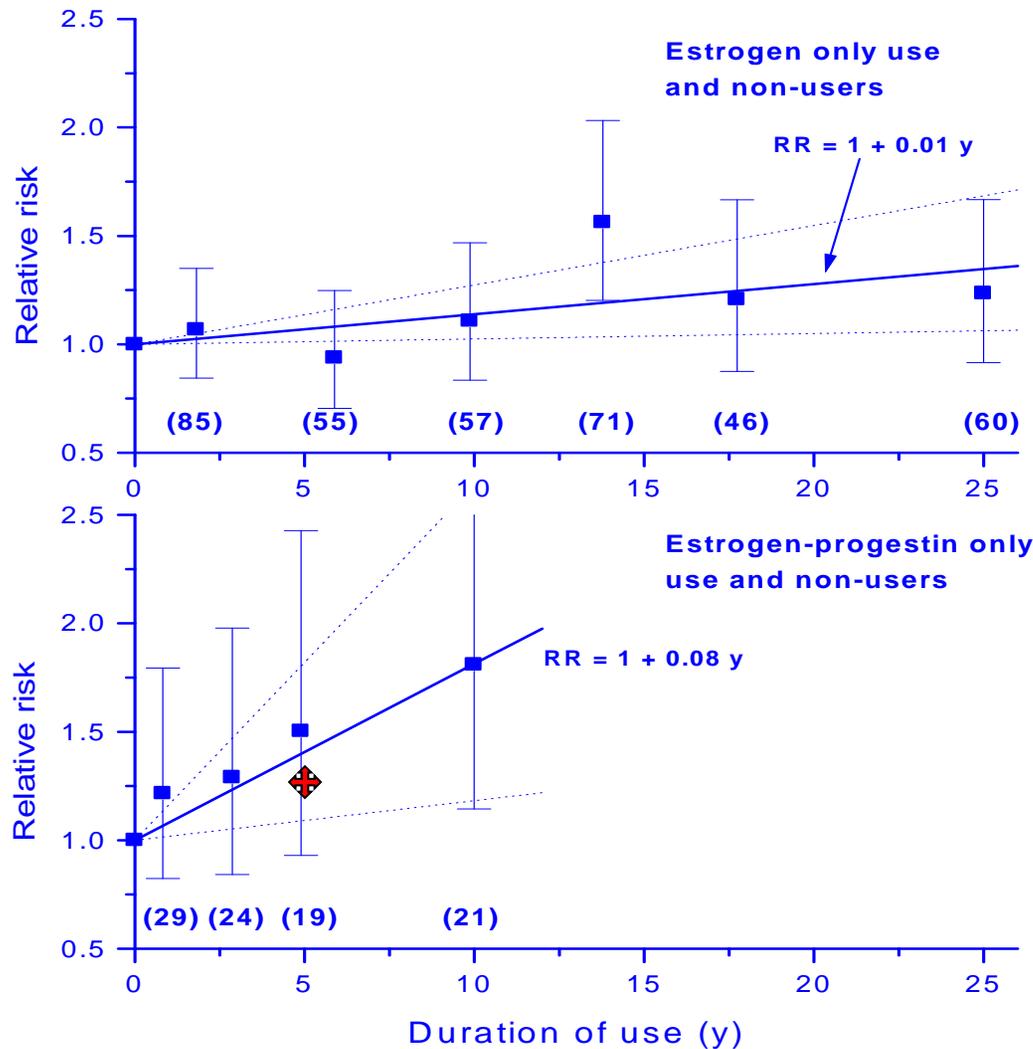
- Age
- Duration
- Recency

Relative Risk (RR) of Breast Cancer: Never Users, Recent Users, and Past Users

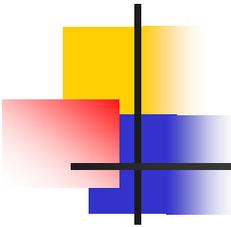
Duration of use and time since last use	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.021)	
Last use <5 years before diagnosis			
Duration <1 year	368/860	0.99 (0.085)	
Duration 1-4 years	891/2037	1.08 (0.060)	
Duration 5-9 years	588/1279	1.31 (0.079)	
Duration 10-14 years	304/633	1.24 (0.108)	
Duration ≥15 years	294/514	1.56 (0.128)	
Last use ≥5 years before diagnosis			
Duration <1 year	437/890	1.12 (0.079)	
Duration 1-4 years	566/1256	1.12 (0.068)	
Duration 5-9 years	151/374	0.90 (0.115)	
Duration ≥10 years	93/233	0.95 (0.145)	

0 0.5 1.0 1.5 2.0

Relative Risk of Breast Cancer by Duration of Estrogen-Only and Estrogen-Progestin-Only Use Among Recent HRT Users



◆ = WHI

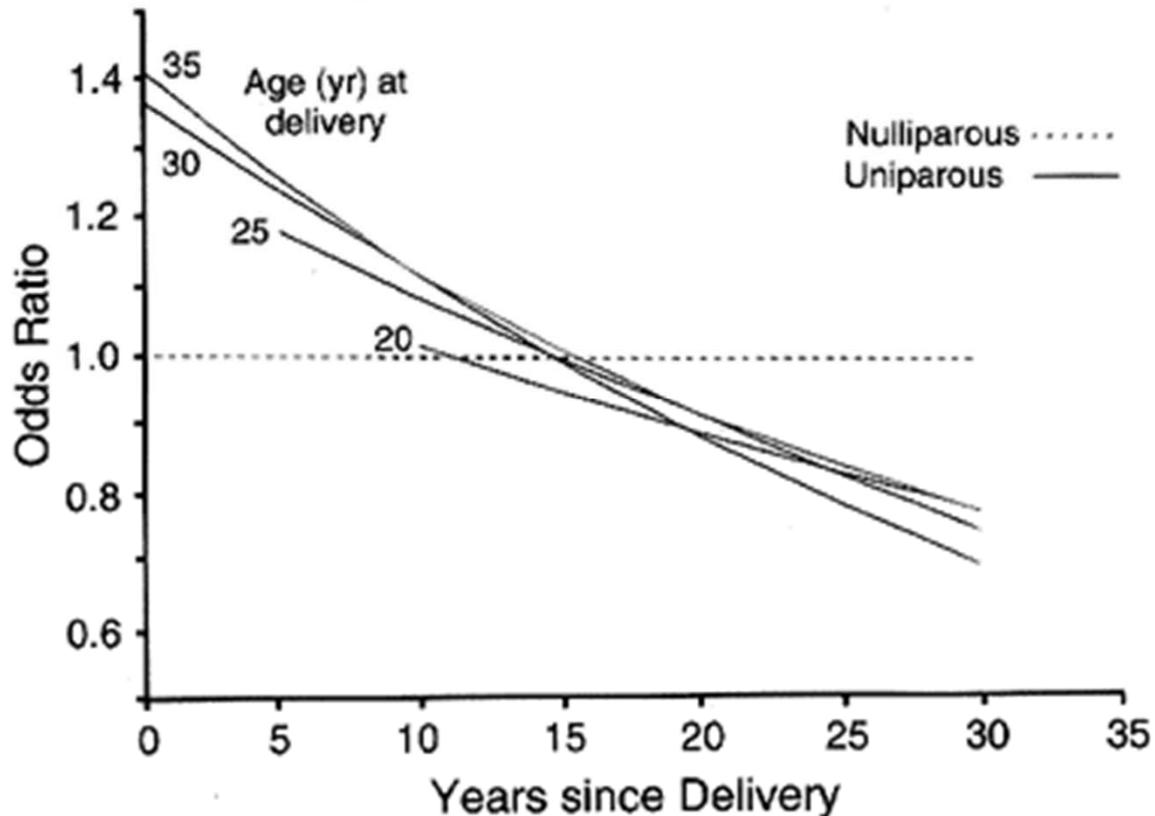


Relative Risk of Breast Cancer: Recent Weight Change

	No	<u>Weight gain, pounds</u>			
	<u>Weight Change</u>	<u>1-5</u>	<u>6-10</u>	<u>> 11</u>	<u>p</u>
Relative Risk	1.0	1.01	1.38	2.26	0.002

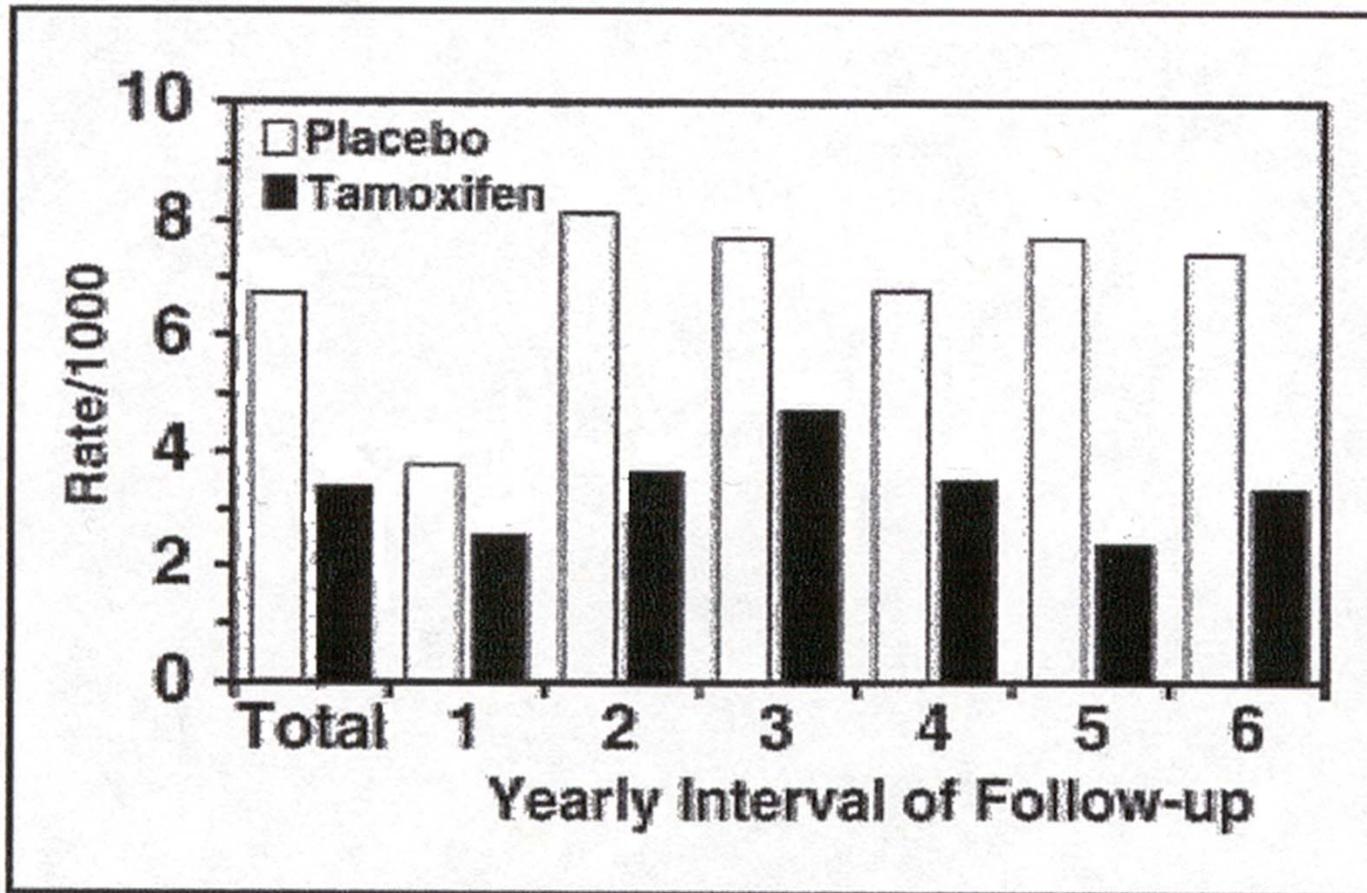
Ziegler JNCI 1996;88:650-60

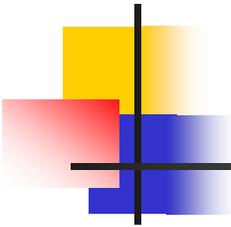
Risk of Breast Cancer for Parity According to the Number of Years Since Delivery



Lambe M, Hsieh C-C, Trichopoulos D, Ekblom A, Pavia M, Adami H-O. Transient Increase in the Risk of Breast Cancer after Giving Birth. *New Engl J Med* 1994;334(1):5-9.

Rates of Invasive Breast Cancer Occurring in Participants Receiving Placebo or Tamoxifen, by Yearly Interval of Follow-up

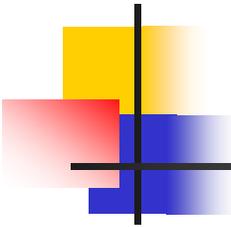




Length of Gestation in First Live Births in Relation to Breast Cancer Risk

<u>Length of Gestation</u>	<u>Cases</u>	<u>Rate Ratio</u>	<u>95% C.I.</u>
<u>≥40</u>	3467	1.0	Reference
32-39	1639	1.03	(0.95-1.05)
32-36	291	1.11	(0.97-1.19)
<32	77	1.22	(0.97-1.53)

From: Vetter et al. Brit J Cancer, 2002



In-Utero “Hormonal” Risk Factors

Risk Factor

Change in Risk

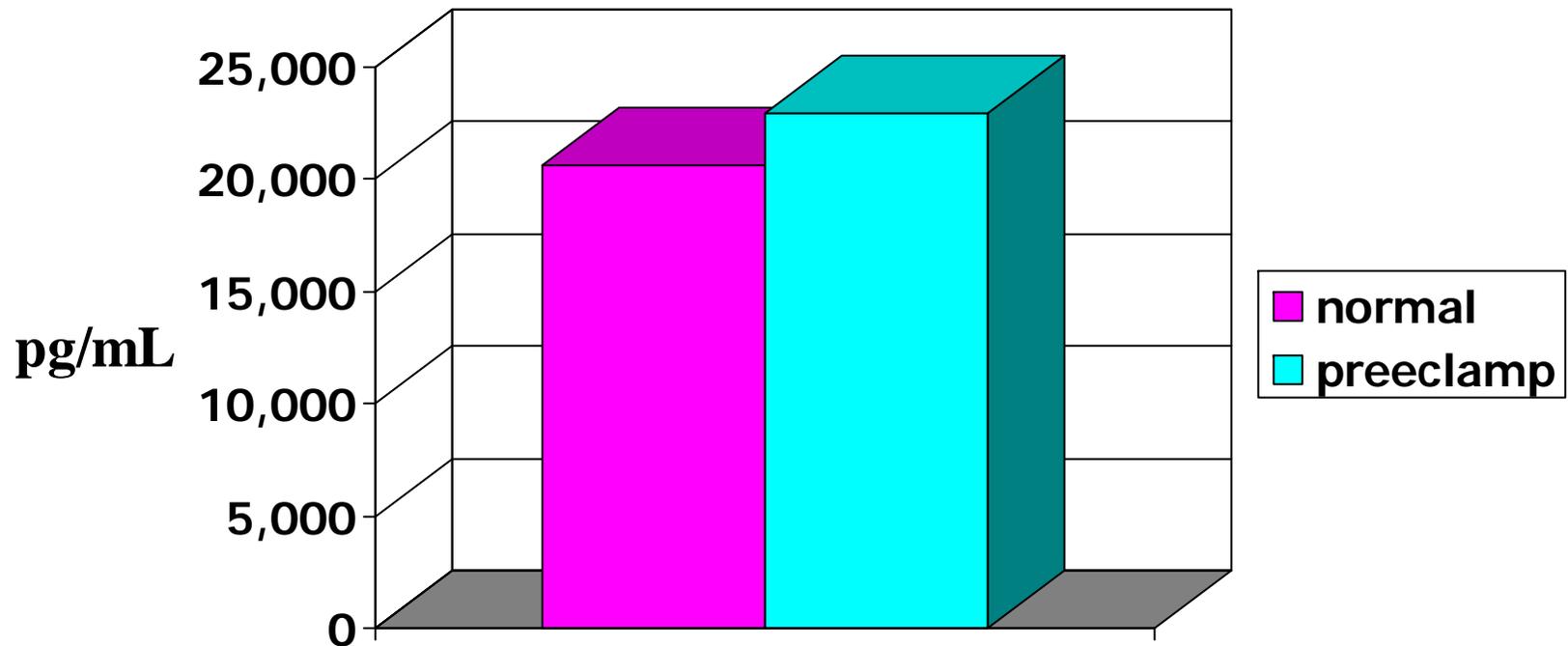
Preeclampsia



Birth Weight



Maternal Estradiol

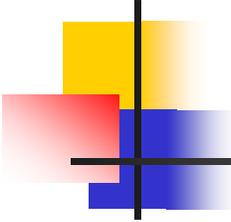


- $P=0.22$, adjusted for age, race and length of gestation
- Troisi and Hoover, unpublished data

Cancer Incidence in Females Exposed In-Utero (daughters) to Diethylstilbestrol

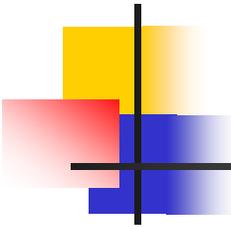
Follow-up through 1998

	Observed	Expected	SIR (95% CI)
All Cancer	89	89.8	1.0
Breast	43	41.2	1.0 (0.8 – 1.4)
Uterine	4	4.3	0.9 (0.4 – 2.5)
Ovary	6	6.3	1.0 (0.4 – 2.1)
Clear Cell Adenoca	4	0.09	46.8 (18 – 125)



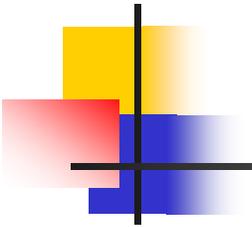
Candidate Hormones

- Estrogens
- Progestins
- Androgens
- Follicle Stimulating Hormone
- Luteinizing Hormone
- Prolactin
- Human Chorionic Gonadotropin
- Corticosteroids
- Insulin
- Insulin-like Growth Factors
- Growth Hormone



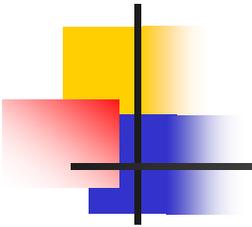
The Effect of Pregnancy and Parity on Basal Serum Prolactin Levels

Variable	No.	Serum Prolactin <i>Ng/ml</i> <i>(mean\timesSE)</i>	P Value*
Pregnancy			
Nulliparous	19	8.85 \times 1.39	
Parous	29	4.77 \times 0.43	<0.01
No. of pregnancies			
1	10	5.18 \times 0.47	
2	14	4.61 \times 0.48	
3	5	4.40 \times 0.35	NS



Hormones Responsible for Risk Factors

- **Estrogens**
 - Elevated estrogens act relatively late in carcinogenesis (most likely tumor promoters or growth enhancers)
 - Role in explaining risk factors earlier in carcinogenesis less clear
 - Some evidence that cumulative lifetime exposure may not be a “unifying” hypothesis
- **Progesterone – similar to estrogens**
- **Other hormones – a role is likely and under-explored**



Challenges in Conduct of Hormonal Epidemiology

Laboratory Assay Variability

Circulating and excreted hormones vs. tissue levels

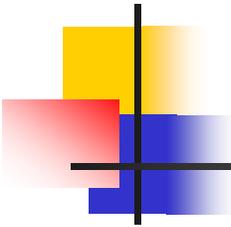
Relevant time

Determinants of levels

Covariates

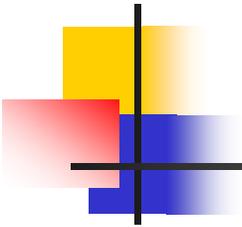
Relevant measures

Lack of understanding of normal and abnormal
biologic mechanisms-of-action of hormones



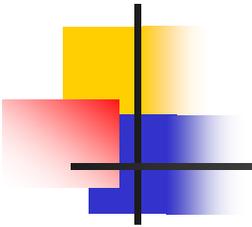
New Research Opportunities

- **Advances in Molecular Science**
 - Basic Science
 - Molecular Epidemiology



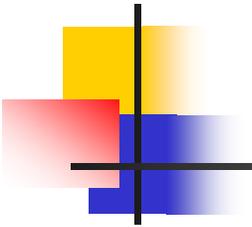
Molecular Epidemiology - Opportunities

- **Measurement of Exposures**
- **Measurement of Outcomes**
 - More Etiologically Relevant Definition of Disease
 - Intermediate Outcomes on Pathway to Malignancy
- **Susceptibility**
- **Mechanistic Insights**



Molecular Epidemiology: Current Needs

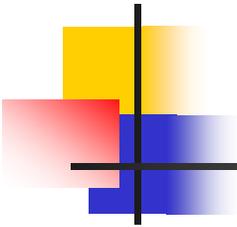
- Very large analytic studies
- Rigorous design, conduct, analysis and interpretation
- More than one such study
- Ideally, in diverse groups
- Available to test important ideas from entire biomedical research community



Emerging New Research Paradigm

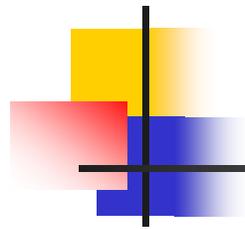
Consortia

- Cohort
- Case-Control
- Epidemiologists, Clinical and Molecular Scientists
- Intensely Collaborative
 - Common Protocol and Methods
 - Coordinated Parallel and Pooled Analyses
- Development of a Resource for testing hypotheses from entire research community



Cohort Consortium Study

	Cases	Controls
Harvard (3 cohorts)	1800	1800
Multiethnic (USC-Hawaii)	1990	1990
EPIC (IARC)	2200	2200
CPS-II (ACS)	1500	1500
PLCO (NCI)	600	600
Total	8090	8090



Cohort Consortium Study

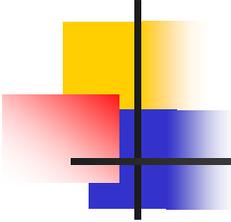
Genomics Collaborating Institutions

Whitehead, USA

CEPH, France

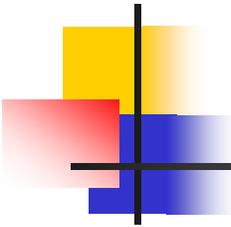
NCI, USA

Cambridge, England



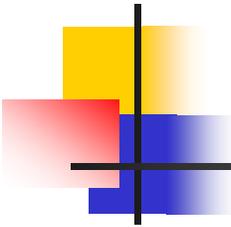
Cohort Consortium Study

- **Hormonal, Dietary and Other Risk Factors**
- **Hormone Levels**
- **Genetic Analysis**
 - 54 genes centrally involved in steroid hormone and IGF synthesis, metabolism and action
 - Specific Polymorphisms
 - Haplotypes



The Hormonal Epidemiology of Breast Cancer, 2002

- **Public Health Imperative:**
 - Need to understand the biologic mechanisms underlying hormonal risk factors
- **Assess a broad spectrum of credible hypotheses**
- **Tools available to do this through interdisciplinary collaborations**



Workshop Being Planned

Early Reproductive Events

and

Breast Cancer Risk