

The Women's Health Initiative, and its implications for Cohort Studies

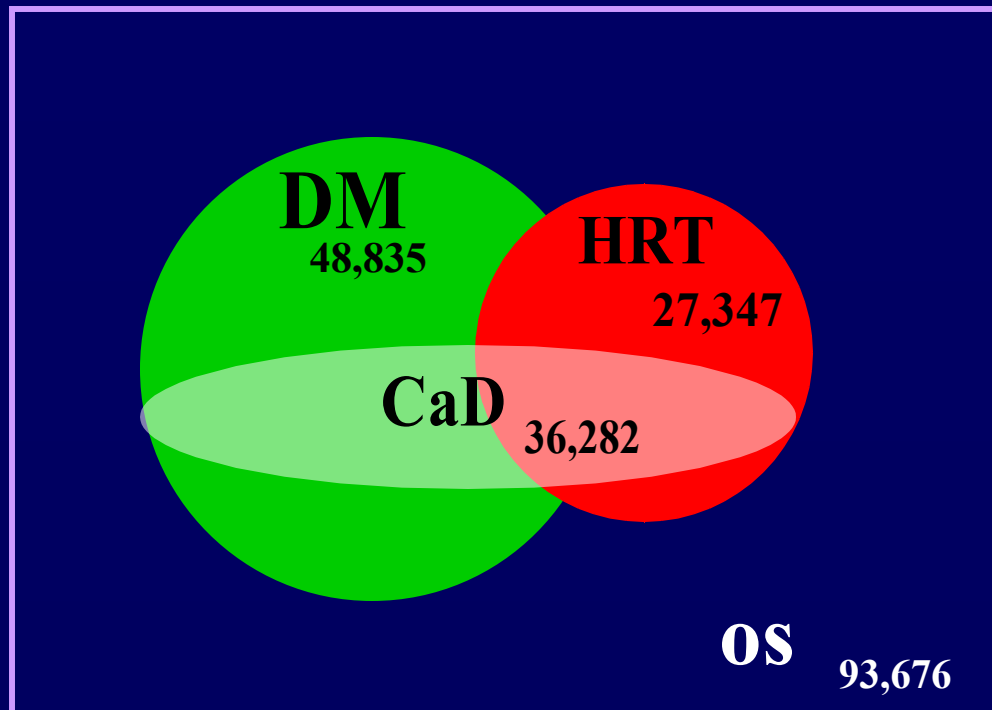
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How can we obtain answers concerning health benefits and risks of behavior changes (interventions), and know that the answers are reliable?

- The WHI cohorts and specimen repository
- The RCT and cohort study interface/ examples of postmenopausal hormone therapy and a low-fat dietary pattern
- The population science research agenda: needs and opportunities

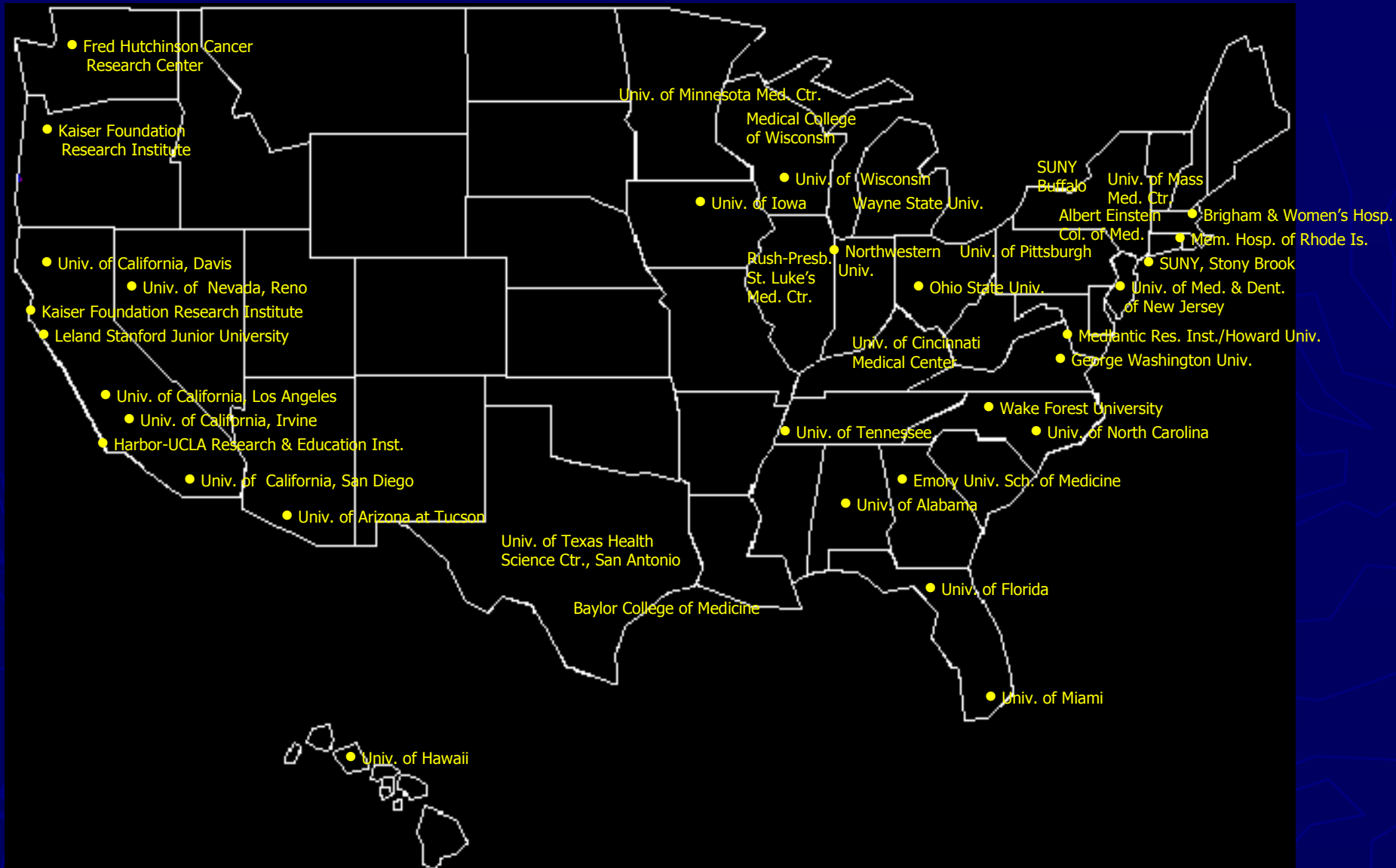
Design of WHI



CT=68,132

WHI =161,808

Women's Health Initiative Clinical Centers



Aliquots Collected and Stored at Each of Two Collections

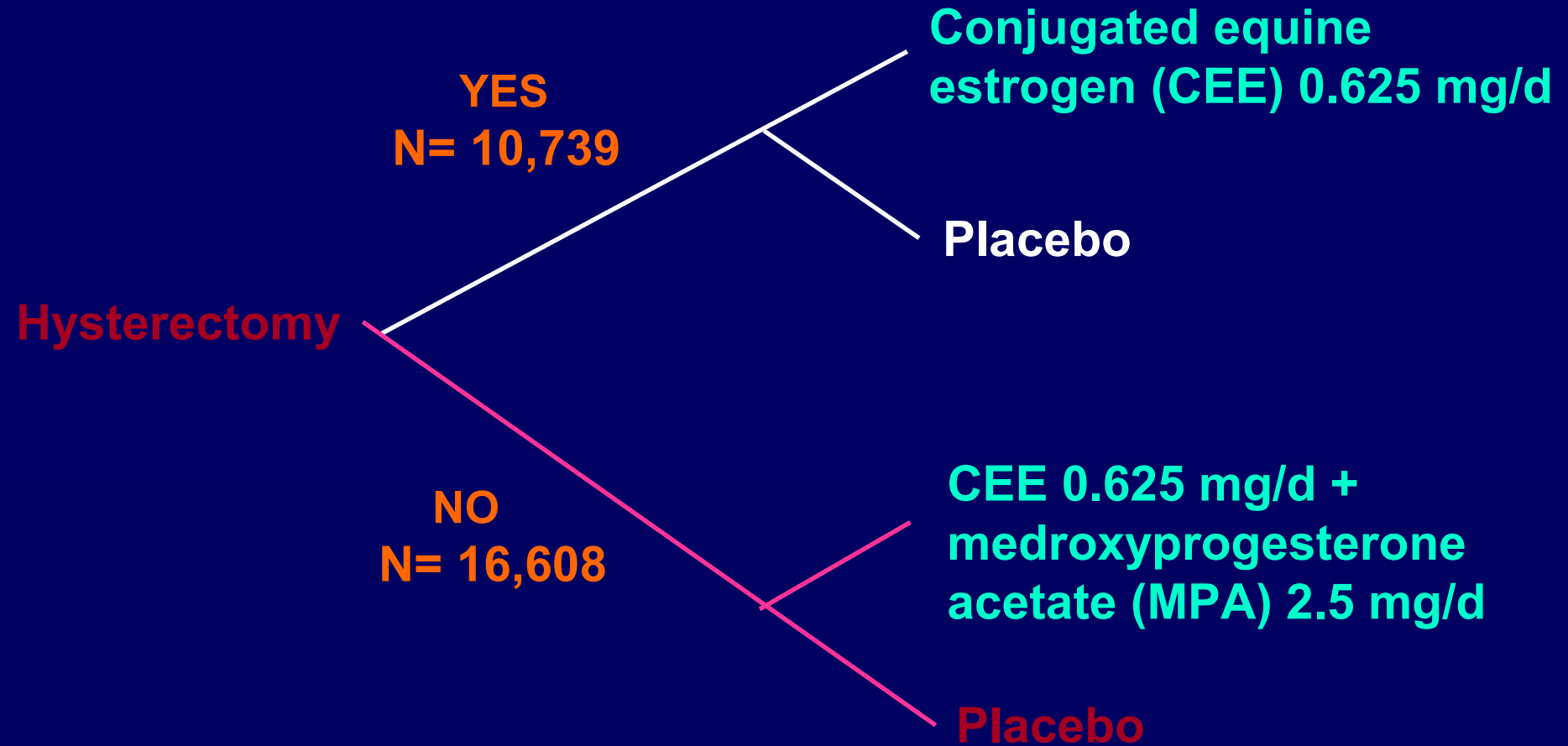
(Baseline and Year 1 in CT, Baseline and Year 3 in OS)

Specimen	VOLUME	ALIQUOTS
Blood		
Serum	7.2 ml	4 x 1.8 ml aliquots
Citrate plasma	5.4 ml	3 x 1.8 ml aliquots
EDTA plasma	5.4 ml	3 x 1.8 ml aliquots
RBC (CT baseline only)	1.8 ml	1 x 1.8 ml aliquot
DNA	200 mcg (< 1996) ~400 mcg (≥ 1996)	2 aliquots buffy coat
Urine	5.4 ml	3 x 1.8 ml aliquots

Approximate Numbers of Cases of Selected Cancer in WHI Clinical Trial and Observational Study (as of 8/15/08)

	CT	OS
Breast	3475	5031
Invasive	2822	4189
Non-invasive	693	880
Ovary	307	442
Endometrial	457	691
Colorectal	904	1109
Bladder	223	275
Kidney	176	228
Leukemia	186	247
Lung	751	990
Lymphoma (NH)	351	504
Melanoma	491	631
Pancreas	192	232

WHI Hormone Program Design



Clinical Outcomes in the WHI Postmenopausal Hormone Therapy Trials

(WHI Study Group, JAMA 2002; Anderson et al, JAMA 2004)

Outcomes	E+P Trial		E-Along Trial	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Coronary heart disease	1.29	1.02 - 1.63	0.91	0.75 - 1.12
Stroke	1.41	1.07 - 1.85	1.39	1.10 - 1.77
Venous thromboembolism	2.11	1.58 - 2.82	1.33	0.99 - 1.79
Invasive breast cancer	1.26	1.00 - 1.59	0.77	0.59 - 1.01
Colorectal cancer	0.63	0.43 - 0.92	1.08	0.75 - 1.55
Endometrial cancer	0.83	0.47 - 1.47		
Hip fracture	0.66	0.45 - 0.98	0.61	0.41 - 0.91
Death due to other causes	0.92	0.74 - 1.14	1.08	0.88 - 1.32
Global index	1.15	1.03 - 1.28	1.01	0.91 - 1.12
Number of women	8506	8102	5310	5429
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	81.6 (19.3)	81.9 (19.7)

Postmenopausal Hormone Therapy (E+P) and Cardiovascular Disease

Women's Health Initiative study of estrogen plus progestin among postmenopausal women in the age range 50-79 at baseline*

	CT			OS		
	Placebo	E+P	Age-adj HR	Control	E+P	Age-adj HR
Number of women	8102	8506		35,551	17,503	
Number of events:						
CHD	147	188	1.21	615	158	0.71
Stroke	107	151	1.33	490	123	0.77
VT	76	167	2.10	336	153	1.06

*Prentice RL et al. *American Journal of Epidemiology* 162:404-414; 2005.

CVD Hazard Ratios for E+P Use, in Joint Analyses of Data from CT and OS Cohorts, Controlling for Potential Confounding Factors

Factor	HR (95% CI) CHD	HR (95% CI) Stroke	HR (95% CI) VT
E+P in CT	1.27 (1.00, 1.61)	1.21 (0.93, 1.59)	2.13 (1.59, 2.85)
E+P in OS	0.87 (0.72, 1.05)	0.86 (0.70, 1.07)	1.31 (1.07, 1.61)
E+P in OS/E+P in CT	0.70 (0.52, 0.95)	0.72 (0.52, 1.02)	0.62 (0.43, 0.88)

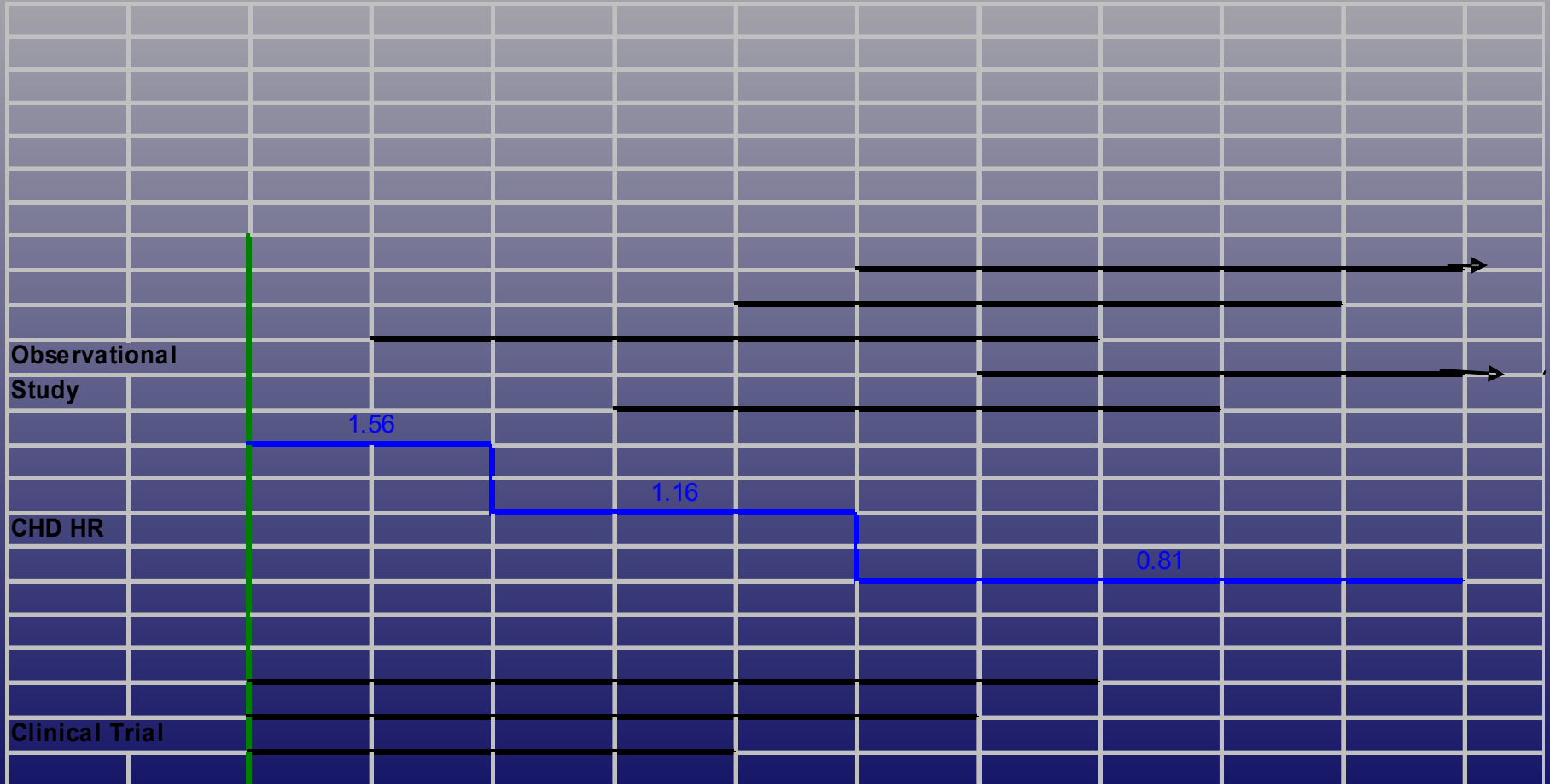
Adjusted for age (linear), ethnicity, bmi (categorical plus linear), education, smoking, age at menopause, physical functioning.

E+P Hazard Ratio in the CT and OS as a Function of Time from Initiation of E+P Use

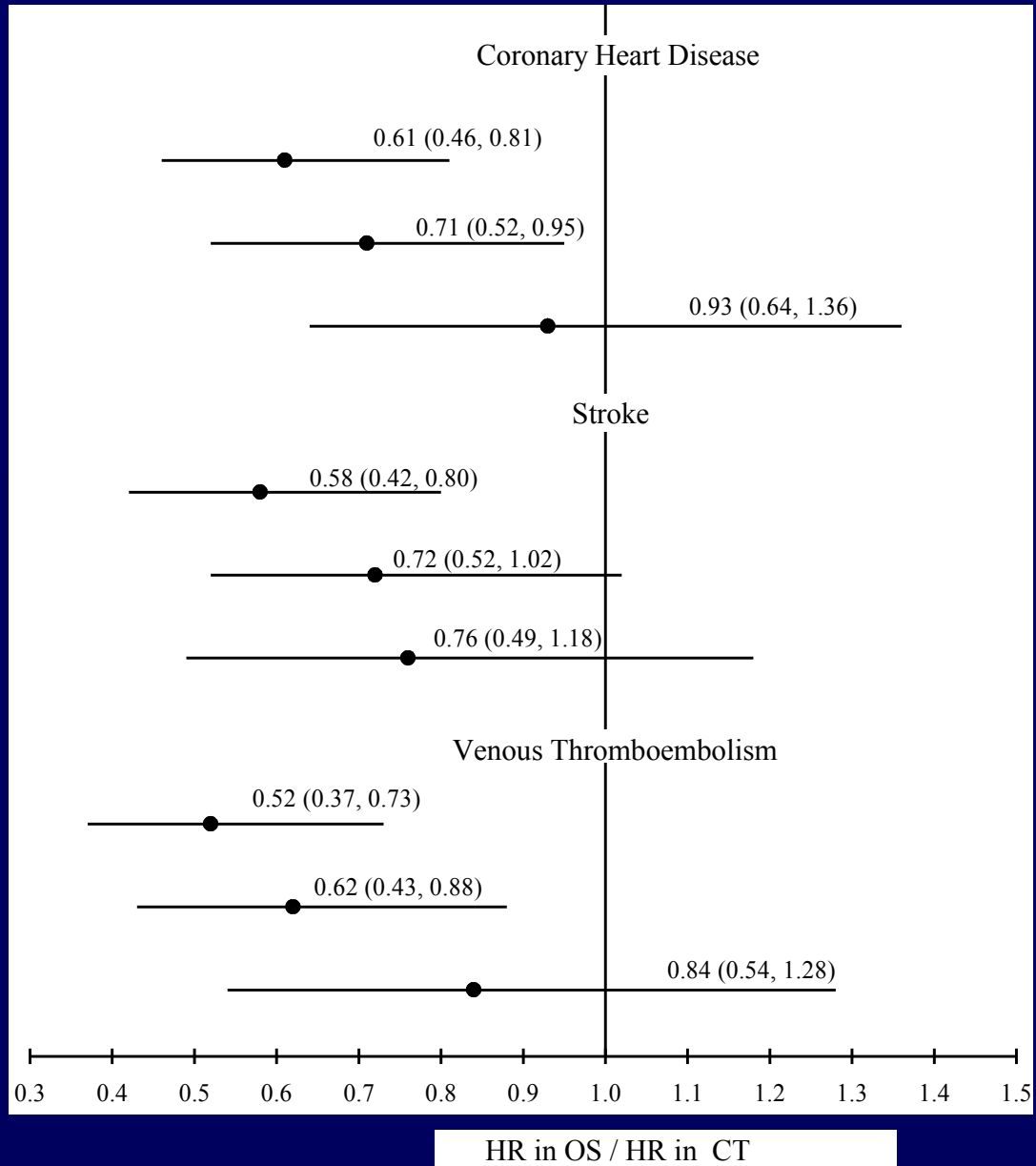
Coronary Heart Disease

Years From E+P Initiation	HR in CT	HR in OS	HR in CT Under Constant OS to CT Ratio	HR Common to CT and OS
< 2	1.68 (1.15, 2.45; 80)	1.12 (0.46, 2.74; 5)	1.58 (1.12, 2.24)	1.56 (1.12, 2.19)
(2, 5)	1.25 (0.87, 1.79; 80)	1.05 (0.70, 1.58; 27)	1.19 (0.87, 1.63)	1.16 (0.89, 1.51)
> 5	0.66 (0.36, 1.21; 28)	0.83 (0.67, 1.01; 126)	0.86 (0.59, 1.26)	0.81 (0.67, 0.99)
E+P in OS/ E+P in CT			0.93 (0.64, 1.36)	

Difference in Distribution in Years from E+P Initiation between WHI Cohorts



Ratio of OS to CT Hazard Ratios for E+P Use



Postmenopausal Estrogen-alone and Cardiovascular Disease

(Prentice RL, et al. AJE 163:589-599,2006)

	CT			OS		
	Placebo	E-alone	Age-adj HR	Control	E-alone	Age-Adj HR
Number of women	5,429	5,310		16,411	21,920	
Number of events:						
CHD	201	217	0.96	548	421	0.68
Stroke	127	168	1.37	408	431	0.95
VT	86	111	1.33	274	265	0.78

Hormone Treatment Hazard Ratios (95% CIs) in the Estrogen (E-alone) Clinical Trial (CT); and in the Estrogen and Estrogen plus Progestin (E+P) Clinical Trials and Corresponding Observational Study Samples

Years from Hormone Treatment Initiation	E-alone HR (95% CI)	E+P HR (95% CI)
Coronary Heart Disease		
< 2	1.11 (0.73, 1.69)	1.58 (1.12, 2.24)
2 - 5	1.17 (0.88, 1.56)	1.19 (0.87, 1.63)
> 5	0.81 (0.62, 1.06)	0.86 (0.59, 1.26)
<i>Hormone Therapy: HR in OS/HR in CT</i>	0.89 (0.67, 1.19)	0.93 (0.64, 1.36)
Stroke		
< 2	1.48 (0.89, 2.44)	1.41 (0.90, 2.22)
2 - 5	1.18 (0.83, 1.67)	1.14 (0.82, 1.59)
> 5	1.48 (1.06, 2.06)	1.12 (0.73, 1.72)
<i>Hormone Therapy: HR in OS/HR in CT</i>	0.68 (0.48, 0.97)	0.76 (0.49, 1.18)
Venous Thromboembolism		
< 2	2.18 (1.15, 4.13)	3.02 (1.94, 4.69)
2 - 5	1.22 (0.80, 1.85)	1.85 (1.30, 2.65)
> 5	1.06 (0.72, 1.56)	1.47 (0.96, 2.24)
<i>Hormone Therapy: HR in OS/HR in CT</i>	0.82 (0.54, 1.23)	0.84 (0.55, 1.28)

Invasive Breast Cancer Incidence Rates in the Clinical Trial Hormone Trials (HT) and the Observational Study (OS) Subcohort*

	E-alone					
	CT			OS		
	Placebo	E-alone	Ratio	Control	E-alone	Ratio
Number of Women	5,429	5,310		14,458	21,663	
Mean age	63.6	63.6		65.3	63.0	
Mean years of follow-up	7.1	7.1		7.0	7.2	
Number of Events	133	104		380	626	
Age-Adjusted [†] Annualized Incidence (%)	0.35	0.28	0.80	0.36	0.41	1.13

	E+P					
	CT			OS		
	Placebo	E+P	Ratio	Control	E+P	Ratio
Number of Women	8,102	8,506		32,755	17,382	
Mean age	63.3	63.2		64.7	61.1	
Mean years of follow-up	5.6	5.6		5.5	5.6	
Number of Events	150	199		610	583	
Age-Adjusted [†] Annualized Incidence (%)	0.33	0.42	1.25	0.33	0.65	1.94

*Prentice RL et al. AJE, 2008 (March E+P; April E-alone).

[†]Age-adjusted to the 5-year age distribution in the CT cohort.

Invasive Breast Cancer Hazard Ratios for HT Use Adjusted for Potential Confounding Factors, in Combined Analyses of Data from the CT and OS

Factor	E-alone HR* (95% CI)	E+P HR* (95% CI)
HT in CT	0.71 (0.53, 0.97)	1.20 (0.95, 1.52)
HT in OS	1.28 (1.05, 1.56)	1.71 (1.38, 2.13)
HT in OS/HT in CT	1.79 (1.25, 2.58)	1.42 (1.03, 1.96)

*Adjusted for age (linear), ethnicity, bmi (categorical and linear), education, smoking history, alcohol consumption, prior HT use, general health, physical activity, Gail risk score

Distribution of Women in the WHI Hormone Therapy Clinical Trials (CT), and in Corresponding Observational Study (OS) Subcohorts, According to Prior Use of Postmenopausal Hormone Therapy (HT) and Gap Time from Menopause to First Use of HT, Among Hormone Therapy Users

Prior HT	CT						OS					
	No			Yes			No			Yes		
	< 5	5 - 15	> 15	< 5	5 - 15	> 15	< 5	5 - 15	> 15	< 5	5 - 15	> 15
Gap time (yrs)	< 5	5 - 15	> 15	< 5	5 - 15	> 15	< 5	5 - 15	> 15	< 5	5 - 15	> 15
CEE Users												
Number of women	198	618	1136	2129	294	113	6626	1454	597	1662	213	30
% of Women	10%	32%	58%	84%	12%	4%	76%	17%	7%	87%	11%	2%
CEE/MPA Users												
Number of women	952	2338	2160	1864	302	63	4257	1115	338	916	113	17
% of Women	17%	43%	40%	84%	14%	3%	75%	20%	6%	88%	11%	2%

*Prior HT is defined relative to WHI enrollment in the CT and in the non-user groups in the OS. Prior HT in the user groups in the OS is defined relative to the beginning of the on-going HT episode at enrollment.

Breast Cancer Hazard Ratio Estimates according to Prior Postmenopausal Hormone Therapy Status, Years from Hormone Therapy Initiation, and Gap Time from Menopause to Hormone Therapy Initiation, among Women Adhering to their Baseline Hormone Therapy Status

Gap Time Periods*	Prior HT	No Prior HT		
	HR (95% CI)	<5 HR (95% CI)	5-15 HR (95% CI)	>15 HR (95% CI)
CEE				
Years from HT Initiation				
< 2	1.52 (0.63, 3.65)	1.08 (0.14, 8.19)	0.56 (0.13, 2.43)	0.92 (0.34, 2.47)
2 - 5	0.76 (0.40, 1.45)	1.61 (0.67, 3.88)	0.76 (0.29, 1.99)	0.61 (0.25, 1.46)
> 5	0.85 (0.46, 1.58)	0.98 (0.54, 1.75)	0.77 (0.40, 1.50)	0.76 (0.35, 1.64)
HT in OS/HT in CT	1.07 (0.61, 1.89)			
CEE/MPA				
Years from HT Initiation				
< 2	1.61 (0.76, 3.41)	1.32 (0.56, 3.11)	0.73 (0.35, 1.52)	0.37 (0.13, 1.06)
2 - 5	3.51 (1.81, 6.81)	1.85 (1.03, 3.34)	1.61 (1.00, 2.59)	0.81 (0.44, 1.48)
> 5	2.76 (1.31, 5.79)	2.75 (1.73, 4.39)	2.00 (1.19, 3.36)	1.23 (0.53, 2.86)
HT in OS/HT in CT	1.15 (0.74, 1.80)			

*Gap time in years from menopause to first use of HT

Comparative and Joint CT and OS Analysis of Postmenopausal Hormone Therapy Effects

- CT/OS analyses also include Prentice et al 2009 CEBP on colorectal cancer, and Prentice et al 2009 AJE on overall health risks and benefits
- Ability to control prescription/confounding biases in OS may differ by clinical outcome (e.g., stroke, hip fracture).
- Careful design and analysis methods needed to obtain accurate information from observational studies (allow for departures from proportional hazards, possible effect modification, ...).
- Clinical trial and observational study data may be able to be combined to obtain useful benefits and risk assessments (important subsets, longer durations, ...).
- Intervention trials may be needed if public health implications are sufficiently great.

Low-Fat Dietary Pattern Trial: Findings and Methodology

Intervention Group Goals:

- 20% energy from fat
- 5 or more fruit and vegetable servings daily
- 6 or more grain servings daily



Photos courtesy of USDA Agricultural Research Service

Mean (SD) of Nutrient Consumption by Randomization Group

	Year 1		Year 1		Year 3		Year 6	
	Intervention	Control	Difference		Difference		Difference	
Fat (% of calories)	24.3 (7.5)	35.1 (6.9)	-10.7*	(7.0)	-9.5*	(7.4)	-8.1*	(7.8)
Total Fat (g)	40.8 (21.4)	63.0 (31.0)	-22.4*	(31.1)	-20.1*	(32.0)	-18.4*	(33.5)
Saturated Fat (%)	8.1 (2.8)	11.8 (2.9)	-3.7*	(2.9)	-3.3*	(3.1)	-2.9*	(3.3)
Polyunsaturated Fat (%)	5.2 (1.8)	7.2 (2.1)	-2.0*	(2.1)	-1.7*	(2.2)	-1.4*	(2.3)
Monounsaturated Fat (%)	8.9 (3.1)	13.3 (2.9)	-4.4*	(3.0)	-3.9*	(3.2)	-3.3*	(3.4)
Energy (kcal)	1500.5 (544.2)	1593.8 (644.0)	-95.8*	(616.2)	-92.5*	(632.1)	-119.9*	(662.9)

*Difference significant at $p < 0.001$ from a two sample t-test

Comparison of Cancer Incidence Rates between Intervention and Comparison Groups in the Women's Health Initiative (WHI) Dietary Modification Trial*

Prentice et al (JAMA, 2006; JNCI, 2007); Beresford et al (JAMA, 2006)

Cancer Site	Incidence per 1000 person- years		P [†]	HR (95% CI) [‡]
	(Number of patients)			
	Intervention	Comparison		
Ovary	0.36 (57)	0.43 (103)	.03	0.83 (0.60 to 1.14)
Endometrium	0.79 (125)	0.71 (170)	.18	1.11 (0.88 to 1.40)
Breast	4.15 (655)	4.52 (1072)	.09	0.91 (0.83 to 1.01)
Colorectal	1.27 (201)	1.18 (279)	.29	1.08 (0.90 to 1.29)
All other sites	4.56 (720)	4.81 (1140)	.30	0.95 (0.86 to 1.04)
Total cancer	10.69 (1687)	11.22 (2661)	.10	0.95 (0.89 to 1.01)

*Trial includes 19,541 women in the intervention group and 29,294 women in the comparison group.

†Weighted log-rank test (two-sided) stratified by age (5-year categories) and randomization status in the WHI hormone therapy trial. Weights increase linearly from zero at random assignment to a maximum of 1.0 at 10 years.

‡HR= hazard ratio; CI =confidence interval, from a proportional hazards model stratified by age (5-year categories), and randomization status in the WHI hormone therapy trial.

Are Biases in Dietary Assessment Dominating Nutritional Epidemiology?

- Bingham et al (2003, *Lancet*) report a positive association between breast cancer and total and fat when consumption was assessed using a 7-day food diary, but the association was modest and non-significant when consumption was assessed with a FFQ. Very similar results from 4-day food record and FFQ analyses among DM comparison group women (*Freedman et al 2006, IJE*).
- Objective measures (biomarkers) are needed to make progress in this important research area. Biomarker assessments in substudies (such as DLW measures of total energy expenditure) can be used to calibrate self-report assessments.

Nutrient and Physical Activity Biomarkers in the WHI

- 544 women completed two-week DLW protocol with urine and blood collection and with FFQ and other questionnaire data collection (50% intervention, 50% control). A 20% reliability subsample repeated protocol separated, by about 6 months from original data collection.
- Biomarker study among 450 women in the WHI Observational Study for calibrating baseline FFQ, 4DFR, and PA questions, and for evaluating measurement properties of prominent dietary and physical activity assessment approaches (frequencies, records, and recalls) and their combination.

Measurement Models for Nutritional Epidemiology

(Carroll, Freedman, Kaaks, Kipnis, Spiegelman, Rosner, Prentice...)

Recovery Biomarkers:

$$X_{\text{biomarker}} = Z + e$$

$$W_{\text{self-report}} = a_0 + a_1 Z + a_2 V + a_3 ZV + r + \varepsilon$$

Can estimate odds ratios (*Sugar et al, 2007, Biometrics*), or hazard ratios (*Shaw et al, 2007*), corresponding to Z from cohort data on W and subcohort data on X .

Regression Calibration Coefficients for Log-Transformed Total Energy, Total Protein and Percent Energy from Protein (Neuhouser et al, AJE,2008)

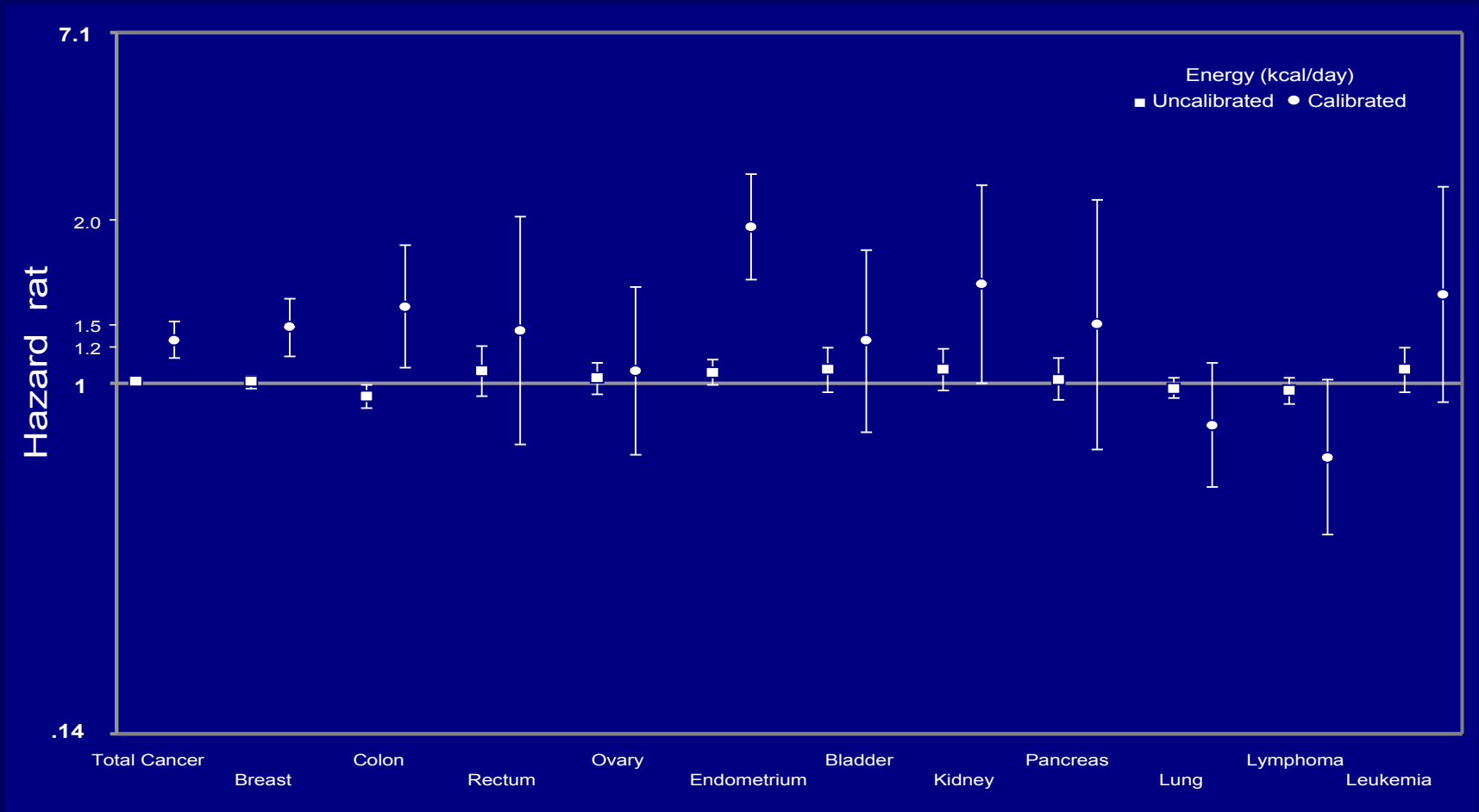
Characteristic	a Coefficient (SE) Total Energy	a Coefficient (SE) Protein	a Coefficient (SE) % Energy from Protein
Intercept	7.61 (0.13)	4.28 (0.024)	2.66 (0.01)
FFQ	0.062 (0.018)	0.212 (0.032)	0.439 (0.058)
BMI	0.013 (0.001)	0.012 (0.002)	-0.004 (0.002)
Age	-0.005 (0.001)	-0.008 (0.002)	-0.005 (0.002)
Black	-0.016 (0.017)	-0.130 (0.047)	---
Hispanic	-0.004 (0.030)	-0.021 (0.056)	---
Other Race	-0.093 (0.027)	-0.100 (0.058)	---

Geometric means and 95% confidence intervals for uncalibrated dietary intakes as estimated by the Women's Health Initiative (WHI) Food Frequency Questionnaire, and for calibrated intakes using nutritional biomarker data in the WHI Dietary Modification trial comparison group (DM) and Observational Study (OS)-Prentice et al, AJE 2009

	Geometric Mean (95 % Confidence Interval)					
	Energy (kcal/day)		Protein (g/day)		% of Energy from Protein	
	Uncalibrated	Calibrated*	Uncalibrated	Calibrated	Uncalibrated	Calibrated
DM	1480.3 (675.9, 3242.2)	2143.1 (1796.5, 2556.5)	60.9 (26.2, 141.6)	78.3 (58.3, 105.0)	16.6 (11.4, 24.1)	14.4 (12.1, 17.2)
OS	1380.2 (642.6, 2964.3)	2059.1 (1726.1, 2456.3)	58.6 (247.0, 138.7)	74.4 (55.5, 99.9)	16.9 (11.5, 25.1)	14.4 (11.9, 17.6)

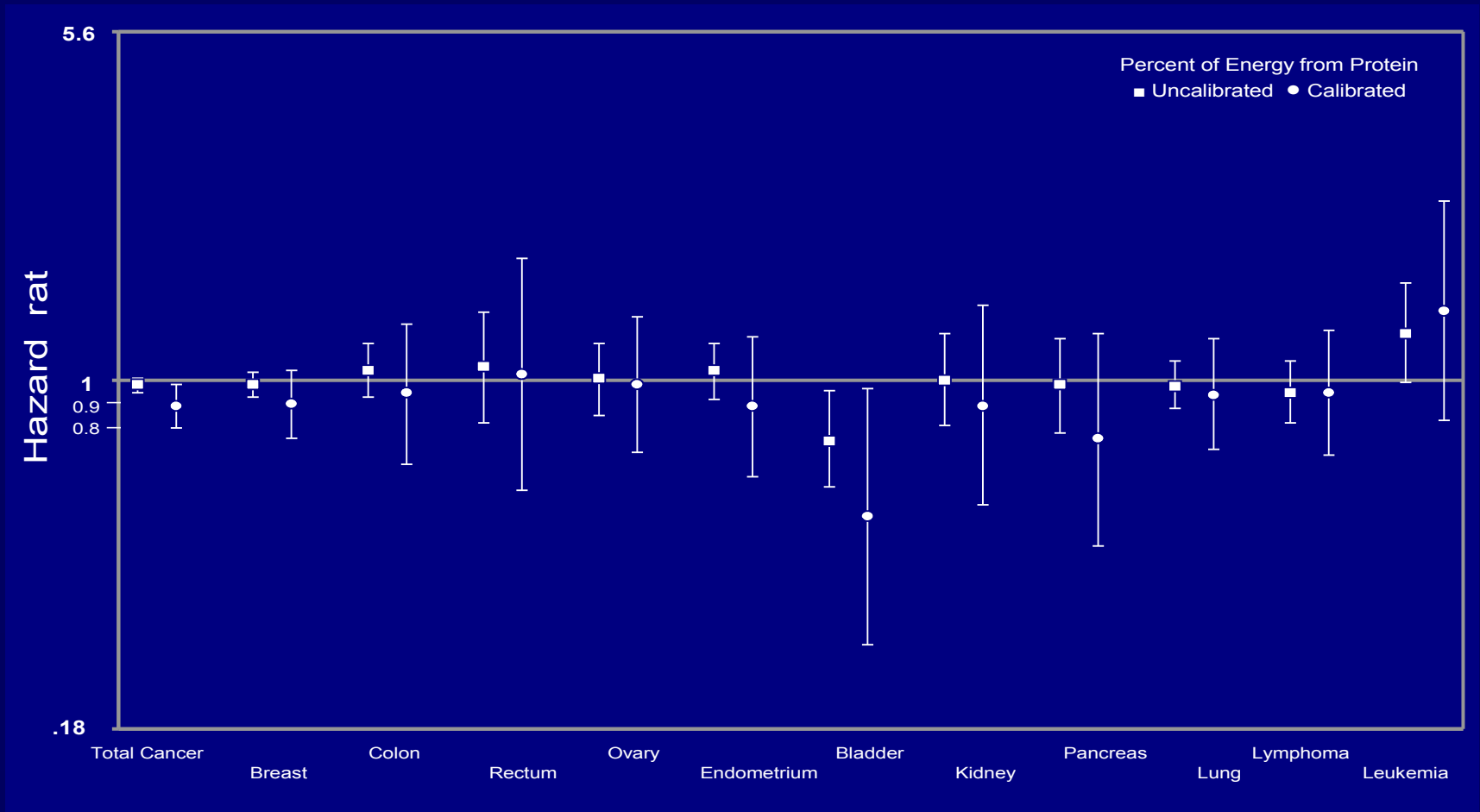
*Calibrated using measurement model A for women in the Nutrition Biomarker Study, and model B otherwise.

Hazard ratios for a 30% increase in energy from combined analysis of data from the Women's Health Initiative Dietary Modification (DM) trial comparison group and Observational Study (OS), without and with biomarker calibration of consumption



*Estimated hazard ratio (HR) for 30% increase in nutrient consumption, and corresponding 95% confidence interval (CI)

Hazard ratios for a 30% increase in percent of energy from protein consumption, from combined analysis of data from the Women's Health Initiative Dietary Modification (DM) trial comparison group and Observational Study (OS), without and with biomarker calibration of consumption (*continued*)



*Estimated hazard ratio (HR) for 30% increase in nutrient consumption, and corresponding 95% confidence interval (CI)

Lessons from Studies of Dietary Consumption Effects on Chronic Disease

- Adequate control of dietary assessment measurement errors key to reliable nutritional and physical activity effects on chronic disease
- Development of biomarkers for other nutrients/aspects of physical activity, or methodologic research as to how to use existing markers needs to have a high priority in nutrition and physical activity research agenda

Population Science Research Needs

- An enhanced preventive intervention development enterprise
- Observational studies of maximal reliability for promising intervention concepts
- Full-scale intervention trials when rationale strong enough, and public health potential sufficiently great
- Vigorous methodology development (e.g., to incorporate exposure and intermediate outcome biomarkers into research agenda)

Infrastructure to facilitate?

Population Science Cooperative Group (USA)

- Identify preventive interventions that merit initial testing or full-scale evaluation
- Receive and evaluate preventive trial proposals and cohort study development/maintenance proposals
- Identify and facilitate needed methodologic research

Group Composition

- Population, basic and clinical scientists
- Leaders in key areas for intervention development
- Leaders in major chronic disease research areas
- Representatives from within and outside of NIH