THE WOMEN'S HEALTH INITIATIVE

IGNITE Presentations

IGNITE 1: Genetic Risk Profiles Inform Personalized Hormone Therapy Decisions: Evidence from the Women's Health Initiative – Huong Le, Fred Hutchinson Cancer Center

IGNITE 2: Harnessing the Power of Multi-Omics to Advance Understanding of Biological Aging and Healthspan in Older Women – Aladdin Shadyab, University of California San Diego

Fred Hutch Cancer Center

Genetic Risk Profiles Inform Personalized Hormone Therapy Decisions: Evidence from the Women's Health Initiative

Huong Le

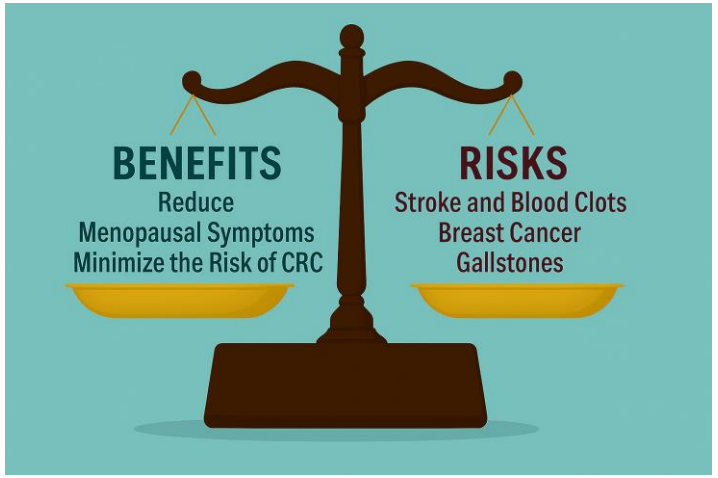
Postdoctoral Research Fellow

Fred Hutchinson Cancer Center

May 2025

Personalizing Hormone Therapy Through Genetics

- ***Genetic profiles may help personalize hormone treatment decisions***
- Hormone replacement therapy (HRT)
  - ➢Effectively treats menopausal symptoms
  - ➢Different women experience different benefits and risks
- Genetic risk profiles may explain these differences
- Understanding genetic modifiers enables personalized medicine approaches



- **Study Goal: Determine how genetic predisposition modifies HRT's effects to optimize the risk-benefit ratio for each woman**

Methods

- Women with genetic data in WHI
  - Two trials: E+P trial and E-alone trial
  - Dietary Modification (people not in the HRT) and Observational Study (DMOS)
  - 2002 for E+P and 2004 for E-alone, when the trials were terminated
- Exposures
  - HRT status : Yes/No
  - Standardized PRS for each disease: continuous variable to measure a genetic risk factor
- Covariates are age, BMI, race/ethnicity, study, education, smoking, first 10 principal components
- Seven outcomes

Coronary Heart Disease (CHD)	Hypertension (HTN)	Breast Cancer (BC)
Stroke	Type 2 Diabetes (T2D)	Colorectal Cancer (CRC)
Venous Thromboembolism (VTE)*		

*: Disease was selected on 2 trials only, not on DMOS

Methods

- Statistical Analyses
  - Logistic regression models for each disease and each study

$$logit\,\{P(G, E)\} = \beta_0 + \beta_1 * PRS + \beta_2 * HT + \beta_3 * PRS * HT + Covariates*$$

  - Multiplicative interaction effects:

$$MI = \exp(\beta_3)$$

  - Additive interaction effects: Relative Excess Risk due to Interaction (RERI)

$$RERI = \exp(\beta_1 + \beta_2 + \beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1 = OR_{11} - OR_{10} - OR_{01} + 1$$

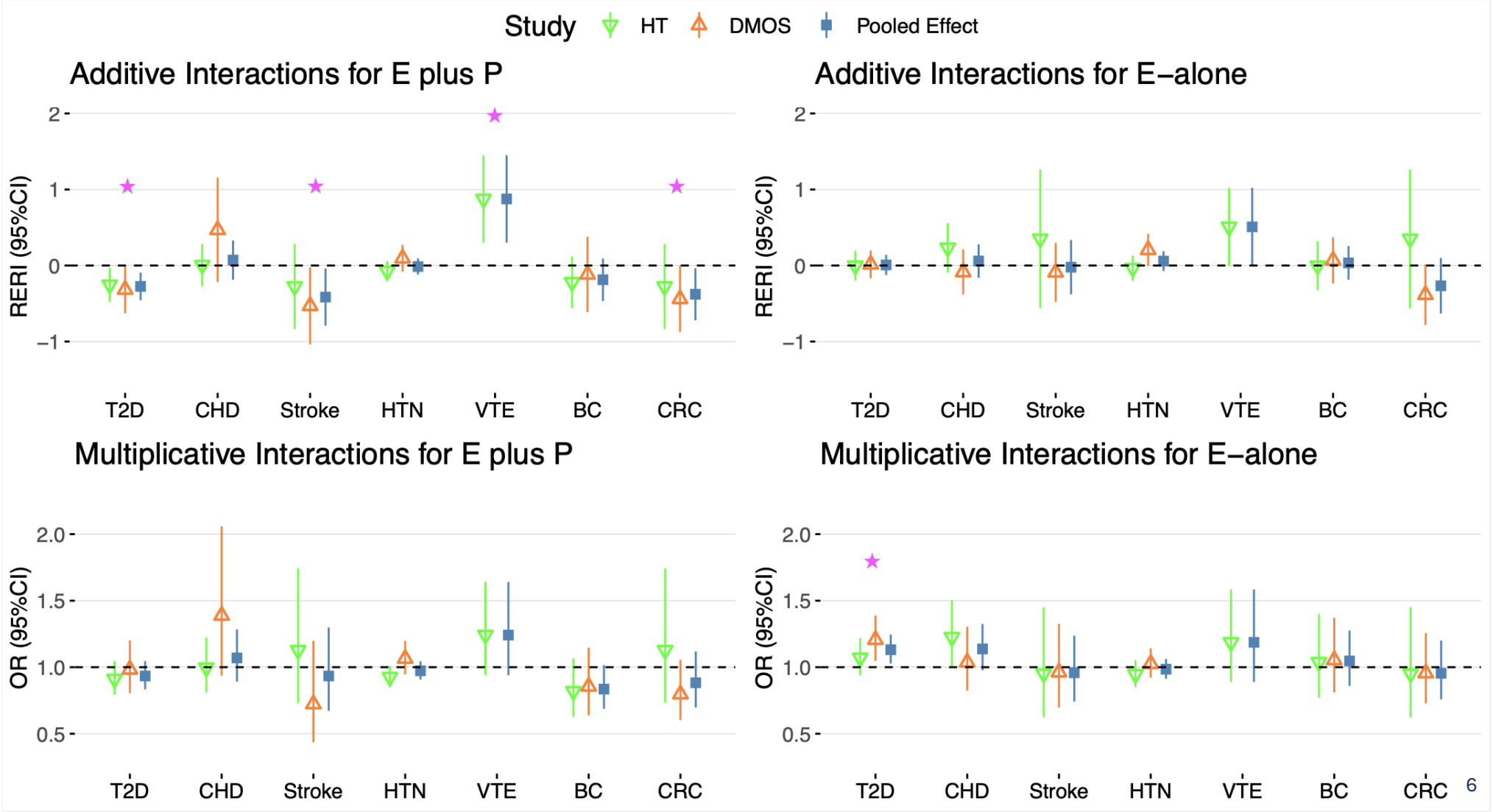
Calculate 95%CI of RERI using delta method

  - Meta-analyses to estimated pooled interactions effects of HT trials and DMOS

Results

Additive and Multiplicative interactions between PRS and HRT

(baseline until 2002 for E+P and 2004 for E-alone)



Absolute disease risks of women in E+P trial during trial phase of ~5.6-year

Disease	Woman 1 (age= 73)			Woman 2 (age= 57)			Woman 3 (age= 72)			Woman 4 (age= 66)		
	PRS	w/o HT	w HT	PRS	w/o HT	w HT	PRS	w/o HT	w HT	PRS	w/o HT	w HT
T2D	74.6	0.16	0.14	**92.3**	**0.05**	**0.04**	54.7	0.07	0.06	30.2	0.01	0.00
CHD	9.0	0.12	0.13	6.7	0.02	0.02	54.3	0.15	0.16	88.1	0.01	0.01
Stroke	**99.6**	**0.18**	**0.14**	**93.5**	**0.02**	**0.01**	38.5	0.10	0.14	39.8	0.00	0.00
HTN	25.4	0.55	0.59	**92.9**	**0.37**	**0.37**	11.3	0.39	0.44	79.2	0.25	0.25
VTE	70.4	0.12	0.21	34.8	0.00	0.01	**92.1**	**0.11**	**0.22**	32.1	0.00	0.00
BC	14.8	0.001	0.001	53.3	0.001	0.001	84.6	0.001	0.001	15.9	0.000	0.001
CRC	70.5	0.012	0.007	55.5	0.001	0.001	**96.2**	**0.023**	**0.016**	**96.9**	**0.016**	**0.011**

Note: We calculated the absolute risk based on the primary results of WHI's papers, except for HTN and HF. Those diseases primary probabilities were calculated from primary data, which includes both women with genetic and without genetic data

Women	Race	BMI	Smoking	Education
1	AA	30	No	3
2	AA	25	Yes	1
8	EUR	25	Yes	4
4	EUR	22	No	4

Note: Education: 1 (Some high school); 3 (High school graduate); 4 (Some college); 5 (College graduate and beyond)[7]

Fred Hutch
Cancer Center

Thank You

(Please join our poster presentation at 4:30 pm today)