FRED HUTCHINSON CANCER RESEARCH CENTER

A LIFE OF SCIENCE

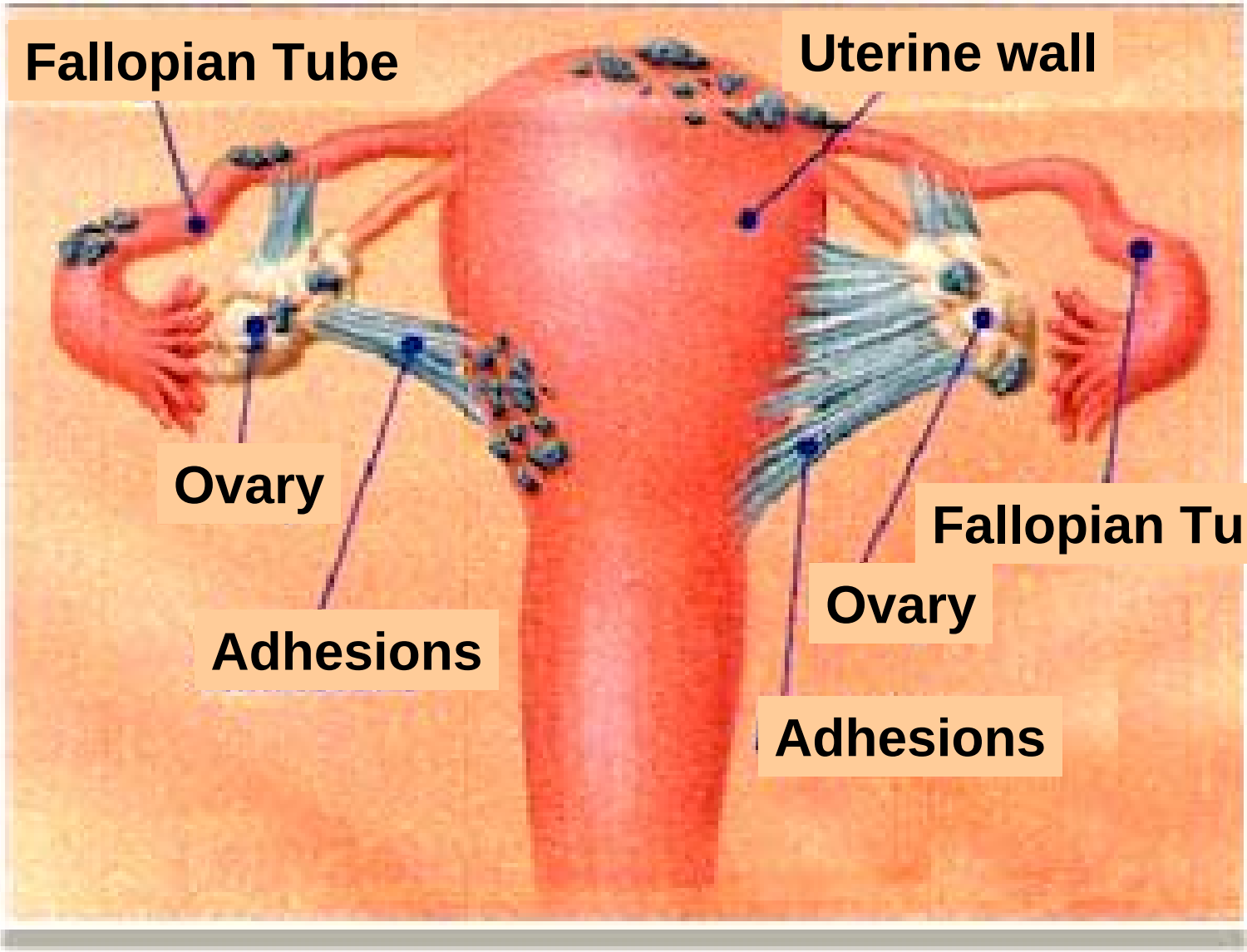
This research is funded by
U.S. EPA - Science To Achieve Results (STAR) Program
Grant # R829438

Persistent Organic Pollutants and Endometriosis Risk

Victoria L. Holt

Fred Hutchinson Cancer Research Center, Seattle, WA

Pelvic endometriosis



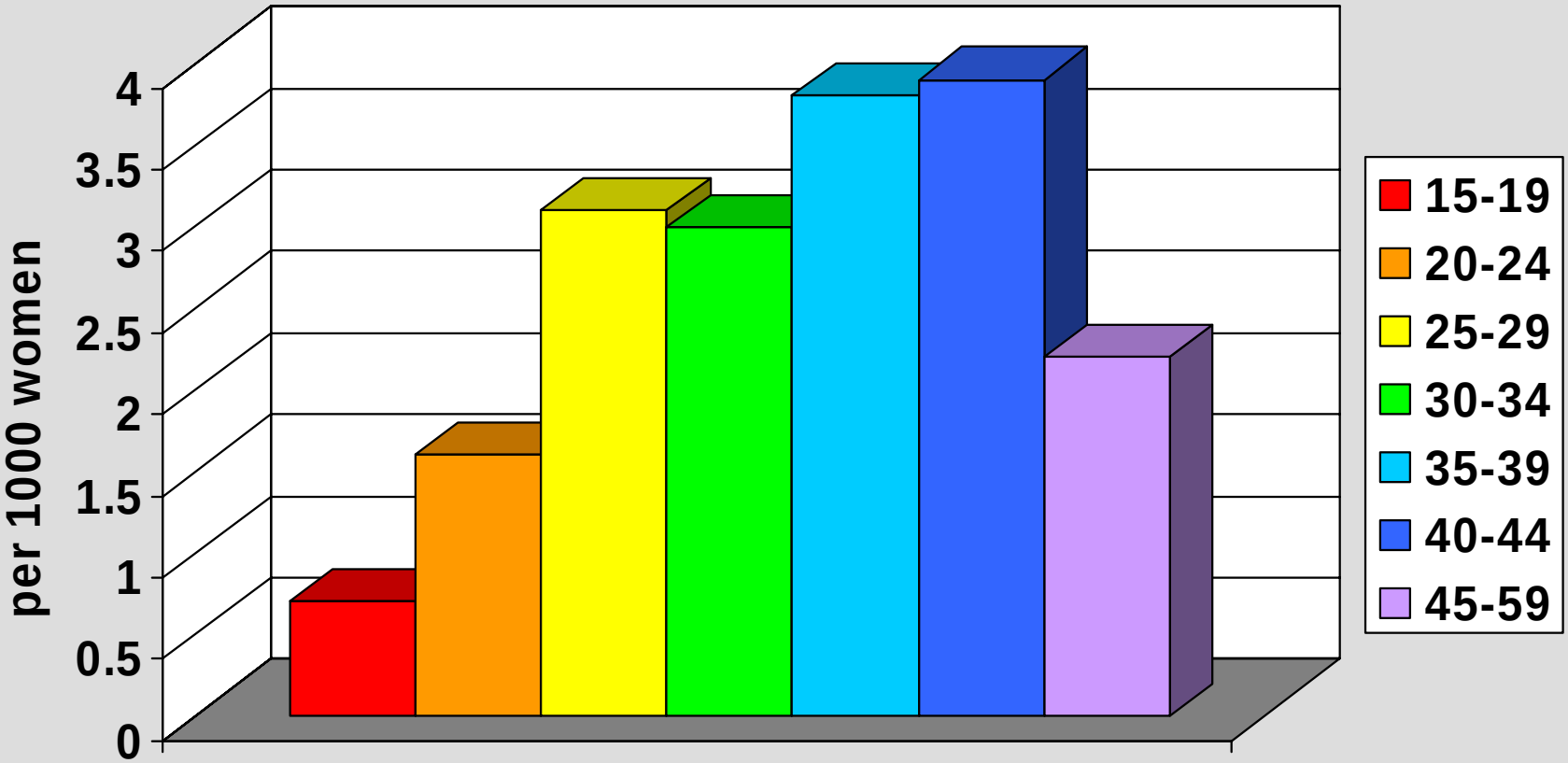
Endometriosis signs and symptoms

Severe menstrual pain
Severe bleeding

Adhesions

Severe chronic pelvic pain
Painful intercourse
Ovarian damage
Infertility

Endometriosis incidence by age group



Houston DE *et al.* Am J Epidemiol 1987; 125:959

Endometriosis treatment

GnRh agonists
Danazol
OCs
Progesterone
Alternative medicine

Lesion resection/ablation
Ovarian cystectomy
Hysterectomy
Oophorectomy

Endometriosis etiology

Menstrual reflux into peritoneal cavity

Immunologic alteration

Estrogen

- ➔ **Occurs from menarche to menopause**
- ➔ **Anti-estrogenic treatments suppress it**
- ➔ **Markers of high estrogen increase risk**
  - **body fat distribution, height, alcohol use**
  - **estrogen-metabolizing genes**

Persistent organic pollutants (POPs) and estrogen

- Estrogenic activity in estrogen receptor binding tests
- Transcriptional activation of estrogen-responsive genes
- Estrogenic effects on breast cancer cells
- Increased uterine weight in mouse studies
- Reproductive toxicity (methoxychlor metabolite HPTE) – decreased fertility in rat studies

POPs associated with endometriosis in animal studies

Low dose dioxin
Dibenzofurans (PCDFs)
Methoxychlor

Not high dose dioxin
Not PCBs

Dioxin

PCBs?

POPs and endometriosis in human studies

Dioxin

– Mayani	Israel	Significantly increased risk
– Pauwels	Belgium	Non-significant increased risk
– Eskenazi	Italy	Non-significant increased risk
– De Felip	Italy/Belgium	No association

PCBs

– Gerhard	Germany	138, 153, 180 increased risk
– Buck Louis	US	Anti-est. PCBs increased risk
– Heilier	France	Dioxin-like PCBs increased risk
– Pauwels	Belgium	No association

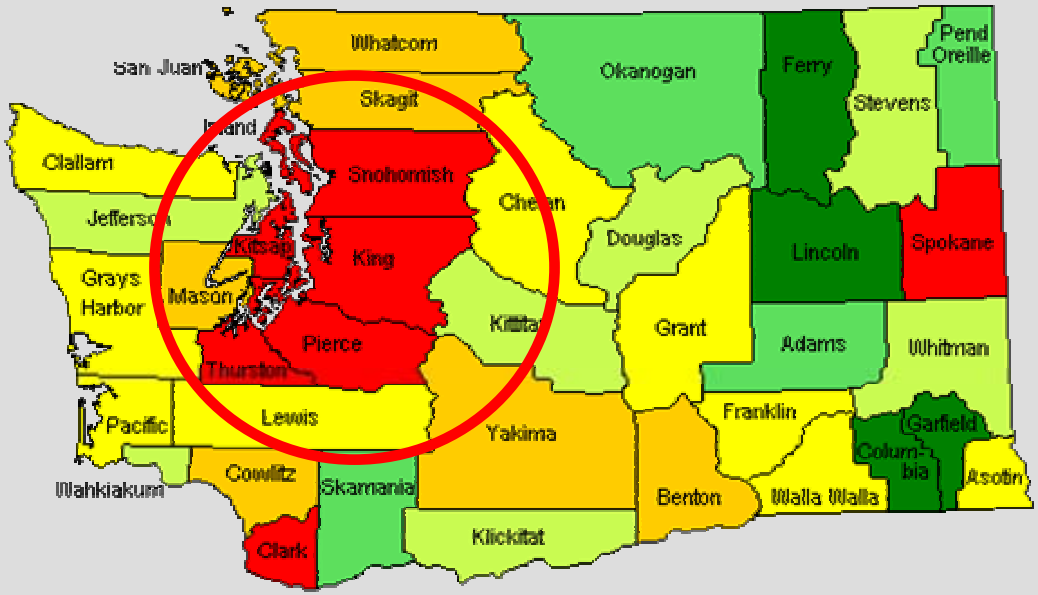
Pesticides

– Lebel	Canada	ß-HCH, DDT, p,p'-DDE

Women's Risk of Endometriosis (WREN) study population

GroupHealth COOPERATIVE

Health maintenance organization
540,000 enrollees
Western Washington State



WREN study design

Case-control study (NICHD R01 HD 33792)

Cases: 341 18-49 year-old female GHC enrollees with first-time endometriosis diagnosis between 4/1/96-3/31/01

Diagnosis confirmed by medical record review

Reference date was date of first visit for endo. symptoms

Minimum 6 months GHC enrollment at reference date

No hysterectomy or bilateral oophorectomy

WREN study design – control selection

Controls: 741 randomly selected 18-49 year-old female GHC enrollees

Assigned reference dates to correspond to cases' dates

Minimum 6 months GHC enrollment at ref. date

No hysterectomy or bilateral oophorectomy

No history of surgically-confirmed endometriosis

WREN study data collection

In-person interviews

- Demographic and behavioral characteristics
- Medical history
- Work history
- Reproductive history

Dietary questionnaires

- Usual diet, plus fish & soy products questions

Body measurements

- Waist, hip, thigh

Blood sample

- GST, COMT polymorphisms

Medical/pharmacy record abstraction

Persistent Organic Pollutants and Endometriosis study aims

- Determine whether risk of endometriosis in women is associated with serum levels of polychlorinated biphenyls (total PCBs + 35 PCB congeners)
- Determine whether risk of endometriosis in women is associated with serum levels of 11 organochlorine pesticides
- Determine whether risk of endometriosis in women is associated with urine levels of the pesticide methoxychlor

Persistent Organic Pollutants and Endometriosis study aims

- Determine whether risk of endometriosis associated with organochlorine pesticide or PCB exposure differs by CYP1A1, CYP1A2, COMT, or GSTM1 genotype
- Determine whether risk of endometriosis associated with organochlorine pesticide or PCB exposure differs by levels of other exposures affecting estrogen levels

Additional activities for POPs and Endometriosis

- **Analysis of collected serum for**
  - **Organochlorine pesticides**
  - **PCBs**
  - **Lipids**
  - **CYP1A1 and CYP1A2 polymorphisms**

- **Collection and analysis of urine for methoxychlor metabolite HPTE**

POPs and Endometriosis results: analysis of interview data

All pesticides combined

	Cases (n=341)	Controls (n=741)	OR*	95% CI
Any exposure	62%	64%	0.96	0.70, 1.33
Occupational exp.	8%	6%	1.22	0.70, 2.12
Nonoccup. exp.	59%	61%	0.91	0.68, 1.23

*Odds ratios adjusted for age and reference year

POPs and Endometriosis results: analysis of interview data

Herbicides

	Cases (n=341)	Controls (n=741)	OR*	95% CI
Any exposure	17%	10%	1.65	1.03, 2.64
Occupational exp.	3%	1%	2.87	0.98, 8.40
Nonoccup. exp.	14%	10%	1.42	0.89, 2.28

*Odds ratios adjusted for age and reference year

POPs and Endometriosis results: analysis of interview data

Fungicides (all subjects)

	Cases (n=341)	Controls (n=741)	OR*	95% CI
Any exposure	5%	2%	2.15	0.99, 4.70
Occupational exp.	3%	1%	2.80	0.95, 8.23
Nonoccup. exp.	3%	1%	1.90	0.69, 5.23

*Odds ratios adjusted for age and reference year

POPs and Endometriosis results: analysis of interview data

Fungicides

COMT low activity allele subjects only

	Cases (n=222)	Controls (n=581)	OR*	95% CI
Any exposure	5.9%	2.5%	2.65	1.11, 6.35
Occupational exp.	3.2%	0.9%	3.94	1.12, 13.87
Nonoccup. exp.	3.2%	1.6%	1.98	0.66, 5.90

*Odds ratios adjusted for age and reference year

POPs and Endometriosis results: analysis of laboratory data

	Cases (n=269)	Controls (n=552)	OR*	95% CI
β-HCH				
geo. mean (pg/g)	**53.6**	**46.1**		
2nd tertile			**1.41**	**0.94-2.12**
3rd tertile			**1.45**	**0.93-2.27**
Trans-nonachlor				
geo. mean (pg/g)	**83.5**	**76.0**		
2nd tertile			**1.12**	**0.75-1.67**
3rd tertile			**1.47**	**0.99-2.33**

*** Odds ratios adjusted for total lipids, age, and reference year**

POPs and Endometriosis results: analysis of laboratory data

	Cases (n=269)	Controls (n=552)	OR*	95% CI
Heptachlor epoxide				
geo. mean (pg/g)	**30.4**	**28.6**		
2nd tertile			**1.35**	**0.89-2.05**
3rd tertile			**1.22**	**0.78-1.91**
Mirex				
geo. mean (pg/g)	**10.5**	**9.7**		
2nd tertile			**1.06**	**0.72-1.55**
3rd tertile			**1.28**	**0.87-1.88**

*** Odds ratios adjusted for total lipids, age, and reference year**

POPs and Endometriosis results: analysis of laboratory data

	Cases (n=269)	Controls (n=552)	OR*	95% CI
p,p'-DDE				
geo. mean (pg/g)	**1796.4**	**1673.9**		
2nd tertile			**1.03**	**0.71-1.50**
3rd tertile			**1.05**	**0.71-1.57**
p,p'-DDT				
geo. mean (pg/g)	**32.5**	**30.4**		
2nd tertile			**0.87**	**0.59-1.27**
3rd tertile			**0.94**	**0.63-1.38**

*** Odds ratios adjusted for total lipids, age, and reference year**

POPs and Endometriosis results: analysis of laboratory data

	Cases (n=269)	Controls (n=552)	OR*	95% CI
PCB 74				
geo. mean (pg/g)	**83.2**	**78.4**		
2nd tertile			**1.39**	**0.93-2.06**
3rd tertile			**1.49**	**0.98-2.26**
PCB 118				
geo. mean (pg/g)	**74.1**	**71.4**		
2nd tertile			**1.25**	**0.84-1.86**
3rd tertile			**1.43**	**0.94-2.17**

*** Odds ratios adjusted for total lipids, age, and reference year**

POPs and Endometriosis results: analysis of laboratory data

	Cases (n=269)	Controls (n=552)	OR*	95% CI
PCB 153				
geo. mean (pg/g)	**223.1**	**206.9**		
2nd tertile			**1.20**	**0.80-1.81**
3rd tertile			**1.34**	**0.86-2.10**
PCB 180				
geo. mean (pg/g)	**136.2**	**137.4**		
2nd tertile			**0.93**	**0.61-1.42**
3rd tertile			**1.00**	**0.64-1.55**

*** Odds ratios adjusted for total lipids, age, and reference year**

POPs and Endometriosis: conclusions and limitations

- The relationship between endocrine disruptor chemical exposure and endometriosis is biologically plausible
- Several epidemiologic studies have shown positive associations with various EDCs
- This study found a fairly consistent pattern of modestly increased risk associated with self-reported exposure and with the top tertile of pesticide and PCB serum levels
- While results were adjusted for age, the possibility exists that there are other noncausal explanations for the associations seen – further modeling will be done
- In a case-control study using post-diagnosis serum the correct temporal sequence is not conclusive, but self-reported pesticide exposure was prior to disease onset

Co-Investigators

Stephen M. Schwartz

Fred Hutchinson Cancer Research Center, Seattle, WA

Delia Scholes

Group Health Cooperative, Seattle, WA

Dana B. Barr

Centers for Disease Control and Prevention, Atlanta, GA

Data analysts

Jen Marino

Fred Hutchinson Cancer Research Center, Seattle, WA

Kara L. Cushing-Haugen

Fred Hutchinson Cancer Research Center, Seattle, WA

Questions and Comments?