# Epidemiologic contribution to understanding environmental impact on women's health:

## Women's Risk of Endometriosis (WREN) Study

Kristen Upson, PhD, MPH (she, her)

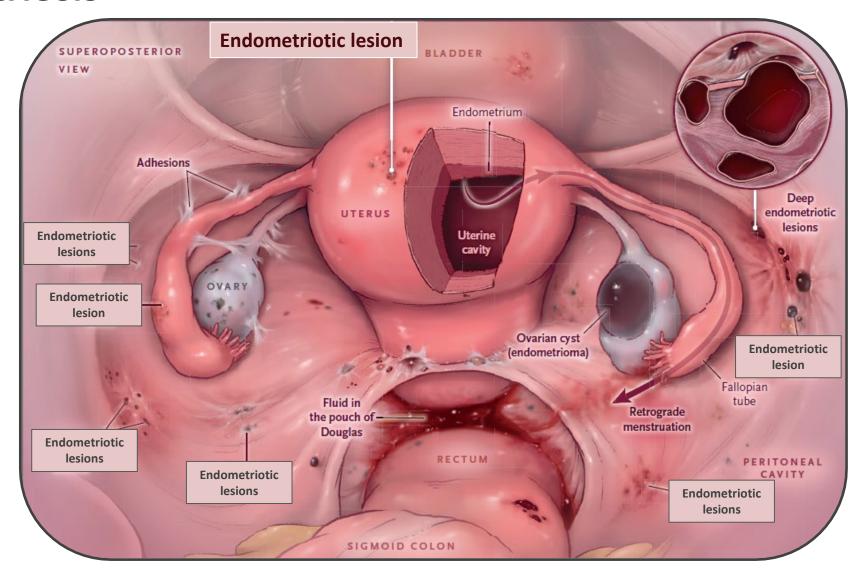
Assistant Professor, Department of Epidemiology and Biostatistics

**Michigan State University** 

Advisory Committee on Research on Women's Health October 18, 2022



### **Endometriosis**



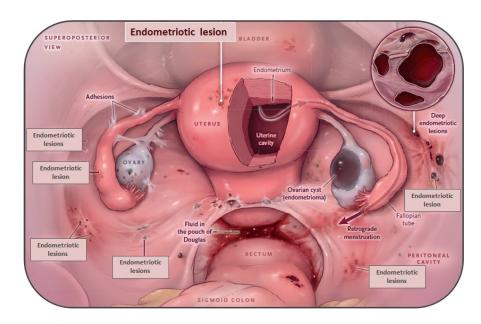
### **Endometriosis**



Chronic pelvic pain Acyclic pelvic pain



Painful menstrual periods





Painful bowel movements
Painful urination

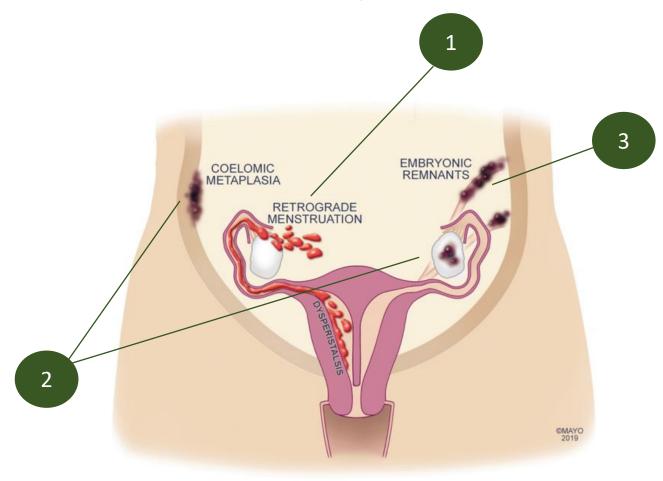


Fatigue



Pain during intercourse

### **Endometriosis: Pathogenesis**



#### Separate etiologic pathways?

- Peritoneal endometriosis
- Ovarian endometriosis
- Deep infiltrating endometriosis

#### Multiple factors involved

- Anatomical
- Genetic
- Hormonal
- Environmental
- Immunological

#### Estrogen

 Regulates key pathological processes

### **Endometriosis: Environmental chemicals**

POSITION STATEMENT

# Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek,

A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Endocrine disrupting chemical

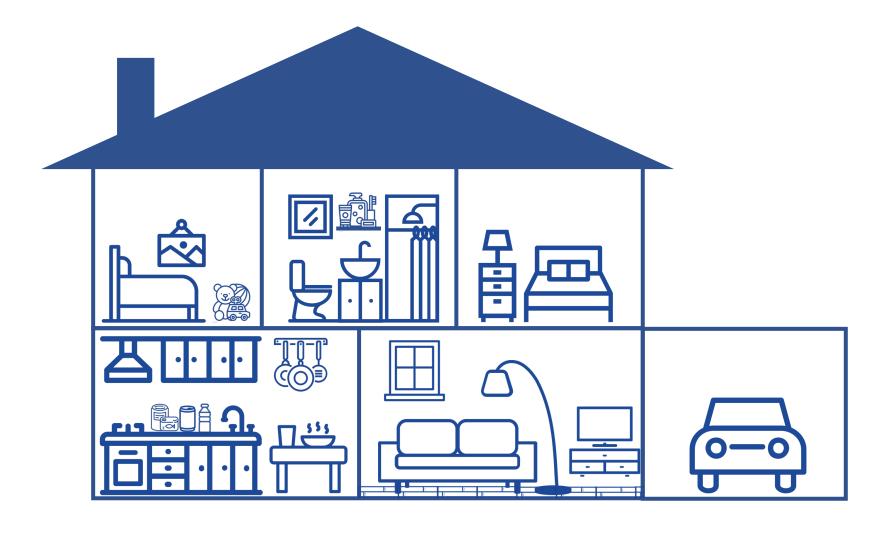
"...is an exogenous chemical, or mixture
of chemicals, that interferes with any aspect
of hormone action."

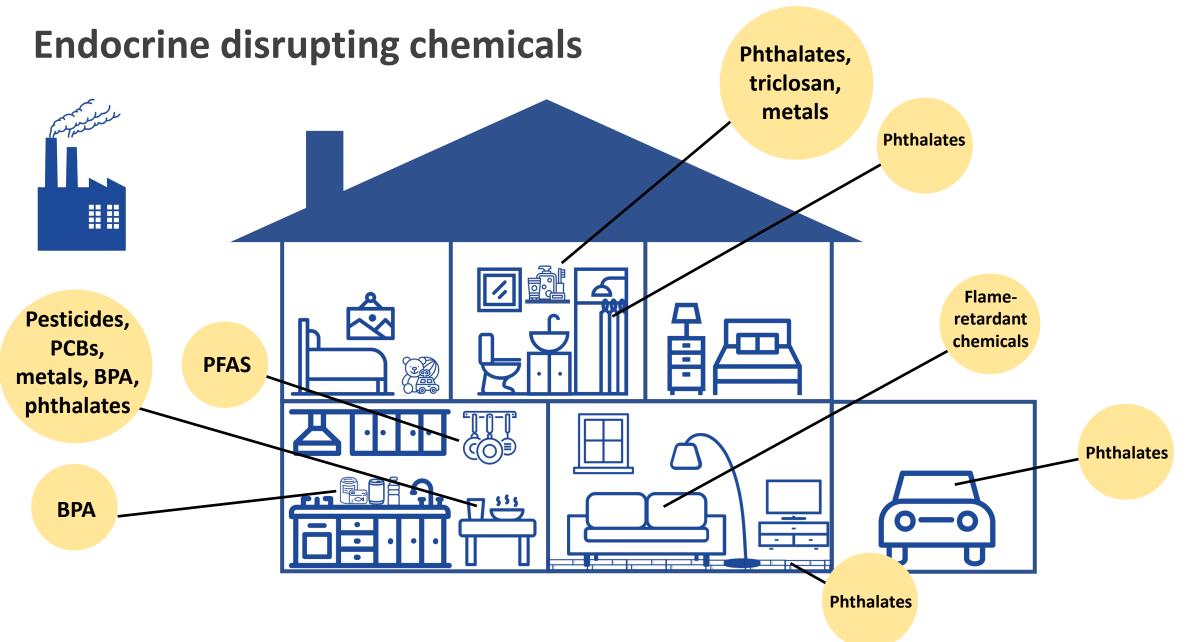
## **Endocrine disrupting chemicals**



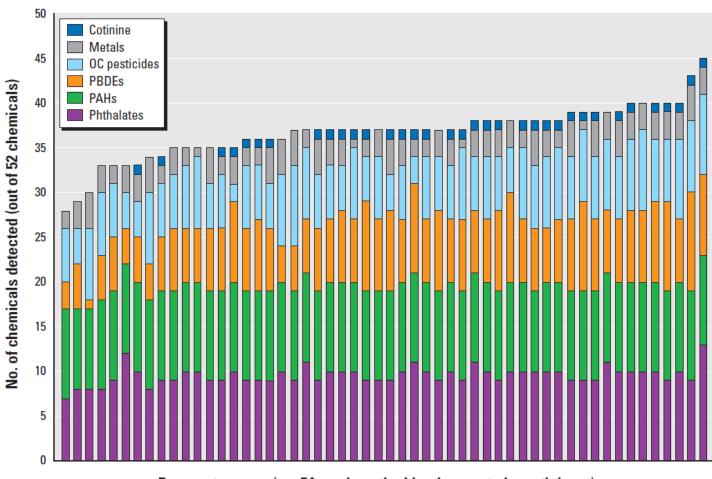
### **Endocrine disrupting chemicals**







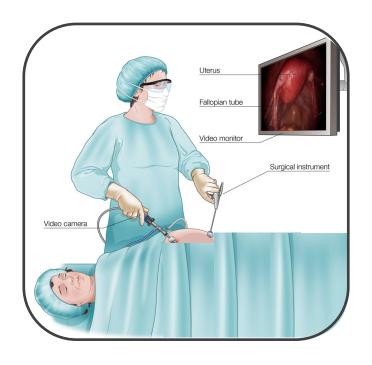
### **Endocrine disrupting chemicals**

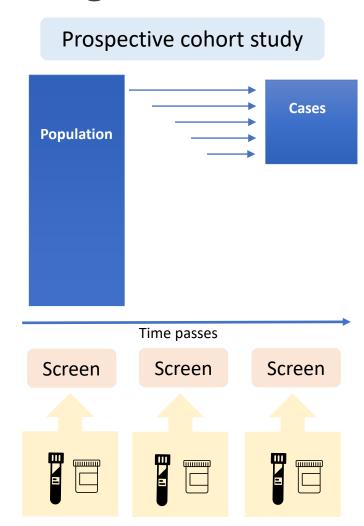


Pregnant women (n = 54; each vertical bar is one study participant)

### **Endometriosis: Major challenge**

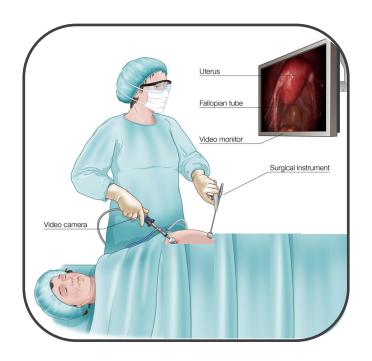
Definitively diagnosed by surgical visualization

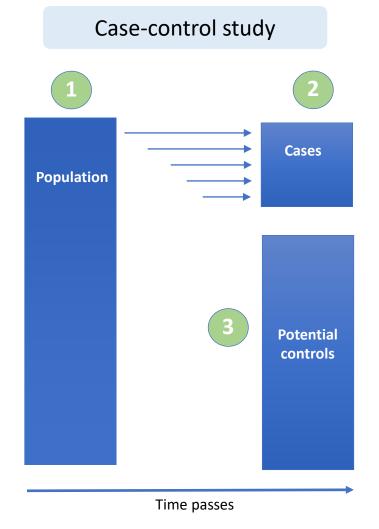


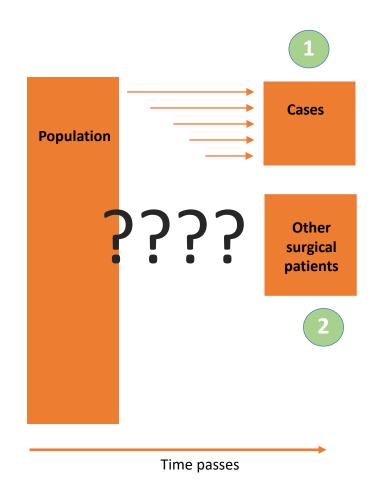


### **Endometriosis: Major challenge**

Definitively diagnosed by surgical visualization



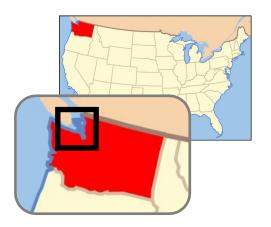




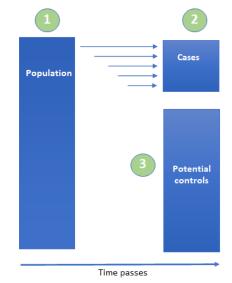
Upson K. Curr Epidemiol Rep 2020;7: 149-170.

Image (modified) from: https://healthjade.com/laparoscopy/









Case-control study

### **Endometriosis cases**

**Population controls** 

Ages 18-49

- Ages 18-49
- Diagnosed years 1996-2001

Randomly selected enrollees

Age-matched to cases

Surgically-confirmed

Victoria Holt, PhD





R01 HD033792

- Ages 18-49
- Intact uterus
- At least one ovary
- No prior endometriosis diagnosis
- reference date

Date of first visit for symptoms leading to endometriosis diagnosis

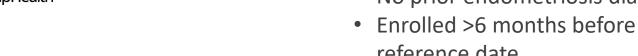
#### **Eligibility criteria:**

- Pre-menopausal



Delia Scholes, PhD







# Endometriotic disease case definition

#### Focus on endometriosis with

- Tissue invasiveness
- Interference with physiologic processes

#### **Benefits**

- † likelihood of observing true etiologic associations
- \$\square\$ frequency of undiagnosed disease in study population

#### Data on:

- Ovarian endometriosis
- Non-ovarian pelvic endometriosis

Table 1. Proposed Standard Definition of Endometriotic Disease for Epidemiologic Studies of Endometriosis	
Status	Signs and Symptoms
Definite disease	Ovarian endometriomas of any size Pelvic endometriotic implants of any size >5 mm deep Pelvic endometriotic implants of any size with adhesions not attributable to another cause
Possible disease	<ul> <li>Pelvic endometriotic implants not meeting above criteria, plus one or more of the following symptoms:</li> <li>Infertility</li> <li>Moderate to severe dysmenorrhea (painful menstrual periods)</li> <li>Moderate to severe dyspareunia (pain during intercourse)</li> <li>Moderate to severe pelvic pain</li> </ul>



### **WREN** participants:

310 Endometriosis cases727 Population controls

#### In-person structured interview

- Conducted by trained female interviewers
- At participant home or Fred Hutch
- Questions covered range of health histories
  - e.g., menstruation, reproductive, pregnancy, contraception
- Methods employed to aid recall









Matrix



Laboratory



Analytes



Funding





11 Organochlorine pesticides (OCPs)
34 Polychlorinated biphenyl

34 Polychlorinated biphenyl congeners (PCBs) (non-dioxin-like)



Science to Achieve Results (STAR) grant R829438





Bisphenol A (BPA)



Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung Institut der Ruhr-Universität Bochum





8 Phthalate metabolites



University of Washington Doctoral Dissertation Small Grants Program

















Median age (IQR)

White race

College graduate

Income (≥\$70,000) BMI (≥30) Current smoker

Nulliparous

**Cases** (n=310)

39 years (IQR: 33-44)

85%

46%

23%

21%

20%

48%

Controls (n=727)

39 years (IQR: 33-44)

83%

41%

28%

20%

17%

30%



Detected in 100% of participants

100 80 % Detected 0 60 20 BPA **Phthalates PCBs** Organochlorine pesticides

Trabert B, et al. *Environ Health Perspect 2010;118: 1280-1285.*Upson K, et al. *Environ Health Perspect 2013;121: 1319-1324.*Upson K, et al. *Environ Res 2013;126: 91-97.*Upson K, et al.. *Hum Reprod 2014;29: 2457-2464.* 







Organochlorine pesticides

2xover



β-HCH (hexachlorocyclohexane)

Q3 vs Q1: OR 2.5, 95% CI: 1.2, 5.2

Q4 vs Q1: OR 2.5, 95% CI: 1.1, 5.3

**Ovarian** endometriosis



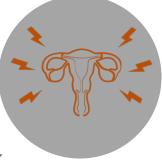


**PCBs** (Polychlorinated biphenyls)

30% Trisk suggested

∑PCBs (non-dioxin-like)

Log-linear ↑: OR 1.3, 95% CI: 0.8, 2.2







Phthalate metabolites

70% risk suggested

MEHP:

Q4 vs Q1: OR 0.3, 95% CI: 0.1, 0.7







Bisphenol A (BPA)

risk suggested

Q2 vs Q1: OR 3.0, 95% CI: 1.2, 7.3

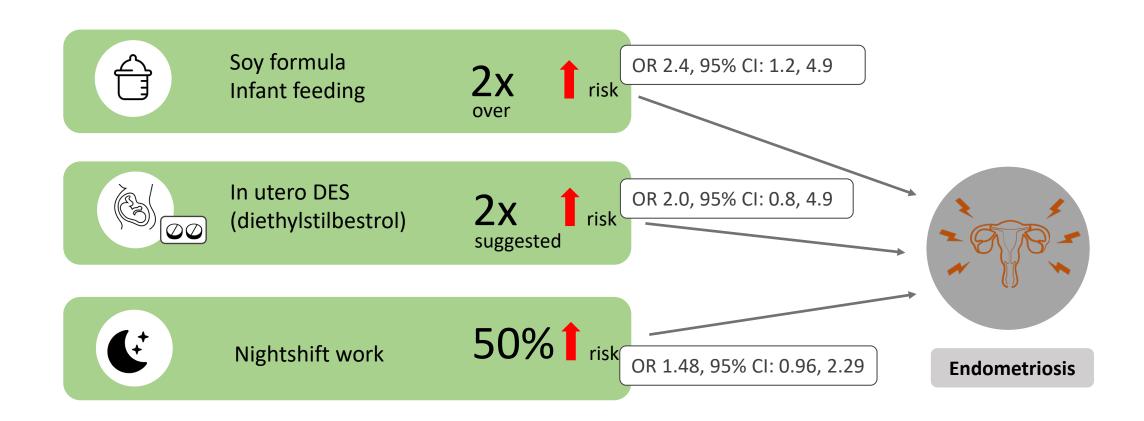
Q3 vs Q1: OR 3.0, 95% CI: 1.1, 7.6

Non-ovarian pelvic endometriosis

Upson K, et al. Environ Health Perspect 2013;121: 1319-1324. Trabert B, et al. Environ Health Perspect 2010;118: 1280-1285. Upson K, et al.. Hum Reprod 2014;29: 2457-2464. Upson K, et al. Environ Res 2013;126: 91-97.

18





Upson K, et al. Fertil Steril 2015.

Marino JL, et al. Epidemiology 2008;19: 477-484.





#### **Limitations**

- Biologic sample collection after case diagnosis
- Single sample for non-persistent chemicals (BPA, phthalates)
- Research conducted before recent developments in mixtures analyses
- Undiagnosed disease among controls



### **Strengths**

- Population-based sampling
- Collection of biologic samples
- Years of biologic sample collection (before EDCs widely known)
- Data on ovarian and non-ovarian pelvic endometriotic lesion location

#### Findings across studies Environmental Risk Factors for Endometriosis: a Critical Evaluation of Studies and Recommendations Review from the Epidemiologic Perspective Organochlorines and endometriosis: A mini-review Kristen Upson<sup>1</sup> **Consistencies within** Jean-François Heilier a,\*, Jacques Donnez b,c, Dominique Lison a 2020 2008 population-based studies Reassessing the evidence for the link 2019 between dioxin and endometriosis: Human epidemiological evidence about the associations between exposure from molecular biology to clinical to organochlorine chemicals and endometriosis: Systematic review and epidemiology meta-analysis German Cano-Sancho<sup>a,\*</sup>, Stéphane Ploteau<sup>b</sup>, Komodo Matta<sup>a</sup>, Evdochia Adoamnei<sup>c</sup>, Sun-Wei Guo<sup>1,†</sup>, Peter Simsa<sup>2,3,†</sup>, Cleophas M. Kyama<sup>2</sup>, Germaine Buck Louis<sup>d</sup>, Jaime Mendiola<sup>c</sup>, Emile Darai<sup>e,f</sup>, Jean Squifflet<sup>g</sup>, Bruno Le Bizec<sup>a</sup>, Attila Mihályi<sup>2</sup>, Vilmos Fülöp<sup>3</sup>, Essam-Eldin R. Othman<sup>4</sup>, Discrepant 2009 Jean-Philippe Antignac<sup>a</sup> and Thomas M. D'Hooghe<sup>2,5</sup> Results 2017 **Review** Dioxin-like PCBs and Endometriosis Polychlorinated biphenyls and its potential role in endometriosis<sup>★</sup> Mengyun Yao <sup>1</sup>, Tingting Hu <sup>1</sup>, Yinfeng Wang, Yongjiang Du, Changchang Hu, Ruijin Wu<sup>\*</sup> Kaylon L. Bruner-Tran and Department of Gynecology, Women's Hospital, School of Medicine, Zhejiang University, 1Xueshi Road, Hangzhou 310006, P.R. China Kevin G. Osteen A recent survey in the United States identified 287 different chemicals in Women's Reproductive Health human cord blood, demonstrating the significant exposure of wor Research Center, Department their children to a wide array of environmental toxicants. While 2010 of Obstetrics and Gynecology, contamination and exposure should be an international priority, it i Vanderbilt University School of appropriate to develop an understanding of the health consequ Medicine, Nashville. TN. USA increasing world-wide industrialization. Endometriosis, a disease of the

Role of environmental organochlorinated pollutants in the development of endometriosis

M.G. Porpora, S. Resta, E. Fugetta, P. Storelli, F. Megiorni, L. Manganaro, E. De Felip

Department of Obstetrics-Gynecology and Urology, "Sapienza" University of Rome, Rome (Italy)

Endocrine disrupting chemicals and endometriosis

Melissa M. Smarr, Ph.D., a Kurunthachalam Kannan, Ph.D., and Germaine M. Buck Louis, Ph.D., M.S.

<sup>a</sup> Office of the Director, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; and <sup>b</sup> Wadsworth Center, New York State Department of Health, Albany, New York

2013



Reasons for disparate results

Study population differences

Exposure measurement

Confounder adjustment

Undiagnosed disease in controls

Environmental Risk Factors for Endometriosis: a Critical Evaluation of Studies and Recommendations from the Epidemiologic Perspective

Kristen Upson<sup>1</sup>

Reasons for disparate results

Study population sampling

Sample collection at diagnosis

Statistical analysis issues

Single disease entity

Heilier JF, et al. Chemosphere 2008;71: 203-210; Guo SW et al. Mol Hum Reprod 2009;15: 609-624; Bruner-Tran et al. Systems biology in reproductive medicine 2010;56: 132-146; Porpora MG, et al. Clin Exp Obstet Gynecol 2013;40: 565-567; Smarr MM, et al. Fertil Steril 2016;106: 959-966; Yao M, et al. Environmental pollution 2017;229: 837-845; Cano-Sancho G et al. Environment international 2019;123: 209-223; Upson K. et al. Curr Epidemiol Rep 2020;7: 149-170.

### Recommendations

1

**Population-based sampling** 

Novel avenues:

 Build capacity to collect endometriosis data in large, epidemiologic cohort studies

2

**Exposure during etiologically-relevant window** 

- Novel avenues:
  - Archived newborn dried blood spots
  - Baby teeth
- Link with existing data (e.g., air pollution)

**3** Disaggregating endometriosis

- Novel avenues:
- Collect operative and pathology reports

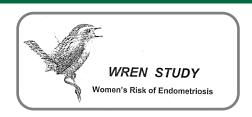
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**Environmental exposures** unique to menstruators

- Novel avenues:
- Menstrual product use
- Menstrual blood loss
- Hormonal contraceptive use

**5** Team science

- Epidemiology
- Exposure science
- Biostatistics
- Gynecology
- Toxicology



#### **WREN Researchers**

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Jennifer Marino, PhD, MPH

Britton Trabert, PhD, MS

Kristen Upson, PhD, MPH

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Sheela Sathyanarayana, MD, MPH
Dana Barr, PhD
Holger Koch, PhD

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National Institute of Nursing Research F31NR009164 (Marino)

University of Washington
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Doctoral Dissertation Small
Grants Program (Upson)

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