# Creating a multi-source, longitudinally-linked dataset to examine the association between birth defects and childhood cancer and between maternal cancer and adverse pregnancy outcomes

**Russell S. Kirby, PhD, MS, FACE**
Distinguished University Professor, Marrell Endowed Chair
Strategic Area Faculty Lead for Population Health Science
College of Public Health
University of South Florida

# Disclosure

- This presentation does not mention specific drugs, medications, or medical devices.
- The presenter has no disclosures relating to the content of this presentation.
- No laboratory animals, family pets or wildlife were harmed to development of this presentation.
- This is a collaborative project involving Florida Department of Health, Centers for Disease Control and Prevention, March of Dimes Foundation, and the USF Birth Defects Surveillance Program.

# Conflict of Interest Statement

- Dr. Kirby has grants and contracts from the Centers for Disease Control and Prevention and the Florida Department of Health, and recently from the March of Dimes Foundation and NIH, and has served as a consultant to UNICEF and AcademyHealth.
- Dr. Kirby chaired the scientific advisory committee for the Nplate pregnancy exposure registry for Amgen Corp, provided technical consultation concerning Botox and pregnancy outcomes for Allergan Corp, and is a member of the scientific advisory committee for the Solriamfetol pregnancy registry for Jazz Pharmaceuticals.
- Dr. Kirby is president of the American College of Epidemiology, past president of the Society for Pediatric and Perinatal Epidemiologic Research and the Association of Teachers of Maternal and Child Health, serves on the executive committee of the National Birth Defects Prevention Network, and on the board of the Perinatal Foundation. He is also treasurer of the 37th Street Foundation, a family charitable foundation. He also leads the USF team in the annual March for Babies in support of the March of Dimes Foundation.
- Dr. Kirby is a bluegrass and roots music fanatic, has been known to travel long distances in search of the true article, and has considered placing the following bumper sticker on his car: "Caution: this car breaks for bluegrass".
- None of these relationships have any bearing on the content of this presentation.

# Objectives and Aims for Linked Data

1. Examine the association between **birth defects** and **pediatric cancers**
2. Examine associations between **maternal cancer** and **adverse outcomes** in subsequent pregnancies
3. Examine maternal risk for **cancer** following birth of a child with an **adverse outcome**
4. Examine risk for **pediatric cancer** following **pregnancy complications**

# Florida Birth Defects Registry

- **Statewide** surveillance registry created in 1998
- **Passive** case ascertainment methodology
- **FBDR inclusion criteria**
  - Infant born alive
  - Mother resident of Florida at time of child's birth
  - Birth defect covered by the FBDR
    - includes major anomalies recommended by the National Birth Defects Prevention Network (NBDPN)
  - Diagnosis prior to one year of age

# Hospital Discharge Data

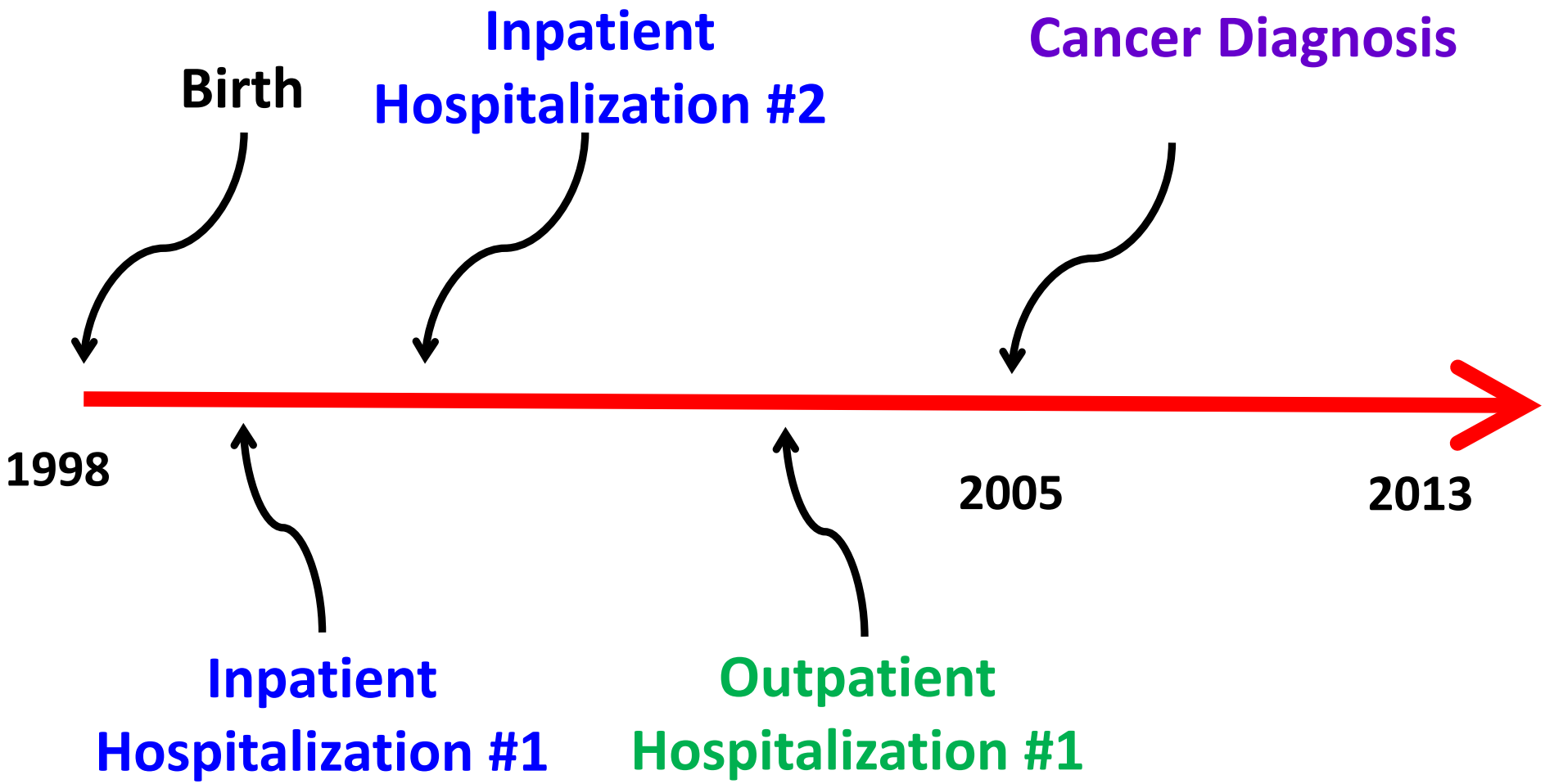
- All non-military hospitals collect information about each patient's hospital stay and reported to AHCA as required under Florida statute chapter 408
- Inpatient, ambulatory, and emergency visits
- Databases contains information on age, sex, ethnicity, ICD-9-CM* diagnosis and procedure codes (up to 31 codes), source of admission, principal payer, and discharge status of all hospitalized patients
- **Component and total charges**

*** ICD-10-CM since 10/1/2015**

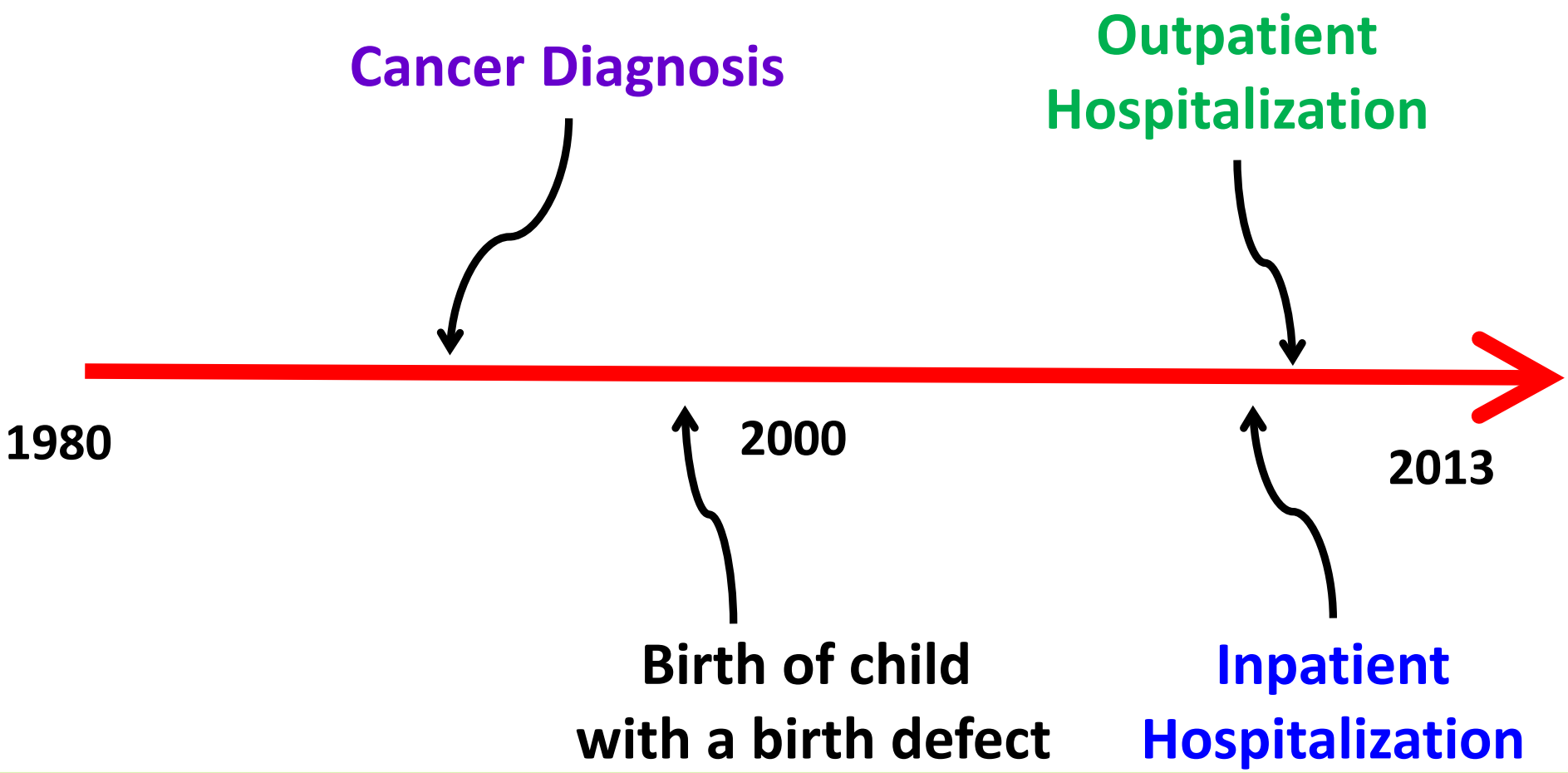
# Florida Cancer Data System

- **Statewide**, **population-based** cancer registry
- **Created in 1978** by the FDOH in collaboration with the University of Miami's Miller School of Medicine
- Under **Florida Statutes**, each hospital and outpatient facility in Florida must report to the FDOH each patient **diagnosed** and **admitted** for **treatment** of cancer
- FDCS is the **largest population-based** cancer incidence registry in the nation
  - Over 4.5 million cancer records, 9.5 million discharge records, 4.9 million mortality records, and 8 million claims records on patients seen at a reporting facility on or after January 1, 1981

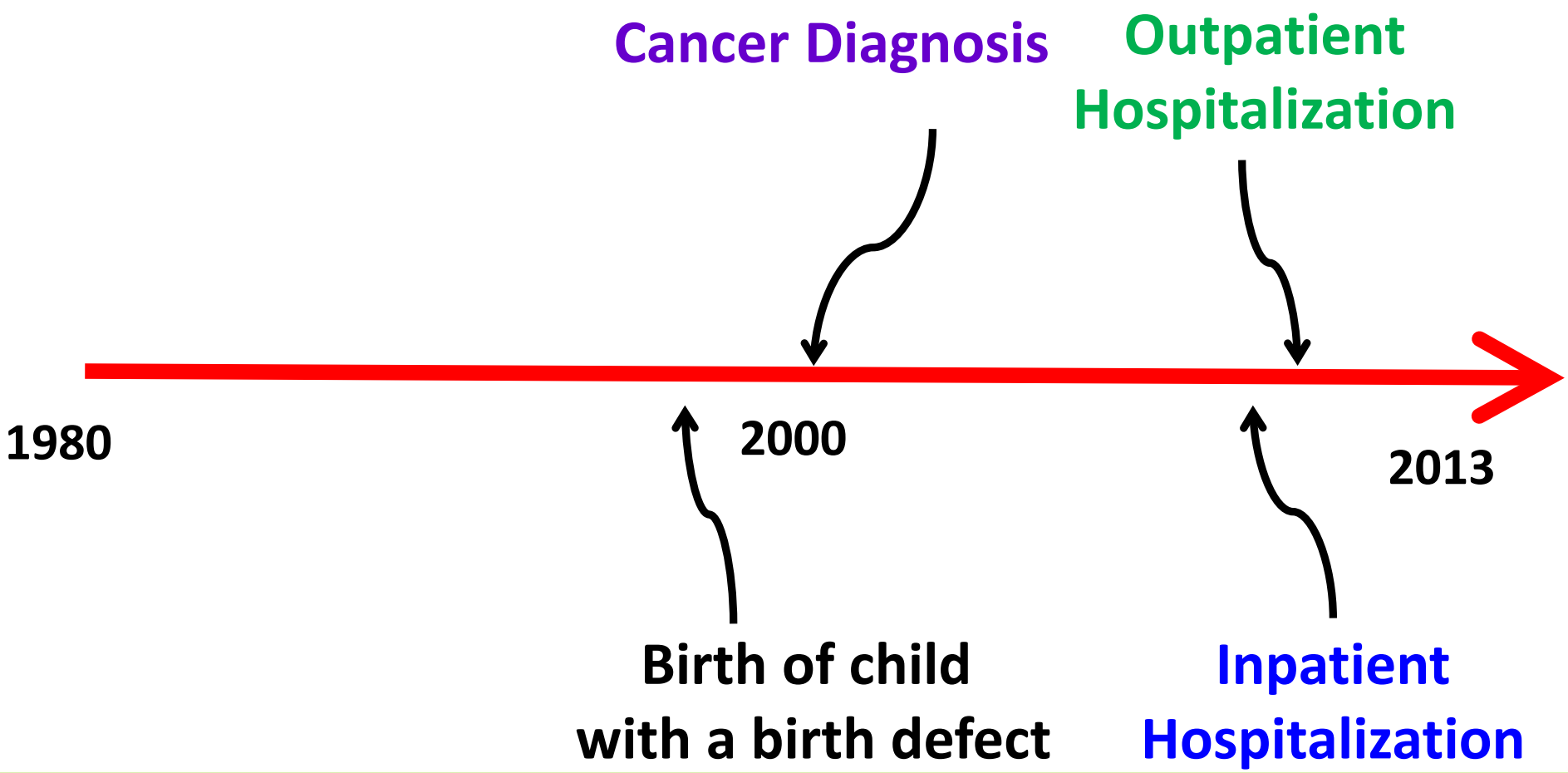
# “Follow” Infants Over Time Through Linkage



# "Follow" Mothers Over Time Through Linkage



# "Follow" Mothers Over Time Through Linkage



# Some Additional Linkage Features

- AHCA data are **longitudinally linked**
  - Live births, child data linked from birth to end of 2014
  - For mothers of live births
    - Linked forward to end of 2014
    - Linked backward to 1998
- Live births are **maternally linked**
  - Live birth sibships enable study of outcomes in pregnancy subsequent to birth with adverse outcome or cancer diagnosis
  - Live births for multiple gestation pregnancies are linked
- **Death certificates** for children are linked to birth certificates through 2014
- Death certificates for mothers are not presently linked, but this is a planned enhancement for the integrated database

# Some Linkage Results

# Vital Statistics and Hospital Discharge Linkage Results

Linkage rates overall and for exclusion subgroups, Florida, 1998-2013

| | | Linked to any infant discharge record in first year of life | Linked to infant's birth hospitalization record | Linked to BOTH maternal delivery AND infant birth hospitalizations |
|---|---|---|---|---|
| | N | % | % | % |
| All resident live births | 3,398,416 | 92.6 | 91.3 | 91.1 |
| **Subgroups excluded (not expected in AHCA)** | | | | |
| Born outside FL | 9,809 | 0.6 | 0.1 | 0 |
| FL birth in non-hospital | 38,717 | 19.4 | 12.4 | 11.0 |
| FL birth in military hospital | 40,027 | 6.7 | 1.1 | 0.1 |
| **Subgroups included** | | | | |
| FL birth in non-military hospital | 3,309,863 | 94.7 | 93.5 | 93.4 |

# Linkage of Birth Certificates with Cancer Data System

- Florida Cancer Data System (1981-2012):
- 4,651 Infants in FCDS linked to a Florida birth certificate (1998-2012)
- 14,728 mothers in FCDS linked to a Florida birth certificate (1998-2012)

# Cancer Sites Among Birth Mothers

Ten most common primary tumor sites among mothers of births occurring in Florida from 1998-2012

| Primary Cancer Site* | Mothers (N=14,728) | % |
|---|---|---|
| Breast | 3,946 | 26.8 |
| Thyroid gland | 2,167 | 14.7 |
| Cervix uteri | 1,649 | 11.2 |
| Skin | 1,540 | 10.5 |
| Lymph nodes | 956 | 6.5 |
| Blood, bone marrow, and hematopoietic | 544 | 3.7 |
| Pituitary gland | 529 | 3.6 |
| Brain, & cranial nerves, and spinal cord (excl. ventricle, cerebellum) | 508 | 3.4 |
| Ovary | 392 | 2.7 |
| Large intestine (excl. appendix) | 367 | 2.5 |

*Mothers may have been diagnosed with more than one cancer*

# Pediatric Cancers Among Florida Births

**Ten most common primary tumor sites among births occurring in Florida from 1998-2012**

| Primary Cancer Site* | Infants (N=4,651) | % |
|---|---|---|
| Blood, bone marrow, and hematopoietic | 1,434 | 30.8 |
| Any nervous system | 1,176 | 25.3 |
| Brain, & cranial nerves, & spinal cord, (excl. ventricle, cerebellum) | 818 | 17.6 |
| Kidney | 331 | 7.1 |
| Connective & soft tissue | 291 | 6.3 |
| Adrenal glands | 234 | 5.0 |
| Any eye | 217 | 4.7 |
| Cerebellum | 215 | 4.6 |
| Lymph nodes | 215 | 4.6 |
| Bones and joints | 184 | 4.0 |
| Retina | 187 | 4.0 |
| Liver | 94 | 2.0 |

**Infants may have been diagnosed with more than one cancer*

Research

JAMA Oncology | Original Investigation

# Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births

Philip J. Lupo, PhD; Jeremy M. Schraw, PhD; Tania A. Desrosiers, PhD; Wendy N. Nembhard, PhD; Peter H. Langlois, PhD; Mark A. Canfield, PhD; Glenn Copeland, MBA; Robert E. Meyer, PhD; Austin L. Brown, PhD; Tiffany M. Chambers, MPH; Pagna Sok, MPH; Heather E. Danysh, PhD; Susan E. Carozza, PhD; Saumya D. Sisoudiya, BS; Susan G. Hilsenbeck, PhD; Amanda E. Janitz, PhD; Matthew E. Oster, MD, MPH; Angela E. Scheuerle, MD; Joshua D. Schiffman, MD; Chunqiao Luo, MS; Amir Mian, MD; Beth A. Mueller; Chad D. Huff, PhD; Sonja A. Rasmussen, MD, MS; Michael E. Scheurer, PhD; Sharon E. Plon, MD, PhD

JAMA Oncol. doi:10.1001/jamaoncol.2019.1215
Published online June 20, 2019.

Findings: Children with chromosomal anomalies 11.6 (95% CI 10.4-12.9) times more likely to be diagnosed with cancer, and children with non-chromosomal birth defects 2.5 (2.4-2.6) times more likely to have a cancer diagnosis before age 18 than children with no birth defects. Children with 4 or more birth defects were 5.9 (5.4-6.5) times more likely to have a cancer diagnosis compared to those with no birth defect.

72 specific birth defect-cancer patterns were analyzed, with many showing statistical associations. Cancers most frequently associated with nonchromosomal defects included hepatoblastoma and neuroblastoma.

# Research Opportunities

- Questions related to pediatric cancer
  - **Co-occurrence of birth defects** and **pediatric cancer**
    - Working on this in collaboration with Dr. Philip Lupo and colleagues (Baylor College of Medicine – R01 for GOBACK study involving several other states)
  - **Perinatal risk factors** for pediatric cancer
- Questions related to **cancers in women** of reproductive age
  - What are the **birth outcomes** for women who have undergone **cancer treatment**, or had specific **cancer diagnoses**, and then become pregnant?
  - What are the **risks for cancer** subsequent to a pregnancy?

OBSTETRICS

# Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes

Mary Ashley Cain, MD; Jason L. Salemi, PhD, MPH; Jean Paul Tanner, MPH; Russell S. Kirby, PhD, MS; Hamisu M. Salihu, MD, PhD; Judette M. Louis, MD, MPH

Am J Obstet Gynecol 2016;215:484.e1-14.

This study examined short-term risk of cardiovascular disease (CVD) among women experiencing maternal placental syndrome, preterm birth or small-for-gestational age birth.

Women with any placental syndrome had 19% increased risk of CVD (HR 1.19, 95% CI 1.07-1.32). Those with more than one placental syndrome were are greater risk, and among those experiencing a placental syndrome whose pregnancy resulted in preterm or SGA birth, the risk of CVD increased to 1.45 (1.24-1.71).

Health care-related costs in follow-up were 5-fold greater among women with a placental syndrome who then developed CVD.

# Research Opportunities (continued)

- Women's **health care utilization** subsequent to pregnancy
  - Example: the 'Pregnancy as a window' paper by Cain et al (AJOG 2016)
- **Antenatal hospitalization** or **emergency department use** and pregnancy outcomes, or women's health outcomes
- **Severe maternal morbidity**
  - Demographic and reproductive health characteristics
  - Association with adverse pregnancy outcomes
  - Association with outcomes in subsequent pregnancy

# Future Plans

- During fiscal year 2019-20 we hope to extend the linkages in the integrated data
  - Link birth certificates and FBDR data through 2016 births
  - Link AHCA followup through end of calendar year 2017
  - Link FCDS data for women and children, to most current possible
  - Link death certificates for individuals born 1998 or later, explore linkage of death certificates for women who gave birth 1998 or later

# E-mail Address and Phone Number

- For additional information, suggestions, comments, and constructive criticism, and advice, please contact me at:

  - rkirby@health.usf.edu
  - 1-813-396-2347