Early Life Exposures and Breast Cancer Risk

Michele R. Forman, Ph.D.
Professor
Department of Epidemiology
MD Anderson Cancer Center
Objective

To identify early exposures related to risk for breast cancer by window of susceptibility

Following the yellow brick road of risk factors
What am I going to tell you?

In utero
- Birthweight ~ pubertal stage
- Maternal energy balance in pregnancy ~ daughter’s age at menarche

Infancy
- Age of greatest weight gain ~ pubertal status & age varies by maternal preeclampsia
- Age of greatest weight gain ~ age at menarche

Childhood/youth
- Body size and family conflict ~ earlier menarche in Mexican American girls.
What do we know?
Breast Cancer Risk Factors

- High birthweight ~ premenopausal breast cancer
- Body mass index by menopausal status
- Height ~ premenopausal breast cancer
- Age at menarche, first and last birth
- Age at menopause
- Physical activity in youth and adult years
- Postmenopausal exogenous hormone preparations
Increasing percentage of girls (9-15 y) who are overweight & obese over time

Decline in the mean or median ages of entry into breast stage 2 (onset of puberty) for US studies
Lower correlation between age of onset of puberty & age of menarche over time

Studies: 1-Reynolds; 2- Bielicki; 3-Largo; 4-Taranger; 5-Marshall; 6-de Ridder; 7-NGH
Percent anovulatory menstrual cycles increases with later age at menarche: Finnish schoolgirls

Menarche marks onset of exposure to cyclic hormones

Menarche indicates “intensity” of hormonal exposure during adolescence

Adapted from Apter & Vihko, J Clin Endocrinol Metab, 1983
Are hormone levels in adulthood associated with age at menarche?

• Apter, Vihko and colleagues would say yes:
  - Using recorded age at menarche
    • Early menarche (<12 y) associated with higher estradiol levels in adolescence
    • Early menarche associated with higher follicular but not luteal phase estradiol levels in women 20-31 yr
    • Few women in the later study

Are hormone levels in adulthood associated with age at menarche?

- Among 106 Caucasian and 39 Shanghai Chinese women ages 33-38 y, Bernstein would say maybe No?
  - Using self reported age at menarche
  - No evidence of effect of age at menarche on estrogen (estrone, estradiol or urinary estrogens) in follicular or luteal (Chinese) phase

Bernstein et al. Cancer Causes Control 1991;2,221
What do we know?

Secular trends:
* Increasing rate of obesity
* Earlier age at onset of puberty
* Earlier age at menarche
  But reaching full maturity at same age, so extending the duration of puberty

Ethnic variation in trends, in cyclic fluctuation of hormone levels, & risk of premenopausal breast cancer

African-Americans > Mexican-Americans > non-Hispanic whites
Early life exposures: In utero

High birthweight ~ early breast development in girls aged 8-11 years.

NHANES III
Adjusted OR (95% CI) for Tanner Stage B2 by birthweight

1 = < 2.5 kg; 2 = 2.5 - 2.9; 3 = 3.0 - 3.5; 4 = 3.5 - 3.9; 5 = 4.0+ kg

Odds Ratio

Birthweight

0 1 2 3 4 5 6

1.71
1.05
0.78
0.8

1 = < 2.5 kg; 2 = 2.5 - 2.9; 3 = 3.0 - 3.5; 4 = 3.5 - 3.9; 5 = 4.0+ kg
Adjusted OR (95% CI) for Tanner Stage B3,4,5 by birthweight NHANES 1988-1994 (Olivo-Marston S, Forman MR; 2010)

1 = < 2.5 kg; 2 = 2.5 -2.9; 3 = 3.0-3.5; 4 =3.5-3.9; 5 = 4.0+ kg
Early life exposures: In utero

Physical activity in pregnancy delays age at menarche.
And Gestational weight gain increases risk of early menarche

MOTHERS of the Nurses' Health Study
Maternal Cohort Study: Design

- Maternal reporting of prenatal, infant, and early childhood exposures of nurse daughters by questionnaire
  - Baby books and birth certificates
- Maternal data linked to prospective cohort study of nurse daughters (NHSII)
- Bi-annual follow-up of the nurse cohort
- Sample: Nurses from NHS II who were free of cancer in 2000 and reported their mothers were alive in 1996
- N = 26,512 Nurse Daughters in NHSII
# Delay in Daughter’s Age at Menarche (months) by Maternal Physical Activity during pregnancy

<table>
<thead>
<tr>
<th>Home &amp; Leisure Activity</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>1.00</td>
</tr>
<tr>
<td>Mostly Inactive</td>
<td>0.7 (-1.2, 2.6)</td>
</tr>
<tr>
<td>Active</td>
<td>1.0 (-0.9, 3.0)</td>
</tr>
<tr>
<td>Mostly Active</td>
<td>1.3 (-0.7, 3.3)</td>
</tr>
<tr>
<td>Highly Active</td>
<td>3.0 (0.3, 5.7)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>

(Colbert L, Graubard BI, Michels K, Willett WC, Forman MR CEBP 2008)
In utero exposures

- Maternal physical activity and weight gain—energy balance—influences age at menarche
- Birthweight ~ pubertal status
Life Course: Hypotheses Related to Early Exposures & Cancer Risk or Protection

**In utero**

- Hormones
- Puberty
- Growth
- Physical Activity
- Diet

**Early Exposures**

- Preeclampsia

**Breast Cancer Risk**
**Adjusted OR for breast cancer in the mother or daughter by pre-eclampsia (yes/no)** (Forman MR Cancer Invest 2005)

<table>
<thead>
<tr>
<th>Maternal risk</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polednak (1983)</td>
<td>0.3*</td>
</tr>
<tr>
<td>Thompson (1989)</td>
<td>0.7*</td>
</tr>
<tr>
<td>Troisi (1998)</td>
<td>0.8</td>
</tr>
<tr>
<td>Vatten (2002)</td>
<td>0.8</td>
</tr>
<tr>
<td>Innes (2000)</td>
<td>0.9</td>
</tr>
<tr>
<td>Paltiel (2003)</td>
<td>1.4*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daughter's risk</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekbom (1997)</td>
<td>0.4*</td>
</tr>
<tr>
<td>Sanderson (1998)</td>
<td>0.8</td>
</tr>
<tr>
<td>Innes (2000)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* 95% CI excludes one
### Adjusted RR of Maternal Breast Cancer in Pre-eclampsia & Normotensives: Norway

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Br. Cancer</th>
<th>R.R. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>503</td>
<td>0.86 (0.78-0.94)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>1081</td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

(Vatten LJ, Forman MR: Br J Cancer 2007)
<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Br. Cancer</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sons</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>246</td>
<td>0.79 (0.60-0.90)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>4468</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Daughters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>252</td>
<td>0.94 (0.86-1.06)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>4194</td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

(Vatten LJ, Forman MR: Br J Cancer 2007)
Mean* maternal androstenedione & testosterone levels by gender of the offspring in 86 PE and 86 Normotensive women before delivery

* Means are adjusted for maternal age and gestational age of the neonate.

(Troisi: BrJCa 2007)
Pre-eclampsia

3 to 5 % of pregnant women
Familial clustering: 5-fold risk in first degree relatives
Offspring: ↑ SGA, Preterm, LGA

Clinical Diagnosis:
- DBP > 90mm Hg
- Proteinuria > 0.3 mg/l
- Severity varies by DBP, proteinuria, onset
Stavanger Study

12,804 births from January 1993 to December 1995
307 cases of pre-eclampsia
2 sets of controls Normotensives (NT) per PE case
Design: Nested case-control study
Follow parents and daughters of the nested case-control study population at ages 10.8 y & 12.8 y.
**Maternal characteristics and gestation data by severity of PE and in NT controls: Stavanger Study**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Eclampsia</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe (n=67)</td>
<td>Mild (n=191)</td>
</tr>
<tr>
<td>Maternal age (μ)</td>
<td>26.4</td>
<td>27.2</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>Maternal smoking (%)</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Gestational age at birth (days)</td>
<td>249</td>
<td>270</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>17</td>
<td>8</td>
</tr>
</tbody>
</table>

(Vatten LJ, Obstet Gynecol 2002;99:85-90)
Follow-up of the Stavanger Pre-eclampsia Study

**Aims**

To compare:

Tanner Stage, anthropometrics, and hormone levels in offspring of the pre-eclampsia group to offspring of normotensives.

Expect that offspring of PE will delay puberty, be shorter height-for-age & larger BMI, and have ↓ IGF-1 and ↑ androgens & leptin.
Breast Development 10.8 years: No difference in Tanner Stage.
Pubic hair 10.8 years: No difference

Normotensive
- 74.6%
- 17.1%
- 6.6%

Preeclampsia
- 70.1%
- 23%
- 6.9%

TANNERPH
- 1.00
- 2.00
- 3.00
- 4.00
Breast Development 12.8 years.
PE have higher % pre-pubertal

**Normotensive**
- 24.4%
- 25.6%
- 2.6%
- 47.4%

**Preeclampsia**
- 30.6%
- 13.9%
- 8.3%
- 47.2%

**TANNERB**
- 1.00
- 2.00
- 3.00
- 4.00
Pubic hair 12.8 years. More advanced Tanner score in PE.

Normotensive
- 44.2%
- 29.9%
- 14.3%
- 11.7%

Pre-eclampsia
- 36.4%
- 24.2%
- 24.2%
- 12.1%

TANNER PH
- 1.00
- 2.00
- 3.00
- 4.00
- 5.00
Odds ratio (OR) for Pathway of Pubertal Development in daughters of Preeclampsia compared to Normotensive pregnancies (Ogeland B, Forman MR, Vatten L: Arch Dis Childhd in press)

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Normotensive</th>
<th>Preeclampsia</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenarche</td>
<td>8.1</td>
<td>17.9</td>
<td>2.14 (1.07-4.30)</td>
</tr>
<tr>
<td>(Pubic hair)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetrical</td>
<td>28.8</td>
<td>31.6</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Thelarche</td>
<td>62.9</td>
<td>50.4</td>
<td>0.52 (0.33-0.83)</td>
</tr>
<tr>
<td>(Breast)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Referent group were classified simultaneously as both pubertal for adrenarche/pubic hair and thelarche/breast development of Tanner stage 2.
Age at menarche in girls by infancy weight gain (A) & infancy growth rates (B): Avon Longitudinal Study of Pregnancy and Childhood

Ong, K. K. et al.

J Clin Endocrinol Metab

2009;94:1527-1532
Body size & family conflict are directly related to risk of early menarche in Mexican American girls.
Mexican American Tobacco Use in Children (PI: Spitz MR)

Longitudinal cohort study
Follow-up (3 years)
  Baseline and final home visits
  Phone calls every six months
Home Visit
  Collect buccal sample
  Survey on PDA to maintain privacy
OR (95% CI) for Early age at menarche (< 11y) among Mexican American Girls (Thelus-Jean R, Wilkinson A, Bondy ML, Spitz MR, Forman MR Submitted)

<table>
<thead>
<tr>
<th></th>
<th>N=522</th>
<th>N=461</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI For Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00 (REF)</td>
<td>1.00 (REF)</td>
</tr>
<tr>
<td>Overweight</td>
<td>2.01 (1.24-3.25)</td>
<td>2.15 (1.25-3.71)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.49 (1.01-2.21)</td>
<td>1.06 (0.68-1.67)</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>-----</td>
<td>1.02 (0.96-1.01)</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>-----</td>
<td>0.66 (0.51-0.86)</td>
</tr>
<tr>
<td><strong>Family Conflict</strong></td>
<td>-----</td>
<td>1.60 (1.07-2.37)</td>
</tr>
<tr>
<td><strong>Marriage</strong></td>
<td>-----</td>
<td>1.77 (0.94-3.36)</td>
</tr>
<tr>
<td><strong>Mother’s age at menarche</strong></td>
<td>-----</td>
<td>0.82 (0.73-0.92)</td>
</tr>
</tbody>
</table>
Conclusions In utero Exposures

• High birthweight ~ 70% to 3 fold higher odds of breast development in girls 8-11 years.
• Compared to nurse daughters of inactive mothers, those who had physically active mothers in the index pregnancy delayed menarche by 3 months on average.
• Maternal pre-pregnancy physical activity and weight gain at the extremes are associated with age at menarche in the nurse daughter.
Conclusions

Stavanger Puberty Study:

No differences in breast or pubic hair development at 10 years among PE and NT girls.

Girls of NT pregnancies who experienced the greatest weight gain at 3-6 months had a higher odds of breast development at 10.8 years.

Girls of PE pregnancies who experienced the greatest weight gain at 6-12 months had a higher odds of breast and pubic hair development at 10.8 years.

Higher percent of PE have pubic hair development but lower percent of PE have breast development at 12 years than NT girls.
Conclusions

MATCH:
High BMI and family conflict increase the risk of early menarche.
The later the maternal age at menarche, the lower the risk of early menarche in Mexican American girls.
What am I going to tell you?

In utero
- Birthweight ~ pubertal stage
- Maternal energy balance in pregnancy ~ daughter’s age at menarche

Infancy
- Age of greatest weight gain ~ pubertal status & age varies by maternal preeclampsia
- Age of greatest weight gain ~ age at menarche

Childhood/youth
- Body size and family conflict ~ earlier menarche in Mexican American girls.
In utero exposures plus cumulative adaptive response to environmental exposures—which involve changes in the epigenome, proteome, transcriptome and genome—through the life course lead to risk of: early onset of puberty, early age of menarche, obesity, diabetes, and cancer.

(Burde GC, Lillycrop KA, Jackson AA, Br J Nutr 2009; Burdge GC, Lillycrop KA, Nutrition, Epigenetics, and Developmental Plasticity: Implications for Understanding Human Disease, Annu Rev Nutr 2010;30:315-339)
Collaborators

Stavanger study:
Pal Romunstad
Lars Vatten
Bjorn Ogland
Stein Tore Nilsen
Lisa Colbert
Fred Kadlubar
J. Carl Barrett

MDACC:
Stavanger
Carol Etzel
Rose Thelus
Yong Q. Dong
MATCH
Margaret Spitz
Melissa Bondy
Anna Wilkinson
Yong Q. Dong
MATCH staff

Mothers:
Walter Willett
Karin Michels
Barry Graubard
Alison Stuebe
Lisa Colbert
Renee Boynton-Jarrett
Janet Rich-Edwards

NHANES:
Susan Olivo-Marston
Barry Graubard

Please contact the authors of submitted or unpublished data before use!