Endometrial Cancer
Risk Prediction Model

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Utility of risk prediction models

- Aid in clinical management
- Identify high risk populations for intervention studies
- Understand biologic process of carcinogenesis
Exposures change rate of tissue aging

Colorectal cancer

Endometrial cancer

Breast cancer

Ovarian cancer

Sources:
Pike 1983 Nature
Pike 1987 J Chron Dis
Pike 2004 Oncogene
Reproductive events in breast tissue aging

Figure 5 Model of rate of breast tissue aging model (LMP = last menstrual period; Pike et al., 1983)

Sources:
Pike 1983 Nature
Pike 1987 J Chron Dis
Pike 2004 Oncogene
Can we improve endometrial cancer risk prediction by incorporating timing of exposures?
Study population

- Nurses’ Health Study (NHS)
  - Ongoing prospective cohort
  - 121,700 female registered nurses from 11 U.S. states
  - 30-55 years of age at baseline in 1976
  - Biennial self-administered questionnaires
- High follow-up rates
# Detailed risk factor information

## Do you currently smoke cigarettes?
- No
- Yes
- How many/day?
  - 1–4
  - 5–14
  - 15–24
  - 25–34
  - 35–44
  - 45+

## Have you had your uterus removed?
- No
- Yes
- Date of surgery:
  - Before June 1, 2010
  - After June 1, 2010

## Have you ever had either of your ovaries surgically removed?
- No
- Yes
  - a) How many ovaries do you have remaining?
    - None
    - One

Since June 2010, have you used prescription female hormones? (Not including over-the-counter/herbal/soy preparations.)
- Yes
  - a) How many months did you use hormones since June 2010?
    - 1–4 months
    - 5–9
    - 10–14
    - 15–19
    - 20–25
    - 26–30
    - 31–35
    - 36+ months
  - b) Are you currently using them (within the last month)?
    - Yes
    - No
    - If No, skip to Part d.
  - c) Mark the type(s) of hormones you are CURRENTLY using:
    - Prempro
    - Oral Premarin or conjugated estrogens
    - Patch Estrogen
    - Vaginal Estrogen
    - Other Estrogen (specify in box below)
    - Estrace
    - Estrogen gels, creams, or sprays on skin
    - Estratest
    - Ogen
    - Other Estrogen (specify type)
    - Progesterone
    - Provera/Cycrin/MPA
    - Vaginal
    - Micronized (e.g., Premarin)
    - Other progesterone (specify type)
  - d) If you used oral conjugated estrogen (e.g., Premarin) since June 2010, what dose did you usually take?
    - .30 mg/day or less
    - .45 mg/day
    - .625 mg/day
    - .9 mg/day
    - 1.25 mg/day or higher
    - Unsure
    - Did not take oral conjugated estrogen

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**Type of female hormones first reported**

NHS

1976

1980

1984

1988

1992

1996

2000

2004

2008

2012

[http://www.channing.harvard.edu/nhs](http://www.channing.harvard.edu/nhs)
Case ascertainment

- Self-report incident diagnosis of endometrial cancer
- Women were asked permission to obtain medical records
- Records reviewed by gynecologic oncologist or pathologist
  - Histologic subtype
  - Stage
  - Grade
- Analysis restricted to medical-record confirmed invasive epithelial endometrial adenocarcinoma (Stages IA-IV)
Exclusions at baseline (1978)

- Cancer diagnosis (except non-melanoma skin cancer; N=4,180)
- Hysterectomy (N=24,542)
- Surgical or unknown menopausal status (N=13,673)
- Missing risk factor data (N=12,519)
- Eligible women at baseline: 66,786
Risk factors modeled

- Timing of reproductive events
- Exogenous hormone use
- BMI in low vs. high estrogen environment (menopause/hormone use status)
- Smoking
- Family history of endometrial cancer
- Personal history of diabetes or hypertension
Statistical analysis

- Cox proportional hazards regression model
- Similar exclusions throughout follow-up
- Follow-up ended in June 1, 2010
- Total incident cases diagnosed throughout follow-up: 648
Statistical analysis

- Relative risks (RR)
  - Dichotomous variables: \( \exp(\beta) \)
  - Continuous variables: \( \exp(\beta \times \text{contrast in risk factor}) \)

- C-statistic for overall discriminatory ability
Preliminary Results
NHS endometrial cancer incidence rates

![Graph showing incidence rate per 100,000 person-years across different age categories (35-39 to 75-79 years). The incidence rate increases with age,达到最高点后下降。]
Duration of premenopausal period

<table>
<thead>
<tr>
<th>Age at natural menopause</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 years of age</td>
<td>1.00</td>
</tr>
<tr>
<td>50 years of age</td>
<td>1.75</td>
</tr>
</tbody>
</table>
# Number and timing of births

<table>
<thead>
<tr>
<th>Age at births</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>1.00</td>
</tr>
<tr>
<td>20</td>
<td>0.68</td>
</tr>
<tr>
<td>20, 23,</td>
<td>0.53</td>
</tr>
<tr>
<td>26, 29</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Oral contraceptive use

<table>
<thead>
<tr>
<th>Duration</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.00</td>
</tr>
<tr>
<td>10 years</td>
<td>0.42</td>
</tr>
<tr>
<td>Type, Duration</td>
<td>RR</td>
</tr>
<tr>
<td>------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Never</td>
<td>1.00</td>
</tr>
<tr>
<td>Oral E, 5 years</td>
<td>3.91</td>
</tr>
<tr>
<td>Oral E+P, 5 years</td>
<td>2.06</td>
</tr>
<tr>
<td>Other, 5 years</td>
<td>2.72</td>
</tr>
</tbody>
</table>
Body mass index (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 kg/m²</td>
<td>1.00</td>
</tr>
<tr>
<td>30 kg/m²</td>
<td>3.58</td>
</tr>
</tbody>
</table>
Pack-years of smoking

<table>
<thead>
<tr>
<th>Duration</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.00</td>
</tr>
<tr>
<td>20 pack-years</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Medical history

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td>Family history of endometrial cancer</td>
<td>1.48</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.34</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.19</td>
</tr>
</tbody>
</table>
Comparison of discriminatory ability (Internal population)

<table>
<thead>
<tr>
<th>Pfeiffer et al. model</th>
<th>Current model</th>
<th>Difference between models</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.766 (±0.009)</td>
<td>0.793 (±0.009)</td>
<td>-0.027 (±0.007)</td>
<td>0.0000 3</td>
</tr>
</tbody>
</table>
Limitations

**Trends in Overweight and Obesity among Adults, United States, 1962–2010**

- **Overweight**
- **Obesity**
- **Extreme obesity**

**Data for 1960–1980 are for adults ages 20 to 74; data for 1988–2010 are for adults age 20 and older.**


**Source: Zbuk 2012 J Epidemiol Community Health**
Conclusions

- Incorporating timing of exposures may improve risk prediction of endometrial cancer

- Reproductive years may be particularly relevant period for intervention
Future directions

- Further explore relation with timing of birth
- Validate model in independent population (PLCO)
- Can we improve upon base model?
  - Suggestive factors (e.g., coffee intake)
  - Plasma biomarkers and/or genetic variants
  - By histologic or molecular tumor subtype
Acknowledgments

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- Immaculata De Vivo
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- Shelley Tworoger
- Akila Viswanathan

PLCO
- Nicolas Wentzensen

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