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Reproduction and Neoplasia

• **Female neoplasia**
  – Benign breast tumors, breast cancer
  – Uterus: Fibroids and endometrial cancer
  – Ovarian cancer
  – Pituitary adenomas
  – Liver: Benign and malignant liver tumors

• **Males**
  – Testicular cancer
  – Benign prostatic hypertrophy and prostate cancer
**Benign Breast Disease (BBD)**

**Pathology**
- Fibro-adenoma
- Fibrocystic disease

**BBD and breast cancer**
- Well differentiated tumors are benign,
- Hyperplasia or proliferative tumors increase risk of breast cancer RR ~ 2

**Epidemiology**
- Highest incidence ages 20-45.
- Decreases after menopause
- Oral contraceptives reduce the risk RR = 0.5 after 2 years use
- Oral contraceptives effects are more pronounced with higher estrogen
Incidence of fibrocystic breast disease (FBD) and fibro-adenoma

Adapted from Goehring C, Morabia A. Epidemiology of benign breast disease, with special attention to histologic types. Epidemiol Rev 1997;19:310-327
Breast Cancer
Incidence and mortality

• US incidence increased from 75/100,000 (1940’s) to 98/100,000 (1990’s).
  - improved registration (since the 1980’s),
  - improved screening, and diagnosis (since 1980, increased detection of small tumors less than 2 cm).
  - Partly a true increase in incidence?

• Incidence increases with age. 13% of cancers occur under age 45 and 87% of cancers postmenopausal.

• Mortality ~ 30,000 death py, ~13% decline in 1990s

• ~13% of U.S. women will have a breast cancer diagnosis and 3.5% will die of breast cancer.

• Breast cancer mortality is declining in most developed countries
Breast cancer incidence US 1975-2003 (SEER data)
Reproductive risk factors for breast cancer

- **Age**: Increased incidence after menopause
- **Age at menarche**: Younger menarche $\leq$ 12 years, RR = 1.3, vs $\geq$ 15 years
- **Age at menopause**: Later menopause $\geq$ 55 years, RR = 2.0 vs <45
- **Oophorectomy** < 35 reduces risk
- **Age at first full-term pregnancy**: Older age higher risk (> 40, RR = 1.6 vs < 18)
- **Parity**: Lower parity higher risk (parity 1 RR = 1.7 vs parity $\geq$ 7)
- **Infertility**: Higher risk in subfertile, but findings not consistent
Reproduction risk factors for breast cancer,

• **Age at last birth**: Later age at last birth higher risk (age ≥ 41 years, OR = 1.95 vs <28)
  – Transient increased risk after each birth (approximately 10 years), greater for older age at delivery

• **Menstrual cycle**: Short cycle (♀ 21 days) higher risk

• **Receptor status**: 50% of tumors have estrogen receptors (ER+). Premenopausal cancers have a lower proportion ER+

• No clear association between steroid levels in urine or blood and cancer risk

• **Obesity** associated with postmenopausal cancers (increased estrone from adipose tissue?)

• **Dietary fat**: Ecologic associations, but not a risk factor in most individual level observational studies and trials
• **Reproduction risk factors for breast cancer**

  • *Lactation*: Prolonged breast feeding lowers risk (lactation > 25 months, OR = 0.7 vs no breastfeeding).

  • *Abortion*:  
    - No association with spontaneous abortion.
    - Induced abortion, probably no effect for abortions < 18 weeks gestation, question with regard to later abortions.
    - Problem of underreporting of induced abortions in retrospective studies. Prospective studies show no effects in first trimester.
Breast cancer and induced abortion

- Several retrospective studies suggest that induced abortion increases breast cancer risk.
  - Findings are not consistent
  - Problem of recall bias
- Prospective Danish study of 1.5 million women (Melbye M, et al. Induced Abortion and the Risk of Breast Cancer. NEJM 1997;336:81-85)

<table>
<thead>
<tr>
<th>History</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any abortion</td>
<td>1.0 (0.94-1.06)</td>
</tr>
<tr>
<td>Week of gestation</td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>7 to 8</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>9 to 10</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>11 to 12</td>
<td>1.1 (1.0-1.3)</td>
</tr>
<tr>
<td>13 to 14</td>
<td>1.1 (0.5-2.5)</td>
</tr>
<tr>
<td>15 to 18</td>
<td>1.2 (0.8-2.0)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>1.9 (1.1-3.2)</td>
</tr>
</tbody>
</table>
Etiologic Hypothesis Regarding Hormonal Risk Factors

- Breast cancer initiation probably occurs in adolescence and early adulthood
- Latent period unknown, probably > 20 years
- Promotion affected by births, lactation and exogenous steroid hormones
- Birth has a dual effect on risk. Pregnancy increases short-term risk due to proliferation of initiated cells (i.e., promotion), but confers long term protection by inducing differentiation of normal mammary cells
Other Non-Reproductive Risk Factors for Breast Cancer

Major increased risk

- Place of birth (North America or Europe)
- Family history (first degree relatives) ~ 12% of cases (1 relative RR = 1.8, 2 relatives RR=2.9, 3+ relatives RR= 3.0)
- Breast Cancer Genes (BRCA 1,2) ~ 4% in all cancer, 25% of cancers < age 40 have BRCA 1,2 mutations.
- Breast cancer in one breast (recurrence)

Moderate increased risk

- Dense mammogram, biopsy confirmed BBD
- Radiation

Minor risk

- Higher SES
- Race (under 40 years, Black > Caucasian > Asian)
- Religion (Jewish > Seventh-day Adventist > Mormon)
- Alcohol consumption?
# International differentials in breast cancer incidence

## Breast cancer incidence in selected countries

<table>
<thead>
<tr>
<th>Country, area or population group and period of study</th>
<th>Age-standardized annual incidence rates per 100 000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA: Connecticut (1968–1972)</td>
<td>71.4</td>
</tr>
<tr>
<td>Switzerland: Geneva (1970–1972)</td>
<td>70.6</td>
</tr>
<tr>
<td>Israel: Jewish population (1968–1971)</td>
<td>55.5</td>
</tr>
<tr>
<td>Denmark (1963–1967)</td>
<td>49.1</td>
</tr>
<tr>
<td>Colombia: Call (1967–1971)</td>
<td>27.8</td>
</tr>
<tr>
<td>India: Bombay (1968–1972)</td>
<td>20.1</td>
</tr>
<tr>
<td>Singapore: Malay population (1968–1972)</td>
<td>17.6</td>
</tr>
<tr>
<td>Japan: Miyagi Prefecture (1968–1971)</td>
<td>13.0</td>
</tr>
</tbody>
</table>

* Age standardized to the world population.
Randomized Trials of Screening for Breast Cancer Mortality Reductions

  - Mortality women aged 50-69 years RR = 0.71
  - Mortality in women 40 - 49 years RR = 0.87
- Kerlikoske et al. *JAMA* 1995;273:149. Meta-analysis,
  - Mortality in women 50 - 74 years RR = 0.87
  - Mortality in women 40-49 years RR = 0.93
  - Mortality ages 50-74 years RR = 0.66
  - Mortality 40-49 year olds RR ~ 1
  - Mortality > 50 yrs RR = 0.50 ns
  - Mortality < age 50 RR = 0.83 ns
  - Mortality > 50 yrs RR = 0.77 ns
  - Mortality ≥ 49 yrs RR = 0.78 ns
Critique of Mammography Trials
Gotzsche & Olsen Lancet 2000;355:129

- Criticized trial design, imbalances etc.
- Claimed detection of tumors with low malignant potential leads to unnecessary surgery
- No effect of mammography on all cause mortality
Swedish Trials with long-term follow up
Nystrom Lancet 2002;359:909

- 129,750 mammography vs 117,260 controls
- Median fu time 15.8 years. Linked to cancer and death registries

- Age-adjusted breast cancer mortality
  - RR = 0.85 (0.77-0.94)

- Benefit observed after 4 years and increased up to 10 years

- Benefit significant > age 55, but not ages 40-54

- Age adjusted all cause mortality
  - RR = 0.98 (0.96-1.00)
Treatment

- Surgery: Lumpectomy, mastectomy, node resection
- Chemotherapy
- Radiation
- Anti-estrogens (tamoxifen, 41% reduction in recurrence rate, aromatase inhibitors, ovariectomy)
The effects of mammography and chemotherapy on breast cancer mortality US.

Figure 2. Estimated and Actual Rates of Death from Breast Cancer among Women 30 to 79 Years of Age from 1975 to 2000 (Panel A) and under Hypothetical Assumptions about the Use of Screening Mammography and Adjuvant Treatment (Panel B).

Panel A, which compares the model-based results with the actual rates in the United States from 1975 to 2000, shows the variability across the model estimates. Some of the models were calibrated according to the observed rate of death from breast cancer in the United States, and some were not. Panel B shows the results from model W (the University of Wisconsin–Madison) of estimated mortality trends for the four scenarios considered: no screening and no adjuvant treatment; base-case screening, but no adjuvant treatment; no screening, but base-case adjuvant treatment; base-case screening and adjuvant treatment. Rates in both panels are age-adjusted to the 2000 U.S. standard.

Methods in Studies of oral contraceptives (OC) and Hormone replacement therapy (HRT) use associated with Breast Cancer

• **Dose of steroid** inferred from duration of use and type of drug (i.e. amount of steroid in OC, HRT).

• **Latent interval** inferred from time of first use to time of diagnosis

• **Promotion** inferred from time of last use to diagnosis (recent use)
  – Need to reconstruct lifetime history of use (event calendar, books of pill packages, clinical records, prescription records)
  – Promotion of existing disease (associated with recent use), expect more rapid growth therefore later stage disease

• **Disease stage** (smaller, localized tumors early, larger disseminated tumors advanced later stage)
Bias and Confounding in studies of hormones and breast cancer

• **Confounding** between reproductive patterns and contraception
  – Delayed first birth, nulliparity, early menarche, etc.

• **Diagnostic or screening bias**
  – More frequent breast exams (self exam, physician exam, mammography, etc) more likely to detect early tumors in hormone users
  – Lead time bias. Need to measure for screening effects.

• **Index of suspicion**.
  – If physician more likely to investigate a lump among hormone users than non-users

• **Unmasking/Detection bias**
  – Breast lumps can obscure tumors. Hormones decrease BBD and reduce lumpiness or density of breast tissue, thus facilitating detection of smaller tumors

• **Detection bias**
  – suggested by current or recent exposure or smaller, earlier tumors
Oral Contraceptives and Breast Cancer

Summary

• No increased risk associated with past OC use among women older than 50 yrs. Possible decreased risk of postmenopausal cancers

• Increased risk of breast cancer associated with current or recent OC use in women under age 45

- **Time since use:** Current and recent use (<5 years) RR = 1.24,
- **Stage of disease:** Risk decreased for larger and metastatic tumors
- **Duration of use:** No consistent effects of duration of use, age at first use, use before first birth, or type of hormone
- **Interpretation:** Could be a promotional effect of OCs on existing tumors or a bias leading to an earlier diagnosis of cancer in OC users
# Size of tumors associated with OC use

<table>
<thead>
<tr>
<th>Extent of tumor spread</th>
<th>HRT ever-users/never-users</th>
<th>RR(FSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized to breast</td>
<td>1387/4104</td>
<td>1.00 (0.056)</td>
</tr>
<tr>
<td>Spread to axillary lymph nodes only</td>
<td>940/2827</td>
<td>0.82 (0.060)</td>
</tr>
<tr>
<td>Metastatic beyond breast and lymph nodes</td>
<td>98/312</td>
<td>0.54 (0.173)</td>
</tr>
</tbody>
</table>
Depo Provera (DMPA) and Breast Cancer

• **Toxicology studies**
  • Beagle dog studies suggest that DMPA causes breast cancer.
    – Dose response between duration and dose of DMPA exposure and number and early onset of breast cancer in dogs.
    – Beagle dog progestin receptors differ from humans and tumor types do not reflect human pathology. WHO and FDA decide beagle dogs are not an appropriate model.
DMPA and human studies

- Epidemiologic studies
- Pooled estimates of risk in 1,768 cases and 13,905 controls (JAMA 1995;273:799)
  - No increase in breast cancer risk with ever use of DMPA (RR = 1.1)
  - No effect of duration of use or age at first use
  - Increased risk with current use or recent use (< 5 years), RR = 2.0
  - No increased risk > 5 years since last use
  - Consistent with either promotion or enhanced detection
Postmenopausal Hormonal Replacement Therapy (HRT) and Breast Cancer

- 1 million UK women 50-64 followed 1996-2001
- **Current use of HRT**
  - Current HRT breast cancer RR = 1.66 (1.58-1.75)
  - Current HRT breast cancer deaths RR = 1.22 (1.0-1.5)
  - E+P RR = 2.0 (1.9-2.1), E only RR = 1.3 (1.2-1.4)
  - Risk increased with longer duration of use
- **Past HRT**
  - Not associated with breast cancer RR = 1.01

  - Lancet 2003;362:419
Women’s Health Intiative (WHI) trial
Chlebowski et al JAMA 2003;289:3243

• Estrogen + Progestin vs placebo
• Invasive breast cancer incidence:
  – HRT = 3.1%, placebo 2.5%; HR = 1.24 (1.01-1.54)
  – Metastatic tumors HRT = 25.4%, placebo 16.0% (p = 0.03)
  – Tumor size HRT = 1.7 cm, placebo = 1.5 cm (p= 0.04)
  – Abnormal mammogram HRT = 9.4%, placebo = 5.4%, p<0.001
  – Trial stopped prematurely
HRT after breast cancer diagnosis

HABITS trial Holmberg *Lancet* 2004;363:453

- Randomized trial of HRT in women with prior breast cancer
- End point “new cancer event” (recurrence or metastases). 2 year fu
- Hazards ratio = 3.5 (1.5-8.1)
- Trial stopped prematurely
HRT and Breast Cancer

Conclusion

• The risks of breast cancer associated with hormone use in observation studies <2.0
  – Data are not consistent with an effect on initiation
  – Possible promotion (e.g., recent use and earlier grade tumors)
  – Possible bias and confounding?
• Two RCTs (WHI and HABITS) show increased risk of invasive breast cancer, larger tumors and more metastases with HRT use
  – Probable true increased risk of breast cancer with exogenous steroid hormones in postmenopausal women
Can Hormones Prevent Breast Cancer? 
Tamoxifen

- Tamoxifen is an anti-estrogen used in prevention of recurrent breast cancer

- Trials of Tamoxifen for prevention of breast cancer in high risk women
  - BCPT (US) RR = 0.55
  - Powle (UK) RR = 0.94
  - Veronesi (UK) RR = 0.91

Genital Neoplasia and Reproduction

- Uterine Fibroids
- Endometrial cancer
- Ovarian cancer
- Cervical cancer
- Vulvar, anal and penile cancers
- Vaginal cancer
- Testicular cancer
- Prostate cancer
- Liver cancer
- Pituitary adenomas
• Uterine Fibroids
  – Benign tumors of uterine muscle
  – Mainly present as bleeding
  – Risk factors suggest hormonal etiology
  – OC reduce risk
  – Most common cause of hysterectomy
## Risk Factors for Uterine Fibroids

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>1.0</td>
</tr>
<tr>
<td>Post-menopause</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td>1.0</td>
</tr>
<tr>
<td>50-</td>
<td>1.7</td>
</tr>
<tr>
<td>55-</td>
<td>2.3</td>
</tr>
<tr>
<td>60-</td>
<td>2.4</td>
</tr>
<tr>
<td>65-</td>
<td>2.6</td>
</tr>
<tr>
<td>70+</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Combined oral contraceptives</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>2-8 years</td>
<td>0.8</td>
</tr>
<tr>
<td>8+ years</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Endometrial Cancer

- Mainly postmenopausal (75%)

- Most cancers estrogen dependent.
  - Excess estrogen results in hyperplasia.
  - Progestins inhibit proliferation.

Combined oral contraception reduces risk by 0.5

- Unopposed estrogen HRT increases risk, partly compensated by progestin supplements

Possible reduced risk during menstruating life due to shedding of precancerous cells.

- Familial links with colon and breast cancer
Incidence of endometrial cancer US (SEER data)

![Graph showing incidence rates of endometrial cancer by race from 1975 to 2003. The graph displays the rates per 100,000 population for all races, white, and black individuals. The rates decrease over time for all races, with white individuals generally having higher rates compared to black individuals.]
## Corpus uteri cancer incidence in selected countries

<table>
<thead>
<tr>
<th>Country, area or population group and period of study</th>
<th>Age-standardized annual incidence rates per 100,000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA: Connecticut (1968–1971)</td>
<td>17.8</td>
</tr>
<tr>
<td>Denmark (1963–1967)</td>
<td>11.4</td>
</tr>
<tr>
<td>Israel: Jewish population (1966–1971)</td>
<td>10.8</td>
</tr>
<tr>
<td>Yugoslavia: Slovenia (1968–1972)</td>
<td>9.1</td>
</tr>
<tr>
<td>England: southern metropolitan region (1967–1971)</td>
<td>8.0</td>
</tr>
<tr>
<td>Colombia: Cali (1967–1971)</td>
<td>5.1</td>
</tr>
<tr>
<td>Singapore: Malay population (1968–1972)</td>
<td>3.8</td>
</tr>
<tr>
<td>Japan: Miyagi Prefecture (1968–1971)</td>
<td>1.3</td>
</tr>
</tbody>
</table>


* Age standardized to the world population.

## Reproductive Risk Factors for Endometrial Cancer

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight by</td>
<td></td>
</tr>
<tr>
<td>9-23 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;23 kg</td>
<td>10</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>2</td>
</tr>
<tr>
<td>Late menopause (&gt;52 years)</td>
<td>2.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.7</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td></td>
</tr>
<tr>
<td>(Unopposed)</td>
<td>6</td>
</tr>
<tr>
<td>Estrogen &amp; progestin</td>
<td></td>
</tr>
<tr>
<td>&lt;10 days/month</td>
<td>3</td>
</tr>
<tr>
<td>10-21 days</td>
<td>1.3</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2</td>
</tr>
<tr>
<td>Combined OC</td>
<td>0.5</td>
</tr>
<tr>
<td>Sequential OC</td>
<td>7</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0.8</td>
</tr>
<tr>
<td>15+</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Source: Rose PG. Endometrial carcinoma. NEJM 1996;335:640-649
### HRT and Endometrial Cancer

**Million Women Study, Lancet 2005**

Relative risk of endometrial cancer according to type of HRT last used.

<table>
<thead>
<tr>
<th></th>
<th>Average use of HRT (years)</th>
<th>Average years since last use of HRT</th>
<th>Cases/population (1000s)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>-</td>
<td>-</td>
<td>763/395.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Continuous combined</td>
<td>5.0</td>
<td>0.2</td>
<td>73/69.6</td>
<td>0.71 (0.56-0.90)</td>
</tr>
<tr>
<td>Cyclic combined</td>
<td>5.1</td>
<td>1.0</td>
<td>242/145.5</td>
<td>1.05 (0.91-1.22)</td>
</tr>
<tr>
<td>Tibolone</td>
<td>5.2</td>
<td>0.7</td>
<td>86/28.0</td>
<td>1.79 (1.43-2.25)</td>
</tr>
<tr>
<td>Oestrogen only</td>
<td>4.6</td>
<td>1.3</td>
<td>33/14.2</td>
<td>1.45 (1.02-2.06)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>2.1</td>
<td>4.5</td>
<td>123/63.7</td>
<td>1.17 (0.96-1.41)</td>
</tr>
</tbody>
</table>

Unopposed estrogen increases risk, continuous progestin use decreases risk.
**Ovarian Cancer**

Incidence increases with age (mainly postmenopausal)

- Case-fatality and mortality high (late diagnosis and poor response to treatment)

- **Risk factors include:**
  - Late age at menopause
  - Nulliparity
  - Infertility (ovulation induction)
  - Oral contraceptives reduce risk for > 10 years since last use
  - Menopausal supplements do not affect risk
  - Familial history, links to breast and colon cancers
Ovarian Cancer, cont.

- Theory that ovarian cancer is due to irritation of the serosal membrane at ovulation (“incessant ovulation”). More ovulation, higher risk. OC may reduce risk by reducing ovulation
- Abdominal surgery (talc) irritant
- Many pathologic types, most common are serosal
Mortality from Ovarian Cancer US

![Graph showing mortality rates from ovarian cancer US over the years. The graph displays data for all races, whites, and blacks. The x-axis represents the year of death (1969 to 2003), and the y-axis represents the rate per 100,000. The graph shows a general trend of decreasing mortality rates over time.]
## Geographic epidemiology

### Ovarian cancer (including fallopian tube and broad ligament) incidence in selected countries

<table>
<thead>
<tr>
<th>Country, area or population group and period of study</th>
<th>Age-standardized annual incidence rates per 100,000 women</th>
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<tr>
<td>Denmark (1963–1967)</td>
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</tr>
<tr>
<td>Israel: Jewish population (1968–1971)</td>
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</tr>
<tr>
<td>USA: Connecticut (1968–1972)</td>
<td>12.5</td>
</tr>
<tr>
<td>England: southern metropolitan region (1967–1971)</td>
<td>11.0</td>
</tr>
<tr>
<td>Yugoslavia: Slovenia (1968–1972)</td>
<td>10.1</td>
</tr>
<tr>
<td>Colombia: Call (1967–1971)</td>
<td>8.0</td>
</tr>
<tr>
<td>Singapore: Malay population (1968–1972)</td>
<td>6.3</td>
</tr>
<tr>
<td>India: Bombay (1968–1972)</td>
<td>4.8</td>
</tr>
<tr>
<td>Japan: Miyagi Prefecture (1968–1971)</td>
<td>2.8</td>
</tr>
</tbody>
</table>


* Age standardized to the world population.

Cervical Cancer

Etiology/Pathology

• Sexually transmitted disease due to Human Papillomavirus (HPV) main high risk types 16, 18, 31, 45. Types 33, 35, 39, 51, 52, 56, 58, 59, 68 moderate risk.

• HPV 16 58.9% cancers, 18 15.0%, 45 6.9%

• Most cancers are squamous cell arising from the columnar/squamous transition zone (T zone) of the cervix. Minority adenocarcinoma.

• > 90% of premalignant and malignant lesions are HPV DNA positive
HPV Epidemiology

• HPV common (incidence 43% over 3 years in sexually active college students)
• Most HPV infections transient (~ 8 months)
• Persistent infections progress to neoplasia (latency ~ 11 years)
• **Molecular Lesions**
  – Minority of persistent infections due to HPV integration into host cell DNA
  – Cause deregulation of E6 & E7 genes which inactivate tumor supressor protein p53, and prevent DNA repair.
Geographic distribution of HPV types

HPV infection by HIV status: Prospective study in Rakai, Uganda

HPV status by HIV

<table>
<thead>
<tr>
<th>HPV status</th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent HPV-</td>
<td>37.01</td>
<td>69.58</td>
</tr>
<tr>
<td>Incident HPV</td>
<td>22.05</td>
<td>15.58</td>
</tr>
<tr>
<td>Prevalent HPV</td>
<td>40.48</td>
<td>14.48</td>
</tr>
</tbody>
</table>
Clearance by HIV status; Rakai

Clearance Rate: By HIV status

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PY</th>
<th>Clear Rate</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>515</td>
<td>820</td>
<td>37</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>343</td>
<td>553</td>
<td>31</td>
<td>0.8</td>
<td>0.7-0.9</td>
</tr>
</tbody>
</table>
The Three Steps of Cervical Carcinogenesis.

The steps can be conceptualized as infection with specific high-risk types of human papillomavirus (HPV), progression to a precancerous lesion, and invasion. HPV infections are usually transient and are often associated with mild cytologic abnormalities. Persistent infection with high-risk types of HPV is uncommon and is required for progression.
Epidemiology and Screening

- Incidence increases with age especially in poorly screened populations,

- Screening increases detection of *in situ* disease and decreases mortality

- Local treatment: cryotherapy, laser, loop electrosurgical excision procedure (LEEP), conization.

- Hysterectomy for invasive disease.
- Screening not available in most developing countries.
- Cervical cancer is the most common cause of female cancer mortality in the developing world (~ 250,000 deaths worldwide)

Katz IT, Wright AA. Preventing cervical cancer in the developing world. NEJM 2006 Mar 16;354:1110. Copyright © 2006 Massachusetts Medical Society. All Rights Reserved.
Mortality from cervical cancer US

Year of Death

Rate per 100,000


All races  White  Black
Risk Factors for Cervical Cancer

• **Risk factors associated with HPV Infection:**
  - age at first intercourse
  - woman’s number sexual partners
  - Male’s number sexual partners.
  - Immunodeficiency (HIV, transplants). Increased HPV prevalence, persistence and shedding, more rapid progression to cancer
  - Lack of male circumcision increases risk

• **Other Risk Factors/co-factors:**
  - Smoking, active or passive. (Co-carcinogen?)
  - Folate deficiency?
  - STDs (other than HPV) possible promotion effect
## SMOKING and CERVICAL CANCER

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoker</td>
<td>3.42</td>
<td>2.1-5.6</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>1.42</td>
<td>0.8-2.5</td>
</tr>
<tr>
<td>Years Smoked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>1.68</td>
<td>1.0-2.8</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>2.17</td>
<td>1.2-3.9</td>
</tr>
<tr>
<td>Passive Smoke (hours/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1-0.9</td>
<td>1.2</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>1.0-2.9</td>
<td>1.6</td>
<td>0.7-4.0</td>
</tr>
<tr>
<td>≥3.0</td>
<td>2.96</td>
<td>1.3-7.0</td>
</tr>
</tbody>
</table>

STD Cofactors?

- Associations reported for HSV-2, chlamydia, gonorrhea
  - possible confounding by sexual behavior?
  - Inflammatory effects of STDs may promote HPV and neoplasia?
Male circumcision, HPV and cervical cancer

• HPV Prevalence in men
  – Circumcised = 5.5%
  – Uncircumcised = 19.6%
  – OR = 0.37 (0.16-0.85)

• Female Cervical Cancer Risk (wives of circumcised vs uncircumcised men)
  – OR = 0.72 (0.49-1.04)

  – Catellsague et al NEJM 2002
HPV vaccines

- Synthetic virus like particles (VLP), encoding for late stage proteins, evoke immune response
  - Include types 16 and 18 (most cancers), and some include types 6 and 11 (for genital warts)
- Trials of prevention of infection
- Trials of therapy ongoing
HPV Vaccine trials

• **Merck**
  – **Monovalent HPV16** (n = 2392): persistent HPV infection intervention 0/control 41 (Koutsky *NEJM* 2002)
  – **Quadravalent HPV 16, 18, 11, 6** (n = 552): persistent HPV intervention 4/control 36 (Villa *Lancet Oncology* 2005)
  – **Quadravalent** 25,000 women Persistent HPV intervention 7/control 111, CIN2-3 intervention 0/control 12 (Mao *Obstet Gynecol* 2006)

• **GSK**
Screening for Cervical Cancer

• Screening methods
  – Cytology (Pap smear, thin prep) → biopsy
  – HPV detection (hybrid capture) → biopsy
  – Visual inspection with acetic acid (VIA) → local excision (developing countries)

• HPV sensitivity > cytology > VIA
Classification of cervical Cancer

- **Cytology (Bethesda System)**
  - Atypical squamous cells of undetermined significance (ASCUS)
  - Low grade squamous intraepithelial lesions (LSIL)
  - High grade squamous intraepithelial lesions (HSIL)

- **Cervical intraepithelial neoplasia (CIN).**

**Histopathology**
- CIN 1 (equivalent to LSIL)
- CIN 2-3 (equivalent to HSIL)
- Invasive cancer
Effects of contraception

- **Barrier methods**
  - Protect from HPV infection and cervical neoplasia

- **Oral contraceptives**
  - Increase risk

- **Injectable contraceptives**
  - Probably no effect?
Barrier contraception and cervical cancer

<table>
<thead>
<tr>
<th>Method</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm</td>
<td>0.67</td>
<td>0.36–1.24</td>
</tr>
<tr>
<td>Foam/Jelly</td>
<td>0.44</td>
<td>0.26–0.74</td>
</tr>
<tr>
<td>Condoms</td>
<td>0.53</td>
<td>0.31–0.89</td>
</tr>
</tbody>
</table>

## OC use and risks of HPV infection

<table>
<thead>
<tr>
<th>Ever use OC</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.1</td>
<td>1.4 to 8.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years of OC use</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1 to 4</td>
<td>2.8</td>
<td>1.1 to 7.7</td>
</tr>
<tr>
<td>5 to 9</td>
<td>2.6</td>
<td>1.0 to 7.5</td>
</tr>
<tr>
<td>10+</td>
<td>5.8</td>
<td>2.0 to 18.0</td>
</tr>
</tbody>
</table>

Possible confounding by sexual behaviors, or effect of OCs?
Confounding of OC use and Cervical Cancer

- Problem of confounding due to sexual behavior (OC users have higher risk behaviors)
- Protective effects of barrier methods (need to adjust for barrier use, or exclude barrier users in analysis)
- Increased case detection (more screening of OC users)
- Smoking (OC users more likely to smoke)
**OC Use and Cervical Cancer**  
IARC Multicenter Case-Control Study  
(Moreno V Lancet 2002;359:1085-92)

HPV-positive women: (minimize bias due to differential sexual behaviors). 1561 cases, 1916 controls

<table>
<thead>
<tr>
<th>OC use</th>
<th>OR Cervical cancer</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>0.73</td>
<td>(0.52-1.03)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>2.82</td>
<td>(1.46-5.42)</td>
</tr>
<tr>
<td>10+ years</td>
<td>4.03</td>
<td>(2.09-8.02)</td>
</tr>
</tbody>
</table>
Prospective study of oral contraceptives and cervical cancer

## Age at first OC use and cervical cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Age at first use</th>
<th>Odds ratio (non-users = 1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parazinni et al. 1990</td>
<td>&lt;25</td>
<td>2.41</td>
</tr>
<tr>
<td></td>
<td>25 to 29</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>1.23</td>
</tr>
<tr>
<td>WHO 1993</td>
<td>&lt;25</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>25 to 29</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>30 to 34</td>
<td>1.218</td>
</tr>
<tr>
<td></td>
<td>35+</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Parazinni et al: adjusted for age, no. of pregnancies, and no. of pap smears.

WHO: adjusted for age, education, calendar year, parity, no. of partners, smoking, and no. of pap smears.
Summary OC and Cervical Cancer

- Cervical cancer risk increased with:
  - Longer duration of OC use
  - Recency of OC use
  - Earlier age at first use

- HPV infection increased with OC use

- Residual confounding by sexual behaviors and screening may exaggerate risk estimates?

- Probable promotion effect (estrogen increases HPV replication)

- Developed countries with screening this not a major public health problem

- In developing countries with high rates of cervical cancer and poor screening, this could be a problem
# DMPA use and Cervical Cancer Case-control studies

<table>
<thead>
<tr>
<th>Study/Site</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>1.2</td>
</tr>
<tr>
<td>Mexico</td>
<td>1.7</td>
</tr>
<tr>
<td>Kenya</td>
<td>0.6</td>
</tr>
<tr>
<td>Thailand</td>
<td>1.2</td>
</tr>
<tr>
<td>Oberle, Costa Rica</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Probably no overall increased risk
Other HPV Related Reproductive Tract Cancers

Vulval cancers

Anal cancers (particularly homosexual males)

Penile cancer (particularly homosexual males)

Laryngeal papilloma in children (infection mainly during delivery)
Diethylstilbesterol (DES) and Cancer

- DES was used for prevention of threatened abortion and preterm birth in 1950s
- **Female Effects:**
  - Defects in development of urogenital tract
  - Women exposed to DES in utero developed clear cell carcinoma (CCA) of the vagina in adolescence & young adulthood
  - Risk of CCA in DES exposed = 40.7 (13.1-126.2)
  - No increase in other cancers
    - (Hatch *JAMA* 1998;280:630-34)
- **Male Effects:**
  - Possible increased risk of testicular cancer
Liver Cancer

• Liver cancer common in developing countries, rare in industrialized countries

• Etiologic factors
  – Hepatitis B
  – Alflatoxin (fungus)
  – Alcohol

• Risk ↑ with number of pregnancies
  – 3-4 births; RR = 1.9
  – 5-6 births; RR = 2.9
  – 7+ births; RR = 3.8
Hormonal Contraception and Liver Cancer

• Older high estrogen dose pills caused benign Hepatocellular Adenomas

• Several small case-control studies find increased risks of 1.5-20.1 for OC use and Hepatocellular Carcinomas

• Need for more studies in developing countries where liver cancer is common
OC use and Pituitary Carcinomas

• Early studies suggested OC use increased pituitary adenomas
• Due to reverse causality
  – Women with adenomas have amenorrhea or cycle irregularity
  – OC prescribed to control menstrual dysfunction
  – OC use for birth control OR = 1.3
  – OC use for cycle regulation OR = 7.7
Male Cancers Related to Reproduction

Prostate cancer
Testicular cancer
Prostate Cancer

• Prostate cancer is common (30% men > 50 have histologic cancers)
• Incidence ~ 100/100,000
• Mortality comparable to breast cancer (~ 40,000 deaths/year in US)
• 5-year survival 75% localized disease, 55% regional spread, 15% if metastatic
• Between 1973-1991; incidence increased 40% and mortality increased by 24%, more recent declines
• Increased incidence in part due to screening
Age-specific incidence of prostate cancer, Sweden

US Death Rates from Prostate Cancer (SEER data)
Geographic Epidemiology

Age-standardized incidence (per 100,000)

Hormones and prostate cancer
(Platz 2006)

• Testosterone decreases with age inversely with prostate cancer incidence

• Men with higher testosterone have less high grade cancer (OR = 0.21 p <0.009), but more low grade cancer (OR = 2.62 p<0.007).

• Testosterone receptor gene on X chromosome has a repeat of CAG sequences. Men with fewer CAG repeats <19 vs 25+ have higher risk of invasive cancer (OR = 1.9, p=0.0002), but no effect on low grade disease

• High testosterone and more receptors appear to protect against high grade cancer, but may increase the risk of low grade cancer
Sexual Activity and STDs and prostate cancer

- Meta-analysis (Dennis & Dawson, *Epidemiol* 2002;13:72)
  - STD history RR = 1.4 (1.2-1.7)
  - Sexual frequency (3/week) RR = 1.2 (1.1-1.3)
  - Number sex life time partners (> 20) RR = 1.2 (1.1-1.3)
- Possible cofactor effect by increased inflammation?
Screening for Prostate Cancer

• **Screening**
  – Prostate Specific Antigen (PSA)
  – Biopsy
  – Transrectal Ultrasound (TRUS)

• **PSA** used since 1987, but never evaluated by randomized trials

• > 20,000/100,000 men >65 have PSA tests

• PSA+ → punch biopsy → radical prostatectomy

• **Prostatectomy risks:**
  – mortality
  – incontinence (8.9%),
  – impotence (59.9%). Increase with age.
## PSA levels and prostate cancer

<table>
<thead>
<tr>
<th>PSA range</th>
<th>Positive biopsies (%)</th>
<th>Biopsies showing aggressive cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.5</td>
<td>7.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>0.6-1.0</td>
<td>10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>17.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>25.0</td>
<td>5.0</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>25.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Thompson IM. Univ Texas Hlth Sci Center 2005
Treatment of prostate cancer

• Localized cancers:
  – US preference for radical prostatectomy,
  – Europeans “watchful waiting”

• Randomized trial of prostatectomy vs watchful waiting (not PSA diagnosis)
  – Mortality due to prostate cancer 4.6% in prostatectomy vs 8.9% with watchful waiting (HR = 0.5, CI 0.3-0.9)
  – All cause mortality HR = 0.8 (0.6-1.2)
  – Erectile dysfunction 80% vs 45%, incontinence 49% vs 21%

Holmberg NEJM 2002;347:781, Steineck NEJM 2002;347:790
Prostatic cancer incidence and mortality in US and UK

Age-adjusted average annual rates per 100,000

- US Incidence
- UK incidence
- US mortality
- UK mortality

Vasectomy and Prostate Cancer

• Some but not all studies suggest an association between vasectomy and prostatic cancer
• Hypothesis that vasectomy reduces prostatic secretions increasing concentration of carcinogens?
• Meta-analysis RR = 1.0
• **Problems of Confounding and bias:**
  – **Self-selection:** men with vasectomy more health conscious, more likely to be screened for prostatic cancer
  – **Medical detection:** Men with vasectomy more likely to see a urologist, and be screened for prostatic cancer
Testicular Cancer

- Testicular cancer peak incidence ages 15-44 years
- Testicular cancer has increased in males 15-44 years in all countries with long term registry data
- Unlikely to be a surveillance bias due to ease of diagnosis
Testicular Cancer

- Increase in both seminomas and germ cell tumors
- No change in incidence in men > 50 years
- No change in mortality rates
Incidence of testicular cancer US (SEER data)
Incidence of testicular cancer (2002 estimates)

Data Source: Figure 1.2 Age-standardised (World) incidence rates for testicular cancer, world regions, 2002 estimates. Cancer Research UK. Accessed April 19, 2007.
Risk factors for prostate cancer

- **Testicular damage before puberty**
  - Undescended testis uncorrected before age 10
  - Unilateral undescended testes, risks increased in the contralateral testis
  - Inguinal hernia at young age (<15 years)
  - Pre-existing infertility (e.g. mumps, orchitis) RR = 1.6 (1.3-1.9)
  - DES exposure in utero RR = 3.1 (0.7-22.0)

- Early age at puberty

- Sedentary lifestyle
Biology of Testicular Damage and Cancer

- Testicular damage $\rightarrow$ reduced testosterone $\rightarrow$ increased FSH

- Testicular cancer is associated with an increase in pituitary gonadotrophins particularly FSH inducing germ cell production (mitosis)

- Rapid mitosis increases risk of mutation
Etiologic Mechanism of Testicular Carcinogenesis

- Testis with Damaged Germinal Epithelium (Atrophic Testis)
  - Gonadotropic Hormonal Drive
  - Mitogenesis
  - Mutagenesis
  - Germ Cell Tumor

- External Insult
- Maternal-Perinatal Factors (Maldescent)
- Conception

Normal Testis

RTD Oliver 1990, 1996
Testicular Cancer as a Sentinel Disease Marker

Testicular cancer possible sentinel disease marker for male reproductive hazards

- Monitor trends in men 15-45
- Easy to diagnose
- Risk is associated with testicular damage, *in utero* or before puberty
Rates of undescended testes (Cryptorchidism) have increased over time
- UK birth cohort 1952 = 1.4%; 1977 = 2.9%
Could be a surveillance bias because of more careful monitoring of boys and early surgical correction
Risk increased with preterm birth
Causes male infertility due to increased temperature of testes
## Undescended testis and maternal smoking

<table>
<thead>
<tr>
<th>Nicotine Content</th>
<th>No. Cases</th>
<th>No. Boys</th>
<th>1 to 9 RR (95% CI)</th>
<th>10 to 19 RR (95% CI)</th>
<th>20+ RR (95% CI)</th>
<th>Adjusted for Daily Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>9</td>
<td>321</td>
<td>0.3 (0.1-1.0)</td>
<td>1.3 (0.6-3.0)</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>43</td>
<td>834</td>
<td>1.0 (0.6-1.6)</td>
<td>1.5 (1.0-2.3)</td>
<td></td>
<td>1.9 (0.9-3.9)</td>
</tr>
<tr>
<td>High</td>
<td>47</td>
<td>781</td>
<td>1.8 (1.2-2.7)</td>
<td>0.8 (0.5-1.5)</td>
<td>3.7 (1.4-9.8)</td>
<td>2.2 (1.0-4.5)</td>
</tr>
</tbody>
</table>

Adjusted for Nicotine Content

1.0 1.0 (0.7-1.5) 1.4 (0.5-3.6)