Cervical Cancer Prevention
In 2013:
Colposcopy and Therapy

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Cervical Cancer Facts
Early 21st Century Stats

Cervical cancer was #1 killer 60 years ago (US)
Cervical cancer accounts for 6% of all cancers in women
Over 65,000 new cases of CIS every year
400,000 Cervical cancer incidence worldwide
– Second most common malignancy
Who Gets Invasive Cervical Cancer?

Optimal Screening Population (70-80%)

Sub-Optimal Screening Population (20-30%)

“Low but not No” Risk Pool

“High” Risk Pool

Cervical Cancer

New cases occur in screened and unscreened

Unscreened less likely to return after outreach: may only have one or two chances to detect precursor or early cancer during their lifetime.

Must ask: Should screening be same for low and high risk patient?

Must ask:
– What is the goal of screening?
– Definition of a precursor “target” lesion.
– Prevalence rate of disease, treatable precursor

Recognize that this is related to a sexually transmitted agent / Human Papilloma Virus.
Overview of Cervical Cancer

Why cervical cancer develops:
- Exposure to agent(s) that promotes development of pre-cancer - probably co-carcinogens
  - HPV - some strains carcinogenic
  - Smoking: oxidative DNA damage
  - Diet: lack of anti-oxidants, vitamin E
  - Estrogen/OCP: length of exposure

Immune Status of Patient
- In the Screened Population:
  - Pre-cursor lesion not found and treated
    - False negative screening test

Risk of Cervical Cancer
A Moving Target

<table>
<thead>
<tr>
<th>Early Adolescence</th>
<th>*GENETIC PREDISPOSITION</th>
<th>*ENVIRONMENTAL FACTORS</th>
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<tbody>
<tr>
<td>Promoters</td>
<td>*INTERCOURSE</td>
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<td></td>
<td>*SMOKING</td>
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<td></td>
<td>*INFECTION</td>
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<td>HPV 16, 18 etc</td>
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<tr>
<td>Inducers</td>
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<tr>
<td>Transformation of the Cervix</td>
<td>*SQUAMOUS METAPLASIA</td>
<td>REPRODUCTIVE AGE</td>
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<td>PROGRESSION</td>
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<tr>
<td>CIN I</td>
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<td>INVASIVE CANCER</td>
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<tr>
<td>CIN II</td>
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<td>CIN III/CA IN SITU</td>
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REGRESSION
Prevention Paradigms

Tertiary Prevention: too late to prevent invasive cancer, detect early and treat to effect a cure. NEED ACCESS, TIMELY CARE.

Primary Prevention: eliminate risk of developing precursors by lifestyle modification or vaccination.

WE ARE NOT VACCINATING IN OB/GYN THE KEY COHORT.

Secondary Prevention: Early definition of the patient “at-risk” who harbors preinvasive cervical neoplasia, with appropriate follow up or treatment. Screening requires infrastructure, patient access and physician expertise. Screening can be organized or opportunistic.

WE ARE WASTING ACCESS, AND $ IN RE-TESTING AND LATE TREATMENT OF MISSED CASES

Risk Assessment through Screening (Secondary Prevention)

Conventional Cervical Cytology (Papanicolaou Smear)

– Easily performed with spatula and brush
– Delay in evaluation and reporting
– Subject to Error: sampling, transfer, fixation, transport, reading, reporting.
– Error may be random (can be overcome with repeated testing) or non-random (error inherent in procedure or patient and may not be overcome)
Cervical Cancer Screening Accuracy
Biopsy Based Comparison to Pap Test

Sensitivity: 35-51% (Fahey and ACHPR)
Specificity: 90% or better
Positive and Negative Predictive Values are sub-optimal with a single pap test.
Has led to Evidence Based Guidelines which describe “low risk” woman as having had 3 consecutive negative screening tests. Flawed: assumed lower false negative rate.
Assumed that Error of Pap Smear was “non-random” event that could be overcome with repetition.

Papanicolaou Smear:
Advantages and Limitations

Reduced Cervical Cancer Incidence Rate and Deaths by 80% after it was introduced (first 20 years).
Average health plan screens ~80-85% of its population in US annually. KP close to 90%
Reduction rate plateau in early 1980’s.
15,000 new cases in U.S., 4-5000 deaths per year in the mid 1980’s…now 12,000 new cases…better screening rates may be responsible, not new technology.
15-20 year old in-vitro technologies have not yet proven to reduce the incidence or death rate from the disease.

– Sawaya, NEJM 2008: Liquid based Pap smear value?
What Do We Get for Our Pap Smear Investment?

Most cervical cancer NOT selected out with Pap smear screening system:
- Symptoms
- Visualized lesions
80-100 M women screened (70% of 130-150M at risk).

4-5 million ASCUS Pap, 2/3 eventually get colposcopy about half get CIN discovered.
- yield 1-1.5M CIN cases/yr

2.5 million LGSIL+ Pap, about 80% get CIN discovered.
- yield 1.5M CIN cases/yr

3-3.5 million CIN cases/yr discovered from cohort of 6 million new referrals to colposcopy. This is conservative estimate (low ASCUS rate).

About 40-50% of CIN 1 and 20% of CIN2+ lesions remain undiagnosed in the screened population. Are we getting our money’s worth?

What it Feels Like
Are You Prepared to Find Disease at an Earlier Stage?

Early detection and an acceptable therapy

Population with precursors are young and in the reproductive age group

Low Grade CIN has been reduced to a “transient infection”.
- Regression rates exceed 60-80% in most series
- Obligated to document the regression with cost
- 20-40% persist or progress – clone of aneuploid cells emerge.

What else is preventing you from treating early stage CIN? …discussion

Is HPV an Anachronism? STI or Cancer Precursor?

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Anachronism

1. The representation of someone as existing or something as happening in other than chronological, proper, or historical order.

**2. One that is out of its proper or chronological order, especially a person or practice that belongs to an earlier time.

(Our current way of thinking regarding HPV infection, its relationship to CIN, and prevention of cervical cancer is inconsistent with an effective earlier lesson from medical history)

Lessons From History

Is there a precursor stage where death is preventable? Morbidity preventable?
Is there an acceptable treatment? Risks vs. benefits?
Who and when to treat with what evidence to base our decision?
Does finding earliest disease = cost effectiveness or just increase costs?
Lessons From History

Is there a precursor stage where death is preventable? Morbidity preventable?
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Tuberculosis Screening
Old Approach

Chest x-ray all adults every year to find active tuberculosis.

Treat with 3 drugs with potential side effects.

Isolate in sanitorium.
**Tuberculosis Screening**

**New Approach (1970’s) (?)**

PPD skin test to find those *infected*: tied to *school entry, employment, universal screen.*

X-ray only positive skin tests

Rx for active disease, and prophylaxis for those with “just infection” (potential pre-disease).

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**Goals of Screening**

**History of Screening & Tuberculosis**

<table>
<thead>
<tr>
<th>Healthy</th>
<th>Infected with TB</th>
<th>Immune recognition</th>
<th>Inactive TB non-infectious</th>
<th>Reactivate Early infiltration</th>
<th>Active TB Cavitary TB</th>
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Many (including Radiologists) warned: “It will break the bank”….too many people needlessly worked up……More than 95% of “infected” will NEVER get active TB! INH can be deadly!
The result of PPD screening:

Active TB in non HIV “native” US population fell to nearly zero over 15 years.
Dramatic / Successful Secondary Prevention Model.
Closed all TB sanitoriums
Cost of TB screening/treatment program fell to 20% of pre-1970 numbers.

Goals of Cervical Screening

Find invasive cancer
Find true precursor lesion(s)
Triage appropriately using
– Clinical test/historical information
– Resources available
Confirm (reliably) absence of disease
HPV and Screening

HPV in most cervical cancers: RR = 30-40. High HPV prevalence in most settings, but transient in most women under age 30. Goal is to find patients with neoplasm with persistent oncogenic high risk HPV. Assumes all HPV infected neoplasms are detectable from cytological sample. Assumption challenged by new data.

Natural History of Cervical Cancer

<table>
<thead>
<tr>
<th>Normal</th>
<th>HPV Infection</th>
<th>Low grade</th>
<th>High grade</th>
<th>CIS</th>
<th>Cancer</th>
</tr>
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<tr>
<td>Pap smear (+)</td>
<td>80%+</td>
<td>100%</td>
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Current discovery goal

- Pap sensitivity for all lesions: 40% - 50%
- Pap sensitivity for high grade: 60% - 80%
- Pap sensitivity for cancer: 85% - 100%
“Old Approach”

Limitations of test push desired discovery to right. Ends justify means?
Limitations of test dictates “desired” algorithms
Limitations of test influence us to view “high grade disease” as only important precursor stage.

Goals of Screening – Move Detection Earlier . . .

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<td>PPD (+) 98%</td>
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Chest x-ray indicates disease <30%

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<td>Pap (+) ~100%</td>
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| HPV testing (+) 90% |
Natural History of CIN I

Definition by colpo/bx or cytology will bias results.
Biopsy can change natural history.
Serves as resevoir for aneuploid clone to progress to CIN 2+.
Although regression documented, up to 1/3 persist or progress.
Use of molecular markers in CIN I may assist in selecting higher risk cohort.

Barriers to the Paradigm Shift towards early detection.

Definition of “true” cancer precursor as CIN 2+ is limiting treatment candidates.
Aggressive nature of treatment modalities in 21st century: majority are ablative or excisional.
Distribution of LG CIN to predominantly younger population: medical-legal fears, future fertility risks.
Are fears overblown?
Lack of consensus on treatment for disease <CIN II.
Lack of treatments with a minor side effect profile seen as inappropriate for CIN I.
When will the Paradigm Shift to Earliest Detection and Treatment?

Treatment modalities are available, safe and benign.

Treatments effectively alter the natural history: improve prognosis (akin to TB prophylaxis).

Treatments are cost effective.

Treatments are either clinician dependent or *patient applied.

Primary prevention including vaccines may be pre-emptive.

HPV and TB morbidity and mortality

More prevalent than TB exposure.

Absolute risk of death lower than TB.

Uncertain prognosis in absence of coincident cervical dysplasia.

– As evidenced by abnl/atypical pap
– As evidenced by visual lesion
– As evidence by proven cervical biopsy.
Non Destructive Treatments for Low Grade Precursors under Study.

Immune modulation agents;
- Topical Immune Modulating Agents: Imiquimod and analogs.
- Biopsy as treatment

Topical Carotenoids
Oral Antioxidants, Folic Acid, Beta Carotene, Vitamin C.
Beta Mannan: Aloe Vera, catechins
Cytokine therapy: Multikine
Therapeutic Vaccine

Conclusion: Accepting the Anachronism

Ability to find all CIN limited with conventional Pap smear testing. Sensitive for high grade CIN so our clinical guideline “structure” paralleled this limited “function”.
Adjuncts such as HPV testing (in-vitro) and visualization (in-vivo) move the detection point towards the earliest precursor. Perceived benefit of this discovery is minimized until early precursor paradigm shift occurs.
Current clinical, financial, and medico-legal “perceived” risks of treatment are preventing moving target toward any CIN from high grade CIN.
Like any capital project, start up cost to find and treat precursors will be offset in long term by reduced prevalence and new cases.
Paradigms need to merge

Gyn Pathology
Search for the “True” Cancer Precursor: CIN2+
Natural History of CIN.
Diagnosis and Prognosis of CIN lesion to guide therapy.
Importance of HPV as oncogenic factor.

Public Health
Exposure and disease prevalence.
Avoiding epidemics.
Willingness to view cervical ca as STI.
*Treatment of all infected patients.

Treat CIN 1 in 2008?
...tell me more

In who?
– Age, ethnicity, screening history, co-morbidity, HPV type, lesion size, correlation with cytology…?

When and Why - What is your definition of “persistent”?


With What?........
– That is the Key issue…..
Treatment Modalities

Colposcopy seen as a risk for psychological fears and harms
Harm of possible over treatment leading to reproductive complications,
Cx Insufficiency and Stenosis
Most are destructive therapies using thermal, freezing, laser or caustic therapy

Treatment of CIN or Adenoca In situ in 2013

CIN 3 or microinvasive
AIS
DX Microinvasive disease is usually a benefit of the excision
If ECC is positive, consider cold knife conization for clear margins
LEEP is electrosurgery with thermal injury at margins; less interpretable for clearance
Evaluation of endocervix with ECC or tophat
LEEP Procedure
Loop Electrical Excision Procedure

Cone Biopsy

More costly and longer procedure that requires some anesthesia
Blood loss risk; sutures and injection of vasopressin used
Indicated for high grade endocervical disease to obtain non-fulgurated margins for accurate interpretation.
May be tailored to the shape of the cervix.
Benefits and Drawbacks of Cryotherapy

Easily performed in the office
Effective for all grades of dysplasia, esp. CIN 1 that persists in lower risk setting, and CIN 2.
No diagnostic sample obtained
3-5 mm iceball, single vs. double freeze, concomitant inflammation may lead to cervical stenosis
Endocervix/Exocervix Cryotherapy

Benefits and Drawbacks of Laser Therapy

Targeted to the transformation zone and helpful when the TZ is large
Shallow depth of vaporization and presumed less scarring and trauma to the cervix
Multifocal disease: cervix, vagina, vulva
Vaporization does not provide a specimen unless the laser is intentionally used to excise vs. ablate the lesion(s).
Laser Conization and VIN Therapy