2019 Scientific Retreat
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Discovery World Pavilion

Together, Taking on Cancer’s Toughest Challenges

NOVEL OPPORTUNITIES FOR ANAL CANCER SCREENING AMONG MEN

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FINANCIAL DISCLOSURES

National Institutes of Health
National Institute for Allergy and Infectious Disease
National Cancer Institute

Medical College of Wisconsin
OBJECTIVES

Review HPV and HPV-associated disease.

Discuss novel opportunities for anal cancer screening.
HUMAN PAPILLOMAVIRUSES ARE COMMON

• HPV is common, but transient.
  • E.g., 82% 2-year period prevalence in heterosexual couples

• Low-risk types may cause anogenital condylomas (e.g., 6 & 11).

• More than a dozen cause cancers like cervical cancer, anal cancer, and oral cavity cancer (e.g., 16 & 18).

• Globally, HPV is responsible for about 5% of all cancers.
CERVICAL CANCER INCIDENCE IS LOW IN HIGH-INCOME COUNTRIES

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, all ages

USA 6.5
Canada 5.7
THE LEGACY OF EXPENSIVE CERVICAL CANCER SCREENING

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, all ages

Nigeria 27.2
Kenya 33.8
Tanzania 59.1
Zimbabwe 62.3
AGE-ADJUSTED CERVICAL CANCER INCIDENCE IN WISCONSIN, 2011-2015

https://gis.cdc.gov/Cancer/USCS/DataViz.html
ANAL CANCER INCIDENCE IS INCREASING


National Cancer Institute, SEER, 2018
US ANNUAL INCIDENCE OF INVASIVE ANAL CANCER

Joseph et al., 2008; Cress et al., 2003, Frisch, 2003; Daling et al., 1982; Chin-Hong et al., 2002; National Cancer Institute, SEER, 2018
## Outcome of Anal Cancer with Squamous Tumor Histology by AJCC Stage Group

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>71.4</td>
</tr>
<tr>
<td>II</td>
<td>63.5</td>
</tr>
<tr>
<td>IIIA</td>
<td>48.1</td>
</tr>
<tr>
<td>IIIIB</td>
<td>43.2</td>
</tr>
<tr>
<td>IV</td>
<td>20.9</td>
</tr>
</tbody>
</table>

Source: National Cancer Database; Cases diagnosed 1998-1999 n=3598
SURGICAL EXCISION FOR EARLY STAGE ANAL CANAL CANCERS IS AN EFFECTIVE STRATEGY

66 French women and men with early invasive anal cancer (≤1 cm tumors);
5-year disease-specific survival was 100%

Ortholan et al., 2005

15 PLWH with T1N0M0 cancer of the anal verge (below the dentate line).
Local excision of tumor with no complications or need of adjuvant therapy.
4-year disease-specific survival was 100%

Alfa-Wali et al., 2016
MEAN ANAL CANAL TUMOR SIZE AT PRESENTATION IN TEXAS IS 3.6 CM IN DIAMETER

Presenting Tumor Size, n = 1,622

- > 5 cm: 18%
- < 1 cm: 13%
- 1 - 1.99 cm: 20%
- 2 - 5 cm: 49%
NATURAL HISTORY OF ANAL HPV INFECTION

Uninfected anal canal → HPV-infected anal canal and persistence → Precancer (lesions) → Cancer

Screen here for anal precancers?
Or screen here for early anal cancer?
Or both?

Adapted from Schiffman, M., & Wentzensen, N., 2010
PREVENT ANAL CANCER STUDY – TWO APPROACHES

Uninfected anal canal → HPV-infected anal canal and persistence → Precancer (lesions) → Cancer

Prevent Anal Cancer Study (PAC Study)

Self-swabbing
Palpation
PAC STUDY GOALS

• Both PAC studies
  • seek to detect cancer earlier when it is more treatable
  • address barriers to screening including embarrassment, cost, and lack of health care infrastructure
  • target communities at highest risk for anal cancer
PREVENT ANAL CANCER STUDY – TWO APPROACHES

Uninfected anal canal → Infection → HPV-infected anal canal and persistence → Progression → Precancer (lesions) → Invasion → Cancer

Prevent Anal Cancer Study (PAC Study)

Self-swabbing, Palpation
PAC SELF-SWABBING STUDY ASSESSES COMPLIANCE AND MOLECULAR MARKERS

Determine compliance with annual anal HPV DNA specimen collection and high-resolution anoscopy.
400 Milwaukee MSM and transwomen randomized to two arms
  • 200 in self-swabbing arm at home
  • 200 in clinician-swabbing arm at a clinic

Determine factors associated with annual screening compliance.
• Modifiable factors: embarrassment, cost, perceived susceptibility
• Non-modifiable factors: age, race, ethnicity

Assess the performance of two molecular markers: HPV DNA persistence and host/viral DNA methylation
PERSISTENCE BIOMARKER PAC SELF-SWAB STUDY

Uninfected anal canal → infection → HPV-infected anal canal and persistence

Baseline swabbing → 12 month swabbing

HPV 16 → HPV 16

progression → Precancer (lesions)

invasion → Cancer

Screen with high-resolution anoscopy
Methylation - addition or removal of a methyl groups on DNA. These changes are epigenetic in nature and can result in the differential expression of proteins.

Lorincz et al., 2017:

Host DNA EPB41L3 (a tumor suppressor gene) + viral DNA methylation predicts high-grade anal canal lesions and cancer.
Methylation scores increase as dysplastic severity increases.

For distinguishing precancer/cancer from benign conditions:

**Sensitivity** 90.6% (95% CI 82.8, 96.9)

**Specificity** 50.7% (95% CI 39.7, 61.6)

**AUC** 82% (95% CI 75%-89%)

Lorincz et al., 2017
METHYLATION – PAC SELF-SWAB STUDY

Uninfected anal canal → infection → HPV-infected anal canal and persistence → progression → Precancer (lesions) → invasion → Cancer

- Baseline swabbing
- HPV DNA + Host DNA methylation

- 12 month swabbing
- HPV DNA + Host DNA methylation

Screen with high-resolution anoscopy
CONCERNS ABOUT A CERVICAL CANCER MODEL FOR ANAL CANCER SCREENING

• It’s expensive
• There is no proven treatment for anal precancerous lesions
• Anal precancerous lesions often regress spontaneously
• Infrastructure for anal cancer screening is poor
PREVENT ANAL CANCER STUDY – TWO APPROACHES

Uninfected anal canal → infection → HPV-infected anal canal and persistence → progression → Precancer (lesions) → invasion → Cancer

Prevent Anal Cancer Study (PAC Study)

Self-swabbing → Palpation
PAC PALPATION STUDY ASSESSES THE ABILITY OF PERSONS TO RECOGNIZE AN ANAL ABNORMALITY

Since most anal cancers have a tumor that can be felt with a finger...
Can MSM and transwomen palpate an anal abnormality?

400 Chicago and 400 Houston participants
PRELIMINARY DATA

• Recruited 200 MSM (61% HIV+; 43% Black; 18% Latino).

• Taught them how to palpate the anal canal.

• Nurse practitioner examined the men’s anal canal/perianal region.

• Men examined their own anal canal/perianal region for an abnormality.
Agreement, 93.0%

False positive, 5.5%
False negative, 1.5%

n=200

The NP found 12 abnormalities and participants found 9 of these.

96% said checking their own anal canal for something abnormal was acceptable.

About one-half said they would prefer to exam themselves rather than get a digital ano-rectal exam from a doctor.

Nyitray et al., 2018
SELF-ANAL EXAMS MAY ADDRESS

• LMIC lack of resources for screening and treatment

• Detection of anal condyloma (warts)

• Lack of knowledge about anal anatomy and increase a sense of self-competency about one’s own body

• Increased self-competence supports self-assurance and possibly increased communication with clinicians
WHY MIGHT SELF-ANAL EXAMS NOT SUCCEED?

• Self-anal exam may be physically too difficult.

• They may be unacceptable to some people.

• Some persons may prefer a doctor’s care.

• Persons may not see a clinician after detecting an abnormality.
FROM FEASIBILITY TO ACCURACY

<table>
<thead>
<tr>
<th>% agreement</th>
<th>sensitivity</th>
<th>specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93</td>
<td>0.75</td>
<td>0.94</td>
<td>0.45</td>
<td>0.98</td>
</tr>
<tr>
<td>0.91</td>
<td>0.71</td>
<td>0.92</td>
<td>0.31</td>
<td>0.99</td>
</tr>
<tr>
<td>0.98</td>
<td>0.80</td>
<td>1.00</td>
<td>1.00</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Legend: All, SAE, PAE
COMMENCE WITH A PUBLIC HEALTH CANCER SCREENING PROGRAM FOR ANAL CANCER?

1) Condition should be an important health problem.
2) There should be an accepted treatment.
3) The natural history of the disease should be understood.
4) There should be a recognizable latent or early symptomatic stage.
5) There should be a suitable test or examination.
6) The test should be acceptable to the population.
7) There should be agreement on whom to treat.
8) Facilities for diagnosis and treatment are available.
9) Cost-effectiveness should be established.
10) There should be compliance with repeat screening.

TAKE AWAY

• Anal cancer is rare overall, but common among MSM, especially MSM with HIV
• There are no uniform guidelines for anal cancer screening
• As guidelines are developed, we should be attentive to the utility of those guidelines in low, middle, and high-resource settings.
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If you want to go fast, go alone.

If you want to go far, go together.

– African Proverb

THANK YOU