Cancer Researchers for Today and Tomorrow: Precision Medicine in Cancer Prevention

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The views expressed are my own and do not necessarily reflect those of NCI/NIH
Outline of Presentation

• Precision medicine is relevant to cancer prevention & screening
• HPV-based screening: an example of precision medicine in screening
• The HPV vaccine: an example of molecularly targeted prevention
Disclosures

- The National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor of this technology.

- The NIH has licensed the L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.

- *I will discuss potential off-label use of the FDA-approved vaccines.*
Some Professional Highlights

• Education: Non-science major as undergraduate; medical school (MD); internal medicine; dermatology

• Research training: Mouse retroviruses, NIH (“yellow beret”); on-the-job

• Principal investigator, intramural program, NCI/NIH
  – Advantages: long-term stable resources; retrospective review; collaborations strongly encouraged; individual & team science; easy to go from “bench to bedside”
  – Disadvantages: difficult to have a large lab
  – My main research areas: HPV; growth regulatory genes; molecular aspects of cancer pathogenesis

• Positions: Principal investigator; Lab Chief; Deputy Director, NCI intramural program; Deputy Director, NCI
Precision (personalized) Medicine

• Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease

• Conventional wisdom: Treatment is the main focus of precision medicine
Precision Medicine in Prevention

• The genetic and epigenetic changes in normal and premalignant tissues are less complex than in cancer

• Therefore, if you like targeted interventions for the treatment of cancer, you will love targeted interventions for the prevention of cancer
Targeted Interventions for Cancer Treatment

• Therapeutic agents that target a specific molecular abnormality in cancer have several shortcomings

• The abnormality may be present in only some of the cancers; e.g., EGFR mutations in lung adenocarcinoma

• Only some patients with the molecular abnormality may respond to the targeted intervention

• Even among those patients who do respond, many become resistant to the treatment, attributable to secondary mutation of the target or to bypass genetic/epigenetic changes
Primary & Secondary Prevention

Primary Prevention: Vaccination Sunscreen

Secondary Prevention: Screening HCV antiviral

Treatment (tertiary prevention)

Normal $\rightarrow$ Pre-cancer $\rightarrow$ Cancer
Targeted Interventions: Primary Prevention

• Primary prevention can target the cause of cancer; e.g., HBV vaccination, HPV vaccination

• *Primary prevention can potentially target all cases attributable to the cause*
  
  – Hepatocellular cancer attributable to HBV infection is heterogeneous; it is difficult to imagine treating all of these cancer cases with a single agent
  
  – HBV infection is the necessary cause of these cancers and can be targeted for prevention by a single agent

• Primary prevention rarely results in resistance
Cancer Screening: Secondary Prevention

• Why are screening for colorectal cancer and for cervical cancer more effective compared with screening for breast, prostate, and lung cancer?

• Doug’s answer: because in colorectal and cervical cancer, there are widely accepted pre-malignant lesions, which are the main focus of screening in these cancer types, leading to substantial reductions in incidence and mortality

• For breast, prostate, and lung cancer, screening is for early cancer, leading to an increase in incidence (because of screening) and more limited reductions in mortality

• Doug’s implication: We need more research to identify and validate pre-malignant lesions in cancer (not just in those cancers for which we already have screening programs)

• It might be possible to use animal models of cancer to study prevention
Cancer Screening: From Pattern Recognition to Molecular Diagnosis

• The primary (initial) *screening tests for breast and lung cancer* (mammography, helical CT) depend on empiric pattern recognition

• The primary *screening test for prostate cancer* (PSA) is a biochemical assay not directly related to cancer

• Primary *screening tests for colorectal cancer* have either been an indirect chemical test (fetal occult blood) or pattern recognition (sigmoidoscopy, colonoscopy); a new molecular test based on hemoglobin plus molecular abnormalities (K-ras + methylation of NDRG4 and BMP3) found in colorectal lesions

• Primary *screening tests for cervical cancer* have gone from empiric pattern recognition (pap smear) to HPV-based testing
Cervical Cancer is Attributable to Multiple HPV Types; HPV16 Predominates

Adapted from Munoz et al, Int J Cancer 111: 278-85, 2004
Cervical cancer rates (USA): Decreasing squamous cell cancer, stable adenocarcinoma

Squamous cell: blacks
Squamous cell: whites

Adenocarcinoma: whites
Adenocarcinoma: blacks
Adenosquamous: blacks & whites

HPV testing is more sensitive than cytology

Pooled cervical cancer incidence from 4 controlled trials of cytology (control arm) vs. HPV testing (experimental arm): POBaSCAM, NTCC, ARTISTIC, and Swedescreeen

**HPV testing reduces adenocarcinoma**
More efficiently than does cytology

* Ratio of incidence with HPV testing vs. incidence with cytology

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Pooled rate ratio* (95% CI)</th>
<th>$I^2$ (p for heterogeneity between studies)</th>
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</thead>
<tbody>
<tr>
<td>Squamous-cell carcinoma</td>
<td>0.78 (0.49–1.25)</td>
<td>0.0% (0.84)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.31 (0.14–0.69)</td>
<td>0.0% (0.59)</td>
</tr>
<tr>
<td>Adenocarcinoma vs squamous-cell carcinoma</td>
<td>0.34 (0.12–0.90)</td>
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*Ronco et al, Lancet 383: 524-33, 2014*
Worldwide Incidence of Cancers Attributable to Infectious Agents

- Infectious agents cause: ~1/6 of cancers worldwide; ~1/4 of cancers in developing world; ~1/12 of cancers in industrialized world
- FDA-approved vaccines have been developed against HPV & HBV, antivirals against HCV

Implications of Identifying HPV as The Main Cause of Cervical Cancer

• 1983/4: Identification of HPV16/18; zur Hausen and colleagues - Nobel Prize 2008

• Natural history of HPV infection/pathogenesis of cervical cancer

• Identification of other HPV-associated cancers
Annual number of cases

- Cervical cancer represents ~10% of all female cancers worldwide; 
- ~14% of all female cancers in developing world

Developing World: Incidence of HPV-Associated Cancers

- Developing world: >90% of HPV-associated cancer is cervical cancer
- ~85% of global cervical cancer occurs in developing world; ~88% of deaths


- Pap screening has reduced cervical cancer incidence by ~80%
- No approved screening tests for other HPV-associated cancers
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased >3-fold

Rapid Acquisition of Genital HPV Infection in Young Women With Their First Sexual Partner

US (18-22 years old; N=130)

UK (15-19 years old; N=242)

20% in 4 months

45% in 26 months

UK data adapted from Collins et al, BJOG 109: 96-98, 2002  
US data adapted from Winer et al, J Inf Dis 197:279-282, 2008
Natural History of Cervical HPV Infection

HPV infection

Spontaneous regression

20%-30% HPV 16/18

60%-70% HPV 16/18

Many years (15++)

Sub-clinical HPV infection

Low-grade precursor

High-grade precursor

Cancer

Annual US Cases

~20,000,000

~3,000,000

~300,000

~12,000
Etiology-based Screening and Vaccination

• HPV-based cervical cancer screening
  – HPV DNA (Hybrid Capture [Digene/Qiagen]; Cervista [Hologic]); Cobas (Roche); Aptima (Gen-Probe)
  – In conjunction with cytology (Pap) testing or as primary screening test (Cobas)

• HPV-based interventions
  – Preventive vaccine
  – therapeutic vaccine, antivirals, etc?
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