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Phase II randomized, double-blind, placebo-controlled evaluation of AHCC for the eradication of HPV Infections in women with HPV positive pap smears

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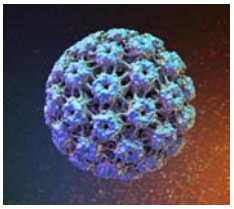
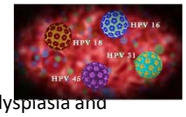
Human Papillomavirus (HPV)



- Non-enveloped dsDNA virus
  - Infects epithelial and mucosal surfaces.
  - First discovered in 1984
- HPV is a very common viral infection
  - Over 200 subtypes of HPV that have been identified,
    - one hundred human subtypes
- HPV 1 most common cause of plantar warts
- 30-40 strains can infect epithelial lining of ano-genital tract
  - HPV 6, 11 causes anogenital warts



- Fifteen of the human HPV subtypes are carcinogenic
  The most common subtypes: HPV 16, 18, 31, 39, and 41
  - HPV appears to be an important co-factor in the development of dysplasia and cancer
    - **HPV does not cause either condition by itself**

Risk Factors

- Increased HPV exposure
  - First intercourse at early age
  - Multiple partners
  - H/O other sexually transmitted diseases
  - Intercourse with uncircumcised males
- Decreased screening
  - Low socioeconomic status
  - Poor access to health care
- Smoking
- HIV/AIDS
- Oral contraceptive use/multiple pregnancies?

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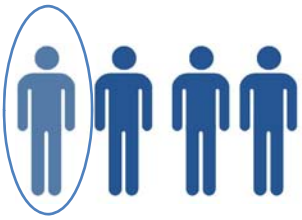
High Risk HPV Infection

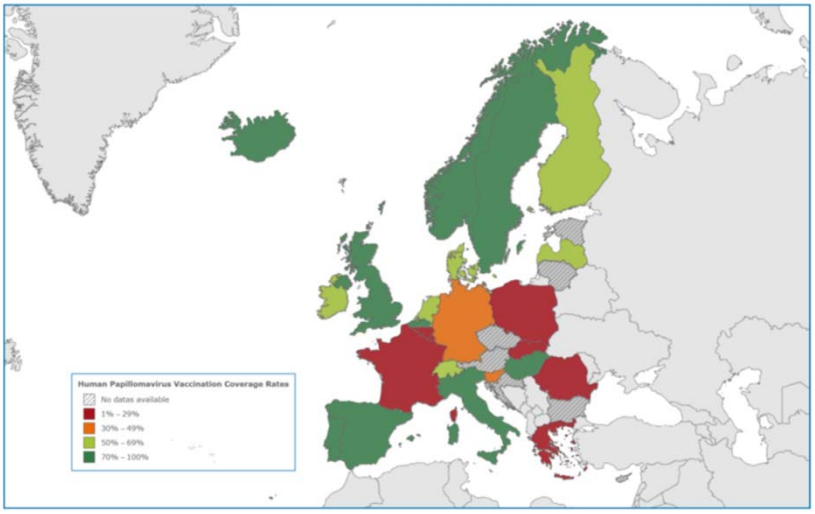


1 in 4 men
CURRENTLY
infected with HIGH-RISK HPV

1 in 5 women
CURRENTLY
infected with HIGH-RISK HPV

https://www.cdc.gov/nchs/products/databriefs/db280.htm

HPV Vaccination Rates in Europe



Nguyen-Huu N., et al 28th ECCMID, April 21-24, 2018

Identifying opportunities to improve HPV vaccination in an "at risk" population

Vaccination Status	Number of patients documented [N]	Number patients with documented HPV infection [N(%)]
Never Vaccinated	50	11 (22.6) *
Incomplete Vaccination	21	5 (23.8) *
Complete Vaccination	18	3 (16.7) *

(*p > 0.05; *no significant difference)*

Lin AS et al, Submitted for publication, July 2019

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Duration of HPV infection

- 608 female college students (age 17-23)
  - Cervicovaginal cells obtained for HPV typing at each (every 6 mo) visit
- Median duration of infection 8 months
  - 60% HPV infected during study
  - Average incidence of HPV 14%
  - Probability of resolving infection decreases
    - 31% after first 6 months
    - 39% after second six months
    - 11% after third six months

Ho G, Bierman R, Beardsley L. et al. N Engl J Med 1998;338:423-8

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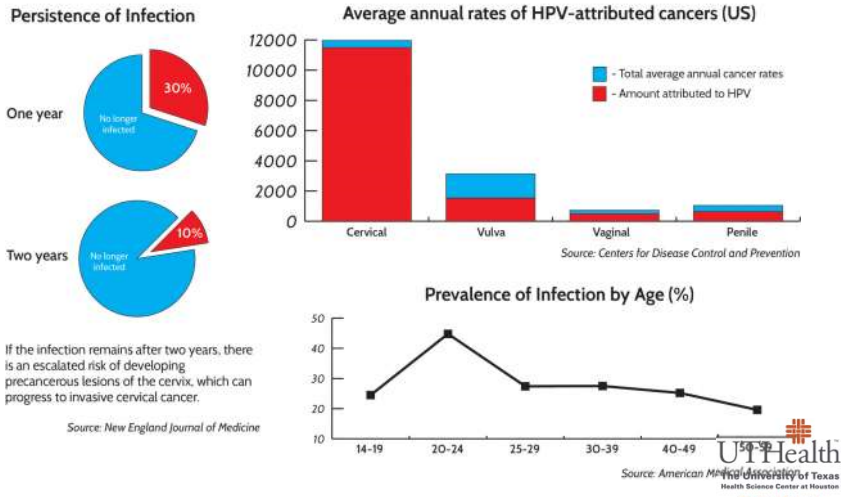
Human papillomavirus (HPV)



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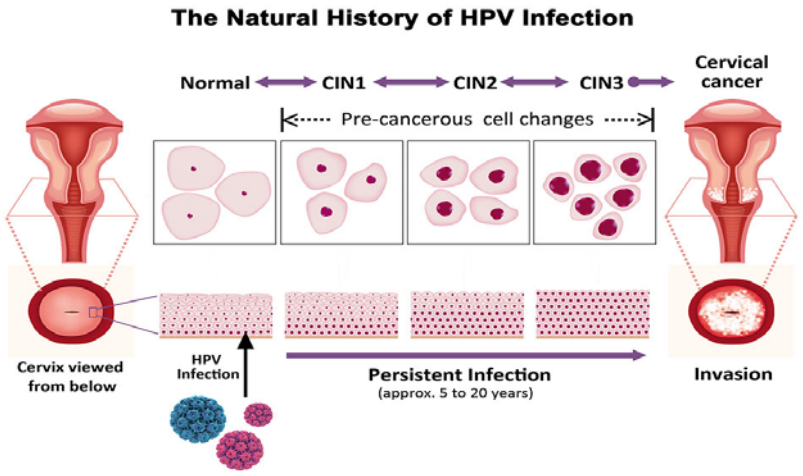
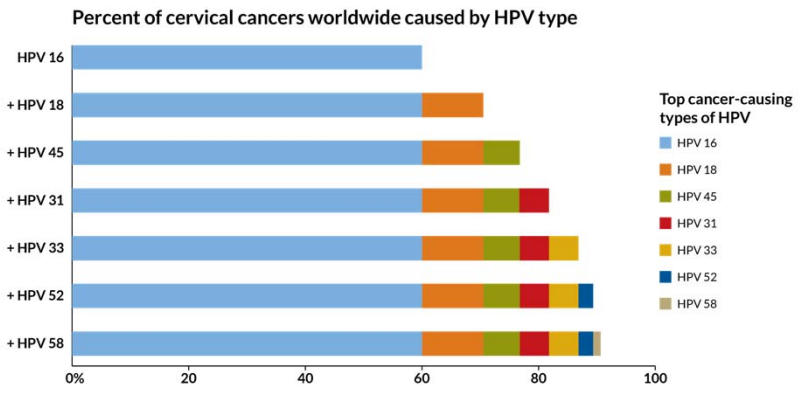
HPV Infection and Cancer



http://www.cuhk.edu.hk/sphpc/hpvselfsampling/en/cc-n-hpv.html

Impact of HPV Worldwide



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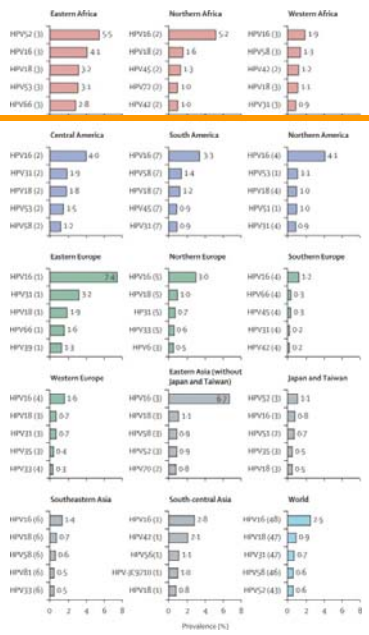

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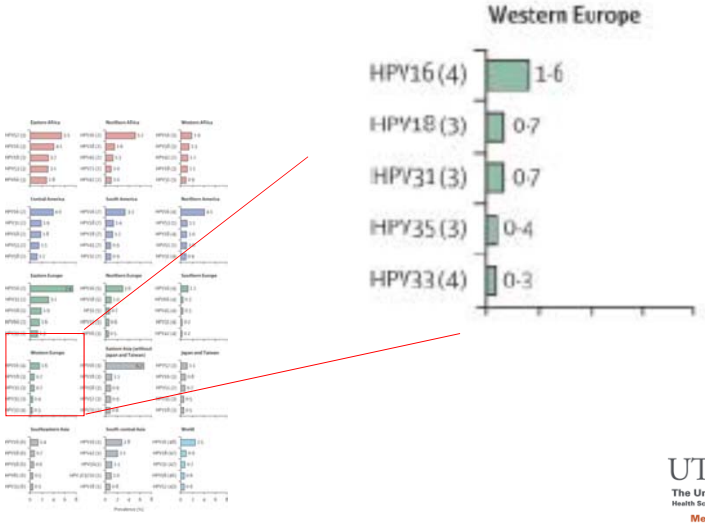

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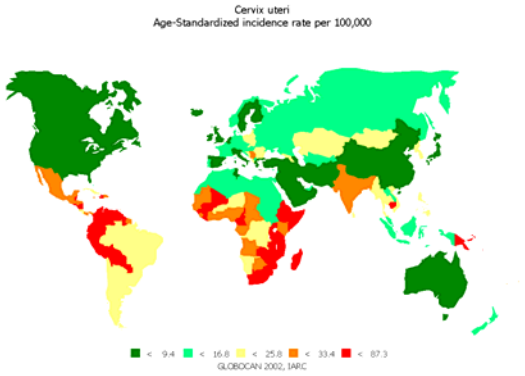
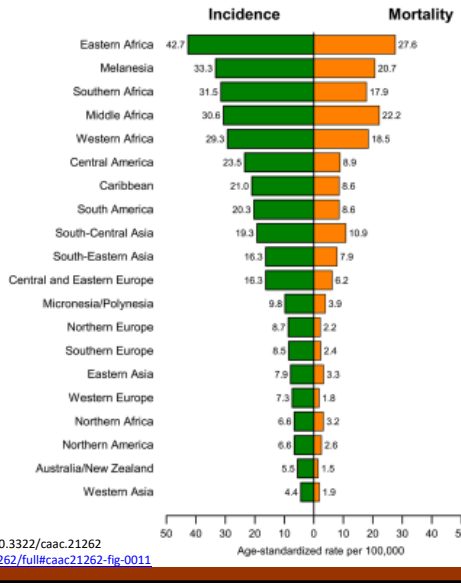
Societal Impact

- 80 percent of the cases occur in developing countries
- 4th leading cancer in women
- Accounts for most cancer deaths in women
- Major public health problem in 3rd world countries



Global cancer statistics, 2012



CA: A Cancer Journal for Clinicians
Volume 65, Issue 2, pages 87-108, 4 FEB 2015 DOI: 10.3322/caac.21262
http://onlinelibrary.wiley.com/doi/10.3322/caac.21262/full#caac21262-fig-0011

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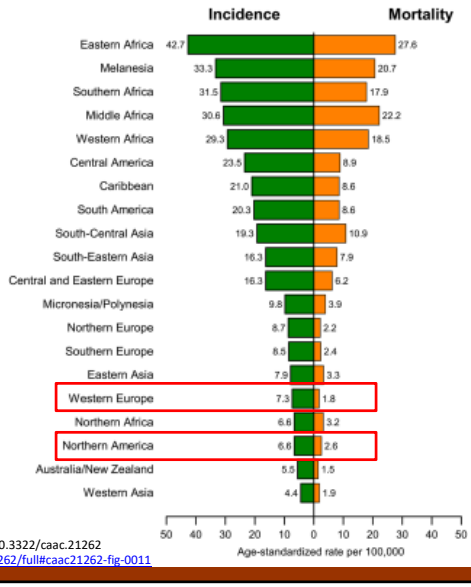
Global cancer statistics, 2012



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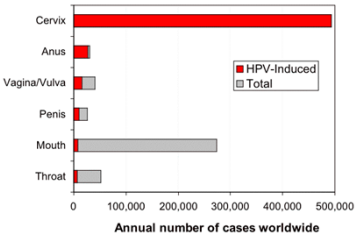
HPV and cancer

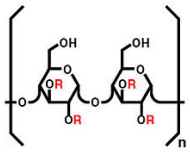
- HPV DNA has been detected
  - 99 % of cervical cancers
  - 95% of anal cancers
  - 60 % of oropharyngeal cancers
  - 65 % of vaginal cancer
  - 50 % of vulvar cancer
  - 35 % of penile cancer



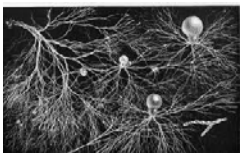
- There is no cure for HPV infections
  - Prevention by vaccination
  - Detection by Pap smear for cervical cancer
  - No current treatment for infection
    - Topical treatments of HPV related genital warts

AHCC

- Prepared from cultured mycelium of a Basidiomycetes
  - Main component of AHCC is acetylated α-glucan
- Proposed benefits
  - *Immunomodulatory*
  - Anti-hepatitis
  - Anti–diabetes
  - Anti-hyperlipidemia
  - Improvement in QOL
  - Anti-tumor effects
    - Safety with chemotherapy



α-1,4 glucan (R: H or CH_3CO-)



Proposed Functions of AHCC

- Anti-tumor effects
  - Increased lymphocytes and leukocytes
  - Production of cytokines
  - Down-regulate tumor markers
- Improvement in QOL
  - **Prevent side-effects of anti-cancer drugs**
  - Increase weight
  - Calm nervousness
- Anti-diabetes
  - Reduce blood sugar levels
  - Reduce A1C
  - Prevents complications
- Anti-hyperlipidemia
- Anti-hepatitis
  - Decreases amount of virus
  - Decreases AST and ALT
  - **Induces enzymes for detoxification and metabolism**
  - Inhibits decrease in platelet level

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www.ahccresearch.com

Preclinical Data Summary

frontiers in Oncology

ORIGINAL RESEARCH
published: 20 March 2019
doi: 10.3389/fonc.2019.00173

***From Bench to Bedside*: Evaluation of AHCC Supplementation to Modulate the Host Immunity to Clear High-Risk Human Papillomavirus Infections**

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Smith et al, Front. Oncol 9(173):1-9 | doi: 10.3389/fonc.2019.00173*, March 20, 2019*

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Summary of Response Data

- AHCC 3 Gram:
  - 4 of 8 (50%) patients had confirmed HPV DNA eradication after 3 months of AHCC 3 grams daily
    - Two patients had less than one month of AHCC during initial stage of study
- AHCC 1 Gram:
  - 4 of 9 (44%) patients confirmed HPV DNA eradication after 7 months of AHCC 1 gram daily
    - One patient has HPV RNA negative result (=suppression)
  - 1 patients withdrawn due to unanticipated pregnancy

Smith et al, Front. Oncol 9(173):1-9 | doi: 10.3389/fonc.2019.00173*, March 20, 2019*

PHASE II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF AHCC® FOR THE ERADICATION OF HPV INFECTIONS IN WOMEN WITH HPV POSITIVE PAP SMEARS

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Study Objectives

Phase II High-Risk HPV Study

- Evaluate the efficacy AHCC® 3 grams by mouth once daily to eradicate HPV infections in women with HPV positive PAP smears.
- Observe the durability of response to AHCC®
- Define the adverse effects of AHCC® compared to placebo.

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Smith et al, submitted for publication July 2019; NIH R03 funded: 1R03CA212935

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Eligibility

Phase II High-Risk HPV Study

Inclusion Criteria

- Women over 30 years of age who have a HPV positive test and normal/negative cytology, atypical cells, ASCUS, or CIN1 or CIN2 cervical dysplasia within three months of study entry. This will minimize potential confounders such as immune modulation that may possibly clear the infection which is common in women under the age of 26.
- Women must have had another HPV positive test with normal/negative cytology within no less than 6 months and more than 24 months prior to study entry. (This is to help establish persistent HPV infection)
- Negative urine pregnancy test within 7 days of therapy start.
- Patients must have adequate hematologic, renal, and hepatic function: ANC >/= 1,500 cells/mm3, platelets 100,000 >/= cells/mm3; Creatinine clearance>/= 60 mL/min (estimated by Cockcroft Gault equation), total bilirubin, SGPT, SGOT, and alkaline phosphatase </= 1.5 times normal.
- Patients must sign an approved informed consent indicating that they are aware of the investigational nature of this study.
- Patients must agree to return to clinic for repeat HPV+ testing and complete medication administration calendar.

Exclusion Criteria

- History of myocardial infarction within past 6 months, unstable angina, CHF, or uncontrolled hypertension (> 140/90).
- Women with a current or prior diagnosis of cancer.
- Women with a current diagnosis of CIN3 cervical dysplasia
- Women that are pregnant or breast feeding.
- Women with a history of Hepatitis (autoimmune, A, B, or C) or antigen positive.
- Patients with history of significant psychiatric disorders (schizophrenia, bipolar, psychosis) or uncontrolled seizures.
- Patients with significant medical co-morbidities at the discretion of the primary Gynecologist. Including immunosuppressive conditions (i.e. HIV+, rheumatoid arthritis, etc.) or taking immune modulation mediations (i.e. immunosuppressants)

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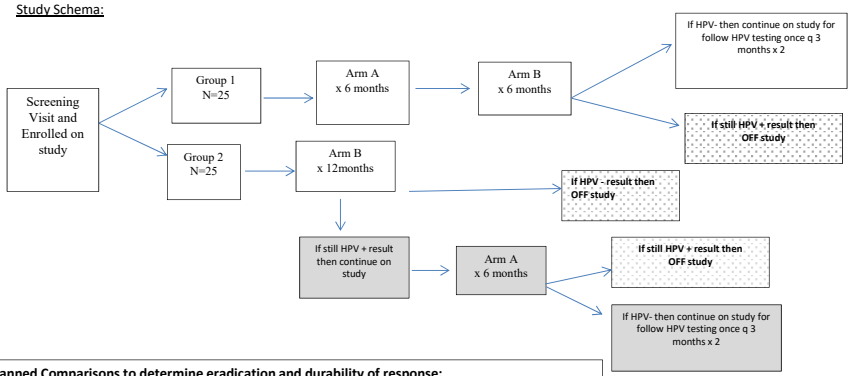
Phase II High-Risk HPV Study Design

Study Schema:



Planned Comparisons to determine eradication and durability of response:

- Group 1 at end of AHCC supplementation will be compared to Group 2 at 6 months on placebo.
- Group 1 at 6 months post end of AHCC supplementation will be compared to Group 2 at 6 months on placebo.
- Group 1 at 9 months post end of treatment will be compared to Group 2 at 9 months of placebo.
- Group 1 at 12 months post end of AHCC supplementation will be compared to Group 2 at 12 months of placebo.

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Study Design

Monitoring

- **HPV testing:**
  - Thin Prep brush sample
    - HPV testing was completed with the
      - **RNA testing: E6/7 assay** (Aptima, Hologic, Inc., Bedford, MA)
      - **DNA testing: (**Cobas, Roche, INC, Pleasanton, CA**)**
  - Outreach Laboratory, *The University of Texas Health Science Center at Houston Medical School (UT Health) – RNA Assay*
  - Methodist Hospital Molecular Pathology Laboratory – DNA Assay
- **Immunological marker monitoring**
  - Core Pharmacology Laboratory, Department of Obstetrics, Gynecology & Reproductive Sciences, UTHealth – McGovern Medical School
  - Blood samples obtained at each visit
    - IgG
    - Interferon (IFN) alpha
    - Interferon (IFN) beta
    - Interferon (IFN) gamma

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Demographics

Data will be inserted here

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Results

Phase II High-Risk HPV Study

Data will be inserted here

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Results

Phase II High-Risk HPV Study

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Results

Phase II High-Risk HPV Study

Note: IFN β is Type 1 IFN
- associated with virulence
- High levels suppress production of IFN γ and NK/T-cell cytotoxic cell immunity

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Results

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Results

Phase II High-Risk HPV Study

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Results

Phase II High-Risk HPV Study

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Results

Phase II High-Risk HPV Study

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Conclusions

Phase II High-Risk HPV Study

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  - Joseph A Lucci, III, M.D.
  - Teresa T. Byrd, M.D.
  - Yu Bai, M.D.
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"The mission of the Women's Health Integrative Medicine Research Program is to advance the progress of the safe and effective use of nutritional and herbal supplements with pharmacologic modalities as it relates to women's health and cancer through innovative thinking, systematic methodology and collaborative interactions throughout the UTHealth System and global research community."