Infections and Epidemiology of HPV

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GYN CANCERS within years

Data of Ministry of Health
Data of Ministry of Health

GYN CANCERS within years

Year | Uterine Corpus | Ovary | Cervix | Vulva |
--- | --- | --- | --- | --- |
2009 | 8.81 | 7.14 | 4.1 | 0.62 |
2010 | 9.02 | 7.34 | 4.1 | 0.64 |
2011 | 9.22 | 7.54 | 4.1 | 0.66 |
2012 | 9.42 | 7.74 | 4.1 | 0.68 |
The First 10 Women Cancers with in years (MoH)

- Memeli: 40.6
- Tiroid: 18.6
- Kolorektal: 13.4
- Uterus Korpusu: 9.3
- Trakea, Bronş, Akciğer: 8.1
- Mide: 8.1
- Ovar: 6.9
- Non-Hodgkin lenfoma: 5.3
- Beyin, sinir sistemi: 5.0
- Uterus Serviksi: 4.5
New Cases vs Mortality in Turkey

Cervix

Ovary

Corpus

- Globocan 2002
- Globocan 2008
- Globocan 2012

New cases:
- 1363
- 1443
- 1686
- 1628
- 1804
- 2400
- 1588
- 1937
- 3787

Mortality:
- 726
- 556
- 663
- 1001
- 1247
- 1588
- 581
- 519
- 951
Cumulative Incidence Risk Through age 74 based on GLOBOCAN
Cervical Cancer

Lifetime risk: 0.68% (1/147)

Median age at diagnosis: 48 yrs

Death rate (Per year): 2.4 per 100,000
Age distribution of İnvasive CC

US 2004-2008

TURKEY 2009
## Stage vs Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>At initial diagnosis</th>
<th>5 year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized Stage</td>
<td>49 %</td>
<td>91.2 %</td>
</tr>
<tr>
<td>Regional LN or beyond primary</td>
<td>35 %</td>
<td>57.8 %</td>
</tr>
<tr>
<td>Distant Met.</td>
<td>11 %</td>
<td>17.0 %</td>
</tr>
<tr>
<td>Unknown (Unstaged)</td>
<td>5 %</td>
<td>58.1 %</td>
</tr>
</tbody>
</table>

**Turkey Data**

- Survival 42.5 mts
- Lokalize: 52.1%
- Bölgesel: 37.3%
- Uzak yayılım: 10.6%
ICC and coverage of Screening

Invasive cervical cancer

National call-recall introduced

Coverage

Incidence Rate per 100,000

Percentage

Year

Incidence of Invasive CC In Scandinavia
Age Adjusted incidence rates
In USA

Based on SEER data base
Causative and cofactors for cervical cancer

HPV 1970 IARC WG

High
Intermediate
Low

Co-factors
- Cigarette
- Multiple partner
- Early age intercourse
- (Immature Metaplasia)

Possible co-factors
- Clamydia
- Herpes II
- HIV
- OC
- Low S.eco status
Profi.Dr.Harald zur Hausen
German Cancer Research Centre
Heidelberg, Germany
HPV Philogenetic Tree
>130 HPV types

- **Mucosal (~40 types)**
  - high risk (16, 18, 31, 33...)
    - low grade cervical abnormalities
    - high grade abn / cancer precursors
    - anogenital cancers
  - low risk (6, 11...)
    - low grade cervical abnormalities
    - genital warts
    - respiratory papillomas

- **Cutaneous (~60 types)**
  - common warts (hand, feet)
### Estimated HPV DNA prevalence in the world

Meta-analysis of 67 studies involving 139,777 cytologically normal women

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated HPV DNA Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>10.2 (10.0-10.5)</td>
</tr>
<tr>
<td>Africa</td>
<td>23.4 (22.0-24.8)</td>
</tr>
<tr>
<td>America</td>
<td>12.8 (12.1-13.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>8.2 (7.9-8.6)</td>
</tr>
<tr>
<td>Asia</td>
<td>7.6 (7.2-8.1)</td>
</tr>
</tbody>
</table>

De Sanjose, Diaz, Castellsague et al. Lancet ID 2007
HPV Type Prevalance at The Different Part of The World

Transmission

- Sexual intercourse
  - Vaginal, oral, or anal
  - Not only penetration but also skin to skin contact

- HPV can be found in women who have never had sexual intercourse,
  (the rate of HPV infection in virgins is 14.8%)

HPV-Age

Life-time risk: %50-80

N. Cytology : %10 HPV

One or multipl type infection

Top 18-30y , 30-40y decreases Postmenoposal incereases

HPV Prevalence Varies With Age in the General Population, NHANES

Overall HPV Prevalence: 26.8%

NHANES = National Health and Nutrition Examination Survey
Data based on self-collected patient samples

HPV Lifecycle in the Cervix

Cervical canal

Mature squamous layer

Squamous layer

Parabasal cells

Basal (stem) cells

Basement membrane

Normal epithelium

Infected epithelium

Shedding of virus-laden epithelial cells

Viral assembly (L1, L2, E4)

Viral DNA replication (E6 & E7)

Episomal viral DNA in cell nucleus (E1 & E2, E6 & E7)

Infection of basal cells (E1 & E2)

Major Steps In Development of Cervical Cancer

• Infection of transformation zone with carcinogenic HPV

• Viral Persistence

• Clonal progression of infected epithelium to cervical cancer

• Invasion
HPV Infection Natural Course

- **HPV Infection**
  - Subclinical HPV infection
  - Low grade SIL
  - HGSIL
  - CANCER

Years later (20+)

USA case no
- 20,000,000
- 1,200,000
- 300,000
- 10,000

- HPV E6, E7 Cellular changes
HPV-DNA Genome

Up Stream Region

Region of Early Genes
  Codes
  E6, E7, E1, E2, E4, E5

Region of Late Genes
  Codes
  L1, L2
Role of Early Proteins

- **E1**: replication
- **E2**: replication and transcription
- **E4**: viral release
- **E5**: immun evasion
- **E6**: bind p53
- **E7**: bind pRb

![Schematic Presentation of the HPV Genome](image)
HPV Genomes in Cervical Cancer

Integration of HPV genomes into host cell DNA can lead to various consequences:

- Frequently deleted during DNA integration
- Opening of the viral ring molecule during integration
- Modulation of viral transcription by host cell promoters
- Chimeric transcripts, increased mRNA lifespan

Diagram showing the integration process with labels for L1, L2*, LCR, E6, E7, E1, E2*.
CERVICAL CARCINOGENESIS

E6

E7

Role of Carcinogenesis

Degradation of p53

Degradation of Rb

Activates Telomerase
Stimulates Cyclin A, E

TSG

p53

Rb
Cervical cancer progression model

- Normal cervix → INFECTION → HPV-infected cervix → PROGRESSION → Precancer → INVASION → Cancer
- HPV-infected cervix → CLEARANCE → Normal cervix
- Precancer → REGRESSION → Cancer
**Population**

Exposure to HPV

**Exposure to high-risk HPV**

**Persistent high-grade CIN**

1.3% Invasive Disease

0.4% Death

75%

50%

10%

1.3%

0.4%
Progression of Cervical Disease

* With increasing probability of viral DNA integration.

CIN = cervical intraepithelial neoplasia; ASCUS = atypical squamous cells of undetermined significance.

HPV related Cancers in Turkey

- HPV'ye Bağlı Kanserler
- Uterus Serviksi
HPV & CERVIX CA

HPV Types That Cause Squamous-Cell Cervical Cancer Worldwide

- HPV 16: 14%
- HPV 18: 3%
- HPV 16 and 18: 52%
- HPV 31: 3%
- HPV 45: 2%
- HPV 52: 3%
- HPV 58: 3%
- HPV negative: 15%
- All other HPV types: 70%

CIN acetowhite lesion
Vulvar papillomas

Vulvar Cancer
Vaginal

Vaginal warts

Vaginal cancer
Being infected with the human papillomavirus (HPV) can affect the risk of developing anal cancer.
Laryngeal papillomatosis refers to the growth of benign epithelial tumors known as papillomas in the larynx and upper respiratory tract. These tumors are caused by infection with the human papilloma virus (HPV). Papillomas originating in the respiratory tract are not considered sexually transmitted diseases.

- Laryngeal papillomas are the most common benign neoplasms affecting the larynx and upper respiratory tract.
- Malignant degeneration to squamous cell carcinoma is rare but can occur.
- The overall prevalence ranges from 2 per 100,000 adults to 4.5 per 100,000 children.
Oral Cavity

• Fifty percent to 90% of Oral Squamous Cell Cancers in the pharynx, tonsil, and tongue are HPV-positive.
HPV is associated with 15% to 35% of head and neck cancers worldwide.\textsuperscript{11}

**Pharyngeal papilloma**

**Oral cancer**

**HPV and HNSCC**
- High-risk HPV specific to tumor cell nuclei
- Clonal virus-tumor relationship
- Viral integration
- Genetic alterations indicative of E6/E7 function
- High viral copy number
- Viral oncoprotein expression
- Reversal of malignant phenotype
Penile

- HPV infection is found in about half of all penile cancers.
- Genital wart infection (HPV) increases penile cancer risk. Around 5 out of 10 men with penile cancer have HPV infection.
Other Warts
Smoking

• Breakdown products (nicotine..)
• BaP(benzo-a-pyrine) in mucus: HPV upregulation
• Persistent cellular proliferation
• Inhibition of apoptosis
• Stimulation of VEGF
• Decrease number of langerhans cells
• Squamous cell carcinoma!!
Other Infections

- C. Trachomatis, N. Gonorrhoeae, HSV-2, T. Vaginalis

- Disruption of epithelial integrity

- Reparative metaplasia associated with acute cervicitis

- Chronic inflammation: Co-inf C. Trachomatis is associated with persistence of HR HPV
Sex Hormones

• Pregnancy
  - Condyloma acuminata increase rapidly in size
  - Maternal estrogen status or immun suppressive effect of pregnancy

• OCP use
  - Reduced metabolism of mutagens with OCP induced folate deficiency
  - Independent of sexual activity
  - Long term Use !!!!
  - There is no demonstrated data
Immunsupression

Iatrogenic
- Transplant patients

HIV
- Increase in prevalence and persistence

Systemic
- Increased incidence and persistence
  (Hodgkin’s Disease, Leukemia, Collagen vasc. Dis.)
Nutritional Factors

Vitamin A, C, E and beta-carotene

**Deficiency** may increase CIN or cervical cancer

High **homocysteine** levels may correlate risk for ICC

High consumption may be protective by increasing the circulating **cis-lycopene**
Circumcision

- Penile HPV decreases from 19.6% to 5.5%.

- HR HPV decreases from 27.9% to 18%.

- 58% lower risk of cervical cancer with circumcised partners.

Castellsague X, N Engl J Med vol.346 no.15 – April 11, 2002
What is HPV prevalence in Turkey?
There are 3 Types of Studies for HPV in Turkey

• Hospital based
• Population based
• Tissue based
Hospital Based Study

Number of patients: 6376

Overall HPV + : 30%

Turkish GOG Study 2012 by using PCR 10centers
<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>HPV detection method</th>
<th>Number of cases</th>
<th>Overall</th>
<th>Women with normal cytology</th>
<th>Women with abnormal cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>İnal, 2007</td>
<td>HC-II</td>
<td>1353</td>
<td>2.14</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td>Dursun, 2009</td>
<td>PCR</td>
<td>403</td>
<td>23</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Ortaç, 2011</td>
<td>HC-II*</td>
<td>501</td>
<td>4.2</td>
<td>3.5</td>
<td>19</td>
</tr>
<tr>
<td>Yüce, 2012</td>
<td>PCR</td>
<td>890</td>
<td>25.7</td>
<td>21.4</td>
<td>48.8</td>
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<tr>
<td>Demir, 2012</td>
<td>AmpliTaq**</td>
<td>530</td>
<td>-</td>
<td>17.9</td>
<td>-</td>
</tr>
<tr>
<td>Tuncer, 2012</td>
<td>PCR</td>
<td>1797***</td>
<td>-</td>
<td>-</td>
<td>22.4</td>
</tr>
<tr>
<td>Akyar, 2013</td>
<td>PCR</td>
<td>1014</td>
<td>69.6</td>
<td>63</td>
<td>75.1</td>
</tr>
<tr>
<td>Turkish GOG, 2013</td>
<td>PCR + HC-II</td>
<td>6388</td>
<td>25</td>
<td>27</td>
<td>57</td>
</tr>
</tbody>
</table>

*Only hr-HPV is studied.

**HPV is studied only in normal cytology.

*** Study is conducted among women with abnormal cytology
Population Based Study

Number of patients: 3500

HPV Prevelance: % 2.9

Population Screening Centers (KETEM Study)
17 centers
Population Based Wart Study

Number of patients: 4,013,084

HPV : 154 / 100,000

Population Screening Centers (KETEM Study)

ö zgül et al
HPV TYPES IN ICC, TURKEY

- HPV prevalence was 93.5% (232/248; 95% CI: 90.5%-96.6%)
- HPV16/HPV18 accounted for 75.4% (95% CI: 69.9%-81.0%)

Usubutun et al. Int J Gynecol Pathol. 2009 Nov;28(6):541-8
Distribution of HPV types Worldwide

- HPV 16
- HPV 18
- HPV45
- HPV 31,33
- Other HPV

Percent

Europe | North America | Central-South America | Africa | Asia
Distribution of HPV types in ICC by Histologic Types

- HPV 16
- HPV 18
- Other HPV
- HPV Negative

**Squamous Cell Carcinoma**
- HPV 16: 60%
- HPV 18: 20%
- Other HPV: 10%
- HPV Negative: 5%

**Adenocarcinoma**
- HPV 16: 70%
- HPV 18: 30%
- Other HPV: 5%
- HPV Negative: 10%

**Adenosquamous Carcinoma**
- HPV 16: 80%
- HPV 18: 20%
- Other HPV: 0%
- HPV Negative: 5%
What is the relation of HPV and abnormal cytology in Turkey? (hospital based)
Abnormal Cervical Cytology in Turkey
A Turkish Gynecologic Oncology Group (TGOG) Study

140,334 patients, 33 centers
Abnormal Cytologic Findings:

(The TBS, 2001)

- **AS cells:**
  - ✔ ASC – US
  - ✔ ASC – H
- **LSIL**
- **HSIL**
- **AG cells**
  - ✔ AGC – NOS
  - ✔ AGC – favor neoplasia
- **AIS**
- **Invasive Cancer**
### Abnormal Cytology (2481/140334)%

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (n)</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC</td>
<td>2341</td>
<td>1.66</td>
</tr>
<tr>
<td>- ASC-US rate</td>
<td>1510</td>
<td>1.07</td>
</tr>
<tr>
<td>- ASC-H rate</td>
<td>100</td>
<td>0.07</td>
</tr>
<tr>
<td>- LSIL rate</td>
<td>429</td>
<td>0.3</td>
</tr>
<tr>
<td>- HSIL rate</td>
<td>243</td>
<td>0.17</td>
</tr>
<tr>
<td>AGC</td>
<td>111</td>
<td>0.07</td>
</tr>
<tr>
<td>Cytologic Ca (SCC+Adeno)</td>
<td>88</td>
<td>0.062</td>
</tr>
</tbody>
</table>
University Hospitals
(n= 82048)

ASC : n=1499

ASC-US : (n=994) %1.2
ASC-H : (n=84) %0.1
LSIL : (n=279) %0.34
HSIL : (n=142) %0.18

AGC : n=101

Cytologic Ca(SCC+Adeno,77) 0.09

0.15
G.Teaching Hospitals (n= 58286)

ASC : 791
-ASC-US : (n=516) 0.88%
-ASC-H : (n=16) 0.02%
-LSIL : (n=150) 0.26%
-HSIL : (n=101) 0.17%

AGC : 10

Cytologic Ca (SCC+Adeno,11): 0.01
## Studies comparing distribution of cervical cytology and HPV

### Abnormal Cervical Cytology

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of cases</th>
<th>Normal (%)</th>
<th>ASCUS (%)</th>
<th>ASCH (%)</th>
<th>LSIL (%)</th>
<th>HSIL (%)</th>
<th>AGC (%)</th>
<th>SCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dursun 2009</td>
<td>403</td>
<td>20</td>
<td>22</td>
<td>51</td>
<td>60</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akyar 2013</td>
<td>1014</td>
<td>17.7</td>
<td>16.9</td>
<td>11.9</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkish GOG 2013</td>
<td>6388</td>
<td>27</td>
<td>20</td>
<td>5</td>
<td>14</td>
<td>10</td>
<td>0.8</td>
<td>3</td>
</tr>
</tbody>
</table>
Primary Prevention

• Stop smoking
• Barrier Contraceptives
• Monogamy
• Diet (Folic, VitB, Caroten etc)
• Vaccination
• Circumcision

Secondary Prevention

• Screening
Conclusion

• Incidence of ICC stable, increasing preinvasive
• HPV burden is higher in hospital based than population based
• HPV Prevelance seems higher in Turkey
• HPV types in Turkey and world are similar
• HPV 16 is higher in squamous type and 18 in adeno type
• Screening reduces ICC and mortality
Thank you for your attention...