Details of HPV-based Cervical Cancer Screening in Turkey

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Cervical Cancer in Turkey

- Incidence: 4-5 /100.000 (Years 2004-2015)
- Annual New Cases: 1,800
- 9. ranking among females
- Life time Risk: 0.55%
- Mortality Rate: 2 /100,000

Stage Distribution
- 55% Have Advanced Disease

<table>
<thead>
<tr>
<th>Country</th>
<th>5 yrs Relative Survival % (Reference Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>62 (2009)</td>
</tr>
<tr>
<td>USA</td>
<td>68 (2006-2012)</td>
</tr>
<tr>
<td>UK</td>
<td>59 (2005-2007)</td>
</tr>
<tr>
<td>Germany</td>
<td>65 (1997-2006)</td>
</tr>
<tr>
<td>France</td>
<td>61 (2000-2007)</td>
</tr>
<tr>
<td>Australia</td>
<td>72 (2008-2012)</td>
</tr>
<tr>
<td>Canada</td>
<td>73 (2006-2008)</td>
</tr>
<tr>
<td>Korea</td>
<td>80 (2008-2012)</td>
</tr>
<tr>
<td>China</td>
<td>74 (2005-2010)</td>
</tr>
<tr>
<td>Japan</td>
<td>72 (2003-2005)</td>
</tr>
</tbody>
</table>

Gultekin, J Gyn Oncol, 2017
Gultekin, M, Int J Gyn Cancer, 2017
Cervical Cancer Globally

✓ Half Million New Cases
✓ 50% Mortality
✓ >90-99.7 % HPV Related
✓ Preventable Cancer
  ✓ HPV Vaccination, Smoking Cessation
✓ Early Detection is Possible
  ✓ VIA-VILI / Smear / HPV / Combination / Others
  ✓ WHO
✓ Eradicable Cancer
Cervical Cancer Last Century

- Cytology based screening programs have reduced more than 75% of incidence and mortality from cervical cancer in the last 50 years.
- Especially in developed countries.
- However, only 12 countries have succeeded in EUROPE (2017).
- And still cervical cancer mortality does not decrease any more even in most developed countries.

UK National Screening Programme

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- Especially in developed countries.
- However, only 12 countries have succeeded in EUROPE (2017).
- And still cervical cancer mortality does not decrease any more even in most developed countries.
Cytology Based Screening: International Problems

✓ Scientific Problems
  • A single Pap-Test has a very low sensitivity for CIN2+ lesions
  • Pap-Test has a high false negative rate
  • Reproducibility of Pap-Test is low
  • Pap-Test is less effective in detecting adenocarcinoma of cervix

✓ Organisational Problems
  • It is a very difficult and complex service to provide.
Previous Turkish Screening Program

- Pap-Smear since 1985, Population Based Since 2004
  - KETEM + GP + Gynecologists
    - However, coverage rates could not exceed
      - 2% for population, 40% for opportunistic plus population based

Reason: Organisational Problems

- Large target population (15 Million)
- Lack of manpower (technician, expert)
- Frequent positional changes in manpower
- Lack of awareness (medical staff and population)
- Geographical limitations (large surface area, seasonal difficulties, transport difficulties)
- Quality control
Why HPV For Turkey?

✓ For Screening Program Directors
  ▪ Higher sensitivity
  ▪ High Negative Predictive Value and Longer Screening Intervals
  ▪ Low HPV positivity (low prevalence)

✓ For Academicians
  ▪ Manpower advantage
  ▪ Central quality control and automatization

✓ For Ladies
  ▪ Shortening the time to final diagnosis
  ▪ Self-testing ability for future a new test for ladies attention
Step By Step Turkish Implementation

- National and international consultations
- Pilot studies
- Preparation of legislations
- Family physicians in-service training and motivation of FP and patients
- National ID number based smart software
New Screening Program

✓ HPV + Conventional Smear in each five years, for women aged 30-65 years old

✓ GP & Nurses
  ▪ 500 / GP or nurse for 5 Years, 10 / month

✓ Cargo to Ankara and Istanbul HPV Lab

✓ Results are on internet in 10 days maximal

✓ HPV Negative, nothing more

✓ HPV Positive, Genotyping Plus Double Blind Smear Evaluation

✓ Samples are stored for five years, smear pictures are also digitally stored

✓ Colposcopy Referral
  ▪ HPV 16/ 18/ Other HPV with Cytological Abnormalities
  ▪ Other HPV with NILM : 1 year later re-screen
Role of HPV in Primary Level Screening
(Per Month; HPV DNA Screening vs. Max Pap-Smear Numbers)
Results: Population Based Cancer Screening

Hacettepe University
Division of Gyn Oncol
HPV Test Results Global Sum (3.222.568)
Positive 4.18%

- Negative (94,95)
- Pozitive (4,18)
- Insufficient Material (0,88)

Data Acces: 20. January. 2018
A total of 3,200,000 were screened by HPV test.

Approximately 12,000 abnormal smear detected (Except ASC-US)

HPV Mapping of Turkey

Turkish HPV Geno-Map (4.18%)
12 NUTS Bölgesi
# HPV Genotypes

**Total Sum (134,568)**

<table>
<thead>
<tr>
<th>HPV TYPES</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only 16</td>
<td>18,507</td>
<td>13,96</td>
</tr>
<tr>
<td>Only 18</td>
<td>3,155</td>
<td>2,35</td>
</tr>
<tr>
<td>16 and 18</td>
<td>534</td>
<td>0,4</td>
</tr>
<tr>
<td>16 and 18 and Others</td>
<td>949</td>
<td>0,72</td>
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<tr>
<td>16 and Others</td>
<td>15,161</td>
<td>11,44</td>
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<tr>
<td>18 and Others</td>
<td>3,654</td>
<td>2,76</td>
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<tr>
<td>Other than 16 and 18</td>
<td>90,634</td>
<td>68,38</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100,00</td>
<td>100,00</td>
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</table>

## Reflex Cytology Results (Positive 134.585)

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
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<tbody>
<tr>
<td>Normal</td>
<td>68.41</td>
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<tr>
<td>Insufficient Material</td>
<td>16.34</td>
</tr>
<tr>
<td>LSIL</td>
<td>7.60</td>
</tr>
<tr>
<td>ASC-US</td>
<td>6.27</td>
</tr>
<tr>
<td>AGC</td>
<td>0.49</td>
</tr>
<tr>
<td>ASC-H</td>
<td>0.53</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.32</td>
</tr>
<tr>
<td>Others</td>
<td>0.04</td>
</tr>
<tr>
<td>AIS</td>
<td>0.00</td>
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</tbody>
</table>

HPV Geno-Type Distribution

- Type 16
- Type 51
- Type 31
- Type 58
- Type 59
- Type 56
- Type 39
- Type 52
- Type 45
- Type 33
- Others
HPV Types Grouped By Their Specific Prevalence

<table>
<thead>
<tr>
<th>TURKEY</th>
<th>WORLD</th>
<th>EUROPE CONTINENT</th>
<th>NORTHERN AMERICA</th>
<th>LATIN AMERICA &amp; CARIBBEAN</th>
<th>ASIA CONTENT</th>
<th>AFRICA CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
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HPV Types Grouped By Their Specific Prevalence

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<th>Types</th>
<th>Prevalence</th>
</tr>
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<tr>
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Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women

Murat Gultekin, Mujdegul Zayifoglu Karaca, Irem Kucukyildiz, Selin Dundar, Guledal Boztas, Hatice Semra Turan, Ezgi Hacikamiloğlu, Kamil Murtuza, Bekir Keskinkılıç and Irfan Sencan

First 1 Million Patients with Colposcopy and Histology Results
Invitations, Acceptence, Attendance & Screening Rates

✓ Acceptance Rate:
  - 36.5% acceptance rate for HPV DNA Screening
  - This rate was 63.5% for ages 30-45y, 32.7% for ages 45-60y and 13.5% for ages 60 years and older.

✓ Attendance Rate: 82.8%.

✓ Invitation:
  - Telephone including SMS (60%)  80-90% Attendance Rates
  - Face to Face (30%)  80-90% Attendance Rates
  - Letter/Brochure/Social Media  30-40% Attendance Rates

✓ Screening Rates:
  - 28.0% (30-34); 33.8% (35-39); 41.6% (40-44),
  - 34.5% (45-49); 32.4% (50-54); 23.3% (55-59); 15.2% (60-65)

Int J Cancer. 2017 Dec 13
DATA COMPLETENESS

- **100% at Primary Level**

- **35% Secondary – Tertiary Level**
HPV POSITIVITY WITHIN AGE GROUPS

Percentage %

- **30-44**
  - HR HPV (+)
  - HPV 16/18 (+)
  - Other HPV (+) With Abnormal Smear (≥ASC-US)

- **45-54**

- **55-65**

- **All**

Hacettepe University
Division of Gyn Oncol
HPV Genotypes among 37,515 HC2 Positive Cases (50,064 different types) by Age Groups (n, %).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case</th>
<th>30-44</th>
<th>45-54</th>
<th>55-65</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV16</td>
<td>10,373</td>
<td>20.7%</td>
<td>22.3%</td>
<td>19.3%</td>
</tr>
<tr>
<td>HPV18</td>
<td>2,561</td>
<td>5.1%</td>
<td>5.3%</td>
<td>5.1%</td>
</tr>
<tr>
<td>HPV31</td>
<td>4,357</td>
<td>8.7%</td>
<td>8.7%</td>
<td>8.8%</td>
</tr>
<tr>
<td>HPV33</td>
<td>1,064</td>
<td>2.1%</td>
<td>2.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>HPV35</td>
<td>2,298</td>
<td>4.6%</td>
<td>4.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>HPV39</td>
<td>2,774</td>
<td>5.5%</td>
<td>5.9%</td>
<td>5.4%</td>
</tr>
<tr>
<td>HPV45</td>
<td>1,603</td>
<td>3.2%</td>
<td>3.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>HPV51</td>
<td>5,420</td>
<td>10.8%</td>
<td>10.8%</td>
<td>10.6%</td>
</tr>
<tr>
<td>HPV52</td>
<td>3,547</td>
<td>7.1%</td>
<td>7.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>HPV56</td>
<td>2,838</td>
<td>5.7%</td>
<td>5.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>HPV58</td>
<td>2,536</td>
<td>5.1%</td>
<td>4.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>HPV59</td>
<td>2,096</td>
<td>4.2%</td>
<td>4.1%</td>
<td>4.3%</td>
</tr>
<tr>
<td>HPV68</td>
<td>2,307</td>
<td>4.6%</td>
<td>4.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>HPV73</td>
<td>4</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>6,286</td>
<td>12.6%</td>
<td>12.0%</td>
<td>13.6%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50,064</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
CROSS TABLES
HPV Genotypes vs.Age and NUTS Regions
Smear Abnormality vs. Age and NUTS Regions
CROSS TABLES:
HPV GENOTYPES VS. SMEAR ABNORMALITIES
DATA COMPLETENESS

- **100% at Primary Level**
- **35% Secondary – Tertiary Level**
Need for Colposcoy Device and Training?

- 5,916 Patients Biopsy Results
- 3,499 Patients Had Colposcopy (59.1%)
- 3,190 Minimal Punch Biopsy (91.2%) (Punch-LEEP-Kone-ECC)

- 2,417 (40.9%) Repeat HPV or Smear or Follow-Up
- 309 (8.8%) Only Colposcopy

- Normal 1,981
- CIN 1 708
- CIN 2 285
- CIN 3 436
- Cancer 85
First 1 Million Results With Biopsy

- **HPV Positivity** 3,87%
  - Over 500,000 Ladies Are Carriers

- **Colposcopy Referral Rate** 1,6%

- **True positivity (CIN2+)** 23%

- **True positivity (CIN3+)** 15%

- **Cancer Incidence Over Age 30**
  - 8,0/100,000 (normal population)
  - 24/100,000 (screening population, range 8.5 - 40)

- **For CIN3+ Lesion Detection**
  - Only Cytology 52%
  - HPV Screening + 16 & 18 Genotyping 88%

- **HPV Genotyping**
  - Real bridge between continents

Int J Cancer. 2017 Dec 13
Cervical Screening: Unpublished Data
Colposcopy Referral, CIN2 Detection Rate, PPCV of Colposcopy to Detect CIN2+

Colposcopy Referral Rates:
- **EU**: 2.1%
- **Turkey**: 1.6%

Cancer (CIN2+) Detection Rates Among Referred:
- **EU**: 4.0%
- **Turkey**: 23%

PPV of Colposcopy to Detect (CIN2+):
- **EU**: 27.0%
- **Turkey**: 25.3%
HPV Mega LAB Video

☑️ https://www.youtube.com/watch?v=IBmAflRjl10&t=213s
✓ Turkey is the first country in the world starting HPV screening among middle income population.

✓ We show that primary HPV screening is feasible within low resource settings and in conservative populations.

✓ However, we face challenges.
Challenges

✓ Resistance of cyto-pathology experts
✓ HPV is a sexually transmitted disease
✓ Resistance of GP for screening
✓ GP and nurses were not well trained for HPV
✓ HPV vaccination was not available
✓ Questions about adult vaccinations
✓ Colposcopy trainings quality and adherance to guidelines
Future for World and For Turkey

✔ World
  - Netherlands, Switzerland, Sweden, Italy, UK, Germany, Australia, Canada, Denmark, Poland, Norway, Austria
  - Countries with National HPV Vaccine Programs
  - HPV Faster
  - Urinary and Self Testing HPV
  - Management of HPV Positives (ESGO –Meta-Analysis)
  - ESGO ENPIGO Statement

✔ Turkey
  - Screening Registry
  - Colposcogy Data Follow Up System
  - HPV Mobile
Thank you for your attention