Epidemiology and Risk Factors for Lung Cancer

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Purpose of Discussion

• Lung Cancer introduction
• Patterns of occurrence
• Epidemiology Globally & MENA region
• Future prediction for MENA (WHO)
• Risk Factors
• Biomarkers and Future Direction
• Summary
• Questions
Lung cancer is the leading cause of cancer death in the world.

In 2008, 1.6 million people received a new diagnosis of lung cancer, comprising 13% of all new cancer diagnoses, and 1.4 million died of lung cancer, which was 18% of all cancer deaths.

# Lung Cancer

## Estimated Incidence, Mortality and Prevalence Worldwide in 2012

<table>
<thead>
<tr>
<th>Estimated numbers (thousands)</th>
<th>Cases</th>
<th>Men</th>
<th>Deaths</th>
<th>5-year prev.</th>
<th>Cases</th>
<th>Women</th>
<th>Deaths</th>
<th>5-year prev.</th>
<th>Both sexes</th>
<th>Cases</th>
<th>Deaths</th>
<th>5-year prev.</th>
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<tbody>
<tr>
<td>World</td>
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<td>1267</td>
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<td>More developed regions</td>
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<td>417</td>
<td>593</td>
<td>268</td>
<td>210</td>
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<td>758</td>
<td>626</td>
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<td>Less developed regions</td>
<td>751</td>
<td>682</td>
<td>674</td>
<td>315</td>
<td>281</td>
<td>288</td>
<td>1066</td>
<td>963</td>
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<td>WHO Africa region (AFRO)</td>
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<td>11</td>
<td>10</td>
<td>6</td>
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<td>5</td>
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<td>WHO Americas region (PAHO)</td>
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<td>113</td>
<td>175</td>
<td>324</td>
<td>262</td>
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<td>WHO East Mediterranean region (EMRO)</td>
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<td>22</td>
<td>7</td>
<td>6</td>
<td>6</td>
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<td>29</td>
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<tr>
<td>WHO Europe region (EURO)</td>
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<td>283</td>
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<td>126</td>
<td>105</td>
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<td>449</td>
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<tr>
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<td>113</td>
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<td>WHO Western Pacific region (WPRO)</td>
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<td>528</td>
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<td>251</td>
<td>220</td>
<td>273</td>
<td>839</td>
<td>748</td>
<td>878</td>
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<tr>
<td>IARC membership (24 countries)</td>
<td>514</td>
<td>438</td>
<td>582</td>
<td>279</td>
<td>219</td>
<td>343</td>
<td>794</td>
<td>857</td>
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<tr>
<td>United States of America</td>
<td>112</td>
<td>92</td>
<td>140</td>
<td>102</td>
<td>76</td>
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<td>214</td>
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<td>China</td>
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<td>653</td>
<td>597</td>
<td>610</td>
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<tr>
<td>India</td>
<td>54</td>
<td>49</td>
<td>24</td>
<td>17</td>
<td>15</td>
<td>8</td>
<td>70</td>
<td>64</td>
<td>32</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>European Union (EU-28)</td>
<td>214</td>
<td>185</td>
<td>234</td>
<td>99</td>
<td>82</td>
<td>106</td>
<td>313</td>
<td>268</td>
<td>340</td>
<td></td>
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</tr>
</tbody>
</table>
Lung Cancer Sats 2012
1.8 million new cases (12.8%)
58 % in less developed regions
Top of the list of men cancers
Most common cause of death worldwide (1 in 5 -19.4% of total)
Estimated Lung Cancer Incidence Worldwide in 2012: Men
Estimated Lung Cancer Mortality Worldwide in 2012: Men
Patterns of Occurrence

• **Survival**
  
  – The 5-year relative survival rate for lung cancer in the United States for the period of 2001 to 2007 is 16.3%, which is up from 12.3% in 1975 to 1977
  
  – 5-year survival depends on the stage but other factors account for survival include being older, male, and African American

• **Sex**

  – Commonest male cancer
  – Lung cancer kills more women than breast cancer
  – Smoking trends peaked two decades earlier in men that’s why women epidemic started late
  – A recent analysis of 2003 to 2007 data for the first time detected a significant downturn in incidence and mortality rates in US women

• **Race and Ethnicity**
  – rates are about 47% higher among African American men than among white men
  – Greater mortality from lung cancer, with the largest disparity in rates being 42% greater than for European American men in 1990; the excess decreased to 25% in 2008.
  – Greater susceptibility of African American smokers to smoking-induced lung carcinogenesis

• Asians
  – Asian ancestry have consistently been observed to have better survival than whites.
  – ?tumor characteristics- the prevalence of epidermal growth factor receptor mutations in lung tumors is much higher in asian than in whites- more responsive to gefitinib

• **Socioeconomic Status**
  
  – Lung cancer is more likely to occur in poorer and less-educated populations- smoking habits
  – Lung cancer is inversely associated with income, education, and social class
  – Positive association with worse prognosis and poor survival

Global Trends

- Age-standardized incidence rates vary 60-fold in both men and women globally.
- In men, the highest annual lung cancer incidence rates are in central and eastern Europe and North America (60+/100,000).
- For both sexes, the lowest incidence rates are in Africa (3 ASR/100,000).
- Lung cancer is now the fourth most frequent cancer of women (513,000 cases, 8.5% of all cancers) and the second most common cause of death from cancer.
MENA Region

• Lower than US and Europe
• Significant variations
  – Lung cancer incidence is about 15 fold times higher in Tunisia than in Sudan for men, and about 10 fold times higher in Bahrain than in Yemen for females.
  – Population growth, aging, increased smoking prevalence particularly in youth and women, as well as increased exposures to environmental pollutants in the region would play in an increase in future
• 2008 data estimate, there were 16,632 newly diagnosed lung cancer cases among the Arab league countries nationals. 13,826 cases (79.7%) of them were males and 2,806 (20.3%) were females. The majority of cases were reported in Arab countries in North Africa such as Egypt (20.6%), followed by Morocco (20.1%), Algeria (15.4%) and Tunisia (10%) for both males and females.

Age-standardised Incidence and Mortality Rates of Lung Cancer in the Arab World in Comparison with Different Parts of the World

Comparison with Different Parts of the World

- Arab countries were all below 5 (Figures 6 and 7).
- African incidence is lower than in African-Americans, in the latter, the rate is 87%.
- Stellman and associates found that lung cancer is frequent in Asian, white, and Northern America men, whereas it is rare in women, the cancer receptor (MET) has been reported in the lowest frequency in the Arab World, both sexes.

Figure 7. Incidence and Mortalities ASRs of Lung Cancer in All Arab Countries

- The survey examined a nearby investigation.
- ASRs refers to age-standardised rates in the range of 60-40 years old.

*Data is a sum of 22 Arab countries extracted from Ferlay et al., (2010).
Incidence & Mortality of Lung Cancer in Arab Countries-Males
Incidence & Mortality of Lung Cancer in Arab Countries-Females
Middle-East and Northern Africa (MENA): Male, all ages

ASR (W)

Lung Prostate Bladder Colonum Liver Stomach Leukaemia Brain, nervous system Larynx Kidney Pancreas Lip, oral cavity Oesophagus Hodgkin lymphoma Thyroid Multiple myeloma Nasopharynx Gallbladder Testis Melanoma of skin Other pharynx Kaposi sarcoma

Incidence Mortality

GLOBOCAN 2012 (IARC) (26.1.2014)
International Agency for Research: Middle-East and Northern Africa (MENA): Both sexes, all ages

![Graph showing ASR (age-standardized rates) for various cancer sites in MENA region for both incidence and mortality.](image-url)
Middle-East and Northern Africa (MENA): Female, all ages

ASR (W)

Breast
Colon/rectum
Cervix uteri
Corpus uteri
Ovary
Lung
Stomach
Liver
Lymphoma
Brain, nervous system
Bladder
Pancreas
Kidney
Esophagus
Lip, oral cavity
Gallbladder
Hodgkin lymphoma
Multiple myeloma
Melanoma of skin
Nasopharynx
Larynx
Other pharynx
Kaposi sarcoma

Incidence
Mortality

GLOBOCAN 2012 (IARC) (26.1.2014)
Cancer in Saudi Arabia
<table>
<thead>
<tr>
<th>Country</th>
<th>Median age at diagnosis</th>
<th>%&lt; 45years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>67.0</td>
<td>15</td>
</tr>
<tr>
<td>Bahrain</td>
<td>69.5</td>
<td>00</td>
</tr>
<tr>
<td>Egypt</td>
<td>60.0</td>
<td>12.1</td>
</tr>
<tr>
<td>U.A. Emirates</td>
<td>63.4</td>
<td>-</td>
</tr>
<tr>
<td>Jordan</td>
<td>63.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Kuwait</td>
<td>70.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Oman</td>
<td>61.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Qatar</td>
<td>60.8</td>
<td>-</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>65.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>
## GLOBOCAN 2012

**Cancer Incidence, Mortality and Prevalence Worldwide**

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated number of new cancers (all ages)</th>
<th>Male</th>
<th>Female</th>
<th>Both sexes</th>
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<tr>
<td>2012</td>
<td></td>
<td>43562</td>
<td>3342</td>
<td>52904</td>
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<tr>
<td></td>
<td>ages &lt; 65</td>
<td>25964</td>
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<td>31095</td>
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<td></td>
<td>ages &gt;= 65</td>
<td>17578</td>
<td>1231</td>
<td>21809</td>
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<td>2015</td>
<td></td>
<td>47666</td>
<td>10366</td>
<td>58032</td>
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<tr>
<td></td>
<td>ages &lt; 65</td>
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<td>5500</td>
<td>25730</td>
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<td>ages &gt;= 65</td>
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<td>4766</td>
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<td>change</td>
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<td>5148</td>
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<td>ages &lt; 65</td>
<td>2524</td>
<td>469</td>
<td>2715</td>
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<tr>
<td></td>
<td>ages &gt;= 65</td>
<td>1870</td>
<td>555</td>
<td>2423</td>
</tr>
</tbody>
</table>

*Population forecasts were extracted from the United Nations, World Population prospects, the 2012 revision. Numbers are computed using age-specific rates and corresponding populations for 10 age-groups.*
Risk Factors

• Concept of interrelationship between;
  (1) exposure to etiologic agents and
  (2) individual susceptibility to these agents

• Synergistic interactions
  – Smoking & asbestos
  – Smoking & Radon
Tobacco Smoking – 80-90% cases
20-fold increase in lung cancer risk
All four types are caused by cigarette smoking
Adenocarcinoma > squamous cell carcinoma in developed countries due probably to change in smoking habits.
Cigar smoking is also an established cause of lung cancer
Environmental and Occupational Agents

• Pipe (shisha) smoking and Bidi (rolled leaf) same risk as cigar—both less than cigarette smoking

• No evidence for marijuana so far

Environmental and Occupational Agents

• Secondhand Smoke Exposure
  – (class A) carcinogen & is a cause of lung cancer among nonsmokers
  – estimated to cause 3,000 lung cancer deaths per year in the United States
  – 20% to 30% increased risk of lung cancer especially if living together


• Never Smokers
  – Global estimate 300,000 lung cancer deaths annually are in never smoker
  – Ranges from 4.8 to 20.8 per 100,000 among individuals aged 40 to 79 years
  – Lung cancer death rates are greater in men than in women and greater in African Americans and in Asians
  – Possible second-hand smoke, radon, and occupational carcinogens


Diet

- Fruits and vegetables inversely associated with lung cancer risk (probable)
- High-dose b-carotene consumption is associated with an increased risk of lung cancer in smokers
- High alcohol consumption in a meta-analysis was associated with high risk of lung cancer
- Low BMI higher risk for lung Ca.


• Physical Activity
  
  – A meta-analysis of leisure activity observed that both moderate and high levels of physical activity are associated with a 13% to 30% decrease in lung cancer risk

Environmental Exposures

• Occupational Exposures
  – Lung cancer is the most common among cancers associated with occupational exposures accounting for around 10%
  – Occupational exposures to soot and tar, metals including arsenic, chromium, and nickel, are also causes of lung cancer


Environmental Exposures

• Asbestos
  – a well-established occupational carcinogen
  – occupational asbestos exposure and lung cancer is greater than a fivefold excess risk
  – Asbestos and cigarette smoking are both independent causes of lung cancer, but in combination, they act synergistically to markedly increase lung cancer risk


Environmental Exposures

• Radiation
  – exposure to ionizing radiation is a risk factor for developing lung cancer;
  (1) low linear energy transfer (LET) radiation (eg, x-rays, g-rays)
  (2) high-LET radiation (eg, neutrons, radon)

• Low-LET Radiation: X-rays and g-rays
  – studied in relation to lung cancer in atomic bomb survivors in Japan
  – Doses from CT scans can be large enough to cause population excess of cancer
  – Risk models indicate that the risks associated with low- dose spiral CT screening before age 50 would likely outweigh the future benefits in mortality reduction


• High-LET Radiation: Radon
  – Radon is an inert gas that is produced naturally from radium in the decay series of uranium
  – Radon in indoor air is associated with an increased risk for lung cancer
  – Cigarette smoking and radon decay products synergistically influence lung cancer risk
  – 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon
Air Pollution

• Atmospheric Air and indoor Pollution
  – Developed world- strong lung cancer risk in never smokers are passive smoking and radon in inpatient pollution
  – Developing world- concern is for unprocessed solid fuels, notably soft coal (a fossil fuel) and bio-mass fuels, for cooking and space heating

Host Factors

• family history of lung cancer is strongly associated with increased risk of lung cancer

• A meta-analysis of 41 published cohort and case-control studies found that having a positive family history of lung cancer was associated with a 1.7-fold increased risk of lung cancer

Presence of Acquired Lung Disease

- **COPD**
  - Positive association
  - moderate or severe obstructive lung disease was associated with a 2.8-fold increased risk of lung cancer
  - a1ATD carriers had a 1.7-fold increased risk of lung cancer

- **Asthma**
  - Evidence is conflicting

- **Pneumoconiosis**
  - Silicosis known lung carcinogen –dose dependent
Presence of Acquired Lung Disease

- **Idiopathic Pulmonary Fibrosis (IPF)**
  - In autopsy studies, high proportions of lung cancer were seen in those with IPF
  - 10-year cumulative incidence of lung cancer in a series of 103 patients with IPF was 55%

- **Systemic Sclerosis (SSc)**
  - Lung cancer is the most frequently reported malignancy in SSc
  - Inflammation and fibrosis cause repeated cellular injury
  - Use of immunosuppressive drugs
Infections

1. TB
2. HIV

- Lung cancer is now the third most frequent neoplasm in individuals with HIV infection (KS, NHL)
- Accounts for 16% of deaths in patients with HIV infection
- Relative risk estimates ranging from 2 to 11
- The average latency between HIV and lung cancer diagnosis is at least 5 years
Biomarkers

• **Tissue-Based Molecular Assays of Carcinogenesis and Risk**
  – The most definitive approach to detecting lung cancer is by directly examining lung tissue, either conventionally (eg, microscopy, immunohistochemistry) or by
  – newer molecular methods - DNA- based genome-wide searches of tumors
  – somatic copy number aberrations (CNAs)
  – Premalignant squamous dysplastic lesions harboring CNAs at specific sites predicted with 97% accuracy the later occurrence of squamous cell cancer at the same site
Biomarkers

• DNA Methylation Markers
  – Progressive DNA methylation, especially in tumor suppressor genes, plays a central role in lung carcinogenesis.
  – Using a candidate gene approach, distinguished by methylation status neoplastic from nonneoplastic lung tissue with 94% sensitivity and 90% specificity


Biomarkers

- Noninvasively obtained tissues in asymptomatic populations include exfoliated cells in sputum or the circulating macro-molecules of blood.
- Commonly used techniques are polymerase chain reaction (PCR) assays of DNA and RNA, and MS-based methods.
- PCR assays have excellent sensitivity.
Biomarkers

- **Blood-Based Markers**
  
  1. DNA-Based Markers - based on carcinogen metabolism, DNA repair, and inflammation pathways - Results inconsistent
  
  2. DNA Methylation – ineffective as diagnostic tool but recent results more encouraging
  
  3. RNA-Based Markers - Blood mononuclear cells are a more robust source than plasma or serum, yielding 76% sensitivity and 82% specificity in lung cancer detection
  
  4. Proteomic-Based Markers
Biomarkers

• Sputum-Based Cytology
  – Standard sputum sensitivity is only 30% to 50% for proximal, slow growing lesions
  1. Sputum for DNA-Based Markers -
  2. DNA Methylation in Sputa
  3. Sputum for RNA-Based Markers - APRIL (a proliferation-inducing ligand) mRNA amplification from sputum appears to be feasible and yielded 82% sensitivity and 97% specificity
  4. Sputum for Protein-Based Markers- in a case-control study, sputum telomerase activity yielded 68% sensitivity and 90% specificity for concurrent lung cancer.
Biomarkers

• Exhaled Breath for Volatile Small Compounds - exhaled breath can be used to identify individual volatile components (e.g., volatile organic compounds [VOC]) or complex volatile mixtures that indicate the presence of lung cancer.

• In simulations, lung cancer cases were discriminated from control subjects with 54% sensitivity and 99% specificity.
Summary of biomarkers

• Innovative approaches are being used to develop biomarkers of lung cancer risk and early detection
• Most of the evidence to date has been based on associations in case-control studies
• Challenge is to translate this into meaningful predictive power for risk of lung cancer in prospective studies
• Validation studies for some of the most promising markers are under way, holding promise for future translation to lung cancer prevention and detection efforts.
## Summary of Risk Factors

### Table 1—Summary of Findings: Key Factors Associated With Risk of Lung Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Single most important causal determinant of individual and...</strong></td>
<td>Active smoking of cigarettes and other tobacco products:</td>
</tr>
<tr>
<td>population risk, most valuable indicator of clinical riskc</td>
<td>Individual risk increases with greater number of cigarettes smoked per day and</td>
</tr>
<tr>
<td></td>
<td>greater number of years of smoking. Population risk increases with the</td>
</tr>
<tr>
<td></td>
<td>prevalence of current smokers because population prevalence predicts lung</td>
</tr>
<tr>
<td></td>
<td>cancer occurrence with a latency period of about 20 y.</td>
</tr>
<tr>
<td><strong>B. Other risk factors causally associated with lung cancerc</strong></td>
<td>Secondhand smoke exposure</td>
</tr>
<tr>
<td></td>
<td>Ionizing radiation, including radon</td>
</tr>
<tr>
<td></td>
<td>Occupational exposures, e.g., arsenic, chromium, nickel, asbestos, tar,</td>
</tr>
<tr>
<td></td>
<td>and soot</td>
</tr>
<tr>
<td></td>
<td>Indoor and outdoor air pollution</td>
</tr>
<tr>
<td><strong>C. Additional clinical risk indicatorsb</strong></td>
<td>The risk factors noted above, plus:</td>
</tr>
<tr>
<td></td>
<td>Older age</td>
</tr>
<tr>
<td></td>
<td>Male sex, particularly among those of African American ancestry</td>
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<tr>
<td></td>
<td>Family history of lung cancer</td>
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<tr>
<td></td>
<td>Acquired lung disease, e.g., COPD, TB, pneumoconioses, idiopathic pulmonary</td>
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<tr>
<td></td>
<td>fibrosis, and systemic sclerosis</td>
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<td></td>
<td>Occupational exposures, such as silica dust</td>
</tr>
<tr>
<td></td>
<td>HIV infection</td>
</tr>
<tr>
<td><strong>D. Examples of associations with consistent evidence but causal role...</strong></td>
<td>Fruit and vegetable intake (decreased risk)</td>
</tr>
<tr>
<td></td>
<td>Physical activity (decreased risk)</td>
</tr>
<tr>
<td></td>
<td>Marijuana smoking (not associated with risk)</td>
</tr>
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</table>
• Thank you

• Any questions