Cancer Screening

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Outline

• Definition and principles of cancer screening
• Cancer incidence and mortality
• Recommendations of screening and diagnostic aspects for each common cancer
Definition of Cancer Screening

- Identify cancer at earlier stage
- **Asymptomatic** individual with **average risk**
- Earlier therapeutic intervention is available
- Lead to **reduction in cancer mortality** or severity of the disease

Levels of Cancer Prevention

- **Disease onset**
  - No disease
  - Primary: Remove risk factors
  - Secondary: Early detection and treatment
  - Tertiary: Reduce complications

- **Clinical diagnosis**
  - Asymptomatic disease
Principles of Cancer Screening

- Important public health problem: frequency and/or severity
- Window of opportunity for early detection: detectable preclinical phase
- Treatment should be available or more effective at the earlier stage
Suitable Screening Test

- Scientifically validated
  - Sensitivity, specificity, positive predictive value

Avoid: over diagnosis
  - increase testing/invasive testing/procedure
  - anxiety of a potential cancer diagnosis

- Cost effectiveness
Cancer Incidence in more developed regions

Cancer Incidence in less developed regions

- Lung: 1066 (13.3%)
- Breast: 883 (11.0%)
- Stomach: 677 (8.4%)
- Liver: 648 (8.1%)
- Colorectum: 624 (7.8%)
- Leukaemia: 211 (2.6%)
- Prostate: 353 (4.4%)
- Oesophagus: 370 (4.6%)
- Cervix uteri: 445 (5.5%)

Other: 2738 (34.2%)

Less developed regions: total 8014

# Cancer Incidence and Mortality: men/women

The table below shows the estimated number of cases and deaths for different types of cancer in more developed and less developed regions.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>More Developed Regions</th>
<th>Less Developed Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu</td>
<td>794</td>
<td>324</td>
</tr>
<tr>
<td>Prost</td>
<td>338</td>
<td>163</td>
</tr>
<tr>
<td>Colorect</td>
<td>210</td>
<td>281</td>
</tr>
<tr>
<td>Stoma</td>
<td>268</td>
<td>186</td>
</tr>
<tr>
<td>Lii</td>
<td>158</td>
<td>221</td>
</tr>
<tr>
<td>Blade</td>
<td>338</td>
<td>230</td>
</tr>
<tr>
<td>Oesophag</td>
<td>168</td>
<td>152</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>100</td>
<td>139</td>
</tr>
<tr>
<td>Kidn</td>
<td>99</td>
<td>186</td>
</tr>
<tr>
<td>Leukaen</td>
<td>89</td>
<td>182</td>
</tr>
<tr>
<td>Lip, oral cav</td>
<td>89</td>
<td>182</td>
</tr>
<tr>
<td>Pancre</td>
<td>61</td>
<td>90</td>
</tr>
<tr>
<td>Brain, nervous system</td>
<td>41</td>
<td>76</td>
</tr>
<tr>
<td>Lary</td>
<td>75</td>
<td>53</td>
</tr>
</tbody>
</table>

The graph on the right illustrates the data in a bar chart, showing the incidence and mortality for each type of cancer.
### Age-standardized incidence rates (ASR) of all cancers

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>33.9</td>
<td>Breast</td>
</tr>
<tr>
<td>Lung</td>
<td>22.7</td>
<td>28.5</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>14.4</td>
<td>Cervix</td>
</tr>
<tr>
<td>Prostate</td>
<td>7.1</td>
<td>Liver</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>6.2</td>
<td>Colon/rectum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.1</td>
</tr>
</tbody>
</table>

Common Cancers

- Hepatobiliary cancer
- Lung cancer
- Colorectal cancer
- Breast cancer
- Cervical cancer
- Prostate cancer
Hepatobiliary Cancer

- Hepatocellular carcinoma
- Cholangiocarcinoma
Hepatocellular carcinoma

Viral infections

- **Hepatitis B virus (HBV)**
  - Common in Asia and Africa
  - Seropositive for HBeAg
  - High serum HBV DNA
  - Family history of HCC

- **Hepatitis C virus (HCV)**
  - Common in Europe, Japan and North America
  - High serum HCV RNA viral load

Non viral causes

- **Cirrhosis**
  - Alcoholic cirrhosis
  - Genetic hemochromatosis
  - Alpha-1 antitripsin deficiency
  - Stage IV primary biliary cirrhosis
  - Porphyria cutanea tarda
  - Wilson disease
  - NAFLD or NASH

- **Environmental exposure to aflatoxin**
### Screening Tests for HCC

<table>
<thead>
<tr>
<th>Methods</th>
<th>Detection rate</th>
<th>False positive rate</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver ultrasound (US)</td>
<td>84%</td>
<td>2.9%</td>
<td>6.6%</td>
</tr>
<tr>
<td>AFP</td>
<td>69%</td>
<td>5.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Combination of US and AFP</td>
<td>92%</td>
<td>7.5%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

RCT of Screening for HCC

- Primary outcome: HCC mortality

Results of RCT

- 58.2% of the screen group completed the screening offered

- HCC mortality rate was significantly lower in the screened group

- Mortality rate ratio of 0.63 (95% CI 0.41, 0.98)

- Biannual screening reduced HCC mortality by 37%

<table>
<thead>
<tr>
<th>Group</th>
<th>Subclinical HCC</th>
<th>Small HCC</th>
<th>Resection</th>
<th>1-yr survival</th>
<th>3-yr survival</th>
<th>5-yr survival</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>52</td>
<td>39</td>
<td>40</td>
<td>65.9%</td>
<td>52.6%</td>
<td>46.4%</td>
<td>32</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>31.2%</td>
<td>7.2%</td>
<td>0%</td>
<td>54</td>
</tr>
</tbody>
</table>

Recommendation for Screening of HCC

Persons at risk for HCC

Liver US and AFP every 6-12 months

Rising AFP / liver nodule

3 phase CT or MRI

Cholangiocarcinoma (CCA)

- Extrahepatic cholangiocarcinoma
  - Hilar cholangiocarcinoma (Klatskin tumor)
  - Distal cholangiocarcinoma
- Intrahepatic cholangiocarcinoma

<table>
<thead>
<tr>
<th>Primary sclerosing cholangitis</th>
<th>Inflammatory bowel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatolithiasis</td>
<td>HCV, HBV, cirrhosis</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>Diabetes, obesity, NAFLD</td>
</tr>
<tr>
<td>Liver fluke infection</td>
<td>Alcohol, tobacco</td>
</tr>
</tbody>
</table>
Recommendation for Screening of CCA

- Screening program is currently not established worldwide
- A 5-year population-based study for CCA screening in Ban Luang District, Nan Province, started in 10/2011
  - Liver US, stool examination for parasites
  - CBC, LFT, HBsAg, HBcAb, CEA, CA19-9, AFP
- CCA was detected in 32 out of 4,225 individuals
- 21/32 cases were at a curative resectable stage
- One- and 2-year OS of CCA patients were 90.9 and 61.5 %
- The Cholangiocarcinoma Screening and Care Program (CASCAP) is ongoing

Lung Cancer

- Leading cause of cancer-related mortality worldwide
- Risk factors for lung cancer
  - Tobacco smoke: active tobacco smoke, second-hand smoke
  - Occupational exposure to carcinogen
  - Residential radon exposure
  - History of cancer
  - Family history of lung cancer
  - History of lung disease: COPD, pulmonary fibrosis
Screening Tests for Lung Cancer

Modalities
- Sputum cytological examination
- Chest x-ray
- Low-dose CT scan

no benefit in reduction of cancer mortality
Low-dose CT scan (LDCT)

• Non contrast CT scan
• Lower radiation exposure when compare with conventional CT scan
• Detect non-calcified lung nodules: size and type
  • Solid
  • Subsolid:
    • Nonsolid or ground-glass opacities
    • Part-solid
Benefits and Risks of Lung Cancer Screening

Benefits
- Improvement of oncology outcomes
- Improvement of quality of life
  - Reduction in disease and treatment related morbidity
  - Increase smoking cessation
  - Reduction in anxiety

Risks
- False-positive results
- False-negative results
- Futile detection of small aggressive tumor
- Futile detection of indolent disease
- Indeterminate results
- Radiation exposure
- Physical complications from diagnostic workup
National Lung Screening Trial

- Large randomized, multicenter trial of current and former heavy smokers

Current and former heavy smokers,* 55-74 yrs of age (N = > 53,000)

Baseline screening

Low-dose CT scan

Stratified by emphysema risk, fibrosis, family history of cancer

Chest x-ray

2 annual follow-up scans

26,722 persons

26,732 persons

*≥ 30 pack-yrs; former smokers quit within last 15 yrs.

- Primary endpoint: lung cancer mortality
- Secondary endpoints: overall mortality, lung cancer incidence, screening- and treatment-related morbidities

### Results

<table>
<thead>
<tr>
<th></th>
<th>LD CT</th>
<th>CXR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td>95%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td><strong>Positive screening test</strong></td>
<td>24.2%</td>
<td>6.9%</td>
<td></td>
</tr>
<tr>
<td><strong>False positive</strong></td>
<td>96.4%</td>
<td>94.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>645</td>
<td>572</td>
<td></td>
</tr>
<tr>
<td><strong>Deaths from lung cancer</strong></td>
<td>247</td>
<td>309</td>
<td>RRR = 20.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI, 6.8 to 26.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.004</td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td>1877</td>
<td>2000</td>
<td>RRR = 6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI, 1.2 to 13.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.02</td>
</tr>
</tbody>
</table>

Recommendation for Screening of Lung Cancer

- Individuals with high-risk factors
  - Age 55 to 74
  - 30 or more pack-year history of smoking
  - Currently smoke or have quit within 15 years

- Screening: LDCT
- Candidates for screening
- Shared decision making
- Multidisciplinary team approach

NCCN Guidelines Version 1.2017
Colorectal Cancer (CRC)

Adenoma-carcinoma sequence

CRC Screening Tools

Fecal-based tests
- Guaiac-based fecal occult blood test (gFOBT)
- Fecal immunochemical test (FIT)
- Multitargeted stool DNA test (FIT-DNA)

Structural tests
- Flexible sigmoidoscopy
- Colonoscopy
- CT colonography
Fecal Occult Blood Testing (FOBT)

- Effect on CRC mortality has been validated by randomized trials
- Simple, non-invasive and cheap
- Relatively poor sensitivity
- Test sensitivity can be increased through repetitive screening
- Two types of FOBT screening are available:
  ◦ Guaiac-based FOBT
  ◦ Fecal immunochemical test (FIT)
- Require evaluation with colonoscopy after positive test
Guaiac-based FOBT

- Peroxidase activity of heme in human blood
- Sensitivity for detecting cancer ranged from 37% to 79%
- Guaiac FOBT should be performed on 3 successive stool specimens
- High false positive rate from reaction with non human heme in food
- A meta-analysis of 4 RCTs involving more than 320,000 participants showed a 16% reduction in relative risk for CRC death (95% CI 0.78,0.90)

Fecal Immunochemical Test (FIT)

- FIT directly detects human globin
- Not require dietary restriction
- A single testing sample is sufficient
- Improved sensitivity compared with gFOBT for detecting CRC
  - Sensitivity 56%-89%
  - Specificity 91%-97%

Bretthauer M, J Int Med 2011;270:87-98
Multitargeted Stool DNA Test (FIT-DNA)

- An emerging screening strategy that combines a FIT with testing for altered DNA biomarkers on cells shed into stool
- Increased single-test sensitivity for detecting CRC compared with FIT alone
- Specificity of FIT-DNA is lower than that of FIT alone
- Cologuard: sensitivity 92% (95% CI 84,97) specificity 84% (95% CI 84,95)

Imperiale TF, et al. NEJM 2014;370(14)1287-1297
Lin JS, et al. JAMA 2016;315(23):2576-2594
Flexible Sigmoidoscopy (SIG)

- Four large RCTs (N = 458,002) evaluated effectiveness of 1 or 2 rounds of SIG in average-risk adults aged 50-74 years
- SIG was associated with lower CRC-specific mortality compared with no screening at 12 years of follow-up: Incidence rate ratio 0.73 (95% CI 0.66, 0.82)
- Mortality benefit was limited to distal CRC: incidence rate ratio 0.63 (95% CI 0.49, 0.84)

Segnan N, JNCI 2011:103(17):1310-1322
Holme O, et al. JAMA 2014;312(6):606-615
Colonoscopy

- Current gold standard for assessing the efficacy of other screening methods
- Allowing entire colon to be examined and polyps to be removed in one session
- Evidence based on case control and cohort studies show significant impact of colonoscopy and polypectomy on CRC incidence (> 50% reduction)
- Invasive procedure, require sedation, bowel cleansing
- Risk of perforation 4 in 10,000; major bleeding 8 in 10,000; Increased risk with increasing age

Lin JS, et al. JAMA 2016;315(23):2576-2594
CT Colonography (CTC)

- Promising technique for CRC screening
- Non invasive, not requiring sedation
- Positive finding requires colonoscopy
- Extracolonic findings were common 27%-69% of examinations
- Cumulative exposure to low dose radiation
- Detection of adenomas ≥ 10 mm: sensitivity 67%-94%, specificity 86%-98% for CTC with bowel preparation

Lin JS, et al. JAMA 2016;315(23):2576-2594
Recommendation for CRC Screening

- Age > 50 years
- No Hx of adenoma
- No Hx of inflammatory bowel disease
- Negative family Hx

Individual at average risk for CRC
# CRC Screening Strategies

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Frequency</th>
<th>Evidence of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBT</td>
<td>Every year</td>
<td>RCTs with mortality EP&lt;br&gt;High sensitivity version</td>
</tr>
<tr>
<td>FIT</td>
<td>Every year</td>
<td>Test characteristic studies</td>
</tr>
<tr>
<td>FIT-DNA</td>
<td>Every 1 or 3 y</td>
<td>Test characteristic studies</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 y</td>
<td>Prospective cohort study with mortality EP</td>
</tr>
<tr>
<td>CT colonography</td>
<td>Every 5 y</td>
<td>Test characteristic studies</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>Every 5 y</td>
<td>RCTs with mortality EP</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy with FIT</td>
<td>SIG q 10 y plus FIT every year</td>
<td>RCT with mortality EP (subgroup analysis)</td>
</tr>
</tbody>
</table>
Breast Cancer

Modalities

• Breast Self Examination (BSE)
• Clinical Breast Examination (CBE)
• Mammography
• Breast MRI
## Recommendation for Breast Cancer Screening

<table>
<thead>
<tr>
<th>Population</th>
<th>Screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACS 2016</strong></td>
<td></td>
</tr>
<tr>
<td>Age 40-44</td>
<td>Have a choice to start mammography</td>
</tr>
<tr>
<td>Age 45-54</td>
<td>Annual mammography</td>
</tr>
<tr>
<td>Age ≥ 55</td>
<td>Mammography q 1-2 y</td>
</tr>
<tr>
<td><strong>NCCN 2016</strong></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 25-39</td>
<td>CBE q 1-3 yrs and breast awareness by BSE</td>
</tr>
<tr>
<td>Age ≥ 40</td>
<td>Annual CBE and annual mammography and breast</td>
</tr>
<tr>
<td></td>
<td>awareness</td>
</tr>
<tr>
<td><strong>USPSTF 2016</strong></td>
<td></td>
</tr>
<tr>
<td>Age 40-49</td>
<td>Individual decision whether to get mammography</td>
</tr>
<tr>
<td>Age 50-74</td>
<td>every 2 y Mammography q 2 y</td>
</tr>
</tbody>
</table>
Cervical Cancer

- Screening with Pap testing has successfully decreased cervical cancer incidence and mortality
- Persistent cervical infection with high-risk HPV genotypes
- Nearly 100% of cervical cancer cases test positive for HPV
  - HPV type 16 accounts for 55-60%
  - HPV type 18 accounts for 10-15%
  - Other genotypes: 25-35%
<table>
<thead>
<tr>
<th></th>
<th>USPSTF 2012</th>
<th>ACS 2012</th>
<th>NCCN 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start screening</td>
<td>Within 3 yrs after sexual activity, ≥21 yrs</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 30 yrs</td>
<td>Pap tests q 3 yrs</td>
<td>Pap tests q 3 yrs (acceptable)</td>
<td>Pap tests q 3 yrs (acceptable)</td>
</tr>
<tr>
<td>Age ≥30 yrs</td>
<td>Pap tests q 3 yrs (acceptable)</td>
<td>Pap tests q 3 yrs (acceptable)</td>
<td>Pap tests q 3 yrs (acceptable)</td>
</tr>
<tr>
<td>HPV DNA testing</td>
<td>age ≥ 30 yrs* q 5 yrs with Pap (prefer)</td>
<td>age ≥ 30 yrs* q 5 yrs with Pap (prefer)</td>
<td>Age ≥ 30 yrs* q 5 yrs with Pap (prefer)</td>
</tr>
<tr>
<td>Stop screening</td>
<td>Age 65 after regular normal Pap</td>
<td>Age 65 after regular normal Pap</td>
<td>Age 65 after regular normal Pap</td>
</tr>
</tbody>
</table>
Prostate Cancer

- A spectrum of disease that ranges from non-aggressive, slow-growing disease to aggressive, fast-growing disease
- PSA testing for early detection of prostate cancer in informed, healthy men in certain age group
- Level I evidence from RCT that observed a reduction in prostate cancer-specific mortality in men who underwent PSA screening
Prostate Specific Antigen (PSA)

- Glycoprotein produced by prostatic epithelium
- Protease activity lyses clotted ejaculate to enhance sperm motility
- Normal level < 4 ng/mL
- Elevated levels
  - Prostate cancer
  - Prostatitis
  - Benign prostatic hypertrophy (BPH)
  - Prostatic trauma, after ejaculation
Prostate Specific Antigen (PSA)

- No single PSA cut-off separates
  - men at high risk for prostate cancer (Pca) from men at low risk
  - men affected with high-grade disease from those with low-grade disease

- 22% of men with a normal DRE and a serum PSA level between 2.6 and 4.0 ng/mL have PCa, and 81% of them have organ-confined disease†

- 15% of men with normal DRE and a serum PSA < 4.0 ng/mL have PCa‡

Percent-free PSA (fPSA)

- Several molecular forms of PSA circulate in blood
- 60-90% of circulating PSA is bound to endogenous protease inhibitors
  - $\alpha$-1-antichymotrypsin (complex PSA, cPSA)
  - $\alpha$-1-antitrypsin
  - protease C inhibitor
  - $\alpha$-2-macroglobulin (AMG)
Percent-free PSA (fPSA)

- Percentage of free PSA is significantly lower in men who have prostate cancer compared with men who do not.
- US FDA approved the use of fPSA for early detection of prostate cancer in men with PSA between 4 and 10 ng/mL.
- Cut-off level 25% fPSA detected 95% of prostate cancer, avoiding 20% unnecessary biopsies.

Partin AW et al. Prostate Cancer Prostatic Dis 1998;1:197-203
Effect of 5-Alpha Reductase Inhibitor

• Decrease in serum PSA levels (30-80%) after 6 to 12 months
• After 1 year on finasteride
  35% had 40-60% decrease in serum PSA
  30% had > 60% decrease in serum PSA

## Population-based Screening Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>N</th>
<th>Screening</th>
<th>Outcome</th>
<th>HR</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERSPC</td>
<td>50-74</td>
<td>182,000</td>
<td>PSA q 4 y DRE</td>
<td>Death from PC</td>
<td>0.79 (0.68, 0.91)</td>
<td>P=0.001  NNT 1055 37 to be treated</td>
</tr>
<tr>
<td>Goteborg</td>
<td>50-64</td>
<td>20,000</td>
<td>PSA q 2 y</td>
<td>Death from PC</td>
<td>0.72 (0.5, 0.94)</td>
<td>NNT 139 13 to diagnose</td>
</tr>
<tr>
<td>PLCO</td>
<td>55-74</td>
<td>76,885</td>
<td>Annual PSA x 6 DRE x 4</td>
<td>Death from PC</td>
<td>1.09 (0.87, 1.36)</td>
<td>Contamination</td>
</tr>
</tbody>
</table>
Recommendation for Prostate Cancer Screening

- Age 45-75 years
- Risk and benefit discussion about prostate cancer screening
- PSA
- Digital rectal examination (DRE)
  - PSA < 1 ng/mL, normal DRE: repeat testing at 2-4 y
  - PSA 1-3 ng/mL, normal DRE: repeat testing at 1-2 y
  - PSA >3 ng/mL or suspicious DRE: repeat PSA, workup for benign disease, TRUS-guided biopsy

Serum Tumor Markers

- Serum tumor markers especially mucin-associated cancer antigens:
  - CEA
  - CA19-9
  - CA125
  - CA15-3
- have no clinical utility as screening tests for any cancer
## Take home message

<table>
<thead>
<tr>
<th>Who</th>
<th>All with &gt;50 yrs</th>
<th>Woman &gt; 40 yrs</th>
<th>High risk 55-74 yrs</th>
<th>Women with sexually active or age &gt; 21 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>How</td>
<td>colonoscopy</td>
<td>mammogram</td>
<td>LDCT</td>
<td>PV+PAP HPV DNA</td>
</tr>
<tr>
<td>How often</td>
<td>every 10 yr</td>
<td>yearly</td>
<td>yearly for 3 yrs</td>
<td>every 3-5 yrs</td>
</tr>
<tr>
<td>Stop screening</td>
<td>No data</td>
<td>As long as good health</td>
<td>&gt; 74 yrs</td>
<td>Age 65-70 after regular normal Pap</td>
</tr>
</tbody>
</table>
References

American Cancer Society (ACS)
National Comprehensive Cancer Network (NCCN)
The U.S. Preventive Services Task Force (USPSTF)
Question & Answer