All you need to know on tumor markers in cancer screening

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Screening

- Detection of disease in the population who have no symptoms of the disease
- To detect disease at an early stage when curative treatment is more effective
- Gold standard: decrease mortality
Tumor Markers

• **CEA** Colon Cancer
  (smoking, ulcerative colitis, liver dysfunction)

• **CA15-3, CA27.29** Breast cancer
  (benign ovarian, breast disease, cirrhosis)

• **CA125** Ovarian Cancer
  (Gynecological conditions, serositis)
Tumor Markers

- **AFP**  HCC, NSGCT,  
  (hepatitis, cirrhosis)
- **ß-HCG**  GCT, GTT,  
  (pregnancy, marijuana, hypogonadism)
- **PSA**  Prostate Cancer  
  (BPH, age, bike riding, ejaculation)
- **Ca19-9**  Pancreatic cancer

NSGCT – non seminomatous germ cell tumor, HCC – hepatocellular carcinoma, GTT – gestational trophoblastic disease, BPH – benign prostatic hyperplasia
Cancers for which tumor markers are recommended as screening tests for the general population

- No cancers are adequately screened by tumor markers in the general population

MOH clinical practice guidelines, Feb 2010, Grade A, Level 1+
Tumor Markers – some key facts:

- **Lack of specificity** (normal does not mean no cancer)
- **Cancer heterogeneity**
- **False negatives** (lack sensitivity)
- **Benign diseases positive CA 125 or CEA**
- **Smokers have raised CEA**
- **Many men (20-40% !?) die with, not from, prostate ca.**
Tumor markers which are used as screening recommended in High Risk Patients

- Hepatocellular carcinoma (AFP)
- Ovarian Cancer (CA125)
- Prostate Cancer (PSA)
AFP screening for HCC

- Only in those at high risk
- Hepatitis B carriers, chronic hepatitis B infection, and cirrhosis
- AFP every 6 months to 1 year with ultrasound
- Start at age 30 in males and 35 in females

Recent studies have shown that AFP lacks adequate sensitivity and specificity and has been dropped from some guidelines (AASLD, Mar 2011). Whether screening improves survival or mortality is unclear.
CA125 screening for ovarian cancer

- Only for those at high risk
- Genetic predisposition BRCA1 or BRCA2 (10% to 60% lifetime risk)
- Annual pelvic exam, TVUS +/- CA125
- Refer to tertiary center

MOH Clinical Practice Guidelines, Feb 2010, GPP
PSA test

• Most hotly debated
• Most widely used tumor marker test for screening (prostate cancer)
• ‘The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation). This recommendation applies to men in the general U.S. population, regardless of age.’

USPSTF, May 2012
• ESRPC study (European Randomized Study of Screening for Prostate Cancer
• 160,000 men aged 55 to 69y
• Reduced prostate cancer mortality (RRR 21%) but not all cause mortality
PSA for prostate cancer screening

- Male more than 50 years old with a family history of prostate cancer below 60 years old
- Not for men above 75 years, or less than 10 year life expectancy
- Must be given in conjunction with counseling

Many aspects of prostate cancer uncertain. High rate of false positives and associated worry, risk associated with biopsy and serious consequences of treatment have to be balanced with small reductions in prostate cancer mortality.

MOH practice guidelines, Grade D, Level 4
Conclusions

• At present there is no conclusive evidence of the benefit of measuring a serum marker as a screening test or ‘test of cancer’ in the general population

• There maybe some use in high risk patients (GPP)
Conclusions

• AFP – maybe of some use for Hepatocellular carcinoma in high risk groups e.g. Hep B carrier, chronic hepatitis, cirrhosis

• CA125 – for those with genetic predisposition, e.g. BRCA1 or BRCA2, should be referred to tertiary center with genetic counselling/cancer risk assessment
Conclusions

• Although screening for prostate cancer with PSA can reduce mortality from prostate cancer, the absolute risk reduction is very small.

• Given limitations in the design and reporting of the randomized trials, there remain important concerns that the benefits of screening are outweighed by the potential harms to quality of life, including the substantial risks for overdiagnosis and treatment complications.
Tumor Markers on Screening

- Tumor markers measurement is a low cost, rapid, accessible, and minimally invasive
- High false alarms and comforts/reassurances
- Inappropriate use of a tumor marker may result in increased anxiety for patients, increased costs, and unnecessary treatment and toxicity
# Levels of evidence and grades of recommendation

## Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.</td>
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<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.</td>
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<tr>
<td>2+++</td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.</td>
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<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td>2−</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.</td>
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<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series.</td>
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<tr>
<td>4</td>
<td>Expert opinion.</td>
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<td>Grade</td>
<td>Recommendation</td>
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<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
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<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
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<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
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<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
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<td>GPP (good practice points)</td>
<td>Recommended best practice based on the clinical experience of the guideline development group.</td>
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CEA

- Normal value <2.5ng/ml in nonsmokers, <5 in smokers
- Raised in 19% of smokers, and 3% of healthy population without cancer.
- Primary tumor: Colorectal Cancer
- Elevated in <25% of early stage cancers and 75% of late stage colon cancers
- False positives in smokers, PUD, Inflammatory Bowel disease, cirrhosis, biliary obstruction, pancreatitis, hypothyroidism
- Maybe raised in breast, gastric, lung, pancreatic, head and neck
Carcinoembryonic Antigen (CEA)

- Found in gastrointestinal mucosal cells and secretions of pancreatobiliary system
- Can occur in smokers patients with cirrhosis, pancreatitis, inflammatory bowel disease and rectal polyps
cea

• Cleared by liver
• Studies show that if cea used as a screening tool, there would be 250 false-positives indications of cancer for every true-positive
• Useful in monitoring activity of disease in recurrent colorectal cancer
Uses of CEA testing

• Antigen produced by many colon cancers
• Cannot be used for screening because it is usually (in 85% of cases) normal in Stage 1 disease.
• Testing is done preoperatively in patients undergoing resection for colon cancer, so that the data can be used for follow-up post operative period.
• Reliable indicator of tumor recurrence
• False positive results in smokers, and other types of cancer
CEA is raised in

- Liver dysfunction, including therapy related
- Gastritis
- Peptic ulcer disease
- Diverticulitis
- Liver diseases
- Chronic obstructive pulmonary disease
- Diabetes
- Any acute or chronic inflammatory disease
CA19-9

- Normal values <37u/mL
- Primary tumor: pancreatic cancer, biliary tract cancer,
- Elevated in 80% to 90% pancreatic cancers and 60% to 70% of biliary tract cancers
- False positives in pancreatitis, biliary disease, cirrhosis
PSA

• <4ng/mL for screening, undetectable after radical prostatectomy
• Primary Tumor: Prostate cancer
• Elevated in more than 75% of organ confined prostate cancers
• 20% to 30% with prostate cancer have normal PSA values
PSA

- Prostatitis
  (PSA levels return to normal within 8 weeks of symptom resolution)
- Benign Prostatic Hyperplasia
  (raised in 30% to 50% w BPH)
- Prostatic trauma
- After ejaculation
  (Waiting for 48h after ejaculation to measure PSA levels is recommended)
- Age
CA125

- <35 units per mL
- Primary Tumor: Ovarian Cancer
- Elevated in about 85% of ovarian cancers, and 50% of early stage disease
- False positives in menstruation, pregnancy, fibroids, ovarian cysts, PID, cirrhosis, serositis, endometriosis
- Maybe elevated in endometrial cancers
β-HCG

- Normal value <5mIU per mL
- Primary Tumor: GCT germ cell tumors), Gestational Trophoblastic disease
- AFP or β-HCG raised in 85% of NSGCT, elevated in 20% of early stage NSGCT
- False positive in hypogonadal states, marijuana
- Rarely raised in GI cancers
AFP

- Normal value <5.4ng/ml
- Primary Tumor: HCC, NSGCT
- False positive in cirrhosis, viral hepatitis, pregnancy
- Elevated in 80% of HCC
Alphafetoprotein (AFP)

- Made by yolk sac and liver of human fetus
- Raised in hepatomas and certain germ cell neoplasms
- Used as a sensitivemarker for disease activity
- Can be raised in acute and chronic active hepatitis