Lecture 6 – Prevention

Understanding the rationale for disease prevention and early intervention (screening)

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Objectives - Concepts

• 1. Primary (1st), Secondary (2nd), and Tertiary (3rd) prevention
• 2. Population-level vs. individual-level prevention
• 3. Screening (secondary prevention)
  • Mass screening vs. case-finding
• 4. Screening concepts
  • Pre-clinical phase, test Se & Sp, importance of trials, DSMR
• 5. Screening Biases (Observational studies)
  • Lead-time, Length-time, and Compliance
• 6. Assessing the feasibility of screening
• 7. Risks (Harms) vs. Benefits

Objectives - Skills

• 1. Identify examples of 1st, 2nd, and 3rd prevention
• 2. Communicate the pros and cons of screening
• 3. Explain the importance of lead-time and length-time bias in screening programmes
• 4. Understand how to evaluate the efficacy of screening (trials)
Primary (1o) Prevention

- **Defn:** the protection of health by personal and community-wide efforts with a focus on the whole population

- **Objectives:**
  - To prevent new cases of disease occurring and therefore reduce the incidence of disease

- **Where and How?**
  - Population-level
  - Individual level

1o Prevention @ Population-level

- By reducing exposure to causal (risk) factors
  - e.g., reducing smoking initiation in teenagers

- By adding a factor that prevents disease
  - e.g., vaccination, water fluoridation

- Usually requires policy and/or legislation
  - Smoking = tobacco taxes, restrictions on smoking indoors
  - Physical activity = structural changes to the environment
    - sidewalks, walking paths, linear parks (Town planning)

- Primary prevention at the population-level works best when it is driven by changes in societal attitudes
  - e.g., drinking and driving

1o Prevention @ Individual-level

- By removing or lowering risk factors in at-risk patients
  - Occurs at the patient-physician level
    - Rationale behind the periodic health exam (PHE)
      - e.g., smoking cessation counselling
      - e.g., risk factor screening in at-risk patients (BP, BC, Physical inactivity, abdominal obesity)

- Distinction between primary prevention and secondary prevention hinges on the presence of existing disease
  - Primary prevention = no existing disease
Secondary (2°) Prevention

- **Defn:** measures available for the early detection and prompt treatment of health problems

- **Objectives:**
  - To reduce the consequences of disease (death or morbidity) by screening asymptomatic patients to identify disease in its early stages and intervening with a treatment which is more effective because it is being applied earlier.
  - It cannot reduce disease incidence

- **Where and how do we screen?:**
  - Population-level or mass screening
  - Individual-level screening or case finding

Screening – two different approaches

- **Population-level screening**
  - National level policy decision to offer mass screening to a whole sub-group of a population
    - e.g., mammography screening (women 40+)
    - e.g., Vision and hearing screening of all Michigan 2nd graders

- **Individual-level screening**
  - Occurs at the individual patient-physician level
  - Also refereed to case finding
    - e.g., BP screening every time you visit MD
    - e.g., PSA screening
  - Also a component of the PHE.
  - Focus is on identifying existing disease in patients who don’t know they have it.

Tertiary (3°) Prevention

- **Defn:** measures available to reduce or eliminate long-term impairments and disabilities, minimize suffering, and promote adjustments to irremediable conditions

- **Objectives:**
  - To reduce the consequences of disease (esp. complications and suffering) by treating disease and/or its direct complications in symptomatic patients.

- **Examples**
  - education about disease management (asthma)
  - regular foot exams in diabetics
  - pain management in hospice patients
Example - Fire Prevention

- **Primary** (prevent fires from starting)
  - Education (Smokey the Bear)
  - Outside fire bans (drought)

- **Secondary** (early detection)
  - Smoke detectors
  - Lookout towers

- **Tertiary** (reduce consequences)
  - Fire resistant construction
  - Fire brigades & smoke jumpers

Prevention – A Reality Check

- Very few preventive interventions are cost saving
  - *e.g.*, childhood vaccination, seatbelts

- Almost all preventive interventions – even those that work well - cost money!!
  - *e.g.*, Mamm screening $40,000 per YLS

- Prof. Geoffrey Rose, 1992
  - *There is only one rationale to do prevention and that is ethical*

Prevention – A Reality Check

- Compared to the traditional clinical treatment (curative) approach, effective clinical prevention is hard to sustain because:
  - Its much less effective (as measured by NNT)
    - NNT for 1 year statin use for stroke 1st prevention = 13,000
    - NNT for lifetime seatbelt use = 400

- Prevention Paradox:
  - A measure that provides large benefit to the community may offer little to most individuals.
Screening - Introduction

- Objective: to reduce mortality and/or morbidity by early detection and treatment.
- Secondary prevention.
- Asymptomatic individuals are classified as either unlikely or possibly having disease.
- Important distinction between mass or population-based screening and case finding.
- The allure of screening brought on by new technology is almost irresistible.

Screening - Introduction

- Effective screening involves both diagnostic and treatment components

Screening differs from diagnostic testing:

<table>
<thead>
<tr>
<th>Screening</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy non-patients</td>
<td>Sick patients</td>
</tr>
<tr>
<td>No diagnostic intent</td>
<td>Diagnostic intent</td>
</tr>
<tr>
<td>Very low to low disease prevalence</td>
<td>Low to high disease prevalence</td>
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</table>
I. Important Concepts in Screening
The Pre-Clinical Phase (PCP)
• the period between when early detection by screening is possible and when the clinical diagnosis would normally have occurred.

Pathology begins  Disease detectable  Normal Clinical Presentation

Pre-clinical Phase (PCP)
• Important to know PCP since it helps determine:
  • Expected utility of screening
    - Colorectal cancer = 7-10 years
    - Childhood diabetes = 2-6 months
  • Required minimal frequency of screening
    - Mam screening women 40-49 = 1-2 years
    - Mam screening women 50-69 = 3-4 years
  • Prevalence of PCP indicates how much early disease there is to detect
  • Prevalence of PCP is affected by:
    • disease incidence, average duration of the PCP, previous screening, sensitivity of the test
    • …….see concept of Prevalence pool (Lecture 3)

Lead Time

Lead time = amount of time by which diagnosis is advanced or made earlier

Pathology begins  Disease detectable  Normal Clinical Presentation

| ← Lead Time → |

Screen
Fig 1. Relationship between screening, pre-clinical phase, clinical phase and lead time

a) No screening - no lead time
5 cases developing over 5 years
(Survival = 2yrs)

b) Screening with resultant lead time
5 cases, 3 identified by screening
(Survival = 5yrs)

Lead Time

- Equals the amount of time by which treatment is advanced or made "early"
- Not a theory or statistical artifact but what is expected and must occur with early detection
- Does not imply improved outcome!!
- *Necessary but not sufficient condition* for effective screening.

II. Characteristics of screening tests

a) Sensitivity (Se) (Prob T+|D+)
- Defn: the proportion of cases with a positive screening test among all individuals with pre-clinical disease
- Want a highly Se test in order to identify as many cases as possible...... but there's a trade off with......
II. Characteristics of screening tests

b) Specificity (Sp) (Prob T-|D-)
- Definition: the proportion of individuals with a negative screening test result among all individuals with no pre-clinical disease.
- The feasibility and efficiency of screening programs is acutely sensitive to the PVP which is often very low due to the very low disease prevalence.
  - e.g., PVP of +ve FOBT for CR CA = < 10%
- N.B. Imperfect Sp affects many (the healthy), whereas an imperfect Se affects only a few (the sick).

III. Evaluation of Screening Outcomes

How do we know if screening is helpful?

RCT
- Compare disease-specific mortality rate (DSMR) between those randomized to screening and those not.
- Eliminates all forms of bias (theoretically).
- But, problems of:
  - Expense, time consuming, logistically difficult, contamination, non-compliance, ethical concerns, changing technology.
- Can also evaluate screening programmes using Cohort and Case-control studies, but they are difficult to do and very susceptible to bias.

The only valid measure of screening is...

Disease-specific Mortality Rate (DSMR)

the number of deaths due to disease
Total person-years experience

- The only gold-standard outcome measure for screening.
- NOT affected by lead time.
- when calculated from an RCT - not affected by compliance bias or length-time bias.
- However, there can be problems with the correct assignment of cause of death (hence some researchers advocate for using all-cause mortality as an outcome).
Example of a RCT reporting DSMR to measure efficacy of FOBT screening on Colorectal CA Mortality (Mandel, NEJM 1999)

IV. Biases that effect screening studies

- Observational studies and especially survival data are acutely sensitive to:

  1. Compliance bias (Selection bias):
     - Volunteers or compliers are better educated and more health conscious – thus they have inherently better prognosis

  2. Lead-time bias
     - Apparent increased survival duration introduced by the lead time that results from screening.
     - Screen-detected cases survive longer event without benefit of early treatment (review Fig 2 in course notes).

  3. Length-time bias
     - Screening preferentially identifies slower growing or less progressive cases that have a better prognosis.

Length-time bias – cases with better prognosis detected by screening

Better Prognosis Cases

Worse Prognosis Cases
V. Pseudo-disease and Over-diagnosis

- **Over-diagnosis**
  - Limited malignant potential
  - Extreme form of length-biased sampling
  - Examp: Pap screening and cervical carcinoma

- **Competing risks**
  - Cases detected that would have been interrupted by an unrelated death
  - Examp: Prostate CA and CVD death

- **Serendipity**
  - Chance detection due to diagnostic testing for another reason
  - Examp: PSA and prostate CA, FOBT and CR CA

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Over-diagnosis – Effect of Mass Pap Screening in Connecticut (Laskey 1976)

<table>
<thead>
<tr>
<th>Year</th>
<th>In-situ</th>
<th>Invasive</th>
<th>Total</th>
<th>% In-situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-54</td>
<td>3.8</td>
<td>18.1</td>
<td>21.9</td>
<td>17</td>
</tr>
<tr>
<td>1955-59</td>
<td>9.7</td>
<td>17.1</td>
<td>26.8</td>
<td>36</td>
</tr>
<tr>
<td>1960-64</td>
<td>18.8</td>
<td>13.6</td>
<td>32.4</td>
<td>58</td>
</tr>
<tr>
<td>1965-69</td>
<td>28.6</td>
<td>11.6</td>
<td>40.2</td>
<td>71</td>
</tr>
<tr>
<td>1970-73</td>
<td>32.8</td>
<td>10.9</td>
<td>43.7</td>
<td>75</td>
</tr>
</tbody>
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VI. Assessing the feasibility of screening

- **Burden of disease**
- **Effectiveness of treatment without screening**
- **Acceptability**
  - Convenience, comfort, safety, costs (= compliance)
- **Efficacy of screening**
  - Test characteristics (Se, Sp)
  - Potential to reduce mortality
- **Efficiency**
  - Low PVP
  - Risks and costs of follow-up of test positives
  - Cost-effectiveness
    - Annual Mam screening (50-70 yrs) = $30 – 50,000 /YLS
    - Annual Pap screening (20-75 yrs) = $1,300,000 /YLS
- **Balance of risks (harms) vs. benefits**
Feasibility

- Three questions to ask before screening:
  - **Efficacy**
    - Should we screen? (scientific)
  - **Effectiveness**
    - Can we screen? (practical)
  - **Cost-effectiveness**
    - Is it worth it? (scientific, practical, policy, political)