Níveis de Evidência, Análise de Decisão e Análise de Sensibilidade

Moysés Szklo
1. BURDEN OF CANCER
  Determine health status
  (mortality, incidence,
   survival, recurrence
   rates)
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2. **ETIOLOGY AND PROGNOSIS**
   Identify risk factors and prognostic factors

Modified from: Tugwell et al, *J Chron Dis* 38(4)
INTERFACE OF EPIDEMIOLOGY AND CANCER CONTROL POLICY

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   Decide relationships between costs and effectiveness across programs/protocols

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   Ongoing monitoring of outcomes
   (Population-Based and Hospital Registries)

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INCA/DECIT/MS: Núcleo de Avaliação de Tecnologias em Saúde -- Processo de Implementação de Políticas de Controle de Câncer Baseadas em Evidências

Aquisição de evidências científicas
- Ensaios aleatorizados
- Estudos de coorte
- Estudos de casos e controles
- Estudos de séries temporais
- Estudos de processo e estrutura
- Outros estudos (ex: sensibilidade/especificidade, pesquisa qualitativa)

Revisões sistemáticas
- Colaboração Cochrane
- Outras fontes (meta-análises publicadas em revistas)
- Meta-análises realizadas no NATS-INCA

Custo-efetividade
- Avaliação de níveis de evidência
- Seleção de opções programáticas (Análise de decisão)
- Recomendações

Políticas baseadas em evidências
- Evidências
- Obstáculos

Aplicação da política:
- Evidências
- Obstáculos

Análise de sensibilidade

Estudos conduzidos no INCA

Tradução de conhecimentos
Políticas de Saúde Baseadas em Evidências

Critérios para julgar a eficácia e efetividade de uma intervenção (medida preventiva ou tratamento)

<table>
<thead>
<tr>
<th>Classificação</th>
<th>Nível de evidência</th>
<th>Descrição do nível</th>
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<tbody>
<tr>
<td><strong>melhor</strong> A</td>
<td>1a</td>
<td>Revisão sistemática de ensaios aleatorizados com homogeneidade – inclusive meta-análise</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Um único ensaio aleatorizado de boa qualidade</td>
</tr>
<tr>
<td></td>
<td>1c</td>
<td>Experimentos “naturais” (exemplo: estreptomicina e meningite tuberculosa) e séries temporais</td>
</tr>
<tr>
<td>B</td>
<td>2a.</td>
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</tr>
<tr>
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<td>2b</td>
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</tr>
<tr>
<td>D</td>
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<tr>
<td></td>
<td>4</td>
<td>Série de casos</td>
</tr>
<tr>
<td><strong>pior</strong> D</td>
<td>5</td>
<td>Opinião de especialistas não baseada em avaliação de resultados de estudos ou dedução lógica, ou sem um critério explícito de avaliação</td>
</tr>
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(Modificado de: NHS R&D Centre for Evidence-Based Medicine. See http://www.indigojazz.co.uk/cebm/levels_of_evidence.asp)
Example of Application of Levels of Evidence
Cervical Cancer – Summary (NCI)

- Evidence strongly suggests a decrease in mortality from regular screening with Pap tests in women who are sexually active or who have reached 18 years of age.

- Level of evidence for preceding statement:
  3 - Well-designed cohort/case-control studies
  4 - Evidence from multiple time series with or without intervention
  5 - Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Screening for Breast Cancer
US Preventive Services Task Force
Recommendations for Breast Cancer Screening (Updated December 2009)

- The USPSTF recommends biennial mammography for women aged 50-74 years
  Grade B recommendation

- The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account including the patient’s values regarding specific benefits and harms
  Grade C recommendation

- The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years and older
  Grade I statement

- The USPSTF recommends against teaching breast self examination
  Grade D recommendation

- The USPSTF concludes that the current evidence is insufficient to assess benefits and harms of clinical breast examination beyond screening mammography in women 40 years and older
  Grade I statement

- The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer
  Grade I statement
THE MAIN THREAT TO META-ANALYSIS

PUBLICATION BIAS: SELECTION BIAS THAT OCCURS EITHER AT THE LEVEL OF ENTIRE STUDIES (STUDY PUBLICATION BIAS) OR AT THE LEVEL OF ENDPOINTS WITHIN PUBLISHED STUDIES (OUTCOME REPORTING BIAS)

## Factors Associated with Publication Odds: Multivariate Analysis
(No. of studies = 285)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% Confidence Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null result</td>
<td>1.00</td>
</tr>
<tr>
<td>Statistically significant at $\alpha=0.05$</td>
<td>2.32 (1.25, 4.28)</td>
</tr>
<tr>
<td>Perceived importance of results by author: low</td>
<td>1.00</td>
</tr>
<tr>
<td>Perceived importance of results by author: high</td>
<td>3.50 (1.45, 8.45)</td>
</tr>
</tbody>
</table>

(Easterbrook et al, 1991)
Odds ratios for publication according to source of funding in meta-analyses

\[
\text{Odds Ratio} = \frac{\text{Odds of Favoring the Product in Published Studies Sponsored by Drug Companies}}{\text{Odds of Favoring the Product in Published Studies Not Sponsored by Drug Companies}}
\]

Funnel Plot Evaluating Publication Bias in Nicotine Replacement Therapy Vs. Control Event Rates at 4 Weeks Post Target Quit Date

(Mills EJ. Harm Reduction Journal 2009;6:25)
Funnel plot of odds ratio (OR) of family history of stroke as a risk factor for stroke vs. precision (i.e., inverse of the standard error of the OR) in case-control (full circles) and cohort studies (empty circles). Note the asymmetry of the plot due to lack of estimates when OR<1 (i.e., small negative studies).

Relações entre meta-análise, análise de decisão e análise de custo-efetividade

Meta-Análise

Sumário da efetividade de intervenções na população

Análise de Decisão

Avaliação do valor relativo de opções programáticas baseada na efetividade de intervenções na população. É baseada na “árvore de decisão”

Análise de custo-efetividade

Avaliação do custo do programa, baseado no valor relativo das opções programáticas
Eficácia e Efetividade

- **Eficácia**: estimada em um ou mais estudos em condições ideais.

- **Efetividade**: estimada em um ou mais estudos em condições não ideais (perdas de seguimento, “cross-overs”, etc)

- **Efetividade na população (inclusive a população de pacientes)**: o que acontece quando o programa é implementado na população alvo.

\[
\text{Eficacia ou Efetividade} = \frac{\text{Incidência}_{\text{controle}} - \text{Incidência}_{\text{intervenção}}}{\text{Incidência}_{\text{controle}}} \times 100
\]
Análise de decisão: Usa uma estratégia quantitativa a fim de avaliar o valor relativo de uma ou mais intervenções, programas ou serviços

Árvore de decisão

- Nódulo de decisão: sob controle do investigador

- Nódulo de probabilidade: fora do controle do investigador
Para os que toleram as terapias, D tem uma mortalidade mais baixa do que C.
Exemplo de árvore de decisão com dois nódulos de probabilidade

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Exemplo de árvore de decisão com dois nódulos de probabilidade

Para os que toleram as terapias, D tem uma mortalidade mais baixa do que C
No entanto, mais pacientes toleram C
Efetividade de C nos pacientes (comparada com D) = \{(37.85\% - 28.30\%) ÷ 37.85\%\} × 100 = 25.20\%
Conclusão: D é mais eficaz (isto é, os que o toleram têm uma mortalidade mais baixa do que C), mas como C tem melhor tolerância, a efetividade no total de pacientes é mais elevada.
Análise de sensibilidade: um instrumento para políticas de saúde

Análise de sensibilidade é uma estratégia baseada em modificações dos outputs esperados de um modelo (por exemplo, mortalidade) como resultado da variação dos seus parâmetros (ou pressupostos) dentro de uma faixa razoável de valores.

### Análise de sensibilidade – pressuposto: tolerância ao protocolo D aumentou de 30% para 50%

#### Tabela 2a – C: menor eficácia, maior tolerância

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<th>Tolerância?</th>
<th>Probabilidade conjunta de morte</th>
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<td>$0.70 \times 0.10 \times 0.10 = 0.007$</td>
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<td>$0.70 \times 0.90 \times 0.20 = 0.126$</td>
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<td>Mortalidade total</td>
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C é ainda um pouco mais efetivo do que D, mas se o custo de D for menor, a custo-efetividade de D pode ser melhor do que a de C.

**Efetividade de C (vis-a-vis D) = \{[29.75\% - 28.30\%] + 29.75\%\} \times 100 = 4.90\% (antes: 25.2\%)**
Selective Screening:

When Should Screening Be Limited to High-risk Individuals?

MOYSES SZKLO, MD, DrPH

Issues related to selective screening are discussed. The distinction between test accuracy and program accuracy is presented in the context of impact on cost/true case detection, which in turn reflects the gain in specificity and loss in sensitivity for the total target population. When two or more risk factors are combined to define high-risk subjects, a gain in program accuracy and a relative reduction in cost/true case found ensue if there is additive interaction between these risk factors. The author also discusses periodicity of screening and emphasizes the inappropriateness of using the notion of risk for disease occurrence as a criterion to define periodicity. Key words: selective screening; high-risk; specificity; sensitivity; cost; periodicity. J GEN INTERN MED 1990; 5(suppl):S47–S49.
### Hypothetical Examples of the Effect of Selective (High Risk) Screening on Program Accuracy and Cost/True Case Detected in a Population of 2 000 Individuals

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(Szklo M. *J Gen Intern Med* 1990;5(Suppl):S47-S49)
RASTREAMENTO DE ALTO RISCO (SELETIVO) PARA CASOS INCIDENTES DURANTE UM ANO EM UMA POPULAÇÃO DE 100 000 MULHERES: EFEITO SOBRE A SENSIBILIDADE

Incidência anual média de câncer de mama feminina em São Paulo, 1998-2000 ≅ 278/100 000, São Paulo

1ª. Fase: Sensibilidade de história familiar de câncer de mama = 0.54*; 2ª. Fase: Sensibilidade da mamografia = 0.93**

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Falsos Negativos

Verdadeiros Positivos

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Rastreamento de Alto Risco → Sensibilidade do Programa = 0.54 × 0.93 = 0.50

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§Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

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†Szklo M. J Gen Intern Med 1990; 5(Suppl):S47-S49
Decision Tree of Hypertension Medication Therapy with One Decision Node Using Average Annual Incidence of Coronary Heart Disease (CHD) as Outcome

Note: This example is based on real data, but from different patient population frames. Thus, it should not be applied to a given target population.

Incidence According to Acceptance of Drug Therapy

Yes: \((0.53 \times 0.68 \times 0.005) + (0.53 \times 0.32 \times 0.011) = 0.0037 = 3.7/1,000\)
No: \((0.47 \times 0.10 \times 0.005) + (0.47 \times 0.90 \times 0.011) = 0.0049 = 4.9/1,000\)

Effectiveness of Drug Therapy

\[
\frac{(4.9 - 3.7)}{4.9} \times 100 = 24.5\%
\]
Decision tree for the treatment of high blood pressure based on 52 hypertensive patients. Values besides each outcome health state are median and inter-quartile range. CVE, cardiovascular event (newly diagnosed angina, myocardial infarction, coronary heart disease, stroke or transient ischemic attack) (Montgomery AA, et al. Shared decision making in hypertension. Family Practice 2001;18:309-313).
Age-Adjusted Death Rate Ratios for Current vs. Non-smokers by Cause of Death: The Harvard Six Cities Prospective Study (adapted from *N Eng J Med* 1993;329:1753-9)

<table>
<thead>
<tr>
<th>Cause of death</th>
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“Smoking was most strongly associated with mortality due to lung cancer, significantly associated with mortality due to cardiopulmonary diseases, but not associated with mortality from (the category) other causes”
### Cause of death

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### A. Incorrect Interpretation of the 95% Confidence Interval

- **Point estimate**: 1.5
- **95% Confidence Interval**: 0.9 - 2.4

[Diagram showing log scale likelihood with point estimate and confidence interval]
B. Correct Interpretation of the 95% Confidence Interval
B. Correct Interpretation of the 95% Confidence Interval

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Log scale → Likelihood

Point estimate = 1.5

Likelihood of most values is >1.0

95% Confidence Interval
What is the basic principle of meta-analysis?

Mantel-Haenszel Formula for Calculation of Adjusted Odds Ratios

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>$a_i$</td>
<td>$b_i$</td>
</tr>
<tr>
<td>No</td>
<td>$c_i$</td>
<td>$d_i$</td>
</tr>
</tbody>
</table>

$N_i$

$$OR_{MH} = \frac{\sum_i \frac{a_i d_i}{N_i}}{\sum_i \frac{b_i c_i}{N_i}}$$

The $OR_{MH}$ is a weighted average of study-specific ORs ($OR_i$), with weights equal to each study:

$$w_i = \frac{b_i c_i}{N_i}$$
Mantel-Haenszel meta-analytic pooling strategy

<table>
<thead>
<tr>
<th>Study</th>
<th>Menopause</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Post</td>
<td>3</td>
<td>171</td>
<td>OR₁ = 2.5</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>10</td>
<td>1428</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Post</td>
<td>14</td>
<td>684</td>
<td>OR₂ = 2.6</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>6</td>
<td>757</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Post</td>
<td>37</td>
<td>1408</td>
<td>OR₃ = 4.0</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>1</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Post</td>
<td>64</td>
<td>1343</td>
<td>OR₄ = 1.2</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>0</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>
Meta-Analysis of Studies of Incidence of Depression and Socio-Economic Status

Point estimate: area is proportional to study’s precision

Odds higher in rich

Odds Ratio

Odds higher in poor

Model Choice in Meta-Analysis

• **Fixed-effects model**: inference is conditional on the studies actually carried out – “Did the treatment produce benefit on the average in the studies at hand?”
  – It incorporates only a within-study component of the variance

• **Random-effects model**: inference is based on the assumption that the studies are a random sample of some hypothetical population of studies – “Will the treatment produce benefit on average”?  
  – It incorporates between-study and within-study components of the variance; thus, it is more conservative

**Note**: When the study results are fairly homogeneous -- which is an important assumption for estimating the pooled effect -- the fixed and the random effects models will provide virtually identical results.

Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

Null hypothesis

Point estimate

95% Confidence Interval

Poor precision

Good precision

Null hypothesis

Meta-analysis pooled OR
Example of Application of Levels of Evidence
Cervical Cancer – Summary (NCI)

- Evidence strongly suggests a decrease in mortality from regular screening with Pap tests in women who are sexually active or who have reached 18 years of age.

- **Level of evidence for preceding statement:**
  3 - Well-designed cohort/case-control studies
  4 - Evidence from multiple time series with or without intervention
  5 - Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

Point estimate: area is proportional to the study’s precision (sample size)
Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

Null hypothesis

1.00

Point estimate

95% Confidence Interval (range of likely values)

Point estimate: area is proportional to the study’s precision (sample size)
Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

- **Null hypothesis**
- **Point estimate**: area is proportional to the study’s precision (sample size)
- **Good precision**
Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

Null hypothesis

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Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)

Main Assumption of Meta-Analysis: Homogeneity
Most studies are consistent with a positive association (odds ratio above 1.0)
**Meta-analysis**: quantitative method that aims at summarizing study results, thus, facilitating the process of inferring effectiveness of an intervention, service or program.

**Steps in Meta-Analysis**
Meta-analysis: quantitative method that aims at summarizing study results, thus, facilitating the process of inferring effectiveness of an intervention, service or program.

Steps in Meta-Analysis

- Identification of studies
**Meta-analysis**: quantitative method that aims at summarizing study results, thus, facilitating the process of inferring effectiveness of an intervention, service or program.

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- Identification of studies
- Definition of eligibility criteria for inclusion/exclusion of studies (e.g., only clinical trials with a minimum follow-up of 5 years)
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• Selection of studies based on quality
• Statistical analysis

Instead of person, the analytic unit is study
Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials

Nathalie Druesne-Pecollo¹, Paule Latino-Martel¹, Teresa Norat², Emilie Barrandon¹, Sandrine Bertrais¹, Pilar Galan¹ and Serge Hercberg¹,³

¹UMR U 557 INSERM, U 1125 INRA, CNAM, Université Paris 13, F-93017 Bobigny, France
²Department of Epidemiology and Public Health, Imperial College, London, United Kingdom
³Département de Santé Publique, Hôpital Avicenne, F-93017 Bobigny, France

The effect of beta-carotene supplementation on cancer incidence has been investigated in several randomized controlled trials. The objective was to review the effect of beta-carotene supplementation on cancer incidence in randomized trials by cancer site, beta-carotene supplementation characteristics and study population. Relevant trials were retrieved by searching PubMed (up to April 2009). Authors involved in selected studies were contacted for additional information. Thirteen publications reporting results from 9 randomized controlled trials were included. Overall, no effect of beta-carotene supplementation was observed on the incidence of all cancers combined (RR, 1.01; 95% CI, 0.98–1.04), pancreatic cancer (RR, 0.99; 95% CI, 0.73–1.36), colorectal cancer (RR, 0.96; 95% CI, 0.85–1.09), prostate cancer (RR, 0.99; 95% CI, 0.91–1.07), breast cancer (RR, 0.96; 95% CI, 0.85–1.10), melanoma (RR, 0.98; 95% CI, 0.65–1.46) and non melanoma skin cancer (RR, 0.99; 95% CI, 0.93–1.05). The incidence of lung and stomach cancers were significantly increased in individuals supplemented with beta-carotene at 20–30 mg day⁻¹ (RR, 1.16; 95% CI, 1.06–1.27 and RR, 1.34; 95% CI, 1.06–1.70), in smokers and asbestos workers (RR, 1.20; 95% CI, 1.07–1.34 and RR, 1.54; 95% CI, 1.08–2.19) compared to the placebo group. Beta-carotene supplementation has not been shown to have any beneficial effect on cancer prevention. Conversely, it was associated with increased risk not only of lung cancer but also of gastric cancer at doses of 20–30 mg day⁻¹, in smokers and asbestos workers. This study adds to the evidence that nutritional prevention of cancer through beta-carotene
Beta Carotene and Gastric Cancer Incidence in Not Only Smokers or Asbestos Workers


<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Beta carotene (mg day⁻¹)</th>
<th>No. of Events/Total</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Blot (1993)</td>
<td>15 NA/NA</td>
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<td>0.84 (0.71-1.00)</td>
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<td>Lee (1999)</td>
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<tr>
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Test for Heterogeneity: \( p = 0.311 \)
Test for Overall Effect: \( p = 0.221 \)

* The area of the rectangle (or dot) is proportional to the study’s precision (sample size)

** The narrower the 95% CI, the better the precision
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Test for Heterogeneity: $p = 0.311$
Test for Overall Effect: $p = 0.221$

When the 95% CI includes 1.0, the association is not significant.

**Inference:** beta carotene is not effective.
## Políticas de Saúde Baseadas em Evidências

Critérios para julgar a eficácia e efetividade de uma intervenção (medida preventiva ou tratamento)

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<tr>
<td></td>
<td>1b</td>
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</tr>
<tr>
<td></td>
<td>1c</td>
<td>Experimentos “naturais” (exemplo: estreptomicina e meningite tuberculosa) e séries temporais</td>
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<tr>
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</tr>
<tr>
<td><strong>B</strong></td>
<td>3a</td>
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<tr>
<td><strong>C</strong></td>
<td>4</td>
<td>Série de casos</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>5</td>
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(Modificado de: NHS R&D Centre for Evidence-Based Medicine. See [http://www.indigojazz.co.uk/cebm/levels_of_evidence.asp](http://www.indigojazz.co.uk/cebm/levels_of_evidence.asp))
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Begg’s funnel plot for assessing publication bias in relation to glutathione S-transferase MI null status and bladder cancer risk

RASTREAMENTO DE ALTO RISCO (SELETIVO) PARA CASOS INCIDENTES DURANTE UM ANO EM UMA POPULAÇÃO DE 100 000 MULHERES: EFEITO SOBRE A SENSIBILIDADE

I incidência anual média de câncer de mama feminina em São Paulo, 1998-2000 = 278/100 000, São Paulo

1ª. Fase: Sensibilidade de história familiar de câncer de mama = 0.54*; 2ª. Fase: Sensibilidade da mamografia = 0.93**

- Falsos Negativos (FN)
- Verdadeiros Positivos (VP)

\[
\begin{align*}
\text{Falsos Negativos (FN)} & = 138 \\
\text{Verdadeiros Positivos (VP)} & \geq 278 \\
\end{align*}
\]

\[
\text{1ª. Fase: Sensibilidade de história familiar de câncer de mama = 0.54*; 2ª. Fase: Sensibilidade da mamografia = 0.93**}
\]

Rastreamento de Alto Risco → Sensibilidade do Programa = 0.54 × 0.93 = 0.50

*Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

*Szkl M. J Gen Intern Med 1990; 5(Suppl):S47-S49
