# Fundamentals of Breast Cancer Screening

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# Plan of Talk

1. Background – Objectives of screening and principles for considering screening.
2. Application of principles to breast cancer screening.
3. Surrogate Outcomes and their biases.
4. Informing Decisions 1: Clinical breast examination.
5. Informing Decisions 2: Screening by Age
6. Informing Decisions 3: Screening Frequency.
7. Conclusions


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Greenland
ARCTIC CIRCLE
Alaska
Hudson Bay
Canada
Pacific Ocean
North America
Great Lakes
USA
Atlantic Ocean
1300 mi
1300 km
Gulf of Mexico
Mexico
Caribbean
Caribbean Sea
Central America
South America
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# Why do Cancer Screening in a Publicly Funded System?

Public Policy Aim: To reduce the mortality rate from cancer.

Specific Cancer Screening Aim: To diagnose cancer at an earlier stage

Cancer Screening Objective: to provide cancer screening services to eligible subjects

# Thus for Breast Cancer Screening

Public Policy Aim: To reduce the mortality rate from breast cancer.

Specific Breast Cancer Screening Aim: To diagnose breast cancer at an earlier stage and provide effective treatment

Breast Cancer Screening Objective: to provide mammography screening to eligible subjects

# Private Pay versus Public Pay

In private pay systems the public health impact is not central and screening decisions are determined by the patient and their medical provider

In this talk I will adopt the public pay viewpoint.

# General Guiding Ideas Underlying Screening

Screening segments of the female population involves the application of scarce medical resources to a large number of women who (mostly) will never develop breast cancer.

This it is important to keep in mind the impact on

- Breast cancer mortality
- Women who will not develop breast cancer
- The general medical system

# Principles

Several authors have attempted to establish a set of principles to guide decisions about disease screening.

The first of these were by Wilson and Jungner[1] who identified 10 principles

These principles have been modified by several authors, for example Miller[2] proposed 5 specifically oriented to cancer screening.

1 Wilson, Jungner WHO Chronicle, 1968;22(11);473

2 Miller AB Cancer Epidemiology and Prevention, 2nd Ed, Oxford, 1433.

# Wilson & Jungner 1968

1. the condition is an important health problem
2. there is an accepted treatment for cases identified
3. the condition is recognisable at an early stage
4. the natural history of the condition is known
5. there is an agreed policy on whom to treat as patients

# Wilson & Jungner 1968

6. harm from a screening program is small in relation to benefits
7. facilities for diagnosis and treatment should be available
8. there should be a suitable test
9. the screening test should be acceptable to the population
10. the costs and effectiveness of the screening should be balanced in relation to expenditure on medical care as a whole

# Wilson and Jungner (W&J) Principles

The screening principles fall into 5 major dimensions:

1. An Important Health Problem (P1)
2. Availability of good screening test (P3,8,9)
3. Be able to handle cases identified appropriately (P2,4,5,7)
4. Harms much less than benefits (P6)
5. Cost-Effectiveness is appropriate for health system (P10)

# W&J Principles as Applied to Breast Cancer

Most of these principles have already been addressed for mammography screening:

1. Breast Cancer is an important health condition (P1)
2. Mammography is effective and acceptable (P3,8,9)
3. Work-up and treatment is well understood (P2,4,5,7)
4. Most harms appear minor and transitory (P6)
5. Cost-Effectiveness is high for health system (P10)

# What are the Harms of Breast Screening?

The harms of screening mammography include:

1. A large number of false-positive results which cause anxiety, waste money and waste time.
2. Patients live longer with the knowledge of cancer even when they don't benefit
3. Some cancer would never have come to light (over-detection) if patients hadn't been screened
4. Small risk of cancer induction

# Context of Application

In applying the screening principles to breast cancer it is important to keep the context in mind.

1. Although Breast Cancer is a major health condition its influence varies by age (P1)
2. The efficacy of mammography varies by age and frequency (P3)
3. The balance between harms and benefits varies with age and frequency of screening (P6)
4. Cost-Effectiveness varies with age and frequency of screening (P10)

# Assessment of Screening

As the primary health goal of breast cancer screening is to reduce deaths from breast cancer studies to inform screening decisions should be randomized and have breast cancer death as an outcome.

However such studies are large, expensive and take a long time to complete: for contemporary policy decisions it is necessary to utilize currently available data as new trials with breast cancer death as an outcome are not feasible.

# Surrogate Outcomes

Because cancer deaths occur multiple years after enrollment in screening it is necessary to use surrogate outcomes wherever possible based on observations on populations exposed to screening.

However, many of the usual clinical measures of cancer outcomes (e.g. survival, stage distribution) are distorted by biases inherent in screening.

# Biased Selection of Screening Subjects

In analyzing non-randomized screening data one frequently compares mortality in subjects who agree to be screened with those who do not. The validity of the resulting comparison then depends upon the similarity of their risk of death without screening.

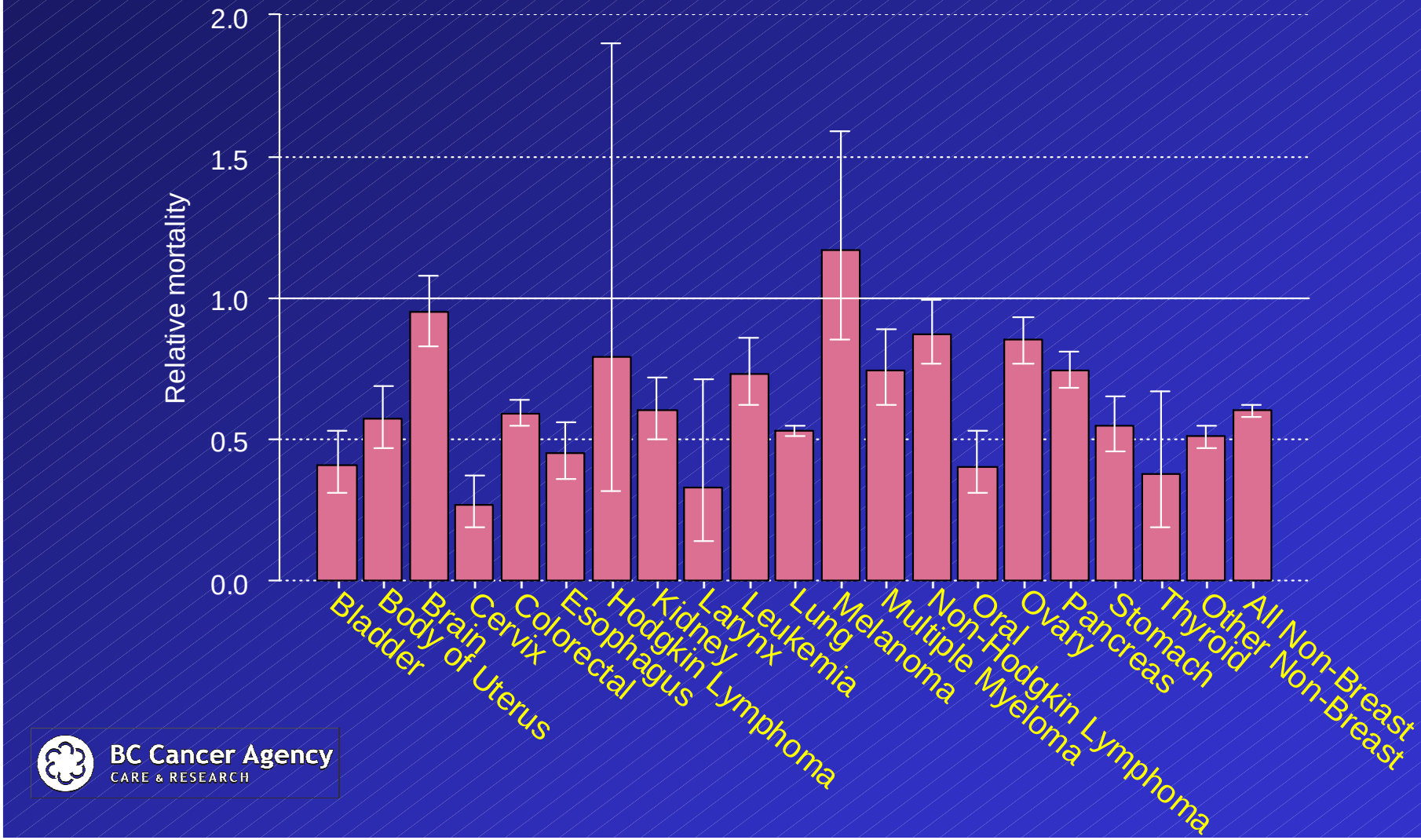
In attempting to improve comparability one may control for age, sex and social class.

# Effect of Volunteer Bias on Mortality Outcomes

There seems ample evidence that this effect is significant.

Example: (MOSS, JECH, 46-362-4) In two regions of the UK with similar historic breast cancer mortality rates, one initiates screening and the other does not. Mortality in those who do not participate in the screening region is 20% higher than the region where there is no screening.

# Ratio of mortality (deaths) by cancer type in SMPBC participants versus non-participants

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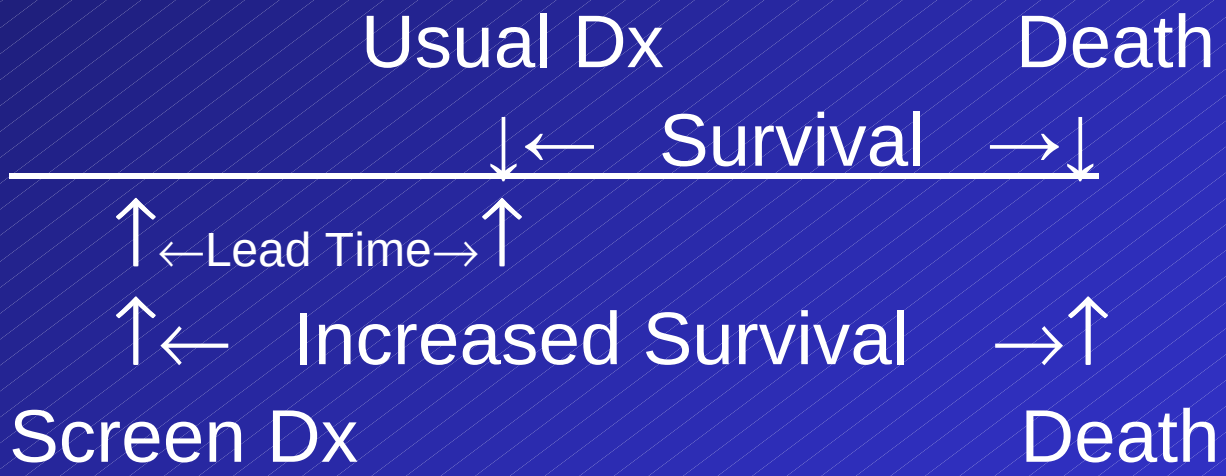
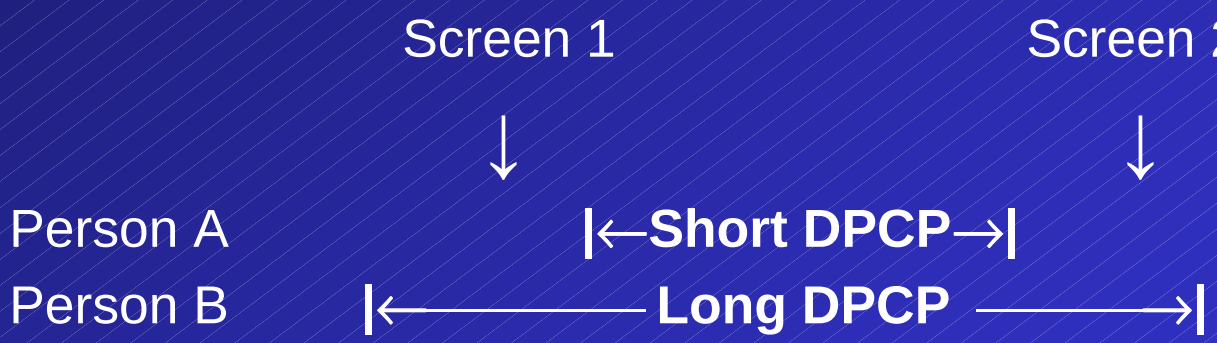
# Lead Time Bias

*Lead time bias* arises in the analysis of survival data where screening subjects have an increased survival by virtue of having an earlier diagnosis.



# Length Bias

*Length bias* arises in the analysis of survival in persons diagnosed by screening where subjects with longer times in the detectable state are more likely to be detected



# Over-Detection

The amount of over-diagnosis is uncertain because it needs to be separated from legitimate early detection. This is difficult to do.

A recent meta-analysis[1] of mammography and breast cancer concluded that the amount had not been reliably estimated. However several authors continue to believe it exists and is substantial.

1: Lancet Oncology. 2008; 8:1129-38.

# Length Bias

If the length of time where disease is detectable is also correlated to the usual survival time then subjects with long periods will also have longer survival and screen detected cases will appear to do much better.

In particular, cancer cases may be detected by screening which would never progress further or may even regress. This is referred to as over-detection, over-diagnosis or pseudo disease detection.

# Informing Decisions

As breast screening programs develop they a variety of decisions:

1. How to screen for breast cancer?
2. Which women will be screened?
3. How often to screen?

These questions are common to all publicly financed screening programs.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# Abnormal Call Rates per 1,000 Women Screened by Mammography And Clinical Breast Examination

| Outcome | Screen Sequence | Modality | Age | | | Ratio |
|---|---|---|---|---|---|---|
| | | | 50-59 | 60-69 | All | |
| Abnormal Call Rate | First | Clinical Breast Exam Only | 25 | 25 | 25 | 4 |
| | | Mammography | 99 | 89 | 98 | |
| | Subsequent | Clinical Breast Exam Only | 9 | 9 | 9 | 5 |
| | | Mammography | 48 | 43 | 46 | |

# Cancer Detection Rates per 1,000 Women Screened by Mammography And Clinical Breast Examination

| Outcome | Screen Sequence | Modality | Age | | | Ratio |
|---|---|---|---|---|---|---|
| | | | 50-59 | 60-69 | All | |
| Cancer Detection Rate | First | Clinical Breast Exam Only | 0.2 | 0.3 | 0.2 | 32 |
| | | Mammography | 5.7 | 8.8 | 6.4 | |
| | Subsequent | Clinical Breast Exam Only | 0.1 | 0.1 | 0.1 | 37 |
| | | Mammography | 3.2 | 4.4 | 3.7 | |
| | | | | | | |

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# Summary of Analysis of Effect of Addition of Clinical Breast Examination

For every 10,000 women screened with mammography once between the ages of 50-69 including clinical breast examination would result in:

- 100 more abnormal results requiring evaluation
- 1 extra case of breast cancer detected at screening

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# Which Women Do We Screen?

This decision about who to screen usually reduces to a decision about age groups to include. This depends upon 3 factors which are linked back to the Wilson and Jungner principles:

- The effectiveness of screening by age (P10)
- The incidence of (mortality from) breast cancer by age (P 1)
- The life-expectancy of women from causes other than breast cancer (P1)

# Screening Effectiveness by Age

There is broad consensus that screening in the 50-69 age group is effective at preventing death from breast cancer

- IARC Breast Screening Handbook, Meta Analysis Odds Ratio (OR)=0.75
- Among compliers, OR~0.6-0.7.

Also there is a widespread opinion that it is as efficacious among women 70+

There is more disagreement regarding 40-49.

# Summary Results for Mammography Trials For Women aged 40-49 at Entry: Odd's Ratios for Breast Cancer Death

| Source: | Type of Study | Odds Ratio for Breast Cancer Death | 95% Confidence Interval | Odds Ratio Corrected for Compliance |
|---|---|---|---|---|
| IARC 2002, Breast Screening Handbook | Meta Analysis, 6 Swedish Trials | 0.81 | (0.65-1.01) | |
| Hendrick, 1997, JNCI, Monograph | Meta Analysis, 5 Swedish trials, 3 Other | 0.82 | (0.71-0.95) | |
| Moss 2006, Lancet | 1 UK Trial | 0.83 | (0.66-1.04) | 0.76 |

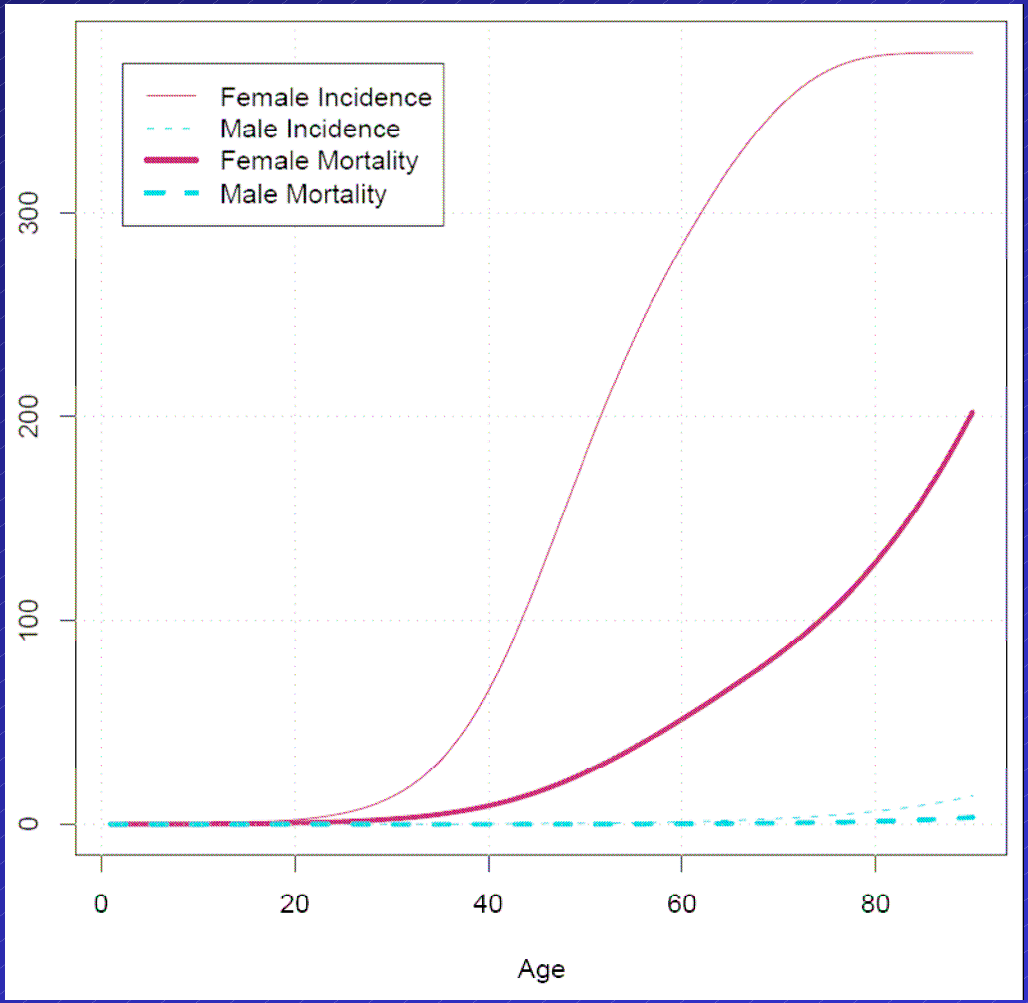
# Effectiveness by Age?

The consistency between the latest UK trial and the previous meta-analyses suggests that (annual) screening in women 40-49 is about 75% as effective (on mortality) as biennial screening in women 50-69.

Mammography screening effectiveness is more dependent on frequency in women 40-49*

*Br J Cancer, 1987, p547

# Age-Incidence and Mortality Rates from Breast Cancer for British Columbia, 1990-1999

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# Breast Cancer incidence, Mortality Rates and Life Expectancy by Age In British Columbia Women

| Age | Breast Cancer Incidence Rate/100,000 | Breast Cancer Mortality Rate per 100,000 | Life Expectancy of Average Woman (years) |
|---|---|---|---|
| 40 | 70 | 10 | 44 |
| 50 | 180 | 30 | 34 |
| 60 | 280 | 50 | 25 |
| 70 | 350 | 80 | 17 |

# Combining the Different Factors

Planning screening requires detailed considerations of demography, costs, resource availability and impact.

However it is possible to develop some simple calculations which provide guidance.

# Main Contributor to Screening Costs and Resource Use

Although effective screening involves more than just mammography it represents the major resource commitment and involves the majority of the costs encountered.

Evaluating the effectiveness of screening plans on a per screen delivered basis provides a way to examine the value of screening approaches and relate them to their resource use. Such a calculation is probably more transferable across countries than actual financial costs.

# Relative Effectiveness Per Screen

Calculating absolute effectiveness (years of life saved per screen delivered) requires specific information for the location.

However we can anticipate that the ratio of effectiveness of different strategies will be more transferable between locations.

# Score

We create a score for a screening strategy by multiplying as follows:

Score (strategy) =

screening interval

× breast cancer incidence rate

× OR for mortality reduction

× Life Expectancy

# Meaning of Score

The score does not really have a useful meaning. But when we take the ratio's of the scores for different screening strategies we obtain the relative effectiveness (as measured on a per-screen basis).

# Interpretation of Ratio

In the following tables the ratio shows how effective different strategies are in comparison to the strategy of biennial screening in a 60 year old woman.

The ratio indicates how many more screens have to be performed to achieve the same effect as a single screen in a 60 year old woman.

# Ratio of Scores For Screening by Age (British Columbia Rates)

| Age | Screening Interval (years) | Score | Score Ratio (Age 60=1.0) |
|---|---|---|---|
| 40 | 1 | 2042 | 5.6 |
| 45 | 1 | 3325 | 3.4 |
| 50 | 2 | 10584 | 1.1 |
| 60 | 2 | 11429 | 1.0 |
| 70 | 2 | 8491 | 1.3 |
| 75 | 2 | 6033 | 1.9 |

# Interpretation of the Ratios

The ratios confirm that the most efficient (improvement in life expectancy) use of mammography (of those considered) is within 50-69 years olds. Across the age-range 50-69 the efficiency does not vary greatly.

Screening younger women is considerably less efficient because of the lower cancer rates and need to screen annually.

Generalization of these findings to Brazil would be facilitated by Brazilian rates and life expectancies.

# Frequency of Screening

It is possible to apply the same methodology to the case of changing screening frequencies in groups in which screening is already performed.

For example for women 50-69 what is the efficiency of annual screening?

The only issue to keep in mind is to make sure we determine the incremental benefit and not the average benefit of annual screening.

# Efficacy of Annual Screening in 50-69

No studies have demonstrated that annual screening provides a statistically significant reduction in mortality. Only one randomized study has been undertaken[1].

Calculations based on mathematic models and some observations indicate that the OR for biennial compared to annual screening in 50-69 is ~ 1.14[2].

1 Eur. J Cancer, 2002, 1458-64
2 Br J Cancer, 2005, 961-6

# Efficacy of Annual Screening in 50-69

Indices were calculated in the same way as for the discussion of screening outside of the 50-69 age-group assuming the preceding odds ratio of 1.14.

Again score ratios were calculated with respect to biennial screening in a 60 year old.

# Ratio of Indices for Annual Screening Ages 50-69 (British Columbia Rates)

| Age | Screening Interval (years) | Score | Score Ratio (Age 60=1.0) |
|---|---|---|---|
| 50 | 2 | 10584 | 1.1 |
| 50 | 1 - added | 1482 | 7.7 |
| 60 | 2 | 11429 | 1.0 |
| 60 | 1- added | 1600 | 7.1 |
| 70 | 2 | 8491 | 1.3 |
| 70 | 1-added | 1189 | 9.6 |

# Interpretation

As anticipated the efficiency of extra mammography used to increase biennial to annual screening among 50-69 years is low and much less than biennial screening in that age group.

# Conclusion

Principles for guiding screening decisions in a public pay framework have been developed.

Their application to specific issues requires the synthesis of local and literature information.

A simple model is described which assists resulting considerations.

Encontro Internacional sobre

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## 16 e 17 de abril
## Rio de Janeiro