CEBM
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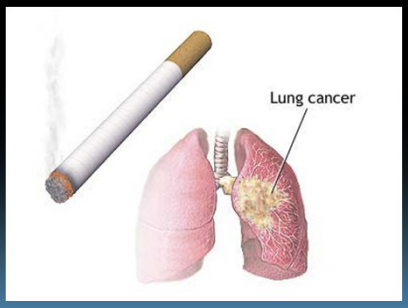
Evidence-Based Practice
Prognostic studies

Dr Kamal R. Mahtani BSc PhD MBBS
Academic Clinical Fellow,
University of Oxford

CENTRE FOR EVIDENCE BASED MEDICINE

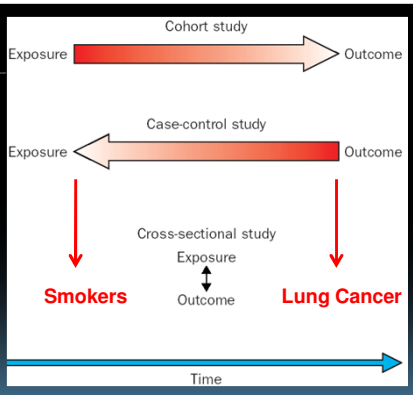
Does smoking cause lung cancer?

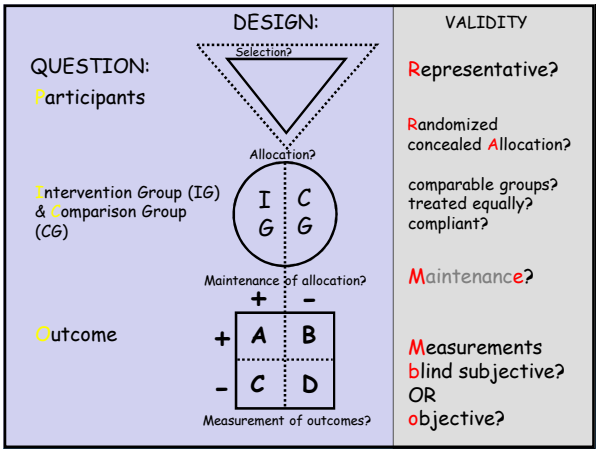


Five steps in EBM

1. Formulate an answerable question
2. Track down the best evidence
3. Critically appraise the evidence for:
   - Validity
   - Impact (size of the benefit)
   - Applicability
4. Integrate with clinical expertise and patient values
5. Evaluate our effectiveness and efficiency

keep a record; improve the process



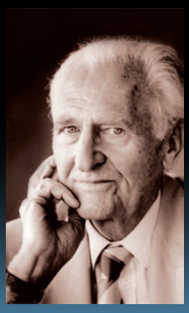


The "ideal" prognostic study

0 Time ∞

Entire population of patients who ever lived who developed the disease followed up from the instant it developed!

Doll and Hill 1956



- 59600 questionnaires to all on the medical register October 1951
- Few simple questions
  - Age, M/F
  - current smoker?
  - Ex smoker?
  - Non (never)-smoker?
- Followed up 4 years and 5 months

- Mr Wilson (age 68) and his wife come to see you. Two months ago you found he had a raised PSA and referred him to Urology.

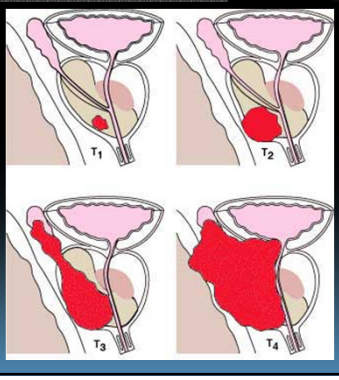
- He has been told he has prostate cancer Stage T1
- They are both very anxious and asks you what this means for the future...

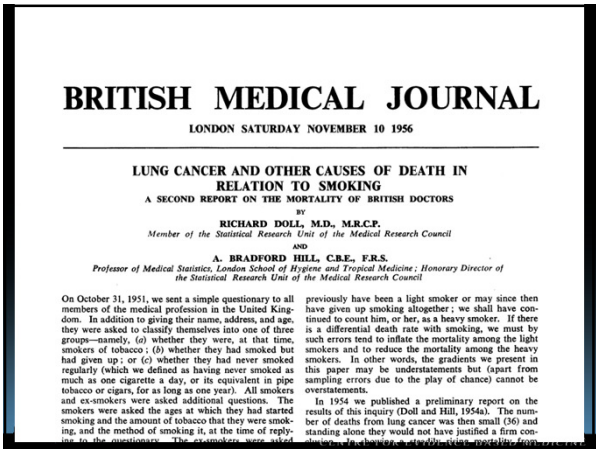
Doll and Hill 1956

- All cause death rate roughly same non-smoker and smokers
- Death from lung cancer 12x higher in smokers than non-smokers
- Death rate in smokers increases in those with highest tobacco consumption

Prostate Ca Staging

T01 implies < 5% tumour tissue in the specimen, and T0d > 5%.





BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 10 1956

LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING

A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS

BY

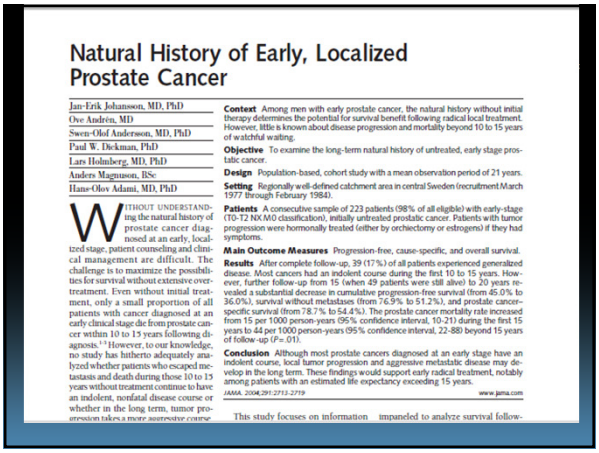
RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., F.R.S.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

On October 31, 1951, we sent a simple questionary to all members of the medical profession in the United Kingdom. In addition to giving their name, address, and age, they were asked to classify themselves into one of three groups—namely, (*a*) whether they were, at that time, smokers of tobacco; (*b*) whether they had smoked but had given up; or (*c*) whether they had never smoked regularly (which we defined as having never smoked as much as one cigarette a day, or its equivalent in pipe tobacco or cigars, for as long as one year). All smokers and ex-smokers were asked additional questions. The smokers were asked the ages at which they had started smoking and the amount of tobacco that they were smoking, and the method of smoking it, at the time of replying to the questionary. The ex-smokers were asked previously have been a light smoker or may since then have given up smoking altogether; we shall have continued to count him, or her, as a heavy smoker. If there is a differential death rate with smoking, we must by such errors tend to inflate the mortality among the light smokers and to reduce the mortality among the heavy smokers. In other words, the gradients we present in this paper may be understatements but (apart from sampling errors due to the play of chance) cannot be overstatements.

In 1954 we published a preliminary report on the results of this inquiry (Doll and Hill, 1954a). The number of deaths from lung cancer was then small (36) and standing alone they would not have justified a firm con-



Natural History of Early, Localized Prostate Cancer

Jan-Erik Johansson, MD, PhD
Ove Andrén, MD
Swen-Olof Andersson, MD, PhD
Paul W. Dickman, PhD
Lars Holmberg, MD, PhD
Anders Magnuson, BSc
Hans-Olov Adami, MD, PhD

Context Among men with early prostate cancer, the natural history without initial therapy determines the potential for survival benefit following radical local treatment. However, little is known about disease progression and mortality beyond 10 to 15 years of watchful waiting.

Objective To examine the long-term natural history of untreated, early stage prostatic cancer.

Design Population-based, cohort study with a mean observation period of 21 years.

Setting Regionally well-defined catchment area in central Sweden (recruitment March 1977 through February 1984).

Patients A consecutive sample of 223 patients (98% of all eligible) with early-stage (T0-T2 NX M0 classification), initially untreated prostatic cancer. Patients with tumor progression were hormonally treated (either by orchiectomy or estrogens) if they had symptoms.

Main Outcome Measures Progression-free, cause-specific, and overall survival.

Results After complete follow-up, 39 (17%) of all patients experienced generalized disease. Most cancers had an indolent course during the first 10 to 15 years. However, further follow-up from 15 (when 49 patients were still alive) to 20 years revealed a substantial decrease in cumulative progression-free survival (from 45.0% to 36.0%), survival without metastases (from 76.9% to 51.2%), and prostate cancer–specific survival (from 78.7% to 54.4%). The prostate cancer mortality rate increased from 15 per 1000 person-years (95% confidence interval, 10-21) during the first 15 years to 44 per 1000 person-years (95% confidence interval, 22-88) beyond 15 years of follow-up ($P=.01$).

Conclusion Although most prostate cancers diagnosed at an early stage have an indolent course, local tumor progression and aggressive metastatic disease may develop in the long term. These findings would support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.

JAMA. 2004;291:2713-2719 www.jama.com

Without understanding the natural history of prostate cancer diagnosed at an early, localized stage, patient counseling and clinical management are difficult. The challenge is to maximize the possibilities for survival without extensive overtreatment. Even without initial treatment, only a small proportion of all patients with cancer diagnosed at an early clinical stage die from prostate cancer within 10 to 15 years following diagnosis.[1-3] However, to our knowledge, no study has hitherto adequately analyzed whether patients who escaped metastasis and death during those 10 to 15 years without treatment continue to have an indolent, nonfatal disease course or whether in the long term, tumor progression takes a more aggressive course.

This study focuses on information impaneled to analyze survival follow-

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Are The Results Valid?

2. Follow-up of patients sufficiently long and complete.

- Too long? Too short?
- Were all patients accounted for?
- "5 and 20" rule:
  - <5% loss little bias
  - >20% loss threatens validity

Are The Results Valid?

1. Assembled a defined, representative sample of patients at a common point in course of disease.

- Early in disease? "Inception Cohort"
- Were they all at the same stage of disease at baseline?
- Were they representative of a normal population?

5 minutes

5 minutes

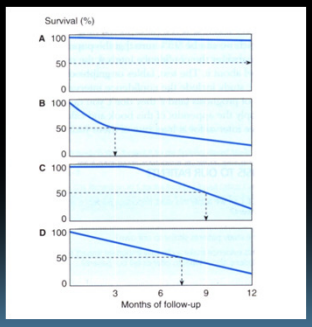
Are The Results Valid?

3. Objective outcome criteria applied in a "blinded" fashion

- How were outcomes measured?
- Were any of the investigators "blinded" to the outcome?
- Did they need to be?

5 minutes

Survival Curves



1 year survival 95%
Median survival unknown
1 year survival 20%
Median survival 3 months
1 year survival 20%
Median survival 9 months
1 year survival 20%
Median survival 7 months

Are The Results Valid?

4. **Were there any subgroups with different prognoses identified?**

- **was there adjustment for important prognostic factors ?**
  - **Demographics?, Age?, Baseline characteristics?**
- **validation in an independent, "test set" of patients?**
  - Reference to a second independent study validating the predictive power of these prognostic factors.

How precise are the results?

6. What are the confidence intervals?

- **How early are the follow up periods?**

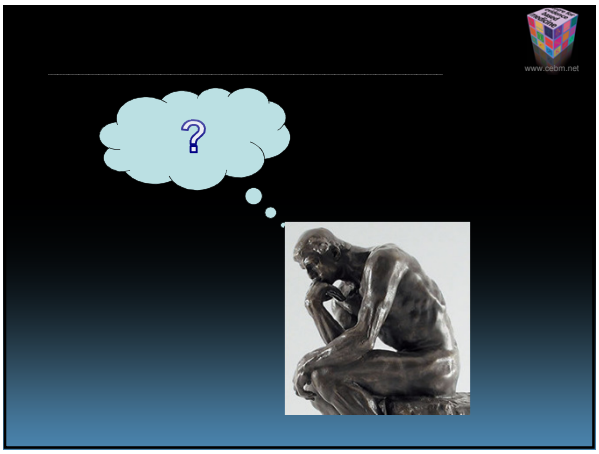
What are the results?

5. **How likely are the results over time? How are results reported?**

1. **% of survival at a particular point in time (1-year or 5-year survival rates**
2. **Median survival (length of follow-up by which 50% of study patients have died)**
3. **Survival curves e.g Kaplan-Meier curves**

Can I apply these results to my patient?

- **Does their baseline characteristics fit with this study?**
- **Are they at a similar stage in their disease?**
- **What will I tell my patient?**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