

Critiques on epidemiology

How were we being misled?

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Outline

- Conflicting nature of observational studies
- Principles and difficulties in radiation epidemiology
- Guidelines for causality

甲状腺がん 疑い含め104人

104 diagnosed and suspected thyroid cancer cases

福島 子どもも30万人調査

Child survey in Fukushima

東京電力福島第一原発事故の被曝による子どもの甲状腺への影響を調べている福島県の検査で、受診した約30万人のうち104人が甲状腺がんやその疑いと判定されたことがわかった。県は「被曝の影響とは考えにくい」としつつも、この結果は24日に公表される。

県「被曝の影響考えにくい」

甲状腺検査は事故当時18歳以下だった県民を対象に実施。県内全域を一巡した今年6月30日現在の結果(暫定値)がまとめられた。

甲状腺がんやその疑いとされた104人のうち、ほとんど確定したのは57人、良性が1人だった。104人の事故当時の平均年齢は14・8歳で、男性36人、女性68人。腫瘍の大きさは約5〜41ミリで平均14ミリ。疑いも含めると10万人当たり30人以上の割合でがんが見つかった計算になる。

事故前から実施されている宮城県などががん登録では、10代後半の甲状腺がんの発生率は10万人当たり1・7人。これに比べると今回の福島県の30人以上はかなり高いが、無症状の人を網羅的に調べてがんを見つけており、症状がある人を調べたがん登録より発生率は高くなるため、単純に比較できない。

また、青森、山梨、長崎の3県で計約4400人の無症状の子どもを調べた環境省の甲状腺検査では、1人ががんと診断され、約3

Thyroid cancer after Chernobyl

SIR — We would like to report a great increase in the frequency of thyroid cancer in children in Belarus, which commenced in 1990 and continues. Table 1 shows the incidence of thyroid cancer in children in the six regions of Belarus and Minsk City from 1986 to the end of the first half of 1992. It can be seen that the overall incidence rose from an average of just four cases per year from 1986 to 1989 inclusive, to 55 in

problems, and is placing great strains upon the health services of our new country. It also provides an opportunity, which we hope will not be repeated, to study the consequences of major exposure of a population to isotopes of iodine from fallout. We are collaborating with several international groups and are preparing detailed reports of various aspects of the problem.

We believe that the only realistic

We examined 11 children who had had operations for thyroid carcinoma and were now hospitalized for post-operative management or evaluation of metastatic disease. We were shown the complete records for these patients, including X-rays and echograms before and after treatment. All were diagnosed during the past 3 years, eight having been living in the Gomel region at the time of the Chernobyl accident and two in the Brest region. The age at diagnosis of the six females and five males was between 4 and 13 years of age; the youngest was born two days after the accident.

We have studied the histological slides from 104 cases of children from Belarus in whom the diagnosis of thyroid carcinoma had been made since January 1989. We agree both with the diagnosis of malignancy and of the type of malignancy in 102 of the cases. We also examined the data on the incidence of thyroid carcinoma in Belarus. There is a marked increase in frequency from 1990 onwards over the average for the years from 1986 to 1990. This increase started only 4 years after the Chernobyl

TABLE 1 Incidence of thyroid cancer in children in Belarus

Region of Belarus	Years							Total
	1986	1987	1988	1989	1990	1991	1992*	
Brest	0	0	1	1	6	5	5	18
Vitebsk	0	0	0	0	1	3	0	4
Gomel	1	2	1	2	14	38	13	71
Grodno	1	1	1	2	0	2	6	13
Minsk	0	1	1	1	1	4	4	12
Mogilev	0	0	0	0	2	1	1	4
Minsk City	0	0	1	0	5	2	1	9
Total	2	4	5	6	29	55	30	131

* Six months of 1992.

Counter arguments

- Limitation of available data
 - The number of people exposed and radiation dose were unknown
- Incidence rate (incidence per person-time) was therefore not reported, making it difficult to interpret data (e.g. comparison with healthy people)

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Counter arguments

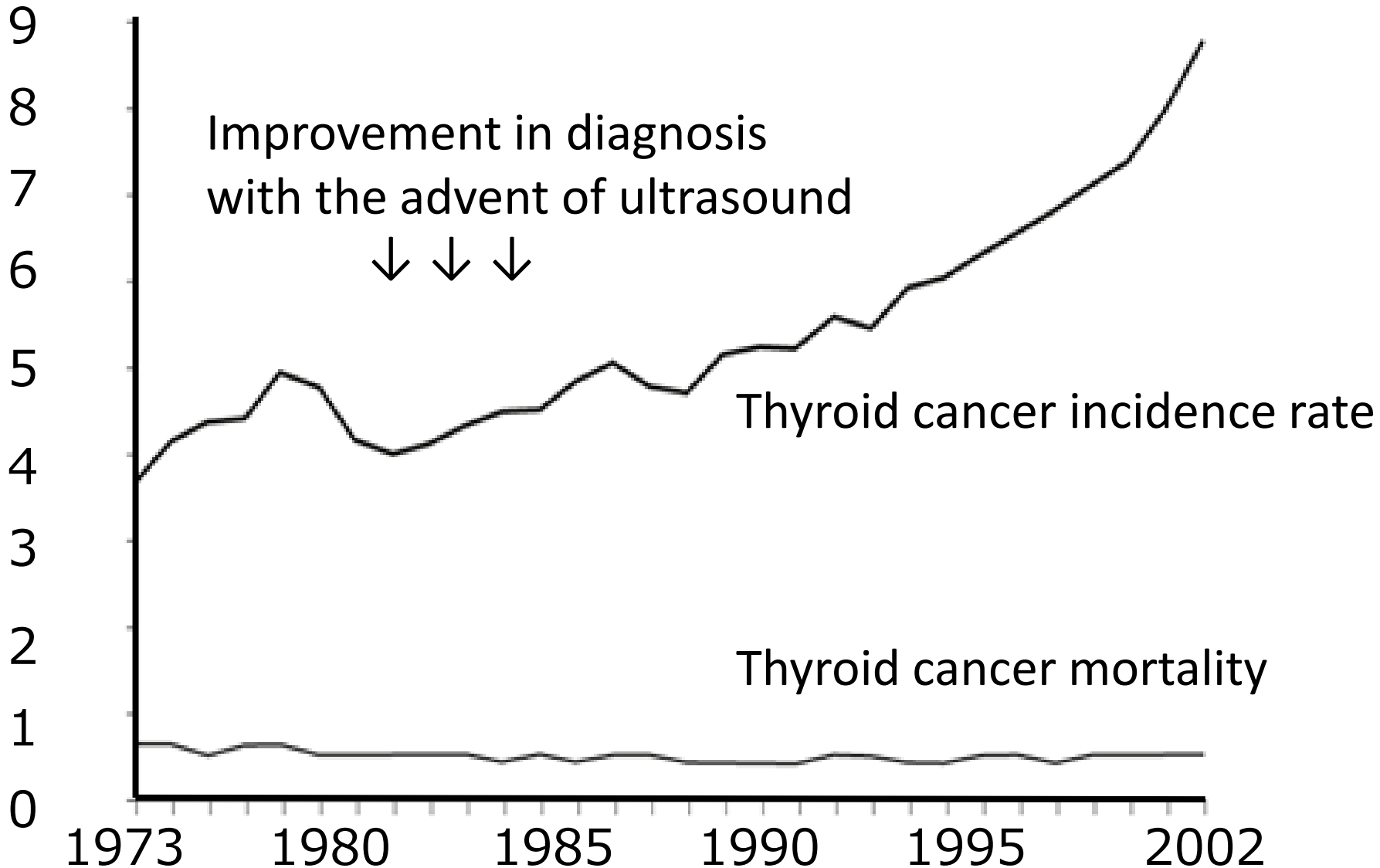
- Dose-response relationships were also unclear
- Potential of screening effect
 - Cancer screening program in Chernobyl began in 1990, which may explain the increasing trend at least partially

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Screening effect in the USA



Examples of the conflicting nature of epidemiological studies

- A Swedish study found a significant association between **residential radon exposure and lung cancer** (ラドンと肺癌) .
- A Canadian study did not.
- Three months later, it was **pesticide residues** (殺虫剤) . A medical journal published a study in April reporting - contrary to previous, less powerful studies - that the presence of DDT metabolites in the bloodstream seemed to have no effect on the risk of breast cancer.
- In October, it was **abortions and breast cancer** (流産と乳癌) . Maybe yes. Maybe no.
- In January it was **electromagnetic fields (EMF) from power lines** (電磁場) . This time a study of electric utility workers in the US suggested a possible link between EMF and brain cancer but - contrary to a study a year ago in Canada and France - no link between EMF and leukemia.

Epidemiology Faces Its Limits

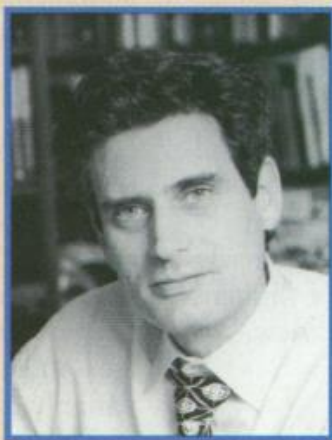
The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty



BARBARA STEINER

“People don’t take us seriously ... and when they do ... we may unintentionally do more harm than good.”

—Dimitrios Trichopoulos



MARNA KENNEDY

“We’re pushing the edge of what can be done with epidemiology.”

—Ken Rothman



KIMBERLY GRANT

“Authors and investigators are worried that there’s a bias against negative studies.”

—Marcia Angell



UNIVERSITY OF WASHINGTON

“People [may] think they have been able to control for things that are inherently not controllable.”

—Norman Breslow



TERRY O'DONNELL

“The sin comes in believing a causal hypothesis is true because your study came up with a positive result.”

—Sander Greenland

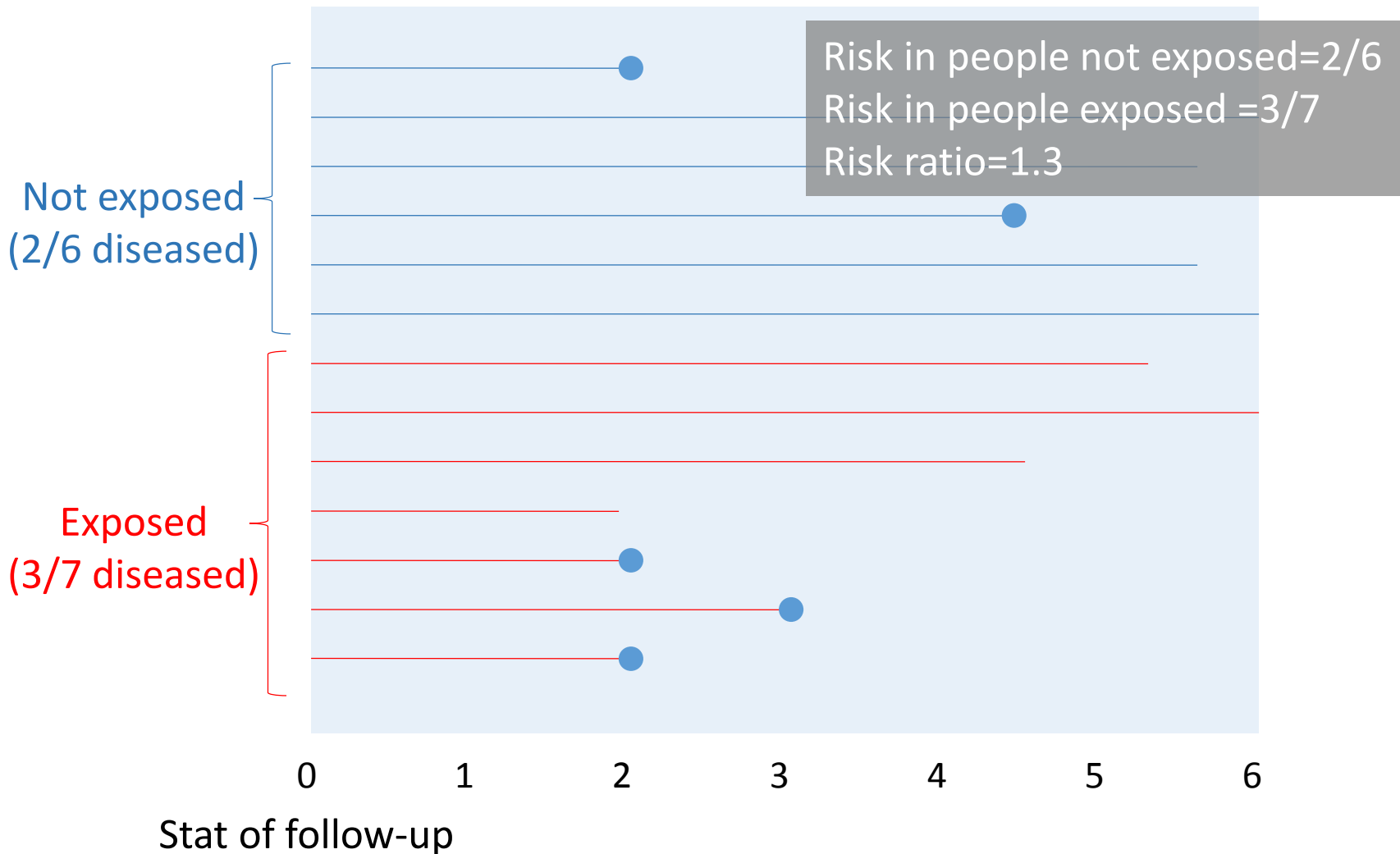
Types of epidemiological studies

	Cross-sectional	Case-control study	Cohort study	Randomized controlled trial
Ex.	Correlation of radiation dose and disease at a specific time	Identify cancer cases and controls and compare radiation dose	Follow-up a population until incidence of cancer	Randomly allocate pre-specified interventions to study subjects
Intervention	No	No	No	Yes
Temporality	No or unclear	Retrospective	Prospective	Prospective
Advantage	Cost effective	Feasible for rare disease	Prospective data collection	High comparability

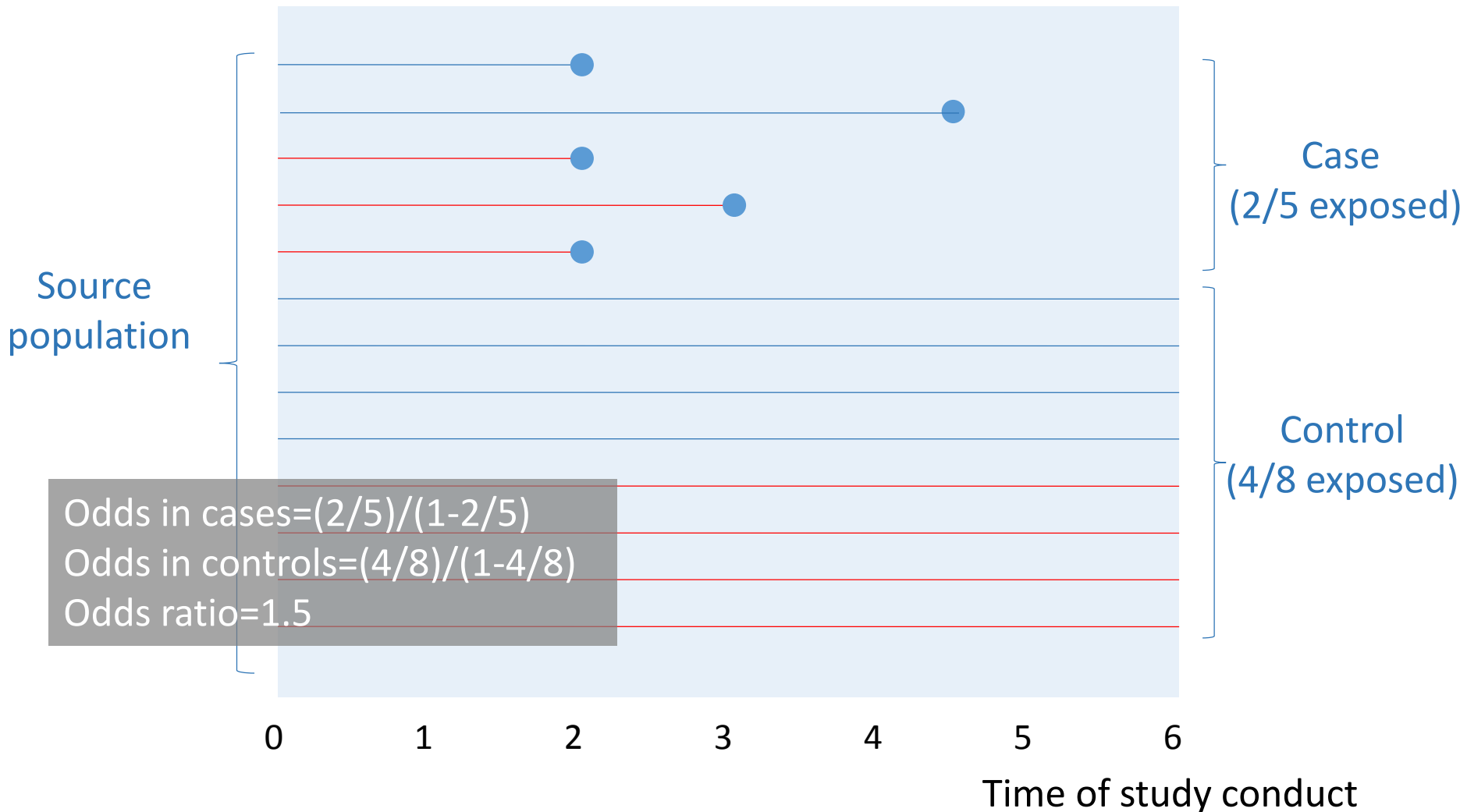
Two paradigms: observation and experiment

- A epidemiological study often examines causal relationships of exposures (e.g. radiation) and outcomes (e.g. cancer)
- Two paradigms toward causality
 - Observational studies
 - Randomized controlled trials (experiments)
- **Observational studies which is typical in radiation epidemiology are not immune to bias, namely systematic deviation of observed associations from truth**

Cohort study and risk ratio



Case-control study and odds ratio



A case-control study in Belarus and Russia

- Compared thyroid radiation dose of cases with thyroid cancer with dose of controls
- Cases
 - 276 patients with thyroid cancer diagnosed in 1992 to 98 in Belarus and Russia
- Controls
 - 1300 people matched to case patients by age, sex, and region of residence at the time of the accident
- Thyroid radiation dose
 - Estimated based on subjects' whereabouts, dietary habits and stable iodine status in 2000's

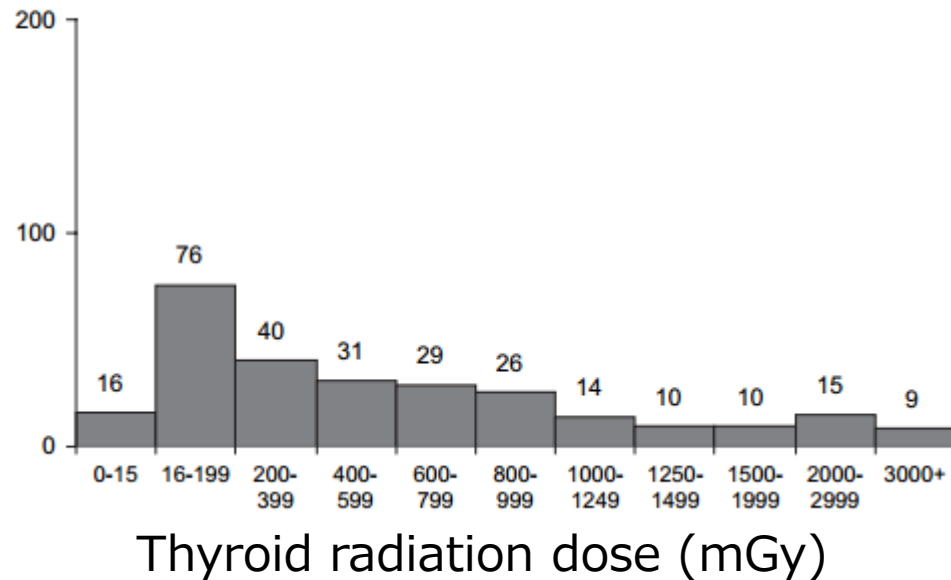
Statistical methods (regression models)

$$\text{Odds ratio} = \frac{\text{Pr}(\text{case}|\text{dose}=d)}{1-\text{Pr}(\text{case}|\text{dose}=d)} \bigg/ \frac{\text{Pr}(\text{case}|\text{dose}=0)}{1-\text{Pr}(\text{case}|\text{dose}=0)}$$
$$= 1 + \beta d + \gamma d^2$$

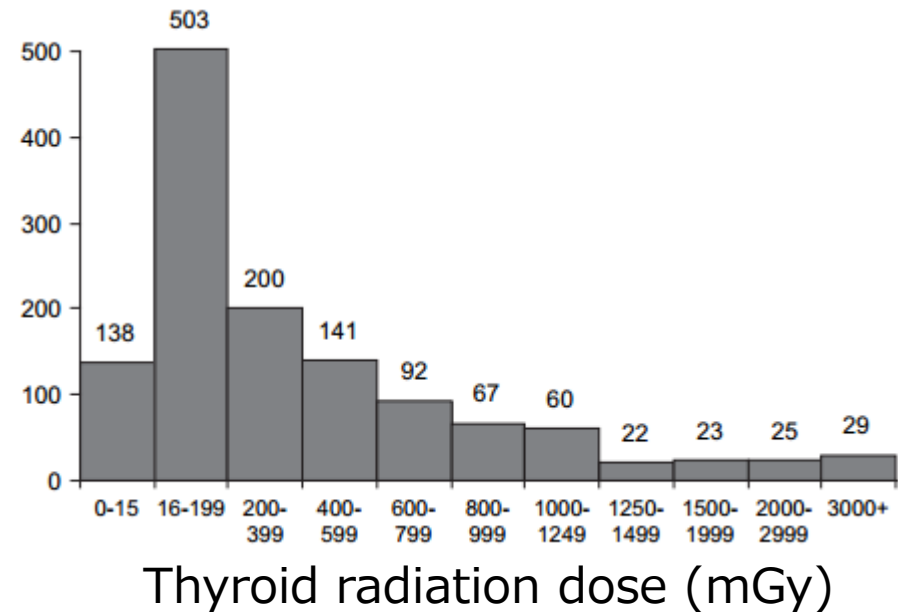
- The radiation effect is expressed as an odds ratio which is a linear-quadratic function of d
 - d : thyroid radiation dose
- Other functional forms were also examined
 - Linear models, i.e. $1 + \beta d$
 - Models fitted to data up to a specific dose (1, 1.5 or 2 Gy)
 - Models with exponential transformation, i.e. $\exp(1 + \beta d + \gamma d^2)$

Thyroid radiation dose in cases and controls

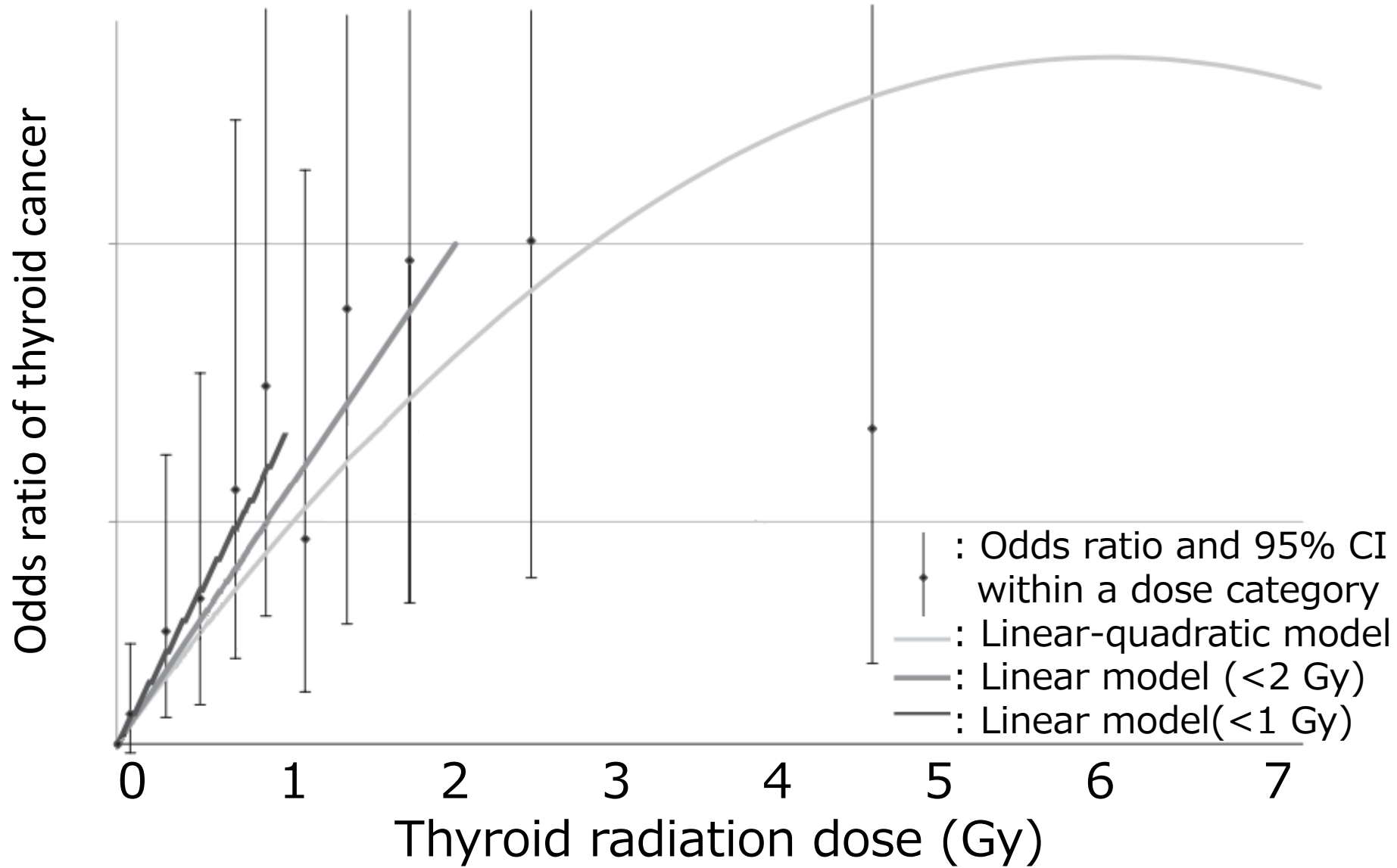
Frequency of cases



Frequency of controls



Dose-response relationships



Underlying assumptions for the validity of statistical analysis

$$\begin{aligned}\text{Odds ratio} &= \frac{\Pr(\text{case}|\text{dose}=d)}{1-\Pr(\text{case}|\text{dose}=d)} \bigg/ \frac{\Pr(\text{case}|\text{dose}=0)}{1-\Pr(\text{case}|\text{dose}=0)} \\ &= 1 + \beta d + \gamma d^2\end{aligned}$$

- Dose of individual subjects, d , is assumed to be estimated without **measurement error**
- d is the unique argument of the function
 - The relationships estimated by fitting the function above can be biased if the truth is Odds ratio = $1 + \beta^*d + \gamma^*d^2 + \alpha^*X$
 - More precisely if there are unmeasured **confounders**

Authors' comments on measurement error

- The main sources of dosimetric uncertainty are as follows
 - Variability of model parameters related to **the transfer of ^{131}I from deposition on the ground to the human thyroid**
 - Uncertainties in information on **individual lifestyle and dietary habits** obtained by questionnaire
 - Uncertainties in **the original direct thyroid measurements made some days or weeks after the accident** and in the dose estimates derived from these measurements.

Authors' comments on measurement error

- Interviews were carried out with case patients and control subjects **years after the Chernobyl accident**
- The possibility of **recall bias** cannot be excluded
- It has not been logistically possible to obtain the questionnaire data for intercomparison with direct thyroid measurements.
- A comparison was made, however, of the estimated doses for a few subjects. **For case patients, the dose derived from model estimates tended to be somewhat lower than the dose derived from direct thyroid measurements, and hence a recall bias related to case patients systematically overestimating their dietary habits appears unlikely.**

Further consideration on measurement error

- Measurement error in dosimetry can lead to both over- and underestimation of the slope of the dose-response relationship, although it is theoretically shown that the direction of bias is toward null in a very simple setting
- In the Ukrainian-US thyroid screening study, the degree of bias due to measurement error was reported to be -7 to +11% according to three statistical methods used for bias-correction

What is a confounder?

- More than 30 years ago, a famous study reported significant associations between coffee drinking and incidence of pancreas cancer (胰腺癌)
- However, we should be careful about the presence of factors other than exposures and outcomes which distort the associations
- Recently the causal effects of coffee were denied

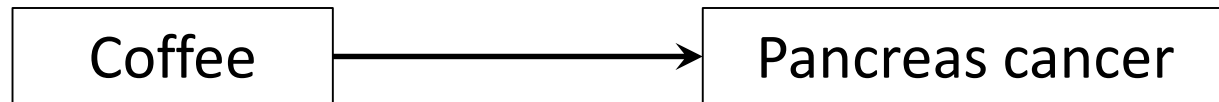




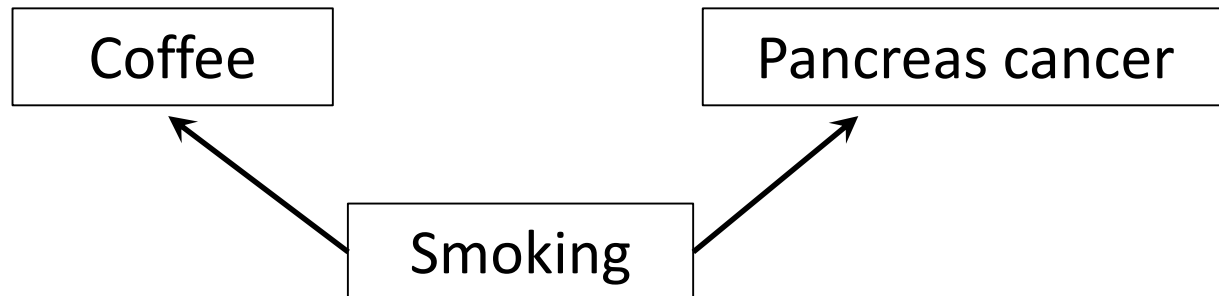
Causality and association



- Causal relationship



- Apparent associations due to confounders

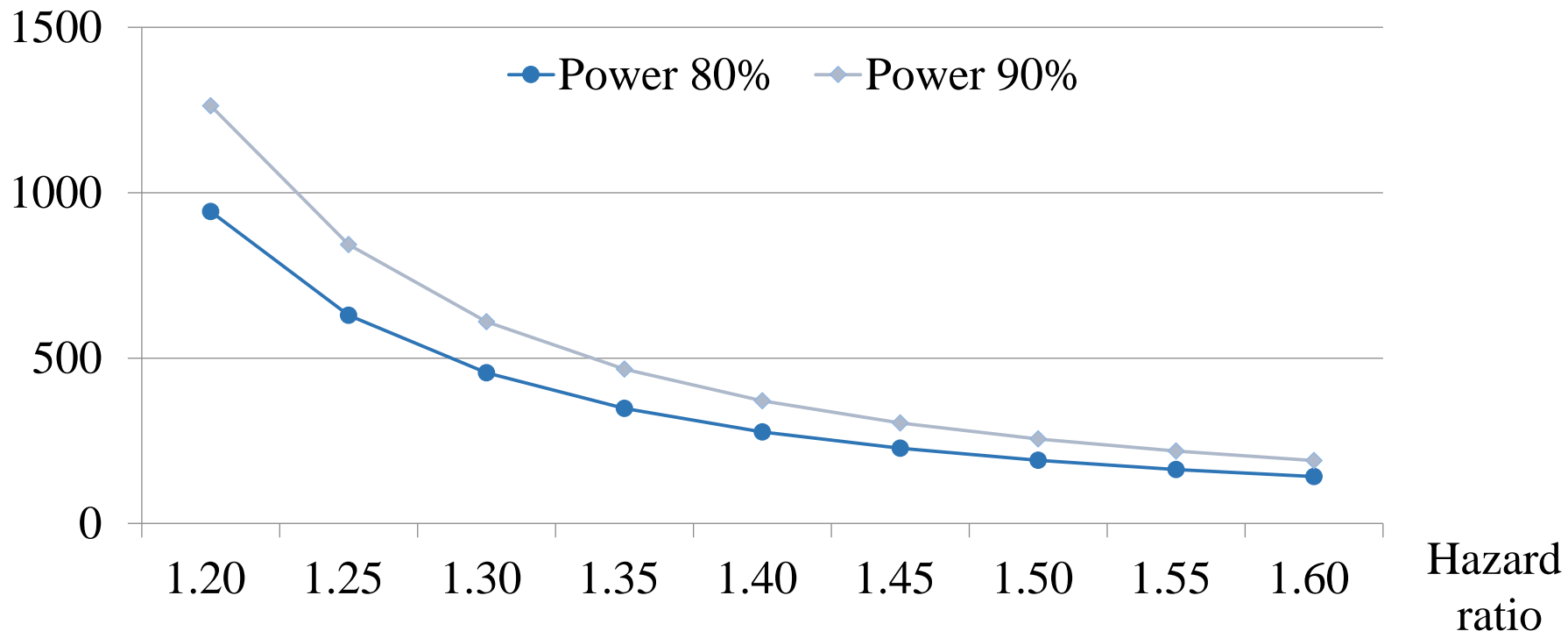


Issues on confounding in radiation epidemiology

- Data on risk factors of cancer such as smoking, diet, and comorbidities are often limited, making it difficult to exclude potential of bias due to confounding
- The validity of external comparison is controversial
 - E.g. the characteristics of emergency workers in nuclear plants may be different from those of general populations
- Confounding is a major difficulty in epidemiological studies on the radiation effects of medical exposure (e.g. CT scan), since patients who used a CT scan are inherently different from patients who did not.

A smaller effect require more data

Number of events required



$$\text{Events required for power of 90\%} = \frac{21}{(\log \text{hazard ratio})^2}$$

$$\text{Events required for power of 80\%} = \frac{16}{(\log \text{hazard ratio})^2}$$

Methodological difficulties in radiation epidemiology

- Screening effect
- Measurement error in dosimetry
- Limited data on subjects' characteristics such as risk factors, and potential of bias due to confounding
- Effects of low-dose radiation are expected to be small, requiring large-scale studies



The Nobel Prize in Physiology or Medicine 2005

The Nobel Assembly at Karolinska Institutet has awarded the Nobel Prize in Physiology or Medicine jointly to **Barry Marshall** and **Robin Warren** for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease. Thanks to this pioneering discovery, peptic ulcer disease is no longer a chronic, frequently disabling condition, but a disease that can be permanently cured.



Royal Perth Hospital

Barry Marshall

Born 1951
Helicobacter pylori
 Research Laboratory,
 Queen Elizabeth II
 Medical Centre,
 Nedlands, Perth,
 Australia.

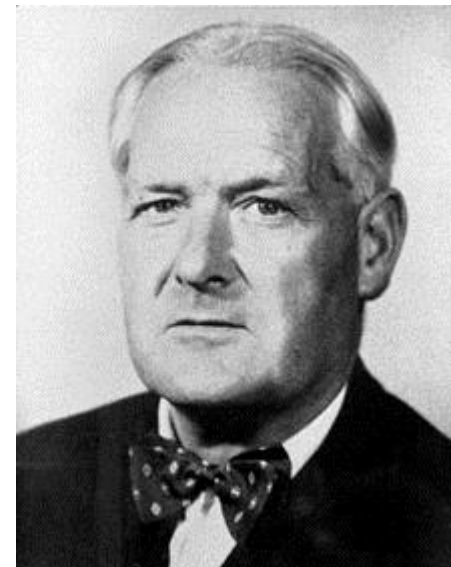
Robin Warren

Born 1937
 Department of
 Pathology, Royal
 Perth Hospital,
 Perth, Australia.

- Now it is well-known that *H. pylori* causes 90% of duodenal ulcers
- How the causality has been established?



Guidelines for the assessment of causality



- Temporality (時間的な前後関係)
- Strength (関連が強いこと)
- Dose-responses relationship (用量反応関係) AB Hill. 1897-1991
- Replication (様々な研究で結果が一致)
- Biological plausibility (もっともらしい作用機序)
- Consideration of alternate explanations (別の説明)
- Cessation of exposure (曝露消失後にどうなるか)
- Consistency (過去の経験や知識との一致)
- Specificity (特異性)

Example: evidence for H. pylori and duodenal ulcer (十二指腸潰瘍)

- Temporal relationship
 - In a study of 454 patients who underwent endoscopy 10 years earlier, 34 of 321 patients who had been positive for H. pylori (11%) had duodenal ulcer compared with 1 of 133 negative patients (0.8%)
- Strength of the association
 - H. pylori is found in at least 90% of patients with duodenal ulcer
 - It has never been found in a population free from H. pylori (Australian aboriginal tribe)
- Dose-responses relationship
 - Density of H. pylori per square millimeter of gastric mucosa is higher in patients with duodenal ulcer

Example: evidence for H. pylori and duodenal ulcer (十二指腸潰瘍)

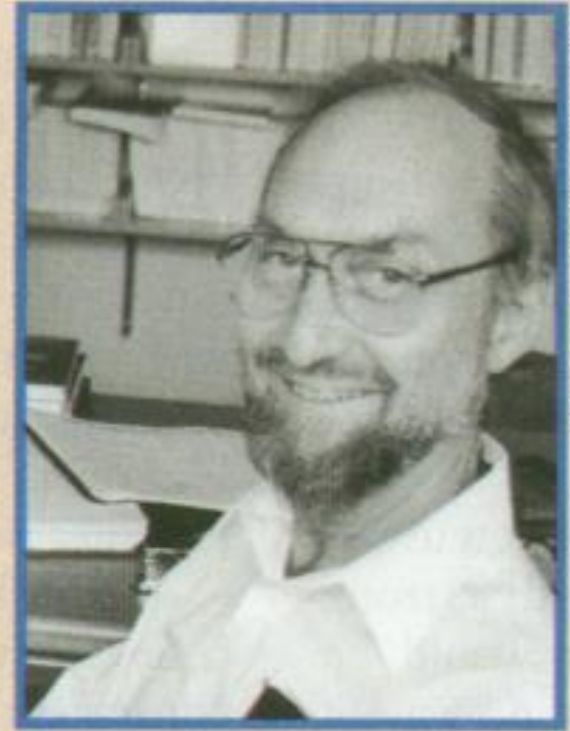
- Replication of the findings
 - Many of observations regarding H. pylori have been replicated
- Biologic plausibility
 - H. pylori has binding sites on antral cells and can follow these cells into the duodenum
 - It induces mediators of inflammation
 - Mucosa is weakened after infection of H. pylori
- Consideration of alternate explanations
 - There are data against confounding due to smoking

Example: evidence for H. pylori and duodenal ulcer (十二指腸潰瘍)

- Cessation of exposure
 - The efficacy of eradication of H. pylori has been confirmed
- Consistency with other knowledge
 - The prevalence of ulcer disease is believed to have peaked in the latter part of the 19th century
 - The prevalence of H. pylori may have been much higher at that time because of poor living condition
- Specificity of the association
 - H. pylori is found in at least 90% of patients with duodenal ulcer but has never been found in a population free from H. pylori (Australian aboriginal tribe)

Conclusion

- Epidemiologists have experienced a huge number of conflicting findings, identifying a variety of source of bias.
- I like the comment by a statistician, Professor Norman Breslow.
- Things to learn is the importance of understanding things controllable and uncontrollable when we interpret data from epidemiological studies and judge causality.



UNIVERSITY OF WASHINGTON

“People [may] think they have been able to control for things that are inherently not controllable.”

—Norman Breslow