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疫学

1. Definition ＜定義＞

- 明確に規定された人間集団の中で出現する健康関連のいろいろな事象の頻度と分布およびそれらに影響を与える要因を明らかにして、健康関連の諸問題に対する有効な対策樹立に役立てるための科学（日本疫学会）
- MacMahon B: Epidemiology is the study of the distribution and determinants of disease frequency in man
- Last JM: the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems（国際疫学会　A Dictionary of Epidemiology より）

Epidemiology is concerning with:

- measuring the frequency of diseases and events (mortality, births, morbidity incidence and prevalence, hospital stays, drug use, injuries, health behaviors);
- solving epidemics;
- looking for causes of disease and risk factors;
- evaluating new diagnostic tests;
- evaluating new treatments;
- surveillance for new diseases and changes in old ones;
- researching health services and their availability; and
- costing out alternative diagnostics, treatments or health service provisions.

2. Purpose ＜目的＞

- 疾病予防　＝　疾病の発生、罹患を防ぐ　←　疾病の原因を明らかにする
  - ①　第1次予防
    - ✧　原因を除去
    - ✧　罹患予防
  - ②　第2次予防
    - ✧　早期発見
    - ✧　早期治療
  - ③　第3次予防
    - ✧　重症化防止

- Disease ＜疾病＞ ←→ Cause ＜原因＞
  - i. Causal association ＜疫学的因果関係＞
    - ✧ Criteria of causal association ＜因果関係の判定基準＞
      1. 強固な関連　strength
      2. 一致した関連　consistency
      3. 時間的な関係　temporality
      4. 生物学的傾きのある関係／量反応関係
         biologic gradient / dose-response relationship
      5. 整合性のある関連　coherence
      6. もっともらしい関連　biological plausibility
    - ✧ Hill's criteria (Above 6 &)
      7. 特異的な関連　specificity
      8. 実験的な証拠の存在　experiment
      9. 類似の関連の存在　analogy

3. Measurement of disease frequency and association ＜疫学指標＞

① Measurement of disease frequency ＜頻度の測定＞
rate / ratio / proportion
- ✧　率　ratio

✧ 比 rate

✧ 割合 proportion

i. 罹患、発生 incidence
罹患率 incidence rate

ii. prevalence ＜有病率＞

iii. 罹患率と有病率の関係

② Measurement of association/effect ＜頻度の比較（効果・関係の強さの指標）＞

i. 絶対効果 Absolute effect ＜絶対効果＞

✧ differences in incidence rate/cumulative incidence/prevalence

rate difference 率差 / **attributable risk (AR) 寄与危険度** / (risk difference)

$$AR = I_{Exp+} - I_{Exp-}$$

ii. 相対効果 Relative effect ＜相対効果＞

relative risk (RR) 相対危険度 / rate ratio 率比 / incidence rate ratio / risk ratio

$$RR = \frac{I_{Exp+}}{I_{Exp-}} = \frac{C \cdot I_{Exp+}}{C \cdot I_{Exp-}}$$

✧ the measure estimates the magnitude of an association between exposure and disease, and indicates the likelihood of developing disease in the exposed group relative to those who are not exposed

✧ time-dependent

iii. Attributable proportion ＜寄与割合＞

✧ absolute effect is divided by the rate of occurrence among the exposed rather than the unexposed

attributable risk percent(AR%) 寄与危険度パーセント

/ attributable proportion / etiologic fraction 原因部分

$$AR\% = \frac{I_{Exp+} - I_{Exp-}}{I_{Exp+}} \times 100 = \frac{RR - 1}{RR} \times 100$$

✧ this estimates the proportion of the disease among the exposed that is attributable to the exposure, or proportion of the disease in that group that could be prevented by eliminating exposure

4. Types of Epidemiological studies ＜疫学研究の種類＞

① 観察的疫学研究 Observational study

i. 記述疫学 descriptive study

A) 地域相関（生態学的）研究 correlation study (ecological study)

B) 症例報告、患者調査 case study and case series

C) 横断研究、時間断面研究 cross-sectional study

ii. **分析疫学** analytical study

A) **横断研究、時間断面研究** cross-sectional study

B) **縦断研究** longitudinal study

- **症例対照研究** case-control study

Exposure Outcome (Disease)
? --------←----------←---- +
? --------←----------←---- －
<starting point>

- design **＜研究デザイン＞**
  - ✓ **症例の定義** definitions of outcome
    - outcome represents etiologically a homogeneous disease
    - strict diagnostic criteria
  - ✓ **対象の選定** selection of
    - **症例の選定** cases
      - ✧ hospital-based
      - ✧ population-based
      - ✧ incident case / prevalent case
    - **対照の選定** controls
      control subjects must be comparable to the cases as well as practical and economically feasible
      - ✧ hospital-based
      - ✧ population-based
  - ✓ assessing
    - **疾病情報の収集** information of outcome
      - ✧ **死亡診断書** death certificates
      - ✧ **疾病登録** case registries
      - ✧ **入退院歴など** hospital record etc.
    - **曝露情報の収集** information of exposure
      - ✧ **面接法**
        interview on study subjects, spouses, and/or family members
      - ✧ **自記式質問票**
        questionnaire on study subjects, spouses, and/or family members
      - ✧ **カルテなど** medical or other records etc.
  - ✓ **対象数** size
    - case to control ratio could be up to 1:4
    - statistical power increases as the ratio increases, but less efficient in the case of 1:5 or less
- **データ解析** data analysis

<u>Estimation of effects</u>

Measure of association and its stability **関係の強さと安定性**

	Disease (+)	Disease (-)	Total
Exposure (+)	A	b	a + b
Exposure (-)	C	d	c + d
Total	a + c	b + d	a+b+c+d

- Measure of association **関係の強さ**
  Odds ratio = OR **＜オッズ比＞**

$$RR \cong OR = \frac{a \cdot d}{b \cdot c}$$

2x2 contingency table

$$OR_1 = \frac{[a/(a+b)]/[b/(a+b)]}{[c/(c+d)]/[d/(c+d)]} = \frac{a \cdot d}{b \cdot c} = \text{disease OR}$$

- Stability indicator 安定性
  Confidence interval; evaluation for role of chance
  p-value

● コホート研究 cohort study
① 後ろ向きコホート研究 retrospective cohort study
② 前向きコホート研究 prospective cohort study

Exposure		Outcome (Disease)
+	--------→----------→----	? (+ or －)
－	--------→----------→----	? (+ or －)
prospective		retrospective
<*starting point*>		<*starting point*>

➢ 研究デザイン design
  ✓ 対象者の選定 Selection of
    ➢ 曝露群の選定 exposed population
    ➢ 比較群（対照群）の選定 comparison group
  ✓ data collection
    ➢ exposure data ＜曝露データ＞
      ✧ pre-existing records
      ✧ interview; questionnaire
      ✧ medical examination
      ✧ laboratory examination
      ✧ job title
      ✧ direct detection of exposure; concentration of chemicals in air/in biological specimens
    ➢ 結果データ outcome data
      ✧ 死亡診断書 death certificates
      ✧ 定期健康診断結果 periodic health examination
      ✧ physicians' records; hospital discharge logs; population-based disease registry
      ✧ self-reported diagnosis followed by additional confirmation procedures
      ✧ whatever the procedures, valid data must be obtained equally (i.e. in the same way) from exposed and non-exposed
      ✧ criteria for diagnosis
  ✓ フォローアップ Follow-up
    ➢ failure to obtain complete follow-up data could be the major source of the bias "*loss to follow-up*"
➢ data analysis ＜データ解析＞
  basic data analysis in a cohort study involves the calculation of rates of the incidence of a specified outcome among the cohorts under investigation, and these rates can be compared between exposed and non-exposed groups

  <u>Estimation of effects</u>
  関係の強さと安定性 Measure of association and its stability
  - "two-by-two (2x2) table" 2x2 表 (contingency table 四分表)
    presentation of count/categorical data

	Disease (+)	Disease (-)	Total
Exposure (+)	a	B	a + b
Exposure (-)	c	D	c + d
Total	a + c	b + d	a+b+c+d

- Measure of association

$$RR = \frac{I_{Exp+}}{I_{Exp-}} = \frac{C \cdot I_{Exp+}}{C \cdot I_{Exp-}}$$

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{a/PY_1}{c/PY_2}$$

SMR
Risk difference (Attributable risk)

- Stability indicators
  confidence interval 信頼区間; evaluation for role of chance
  p-value p 値

② 介入研究 Intervention study / experimental epidemiology
A) 臨床治験 clinical trial
B) 一次予防試験 preventive trial
- design
  - ✓ 対象集団の選定 selection of study population
    - 代表性 generalizability
      - ✧ 性別 sex
      - ✧ 年齢分布 distribution of subjects' age
    - 実現可能性 feasibility
    - 十分な対象者の確保 sufficient sample size
    - 十分な参加割合 sufficient participants (volunteers) (%) and follow up
    - likelihood of
      - ✧ 確実な服用(薬物投与の場合) taking medicine
      - ✧ 十分高い罹患率(予防プログラムの場合) obtaining higher incidence
    - インフォームドコンセント informed consent
  - ✓ allocation
    randomization ＜無作為割り付け＞
  - ✓ maintenance and assessment of compliance ＜コンプライアンス＞
  - ✓ blind assignment and assessment ＜盲検法＞
    single blind ＜単純盲検＞
    subjects
    double blind ＜二重盲検＞
    subjects, researcher
    triple blind ＜三重盲検＞
    subjects, researcher, analyzer
  - ✓ Stopping rules
- data analysis ＜データ解析＞

5. Precision and Validity ＜疫学研究の質＞
reducing errors

random error ＜偶然誤差＞
wrong result due to *chance*
systematic error ＜系統誤差＞
wrong result due to *bias*

- 妥当性 Validity = lack of systematic error
  - 内的妥当性 Internal validity
    - バイアス（偏り） Bias
      - 選択バイアス selection bias
      - 情報バイアス information (observation) bias
        - 思いだしバイアス recall bias
        - interviewer bias
        - 分類の誤り misclassification
          - 方向性のある誤分類 differential misclassification
          - 方向性のない誤分類 non-differential misclassification
      - リードタイムバイアス lead time bias
      - length bias
      - publication bias
      - measurement bias etc. …
    - 交絡因子 confounding factor
  - External validity / Generalizability ＜外的妥当性＞

6. Analysis of data ＜疫学デザイン、データ解析＞

Bias, Confounding factor の制御

① マッチング matching
② 限定 restriction
③ 層化 stratification
④ 無作為化 randomization
⑤ 多変量解析 Multivariate analysis
⑥ 標準化 Standardization

Multivariate analysis ＜多変量解析＞

Multiple linear regression model ＜重回帰分析＞

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_n X_n$$

n = number of independent variable

X_k = data set for each individual

β_k = regression coefficient

- most appropriate when the outcome variable is continuous data

Multiple logistic regression model ＜ロジスティック回帰分析＞

$$\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_n X_n$$

n = number of independent variable

X_k = data set for each individual

β_k = regression coefficient

y = binominal outcome data

or, equivalently

$$p = \frac{e^{\alpha+\beta_1 X_1+\beta_2 X_2+\ldots\ldots+\beta_n X_n}}{1+e^{\alpha+\beta_1 X_1+\beta_2 X_2+\ldots\ldots+\beta_n X_n}}$$

- appropriate when outcome is binary data

7. Screening ＜スクリーニング＞

Purpose

application of a test to people who are as yet asymptomatic for the purpose of classifying them with respect to their likelihood of having a particular disease

not to diagnose illness; those who test positive are sent on for further evaluation by a subsequent diagnostic test

「無自覚の疾病または障害を暫定的に識別すること」

Screening would be

inexpensive ＜安価＞

easy ＜容易＞

minimal discomfort on a subject ＜対象者に不便が最小限である＞

valid ＜有効性あり＞

reliable ＜信頼性あり＞

reproducible ＜再現性あり＞

	Disease (+)	Disease (-)	Total
Screening test result			
(+)	a	b	a+b
(--)	c	d	c+d
Total	a+c	b+d	

a = true positive、b = false positive ＜偽陽性＞、c = false negative ＜偽陰性＞、d = true negative

$$\text{Sensitivity} = \text{Probability}(T^+ \mid Dx^+) = \frac{a}{a+c}$$

$$\text{Specificity} = \text{Probability}(T^- \mid Dx^-) = \frac{d}{b+d}$$

$$\text{Predictive value positive} = \text{Probability}(Dx^+ \mid T^+) = \frac{a}{a+b}$$

$$\text{Predictive value negative} = \text{Probability}(Dx^- \mid T^-) = \frac{d}{c+d}$$

- **sensitivity** ＜敏感(鋭敏)度＞
  probability of test positive if the disease is truly present
- **specificity** ＜特異度＞
  probability of test negative if the disease is truly absent
- **predictive value positive** ＜陽性反応的中率＞
  probability that a person actually has the disease among test positives
- **predictive value negative** ＜陰性反応的中率＞
  probability that an individual truly disease-free among test negatives

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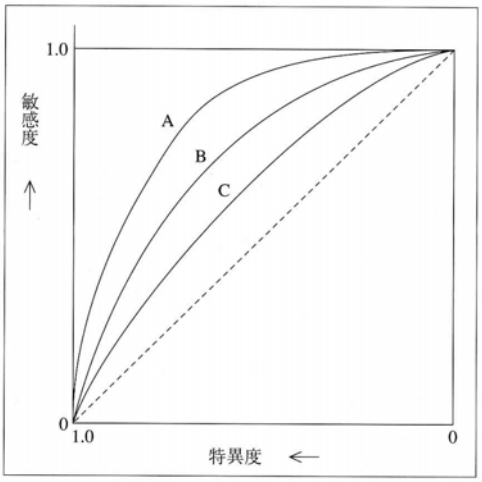
ROC 曲線　Receiver Operating Characteristic curve
（受診者動作特性曲線）

Validity of a screening test ＜スクリーニングの妥当性の指標＞

- 有効性　valid
- 信頼性　reliable
- 再現性　reproducible
- 安価　inexpensive
- 容易　easy
- 対象者の不便が最小限　minimal discomfort on asubject

スクリーニングに生じうるバイアス

volunteer bias (patient self-selection bias) ＜自己選択バイアス＞
lead time bias
length bias



受診者動作特性（ROC）曲線