Estimation of Radiation Risk of Lung Cancer

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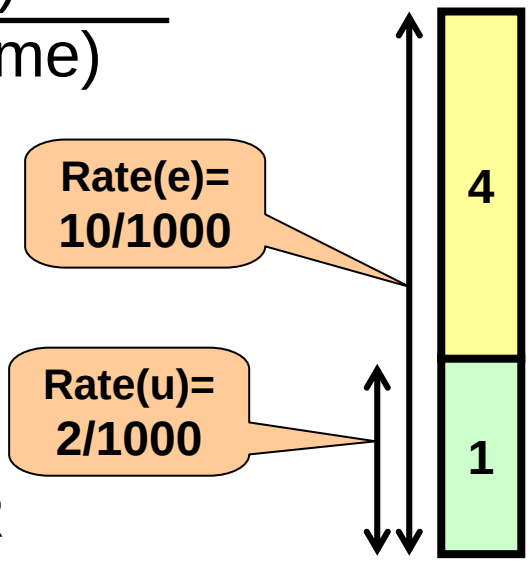
Measurement of Risk

- **Rate** (mortality, incidence)

$$\frac{\text{No. of outcomes (person)}}{\text{Population at risk (person-time)}}$$

- **Risk**
  - Relative risk (RR): ratio of rates

$$\frac{\text{Rate(exposed)}}{\text{Rate(unexposed)}}$$



  - Excess relative risk (ERR): RR=1+ERR
  - Attributable fraction: ERR/RR
  - Excess absolute risk (EAR): difference of rates

Rate(exposed) - Rate(unexposed)

Analytical Models (1)

- **Excess relative risk (ERR) model**

  $\lambda = \lambda_0 (c,s,a,b) [1+ERR(d,s,e,a)]$

- **Excess absolute risk (EAR) model**

  $\lambda = \lambda_0 (c,s,a,b) + EAR(d,s,e,a)$

  – λ: rate at exposure to radiation of dose *d*

  – $\lambda_0(c,s,a,b)$: rate at non-exposure defined by *c,s,a,b*
  (i.e., background rate)

  c: city
  s: code for sex
  a: attained age of an individual (follow-up period)
  b/e: birth year/age at exposure to radiation
  d: dose of radiation received

Analytical Models (2)

ERR, EAR = $\rho(d)\ \varepsilon(X)$

- **Main effect of radiation: $\rho(d)$**
  - **Dose-response relationship**

βd (linear)

- Solid cancer including lung cancer (mortality/incidence)
  - LSS, UNSCEAR

γd^2 (quadratic)

- Leukemia (mortality) – UNSCEAR 2006

$\beta+\gamma d^2$ (linear-quadratic)

- Leukemia (mortality) –LSS, UNSCEAR 2006
- Solid cancer (mortality) –UNSCEAR 2006 (alternative)

Main Effect of Radiation in LSS, 1950-2003

- In full dose range, deviance of the LQ model was the smallest, but not significant than the L model, then the L model was selected
- In dose range of <2Gy, LQ model was the best fit
- LQ component seemed to derive from relatively lower estimates than the linear function around at the level of 0.5 Gy

Ozasa K, Shimizu Y, et al, Radiat Res, 2012

Analytical Models (3)

ERR, EAR = $\rho(d)$ $\varepsilon(X)$

- **Effect modification by X: $\varepsilon(X)$**
  - **Interaction between radiation and X**
  - **Different risk of radiation between various levels/strata of X**

e.g., If the risk of radiation was higher in female, there was effect modification by sex

e.g., If the risk of radiation was higher among the subjects who were exposed to radiation at young, there was effect modification by age at exposure

Analytical Models (4)

$\varepsilon(s,a,e,\ldots)$

- **Effect modification by *s,a,e,…***
  - **Interaction between radiation and *s,a,e,…***

    s: code for sex *a*: attained age of an individual

    e: age at exposure to radiation *a*-*e*: time since exposure

$\exp(\sigma s + \tau e + \upsilon \ln(a))$ – LSS (applied for all individual cancers even if non-significant coefficients)

$\exp(\tau e^* + \upsilon \ln(a/60))$ – BEIR VII (solid cancer mortality/incidence)

- $e^*=(e-30)/10$ ($e<30$), $e^*=0$ ($e\geq 30$)

$\exp(\sigma s + \tau \ln(a-e) + \upsilon \ln(a))$ – UNSCEAR 2006 (all solid cancer mortality)

$\exp(\sigma s + \upsilon \ln(e))$ – UNSCEAR 2006 (all solid cancer mortality)

$\exp(\sigma s)$, **$\exp(\sigma s + \upsilon \ln(a))$** – UNSCEAR 2006 (lung cancer incidence)

Scheme: Effect Modification by Sex

All Solid Cancer Mortality Risk, LSS, 1950-2003

Sex-average ERR=0.42

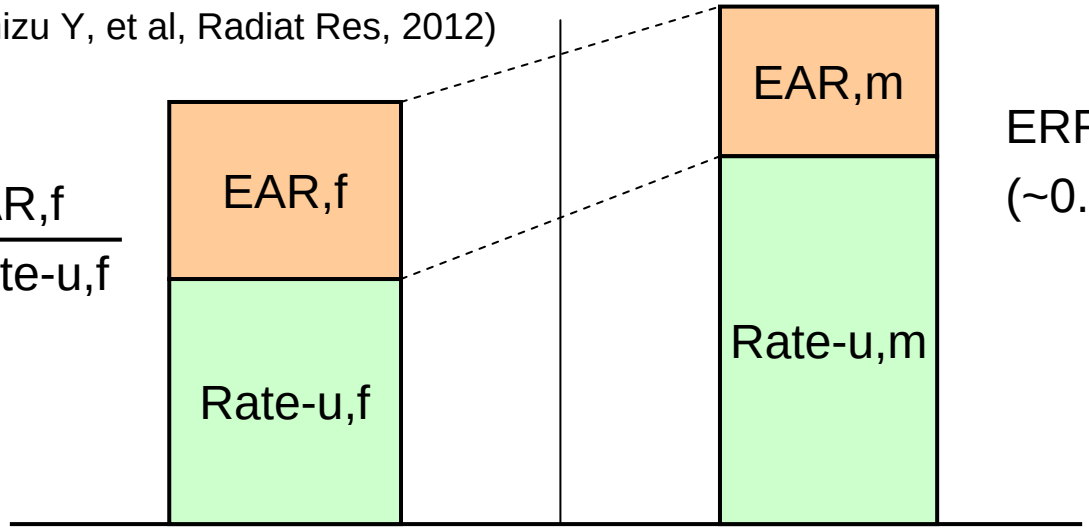
Effect modification of sex on ERR (f/m) =2.1

Sex-average EAR=26.4/10,000 person-years

Effect modification of sex on EAR (f/m) =1.1

(Ozasa K. Shimizu Y, et al, Radiat Res, 2012)

$$ERR,f = \frac{EAR,f}{Rate\text{-}u,f} \quad (\sim 0.6)$$



$$ERR,m = \frac{EAR,m}{Rate\text{-}u,m} \quad (\sim 0.3)$$

$$\frac{ERR,f}{ERR,m} = 2.1$$

$$\frac{EAR,f}{EAR,m} = 1.1$$

Scheme: Effect Modification by Age at Exposure and Attained Age

All Solid Cancer Mortality Risk, LSS, 1950-2003

At attained age of 60

ERR(20)=0.68

ERR(30)=0.48

EAR(20)=15.6

EAR(30)=19.3

At attained age of 70

ERR(20)=0.59

ERR(30)=0.42

EAR(20)=26.4

EAR(30)=32.6

Comparison with RERF, BEIR VII, and UNSCEAR Models, Lung Cancer, Effect Modification by Sex

Effect modification by sex	RERF Mortality 1950-2003 (*p<0.05)	RERF Incidence 1958-1998 (*p<0.1)	BEIR VII Incidence 1958-1998 (*p<0.05)	UNSCEAR Incidence 1958-1998
Sex-average or specific ERR† (female/male)	**0.75* (1.09/0.40)**	**1.33*/0.28***	**1.40*/0.32***	**1.40/0.31**
Sex ratio of ERR† (female/male)	**2.7***	**4.8***	**4.3**	**4.5**
Sex-average or specific EAR†	**6.5* (5.7/7.3)**	**9.1*/6.0***	**3.4*/2.3***	**8.9/5.9**
Sex ratio of EAR†	**0.78**	**1.5**	**1.5**	**1.5**

† ERR and EAR at age 70 after radiation exposure to 1 Gy at age 30
EAR per 10^4 person-years

Comparison with RERF, BEIR VII, and UNSCEAR Models, Lung, Effect Modification by Age at Exposure and Attained Age

Effect modification by:	RERF Mortality 1950-2003 (*p<0.05)	RERF Incidence 1958-1998 (*p<0.1)	BEIR VII Incidence 1958-1998 (*p<0.05)	UNSCEAR Incidence 1958-1998
Age at exposure on ERR†	**-7%**	**20%**	**(-30)§**	**0**
Age at exposure on EAR†	**-16%**	**2%**	**(-41) §**	**0**
Attained age on ERR‡	**-0.04**	**-1.9***	**(-1.4)§**	**0**
Attained age on EAR‡	**6.2***	**4.2***	**5.2***	**4.2**

† Percentage change per 10-year increment, ‡ Power of attained age
§Use the coefficient for all solid cancer

Interaction of Radiation and Smoking on Lung Cancer Risk, Incidence, 1958-99

Risk of radiation for lung cancer:

ERR at 1 Gy was around 0.7 in non-smokers

ERR at 1 Gy was around 2.0 in light smokers who consumed 7-8 cigarettes per day (positive interaction)

No additional increase in risk by radiation in heavy smokers (negative interaction, risk of lung cancer seemed to be saturated by smoking)

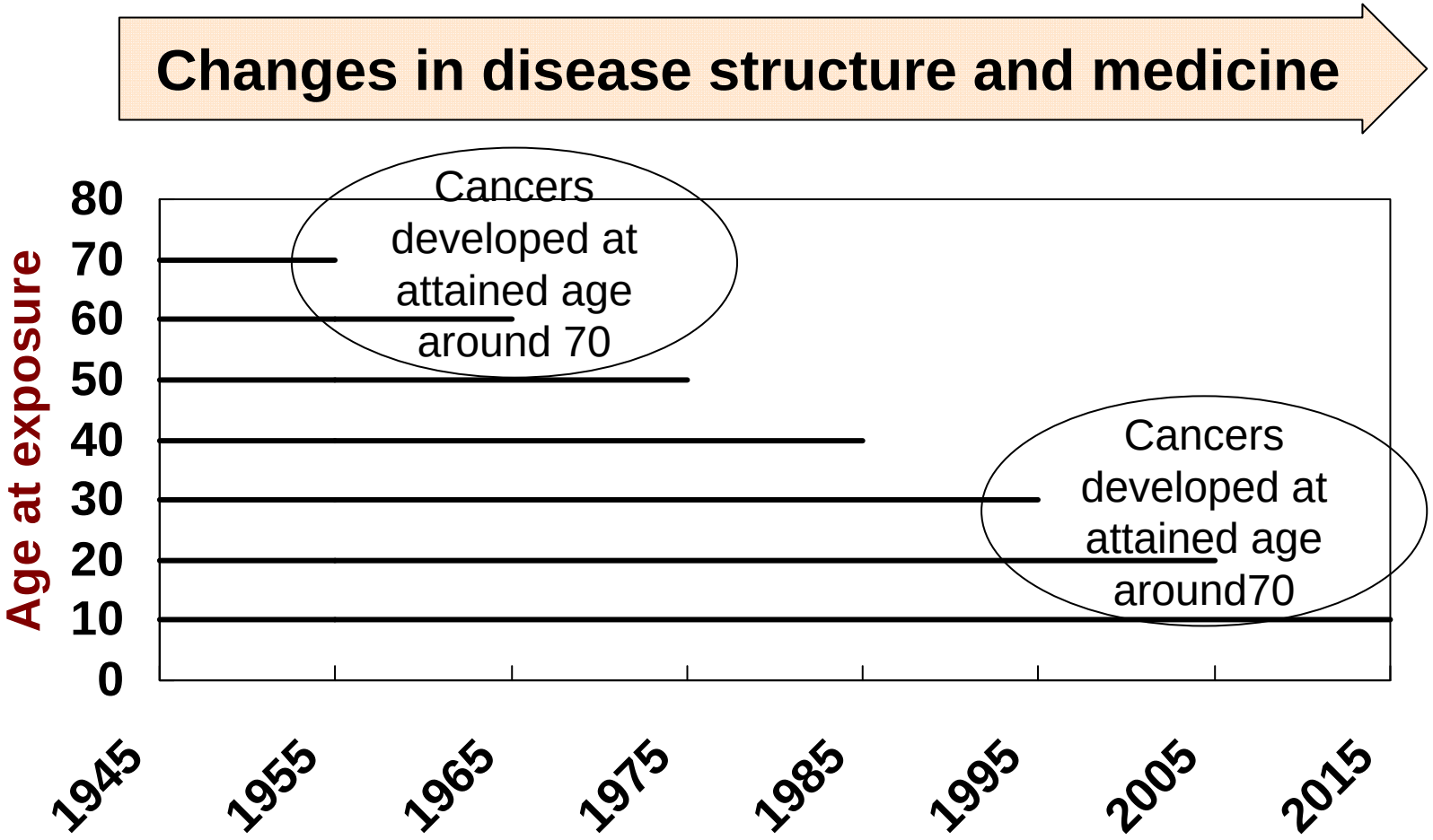
- Risk estimates of radiation on lung cancer may be altered by smoking prevalence and its intensity in the study subjects

Furukawa K, et al. Radiat Res, 2010

Discussion (1)

- **Lung cancer has a high risk of radiation**
  - Estimated risk of radiation exposure on lung cancer may be partially overestimated by the interaction of smoking on lung cancer?
- **Effect modification by sex**
  - ERR is quite different between mortality and incidence data but EAR is rather similar between sex
- **Effect modification by age at exposure**
  - The effect modification on ERR and EAR showed different directions, but not significant, between mortality and incidence data in RERF
  - UNSCEAR assumed no effect modification, BEIR VII applied the values for all solid cancer
  - Substantially no or small effect modification on ERR and EAR?
- **Effect modification by attained age**
  - ERR slightly decreased with attained age or no effect modification
  - EAR increased with attained age

Effects of Age at Exposure Emerged in Different Time periods



Discussion (2)

- Although the background changes might not affect the risk estimation theoretically, the changes need to be kept in mind
  - Difference in preciseness of information on death certificates and cancer registries between the time periods
  - Difference in prognosis of cancer according to medical progress between the time periods

  might cause some differential misclassification on information of outcomes?

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