

# Current Research on Non-cancer Diseases in Atomic Bomb Survivors

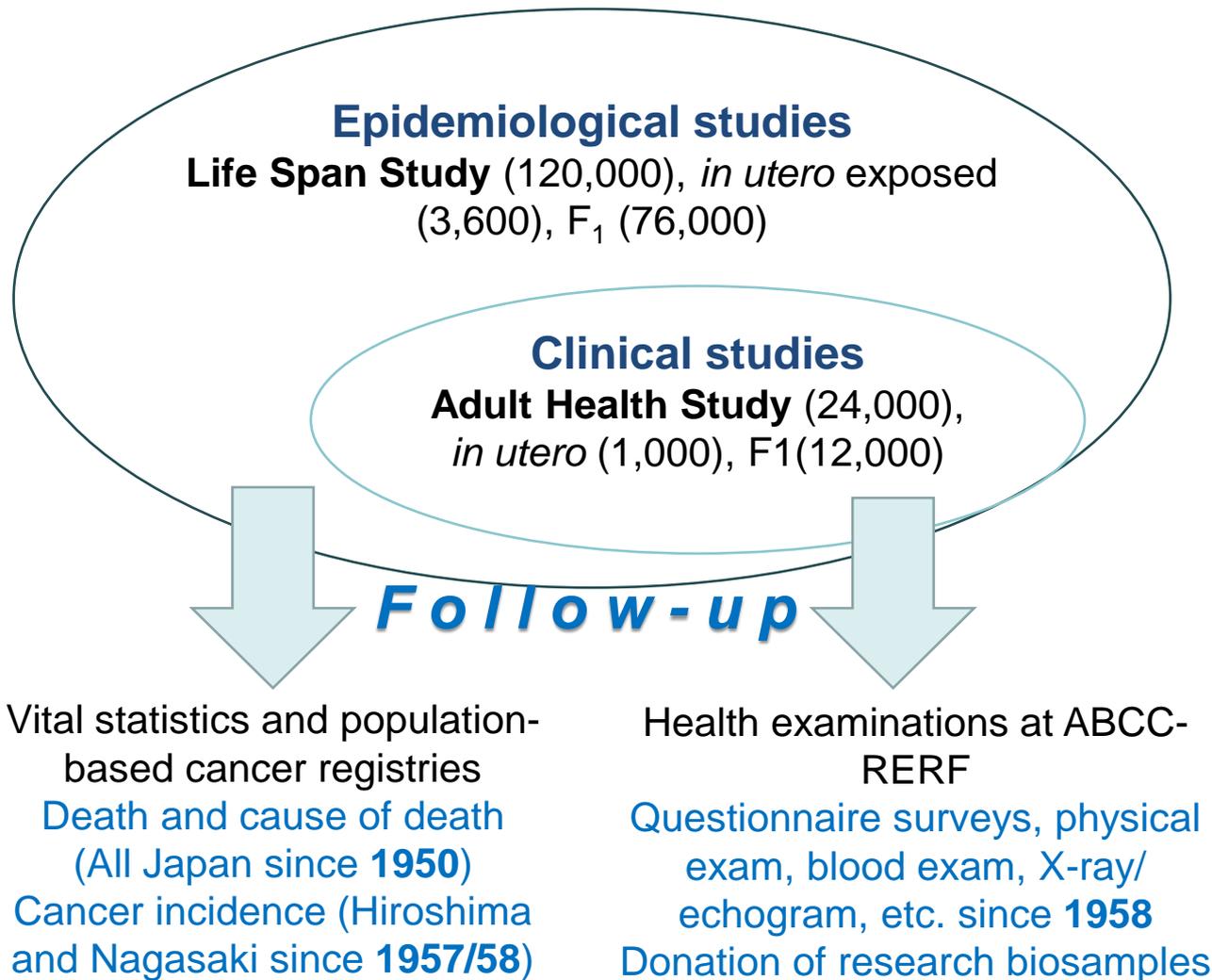
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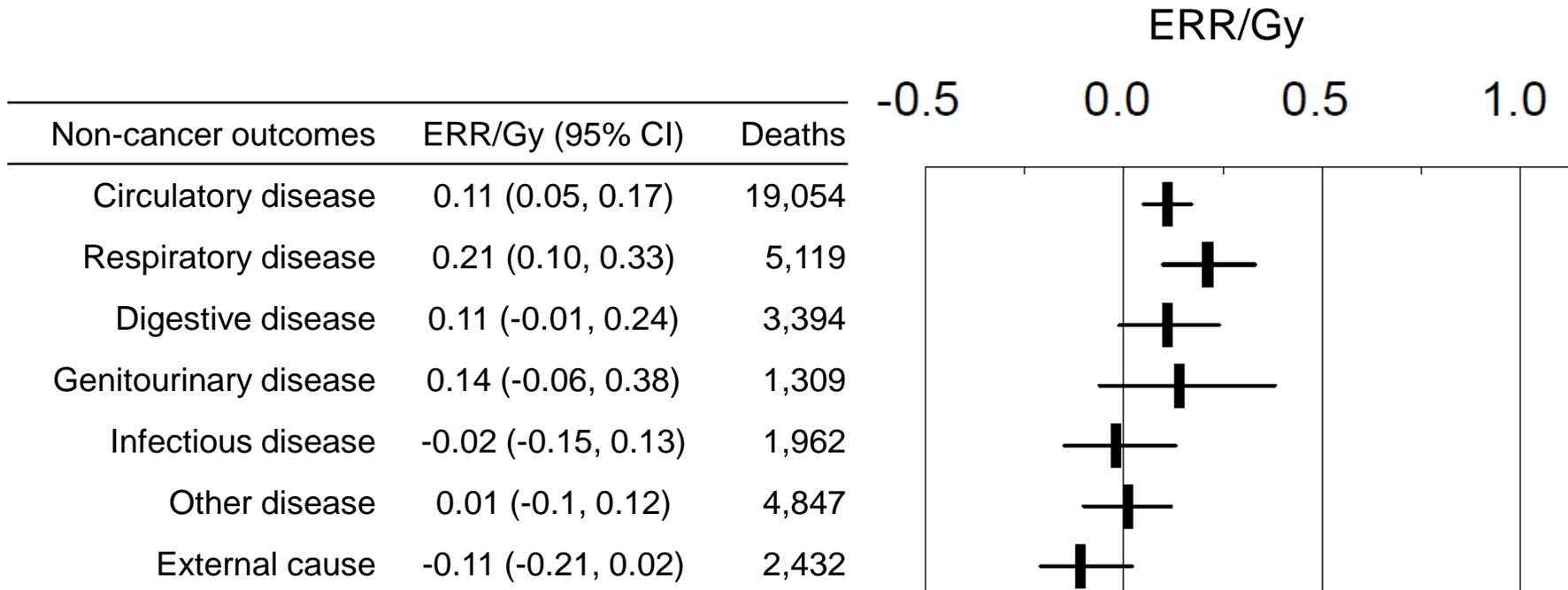
RERF

Hiroshima, Japan

# Life Span Study (LSS) and Adult Health Study (AHS)



# Radiation-associated Non-cancer Diseases among LSS, 1950-2003

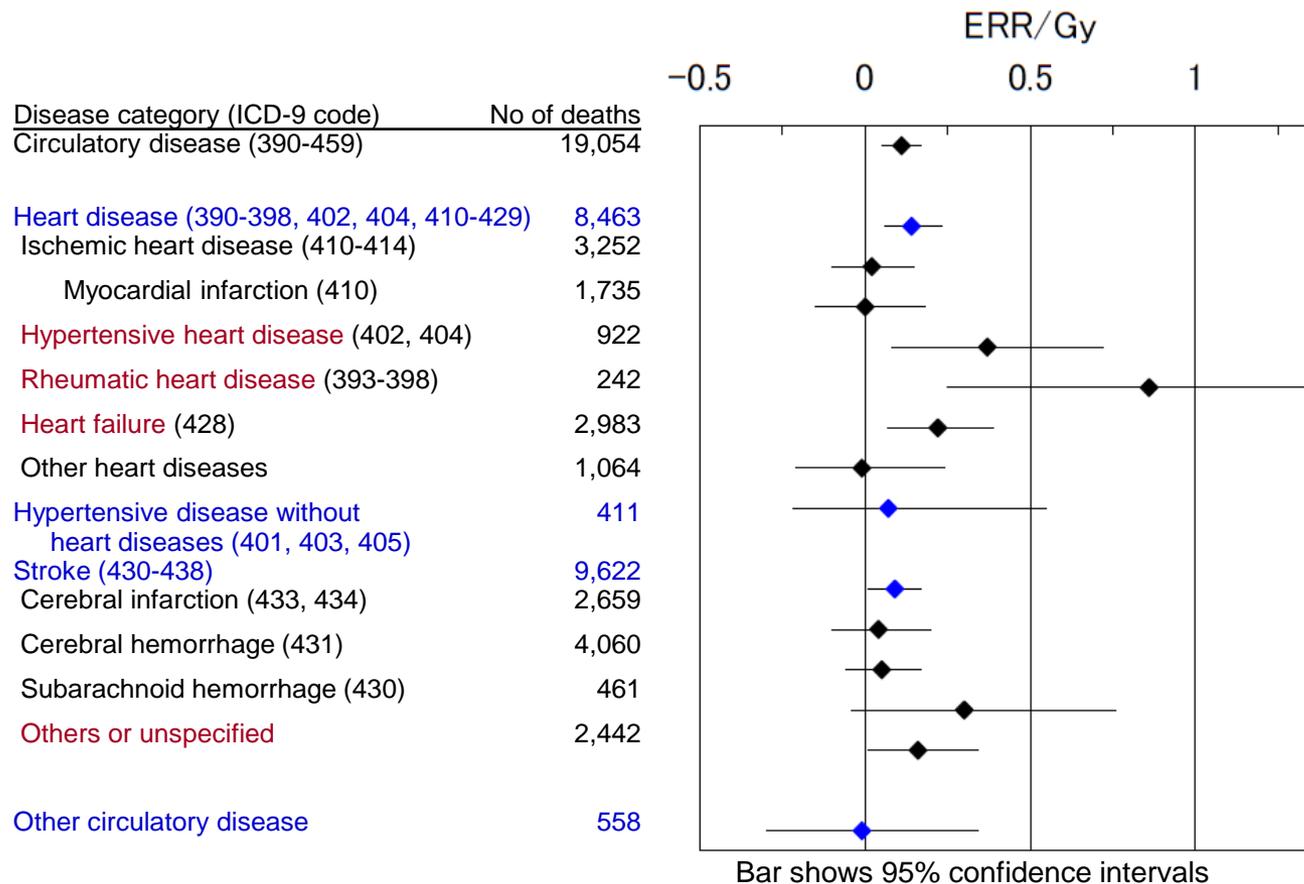


# Cardiovascular Disease (CVD) among Atomic Bomb Survivors

- Radiation-associated CVD among atomic bomb survivors
  - Current knowledge/findings
  - Potential mechanisms of association with radiation exposure
    - Hypertension may be the intermediate pathogenesis
      - Exposure to atomic bomb radiation was systemic irradiation
    - It seems different from the perceived mechanisms
      - i.e., atherosclerotic changes due to endothelial cell injuries or inflammation
    - Another aspect is uncertainty of diagnosis at death in the LSS
- Pathogenesis of CVD in general population of Japan
  - in order to understand the association

# Radiation-associated CVD among Atomic Bomb Survivors (1)

- CVD mortality in LSS (Shimizu, et al. *BMJ*, 2010)
  - Stroke showed a possible upward curvature in dose-response
  - Heart disease showed a linear dose-response
  - Much heterogeneous radiation risks among subtypes of HD and stroke



Data from Shimizu, et al.  
*BMJ*, 2010

## Radiation-associated CVD among Atomic Bomb Survivors (2)

- CVD incidence in AHS (Yamada, et al. *Radiat Res*, 2004)
  - Quadratic dose-response models were significant for hypertension and myocardial infarction (age at the bombing <40 years).
  - However, radiation-related risk was not increased in a linear dose-response model for any CVD subtype
- CVD incidence in AHS (Takahashi, et al. *BMJ*, 2012)
  - Increased risk was shown in hemorrhagic stroke in both sexes (with threshold in females), but not shown in ischemic stroke

## Potential Mechanism- Intermediate Pathogenesis (1)

- Renal disease mortality in LSS (Adams, et al. *Radiat Res*, 2012)
  - A significant quadratic model for chronic kidney disease
- Renal disease incidence in AHS (Sera, et a. *Radiat Res*, 2013)
  - Moderate + severe chronic kidney diseases were associated with radiation exposure

## Potential Mechanism- Intermediate Pathogenesis (2)

- Increase of blood pressure in AHS (Sasaki, et al. *J Clin Epidemiol* 2002)
  - Systolic and diastolic blood pressure levels were higher in exposed subjects than in unexposed subjects among younger birth cohorts, but lower among older birth cohorts
  - The difference was significant, but small, about 1 mmHg/Gy.
- Increase of total serum cholesterol in AHS (Wong, et al. *Radiat Res* 1999)
  - About 2.4 mg/dl at 1 Gy in women and about 1.5 mg/dl in men at most
- Increase of CRP and IL-6 (Hayashi, et al. *Hum Immunol* 2003)
  - Inflammatory markers associated with endothelial cell injuries or inflammation, which induce atherosclerosis
  - Increase by 28% and 9.8% per gray, respectively
- It remains unclear how strong these changes influenced clinically manifested radiation-associated CVD

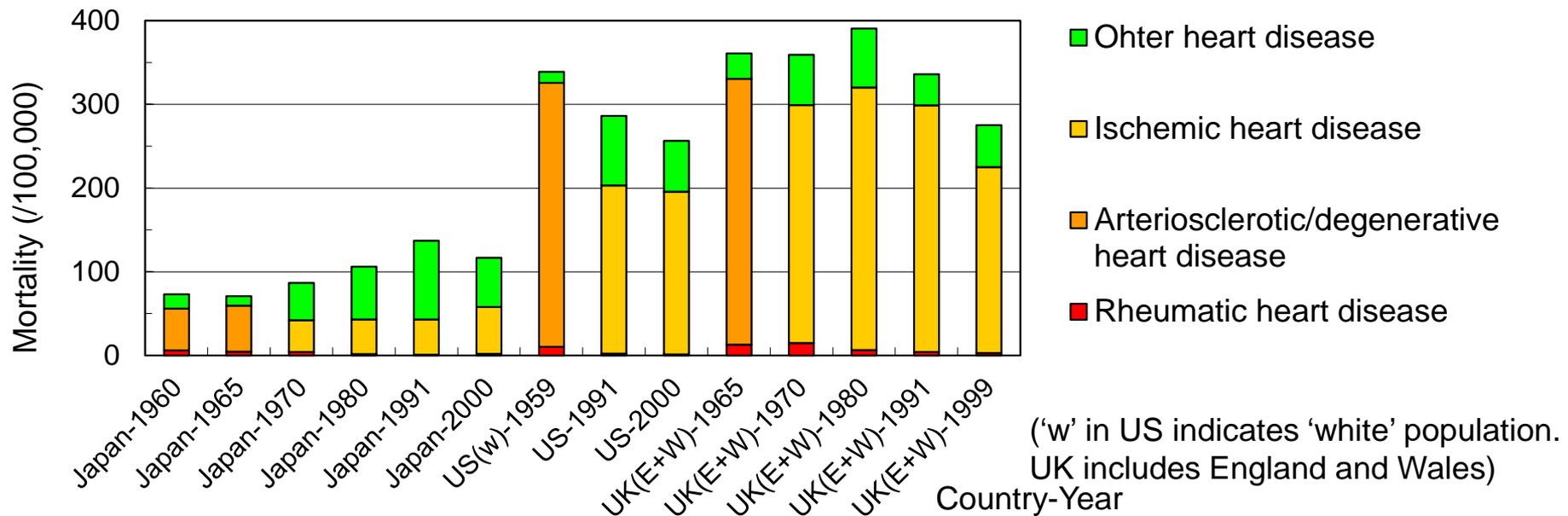
# Summary of Radiation-associated CVD in the LSS and AHS of Atomic Bomb Survivors

- Increased at relatively high-dose levels (>2 Gy) with non-linear dose-response, especially when including non-fatal incidence outcomes
- Rather apparent in those exposed at younger ages
- Intermediate pathogenesis may be hypertension rather than atherosclerosis
  - But, there are some exceptional/remaining issues
- Uncertainty of diagnosis in death certificates (association in LSS)
  - Heart failure and others/unspecified stroke (i.e., ill-defined disease categories) as the underlying cause of death might include undiagnosed malignancies

# Pathogenesis of CVD in Japan

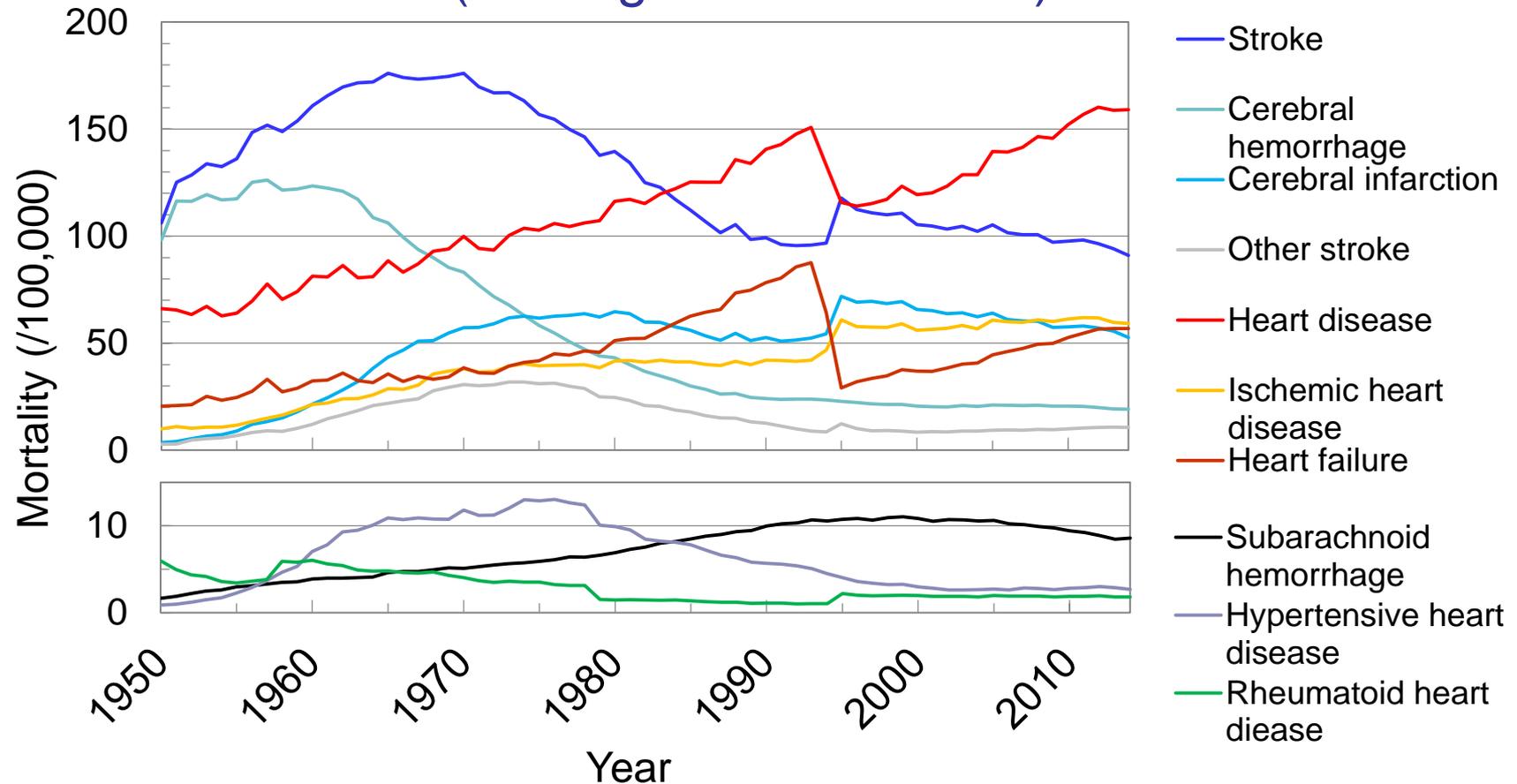
- Difference of CVD profile between Japan and Western countries
- Nutritional and metabolic background of CVD in Japan

# Mortality of Heart Diseases in Japan and Western Countries



- Mortality of heart disease has been much lower in Japan than in US/UK
- Proportion of arteriosclerotic/ischemic heart disease has been smaller in Japan than in US/UK
- Hypertension is the most potent risk factor in Japan for stroke and heart disease including cerebral infarction and ischemic heart disease

# Trend of *Crude* Mortality of Circulatory Disease (Average of both sexes)



- Cerebral hemorrhage had markedly decreased from 1960s to 80s whereas cerebral infarction and heart disease (especially heart failure) had increased
- 'Heart failure' should be avoided for a underlying cause of death then cerebral infarction and ischemic heart disease (mostly myocardial infarction) increased

# Blood Pressure Level of Japanese Population

| Year | Age class | Average blood pressure |                  | Proportion of hypertensive people           |   |
|------|-----------|------------------------|------------------|---|---|
|      |           | Systolic (mmHg)        | Diastolic (mmHg) | Systolic: $\geq 150$ mmHg                   | Diastolic: $\geq 90$ mmHg                   |
| 1960 | 60-64     | M: 154, F: 156         | M: 90, F: 90     | M: 52%, F: 53%                              | M: 48%, F: 46%                              |
| 1970 | 60-64     | M: 152, F: 152         | M: 87, F: 86     | M: 49%, F: 50%                              | M: 40%, F: 38%                              |
|      |           |                        |                  | Sys. $\geq 140$ mmHg or Dia. $\geq 90$ mmHg | Sys. $\geq 160$ mmHg or Dia. $\geq 95$ mmHg |
| 1980 | 60-69     | -                      | -                | M: 69%, F: 65%                              | M: 36%, F: 30%                              |
| 1990 | 60-69     | -                      | -                | M: 63%, F: 61%                              | M: 32%, F: 26%                              |
| 2000 | 60-69     | -                      | -                | M: 56%, F: 52%                              | M: 20%, F: 17%                              |
| 2010 | 60-69     | M: 140, F: 138         | M: 84, F: 81     | M: 53%, F: 46%                              | M: 14%, F: 12%                              |

M: male, F: female

- Blood pressure level of Japanese population was high in the past then consistently decreased

## Nutrition Intake per Person in Japan

| Year          | Energy (kcal) | Protein (g) |        | Fat (g) |        | Salt (g) | % energy from fat |
|---------------|---------------|-------------|--------|---------|--------|----------|-------------------|
|               |               | Total       | Animal | Total   | Animal |          |                   |
| 1950 (urban)  | 1,972         | 70.1        | 21.3   | 21.2    | -      | -        | 9.7               |
| 1950 (rural)  | 2,163         | 66.1        | 13.8   | 15.4    | -      | -        | 6.4               |
| 1960          | 2,096         | 69.7        | 24.7   | 24.7    | 9.2    | -        | 10.6              |
| 1970          | 2,210         | 77.6        | 34.2   | 46.5    | 20.9   | -        | 18.9              |
| 1980          | 2,084         | 77.9        | 39.2   | 52.4    | 27.2   | 13.0     | 22.6              |
| 1990          | 2,026         | 78.7        | 41.4   | 56.9    | 27.5   | 12.5     | 25.3              |
| 2000 (male)   | 2,152         | 84.9        | 45.9   | 61.7    | 31.6   | 13.1     | 25.8              |
| 2000 (female) | 1,764         | 71.1        | 37.8   | 53.5    | 26.4   | 11.6     | 27.3              |
| 2010          | 1,849         | 67.3        | 36.0   | 53.7    | 27.1   | 10.2     | 26.1              |

- Animal protein intake and fat intake, especially animal fat, were low in the past in Japan
- Salt intake was high in the past

# Summary of Pathogenesis of CVD in Japan

- Hypertension was the basic pathogenesis of CVD in Japan
  - Lack of animal protein and fat raised cerebral hemorrhage in the early period
  - A large fraction of cerebral infarction was lacunar type (arteriosclerosis of the cerebral parenchymatous small arteries induced by hypertension)
  - Ischemic heart disease was more attributed to hypertension
- Westernization of lifestyle has increased atherosclerotic change
  - Likely affected younger generations
  - Still at lower level than Western countries
- These background may influence the profile of radiation-associated CVD in atomic bomb survivors

# Non-cancer Respiratory Disease (NCRD) in the Atomic Bomb Survivors

# Radiation Dose-response of ERR for All NCRD in LSS, 1950-2005

## 1950-1964

ERR/Gy=0.11

(95%CI: -0.08, 0.36)

N=849

Increased at the highest dose level

## 1965-79

ERR/Gy=0.08

(95%CI: -0.09, 0.29)

N=1149

Almost no increase over the whole dose range

## 1980-2005

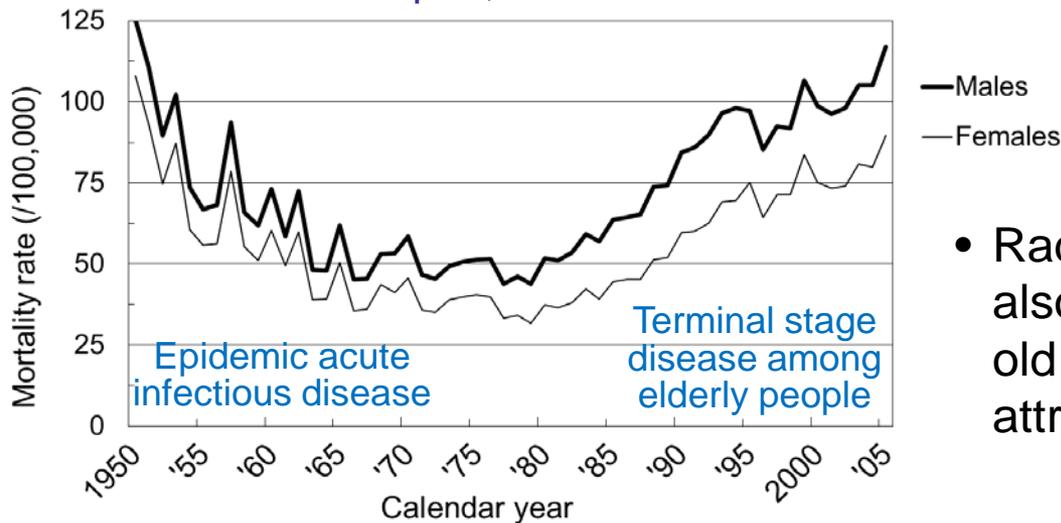
ERR/Gy=**0.21**

(95%CI: 0.10, 0.34)

N=3,517

Linear function was the best fit

Trend of Crude Mortality of All NCRD in Japan, 1950-2005



For 1950-2005, ERR/Gy=**0.17** (95%CI: 0.08, 0.27), N=5,515

Adjustment for cancer incidence reduced the ERR/Gy to 0.12

- Radiation-associated risk of NCRD was also associated with ill-defined death at old ages, which could in part be attributed to coincident malignancies

# *The End*

