به نام خدا

LINEAR –NO-THRESHOLD MODEL (LNT)

HEALTH EFFECTS ASSESSMENT OF LOW DOSE RADIATION

استاد:آقای دکتر مرتضوی

سحر لعل پور

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IS THE LINEAR NO-THRESHOLD DOSE-RESPONSE PARADIGM STILL NECESSARY FOR THE ASSESSMENT OF HEALTH EFFECTS OF LOW DOSE RADIATION?

CONTENTS:

- Ionizing radiation effects
- LNT Definition
- History
- Low dose window and its effects
- Important facts neglected by LNT
- Five risk assessment models
- Low dose radiation researches
- Confounding factors
- Epidemiological studies
- Uncertainties in estimating health risks
- conclusion

Two general mechanisms can explain different types of ionizing radiation effects:

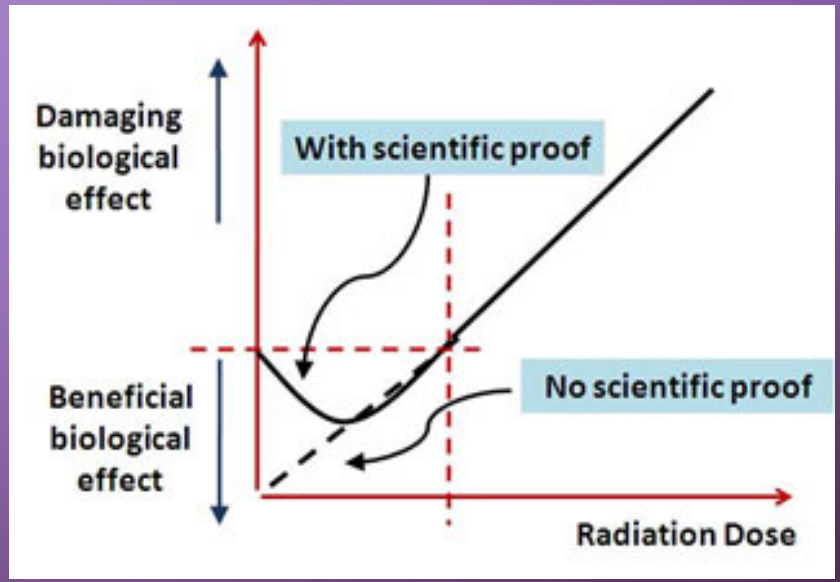
- Target theory

Linear-no-threshold models

- non-targeted effects

Bystander effects

Adaptive response

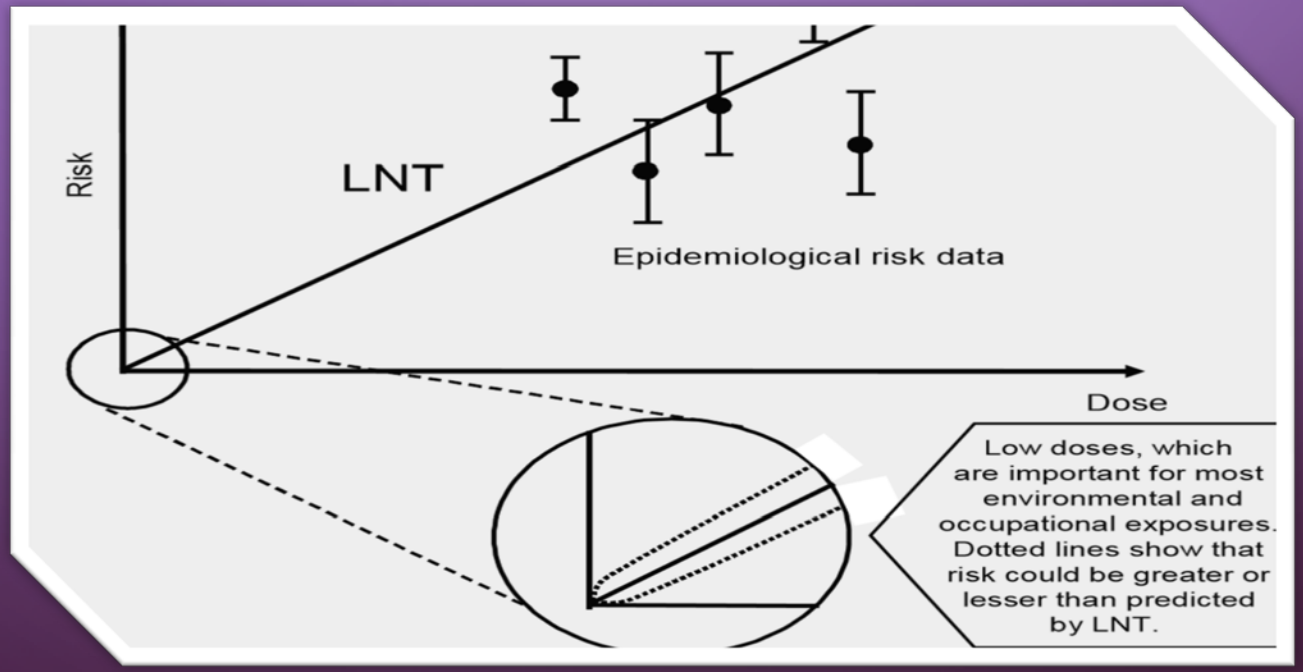


DEFINITION:

- The LINEAR NO-THRESHOLD MODEL (LNT) is a model used in radiation protection to estimate the long-term, biological damage caused by ionizing radiation
- It assumed that the damage is directly proportional ("linear") to the dose of radiation, at all dose levels.
- Radiation is always considered harmful with no safety threshold
- Any low dose of radiation can cause detrimental effects (cancer, heritable genetic mutations) stochastic effects

LNT MODEL:

- High dose: A proportional relationship between cancer risk and effective dose above 200 mSv has been well documented mainly based on Japanese atomic bomb survivor in 1945.(solid scenific evidence)
- Low dose: extrapolation of high dose health effects.(imprecise and often conflicting data)



HISTORY:

- Discovery of X-ray by Roentgen in 1895
- Discovery of radioactivity by Becquerel in 1896
- Use of radiation in diverse fields:

1. *Medical diagnosis and treatment*
2. *Industrial application*
3. *Scientific and educational uses*

In early days after finding radiation, Since its harmful effects hadn't been recognized, Radiathor and Fluoroscope were prevalent all over the industrial fields.

HISTORY:

- Early decades of 20th century

✓The most fundamental radiation dose-response relationships have a threshold. Presence of tolerance levels against radiation exposure

✓No radiation risk at less than a threshold

✓Dose limits for radiation workers and public based on a linear model with a threshold dose.

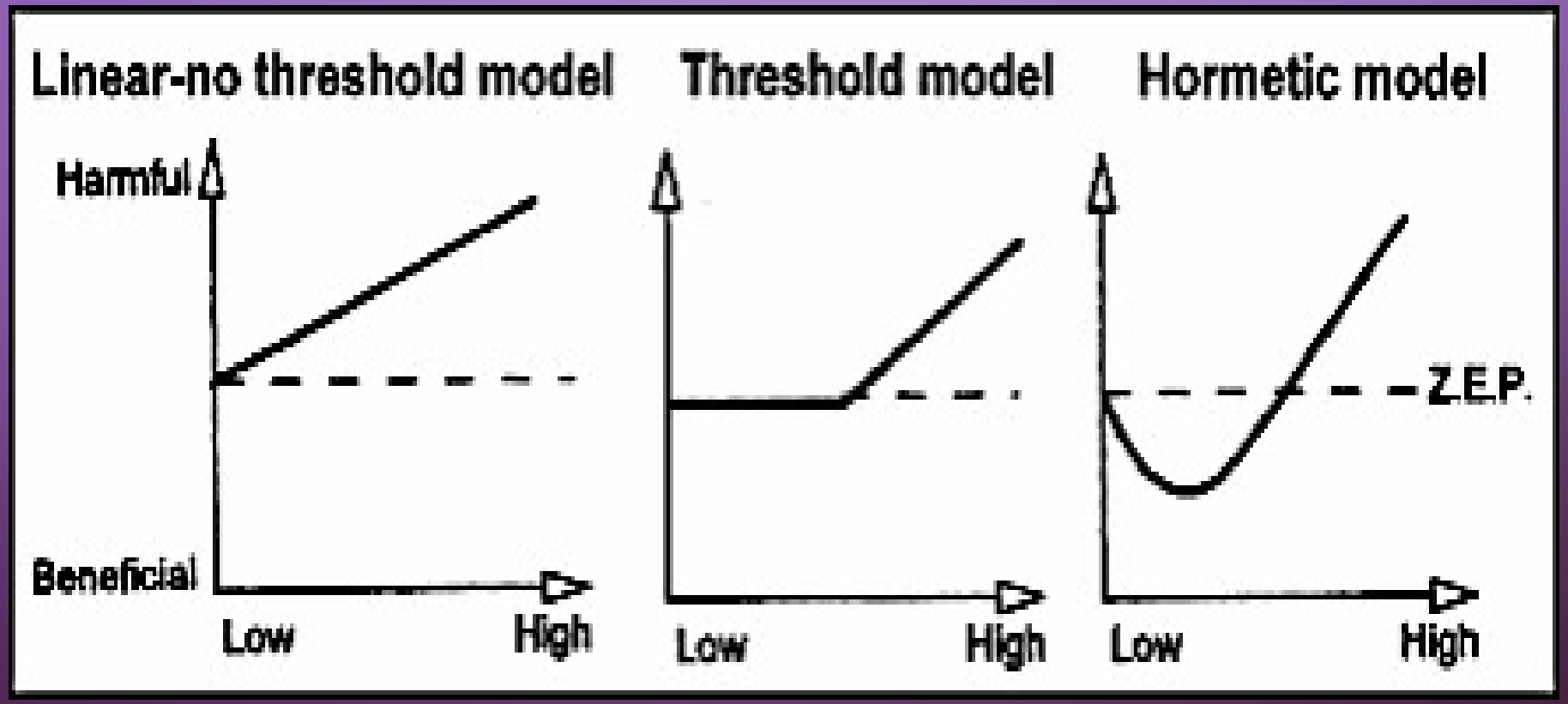
(Vaiserman 2010)

This concept was rapidly changed after atomic bomb disasters.

LNT MODEL:

- First introduced by John Gofman (Berkeley)but rejected by the Department of Energy.
- NAS, in their Biological Effects of Ionizing Radiation report, concluded that “the preponderance of information indicated that there will be some risk, even at low doses”.
- The atomic bomb survivor data and several evidence from various medical exposure groups had reduced the recommended dose limits over the years.
- accepted and published as a guideline of radiation policy by ICRP 1958

RISK ASSESSMENT MODELS:



Why is it so important to develop our knowledge around low dose effects?

- Since most of prevalent irradiations happen in low dose window, it is essential to understand its mechanism of effects .
- Occupational and medical exposures(diagnostic) , natural background radiation , even most of local contaminations in nuclear centers (medical or industrial) are within low dose range.
- Comprehending all aspects will help agencies to choose a rational approach toward low dose radiation protection .

The biological effects of radiation are categorized into two broad classes: stochastic and deterministic effects (or recently termed tissue reactions):

A. STOCHASTIC EFFECTS:

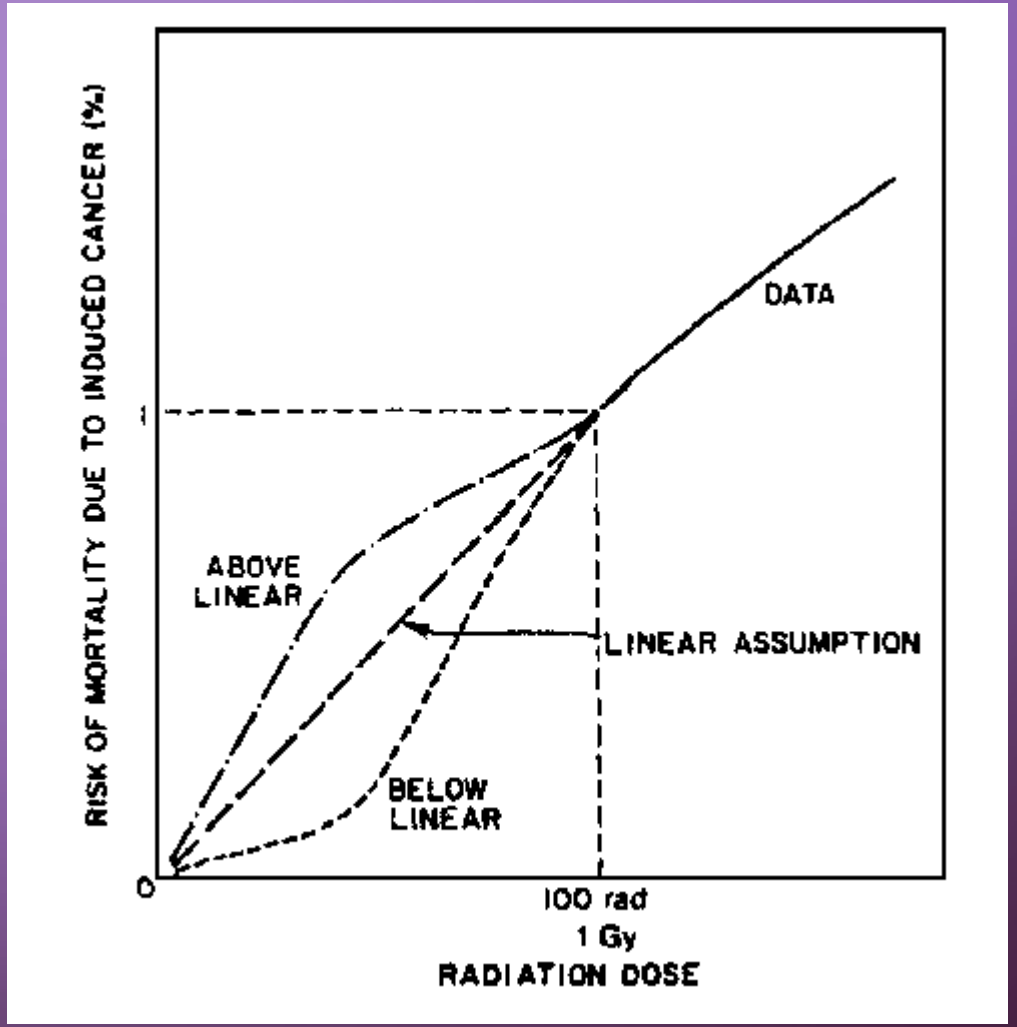
- ✓ Probability of occurrence depending on the irradiated doses without threshold
- ✓ Happening by chance
- ✓ Cancer/genetic defects
- ✓ Show up years after exposure
- ✓ Appearing in individuals under background radiation levels
- ✓ it can never be determined that an occurrence of these effects was due to a specific exposure.

B. non-STOCHASTIC EFFECTS:

- ✓ malfunctions of organs by irradiation at more than threshold
- ✓ Do not exist below their threshold doses.
- ✓ can occur as a result of losing normally functioning large number of critical cells caused by stochastic killing of irradiated individual cells.
- ✓ Tissue reactions=because it was recognized that these effects are not decided at the moment of irradiation and can be modified through various biological responses.(ICRP,P 118)

LOW DOSE WINDOW:

- Health effects of low dose radiation less than 100 mSv have been debated whether they are beneficial or detrimental.
- Low dose health effects are stochastic effects.



COMPLEXITY OF BIOLOGICAL EFFECTS BY RADIATION:

- Damaging various cell components directly(molecule ionization) or indirectly(ROS production)
- Immediate Innate defense mechanisms:

✓Removal of oxidative stress (antioxidant molecules)

✓Removal damaged cells

✓DNA repair: homologous recombination(HR)/non-homologous end joining(NHEJ) → influenced by irradiated dose, dose-rate, nature of radiation, and cell state.

Continued:

1. These systems could be activated by low dose radiation and less effective when the irradiated dose is high.
2. The efficacy of repair in the irradiated cells at low dose would be higher than at high dose .
3. Therefore, the carcinogenic risk seems to be negligible at low doses and low dose-rates irradiation.(Dikomey E, 2000)
4. No induction of the intra-chromosomal inversions and deletions in human irradiation at doses less than 100 mSv.(Zeng G 2006)
5. Programmed cell death (apoptosis) activated by low doses under 200 mSv could remove damaged cells.(Lobrich 2005,Columbano 1996)
6. The number of eliminated cells at low dose irradiation did not affect the tissue function for organism's living.

REPORTS ISSUED BY INTERNATIONAL AUTHORITIES OF RADIATION:

Analysis of great number of experimental data related to low dose radiation :

A. *biological responses of low dose radiation were different from those of high dose radiation with various dose-response relationships.*

B. *low dose effects cannot be concluded to be harmful to human health.*

Recommendation:holistic approaches combining biological system-based methods with epidemiological data to develop more sophisticated dose-response models at low dose levels, considering a dose and dose rate effectiveness factor (DDREF)

(NAS , UNSCEAR , ICRP-publication 99, FAS)

IMPORTANT FACTS NEGLECTED BY LNT MODEL:

1) All living beings on the earth have been evolved and adapted to harsher natural radiation environments for billions of years.
2) There is a growing body of experimental and epidemiological evidence that does not support the LNT model for estimating cancer risks at low doses.(Calabres EJ, 2014)
3) There are also non-targeted DNA mechanisms in low dose radiation response.
4) Low dose radiation effects=complex to investigate, difficulty in prediction for their occurrence due to confounding factors such as pollutants, ages and life styles.

LNT : because risk estimation at low doses is achieved by extrapolation of linear dose-response relationship for high doses without definite scientific evidence, it should be carefully revaluated in the low level of radiation.

Nowadays, five risk assessment models has been discussed:

- focused on primarily cancer risk
- Regarding heritable risk, its nominal risk coefficient in the whole population was estimated as 0.2% per Sv in ICRP 103, which was substantially reduced by a factor of 6-8 compared to the estimates from the former ICRP 60, becoming less of a concern about health risks of low dose radiation.

FIVE RISK ASSESSMEN MODELS:

a) LNT model
b) Linear threshold model
c) Linear Quadratic Model (LQ)
d) Supra-linear model
e) Hormesis Model

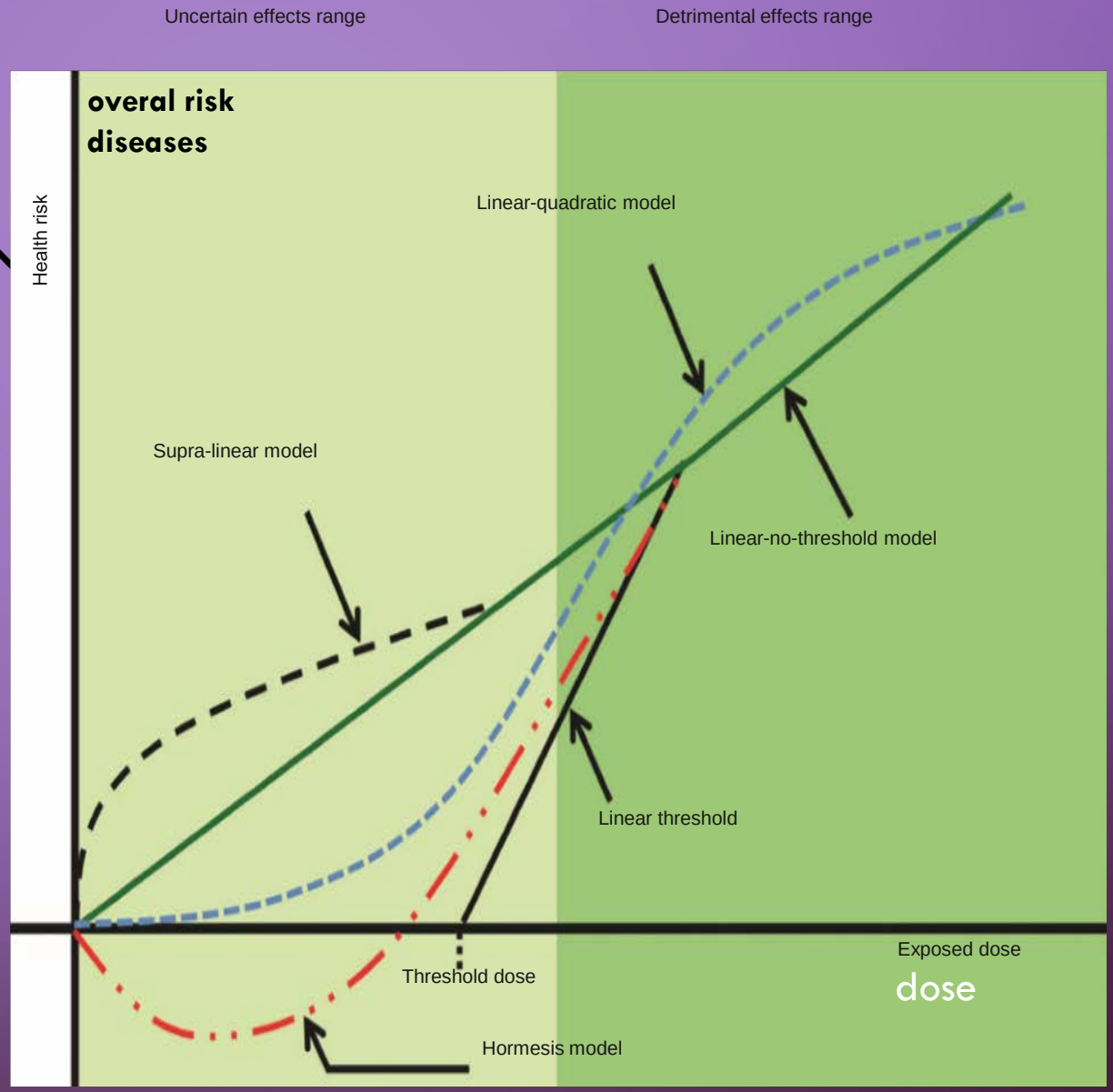


Fig. 1. Schematic diagram illustrating various dose-response models in risk assess

LQ MODEL

- ✓ Viewed in radiotherapy
- ✓ Best fit to leukemia data from life span study(LSS) of atomic bomb survivors

SUPRA LINEAR MODEL

- ✓ Non-targeted effects:Bystander /apscopal effect
- ✓ Low dose hypersensitivity
- ✓ LDHRS decreases with increasing dose and disappears at doses higher than 0.5 Gy due to the biological defense system
- ✓ eliminating potential mutant cells at low doses, thereby reducing the carcinogenic risk

HORMESIS MODEL

- ✓ U-shaped dose-response relationships at low doses
- ✓ low dose radiation induced the activation of protective mechanisms at the cell and tissue levels, against carcinogenic factors other than ionizing radiation and even against spontaneous cancer.(adaptive response/bystander effect)
- ✓ Dose window:

Less than 100 mSv=BS

Less than 500 mGy=AR

EFFECTS OPPOSING LNT:

- **Adaptive response** :

✓Growth of human cells under reduced background radiation increased their sensitivity to acute irradiation at high dose.(Carbon,2009)

✓evidence for the existence of a AR made by normal levels of background radiation.

✓Determined by Genetic background , physiological factors

LOW DOSE EFFECTS OPPOSING LNT:

- **Radiation Hormesis** :

✓ defined as the stimulating effect of small doses of substances which in larger doses are inhibitory.

✓ Upregulation of protective mechanisms at the cell and tissue by low doses can function against spontaneous cancer other than radiation-induced carcinogenesis

✓ irradiation at 10 mGy reduced the rate of spontaneous transformation in culture cells below background level. (Calabres 2004)

✓ irradiated model animals at low dose showed the extension of their lifespan, compared to non-irradiated control. (Calabres 2012)

✓ activation of the specific signal pathway related to mammalian NF-κB in fruit flies. (Seong 2012)

✓ Radiation protection agencies = unwarranted effect

LOW DOSE EFFECTS OPPOSING LNT:

- **Bystander effects/apscopal effect**:

✓ communicating their information to neighboring cells with small molecules

✓ radiation effect in a non-irradiated tissue distant from the irradiated tissue

✓ recent results suggest that irradiated cells also protect neighboring cells, thus acting as a beneficial effect. (Mothersil 2006)

✓ Health effects at less than 100 mSv are argued whether radiation is good or bad in epidemiological approaches

LOW DOSE EFFECTS OPPOSING LNT:

- **Radiation-induced genomic instability:**

✓ acquired DNA damage in cell progeny causing chromosomal aberrations, micronuclei, DNA fragmentation, and aneuploidy.

✓ induced through targeted and non-targeted bystander effects by irradiation

✓ formed by X-ray at doses about 10 mGy, which is regarded to be an early event in radiation carcinogenesis (Huang L,2007)

✓ In contrst, radiation less than 250 mGy of X- or gamma ray showed no genomic instability. (Okada M,2007)

CONTINUED:

- ✓ Exposed individual showed convincing evidence of genomic instability in acute myeloid leukemia and myelo-dysplastic syndrome patients among Japanese A bomb survivors(consequence of the disease or non-targeted effects of irradiation ? _ correlation between instability and development of the diseases ?).
- ✓ radiation-induced genomic instability at low doses affects health risk ??

LOW DOSE RADIATION RESEARCH

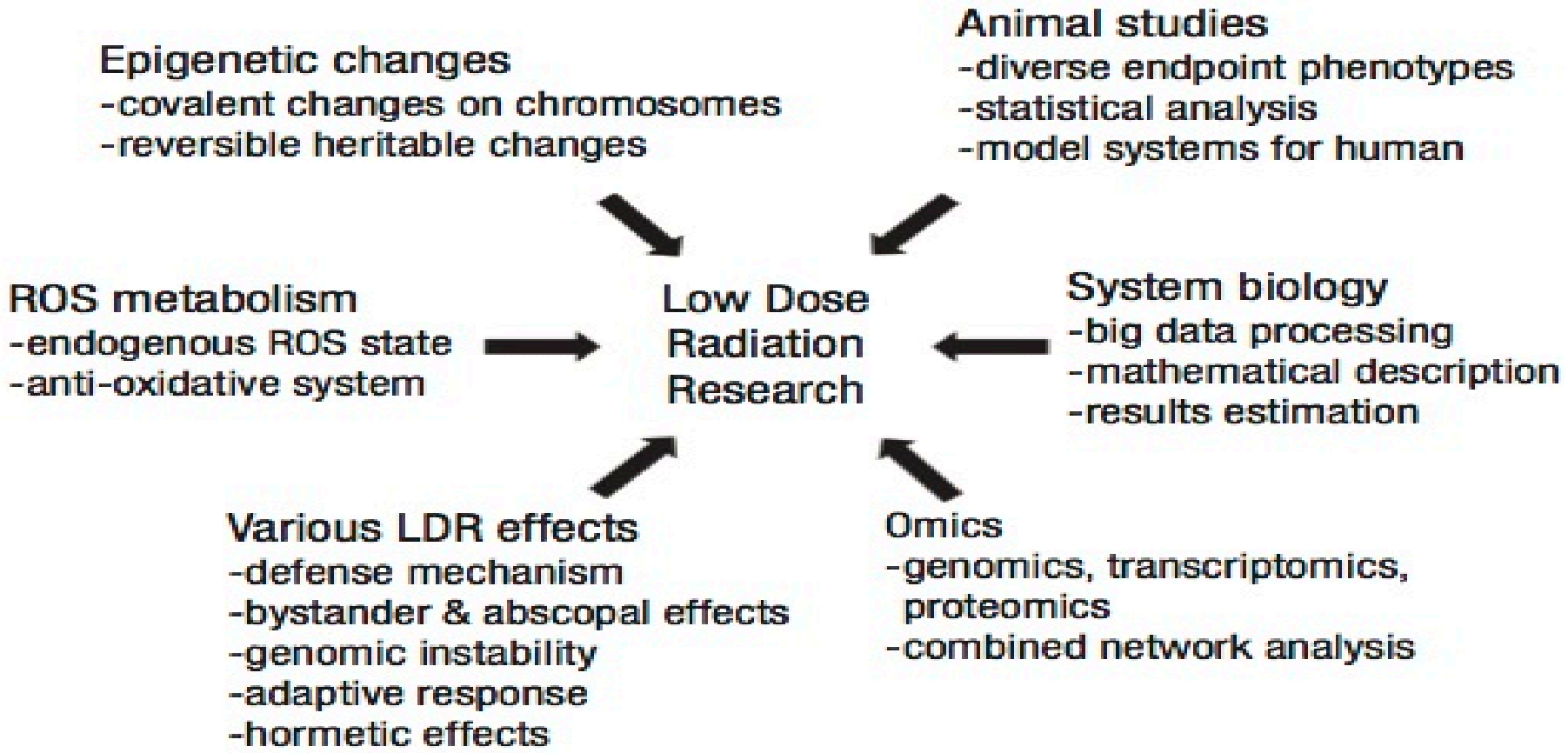


Fig. 2. Recent biological studies on the low dose radiation effects. To increase the consistency and coherence of experimental data on low dose radiation, we should introduce new biological knowledge of emerging area as well as conventional concepts.

NEW BIOLOGICAL RESEARCH FIELDS TO ESTIMATE RADIATION RISK AT LOW DOSES:

- reversible heritable changes on genome without a change in the DNA sequences
- epigenetic changes

Understanding carcinogenesis

- covalent modifications of chromosomal structure(phosphorylation, methylation, acetylation and sumoylation)
- Reactive oxygen species (ROS) :modulates radiation response

ROS state , regulated by irradiation at low doses, which maintained for a period time accompanying with gene expression changes

NEW BIOLOGICAL RESEARCH FIELDS TO ESTIMATE RADIATION RISK AT LOW DOSES

- Omics is another excellent arsenal to reveal the overall cellular signal networks rather than one or two specific signaling

1. it can provide high-throughput screening methods to find biomarkers in radiation response
2. It can deal with multi-factors affecting radiation response and explain the connectivity among signaling networks with mathematical equations produced by computational biology
3. mechanistic model: explanation of radiation response, at low dose, including environmental factors
4. remove the uncertainty and inconsistency from biological specimen.

CONFOUNDING FACTORS:

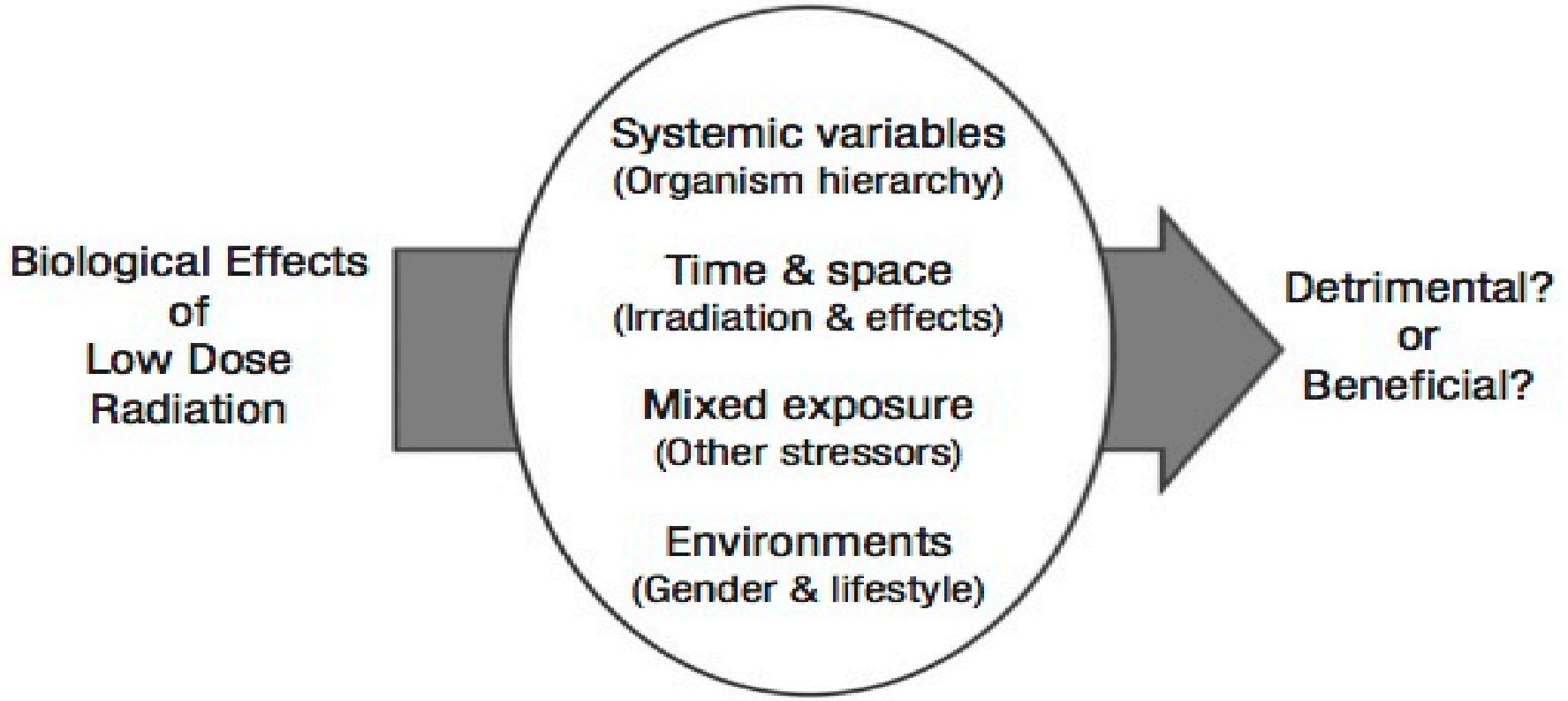


Fig. 3. Confounding factors in the analysis of low dose radiation effects. Biological effects of low dose radiation could be determined by several confounding factors as detrimental or beneficial. For example, systemic variables such as hierarchy, maturity, and ageing of irradiated organism, time of irradiation and phenotype emergence, and interaction with other environmental factors.

EPIDEMIOLOGICAL STUDIES ON THE EFFECTS OF LOW DOSE IONIZING RADIATION

1) Atomic bomb survivors and accidental exposure
2) Occupational exposure (mainly focus on nuclear industrial workers and aircrew)
3) High background radiation exposure
4) Medical exposure (diagnostic/therapeutic)

ATOMIC BOMB SURVIVORS AND ACCIDENTAL EXPOSURE

- proportional relationship between cancer risk and effective dose above 200 mSv (based on Japanese atomic bomb survivor)
- Recent LSS :the additive radiation risk for solid cancers continues to increase with a linear dose-response relationship
- The sex-averaged excess relative risk (ERR) for all solid cancer was 0.42 per Gy (95% CI, 0.32-0.53) at age 70 years after exposure at age 30
- the estimated lowest dose range with a statistically significant ERR (0.56/Gy, 95% CI, 0.15-1.04) was 0-0.2 Gy

(Osaza K,2012)

ATOMIC BOMB SURVIVORS AND ACCIDENTAL EXPOSURE

- Three Mile Island(TMI) 1979 : low level exposure of 0.09-0.25 mSv within 5-mile area around TMI,
- elevated risks for non-Hodgkin's lymphoma, lung cancer and leukemia in a few studies with the first 5 year followup after the accident
- epidemiological data for acute radiation exposure have not provided consistent evidence of health effects in the low dose range.
- ICRP proposed nominal probability coefficients of 5.5% per Sv for detriment-adjusted cancer and 0.2% per Sv for heritable risks for the whole population, using the LNT model with a DDREF of 2.

ATOMIC BOMB SURVIVORS AND ACCIDENTAL EXPOSURE

- Except observed increased in thyroid cancer, no clearly increase in the incidence of other cancers or non-cancer diseases in the residents of the Chernobyl region1986 (UNSCEAR2011)

- Chernobyl liquidators exposed to prolonged low to medium radiation (0-500 mSv), data indicating the increase in the risk of leukemia, cataracts and cardiovascular diseases

ATOMIC BOMB SURVIVORS AND ACCIDENTAL EXPOSURE

- Fukushima Daiichi 2011: ultrasound screening of thyroid in children between Fukushima and other three Japanese prefectures, no significance differences were observed (Hayashida 2013)
- No reported effects
- Minimal lifetime health risk expected=exposure level < 50 mSv during 1st year
- further careful follow-up should be continued in consideration of long latency of radiation effects

OCCUPATIONAL EXPOSURE (MAINLY FOCUS ON NUCLEAR INDUSTRIAL WORKERS AND AIRCREW)

- significant ERR of 0.97 (95% CI, 0.27-1.8) for all cancer mortality
- Mayak nuclear complex:mean cumulative external dose of 810 mGy
- the Mayak cohort studies, elevated risks of certain types of cancer
- Air crew: average effective dose=2-5 mSv/year and 75 mSv for cumulative effecttive dose at career end
- the average effective dose of radiation workers is generally less than 2 mSv/ year

OCCUPATIONAL EXPOSURE (MAINLY FOCUS ON NUCLEAR INDUSTRIAL WORKERS AND AIRCREW)

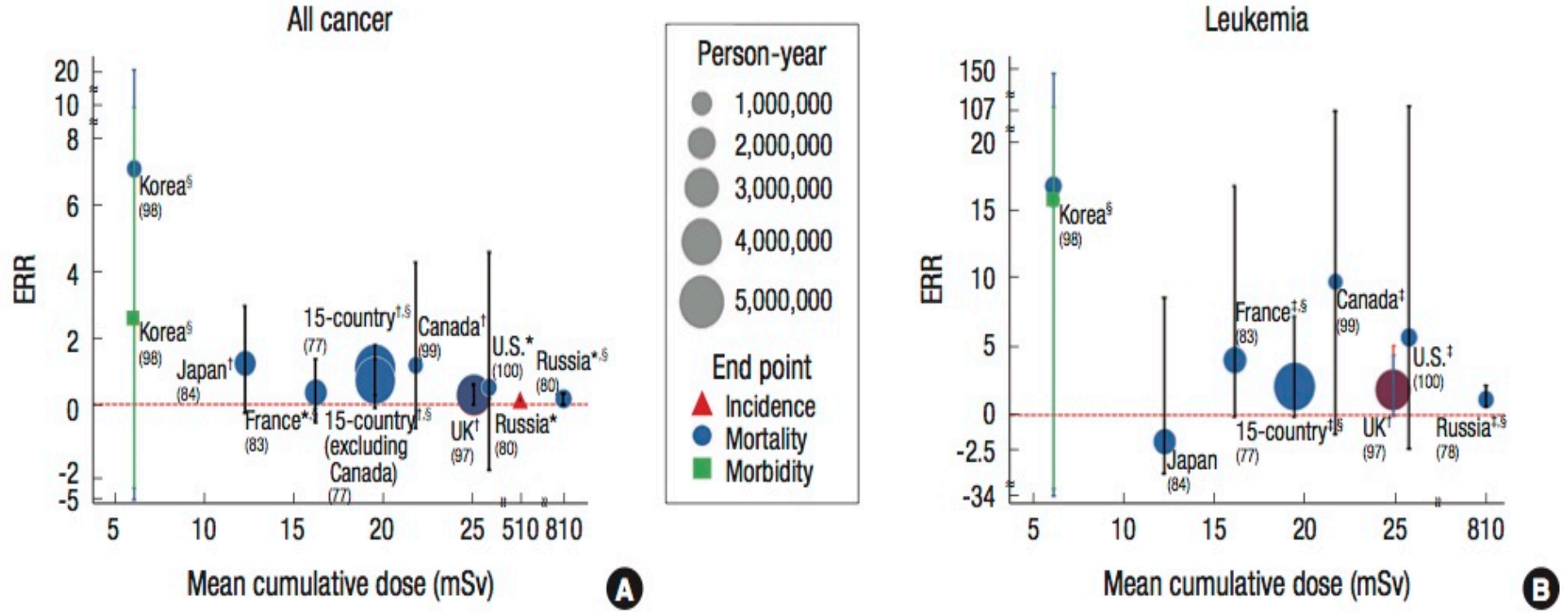


Fig. 4. Excess relative risk (ERR) for cancer in major cohort studies of radiation workers. (**A**) All cancer; (**B**) leukemia. The mean cumulative doses are represented on the x-axis and ERRs for cancer are represented on the y-axis. *Solid cancer only; †All cancer excluding leukemia; ‡Leukemia excluding CLL; §90% confidence interval.

OCCUPATIONAL EXPOSURE:

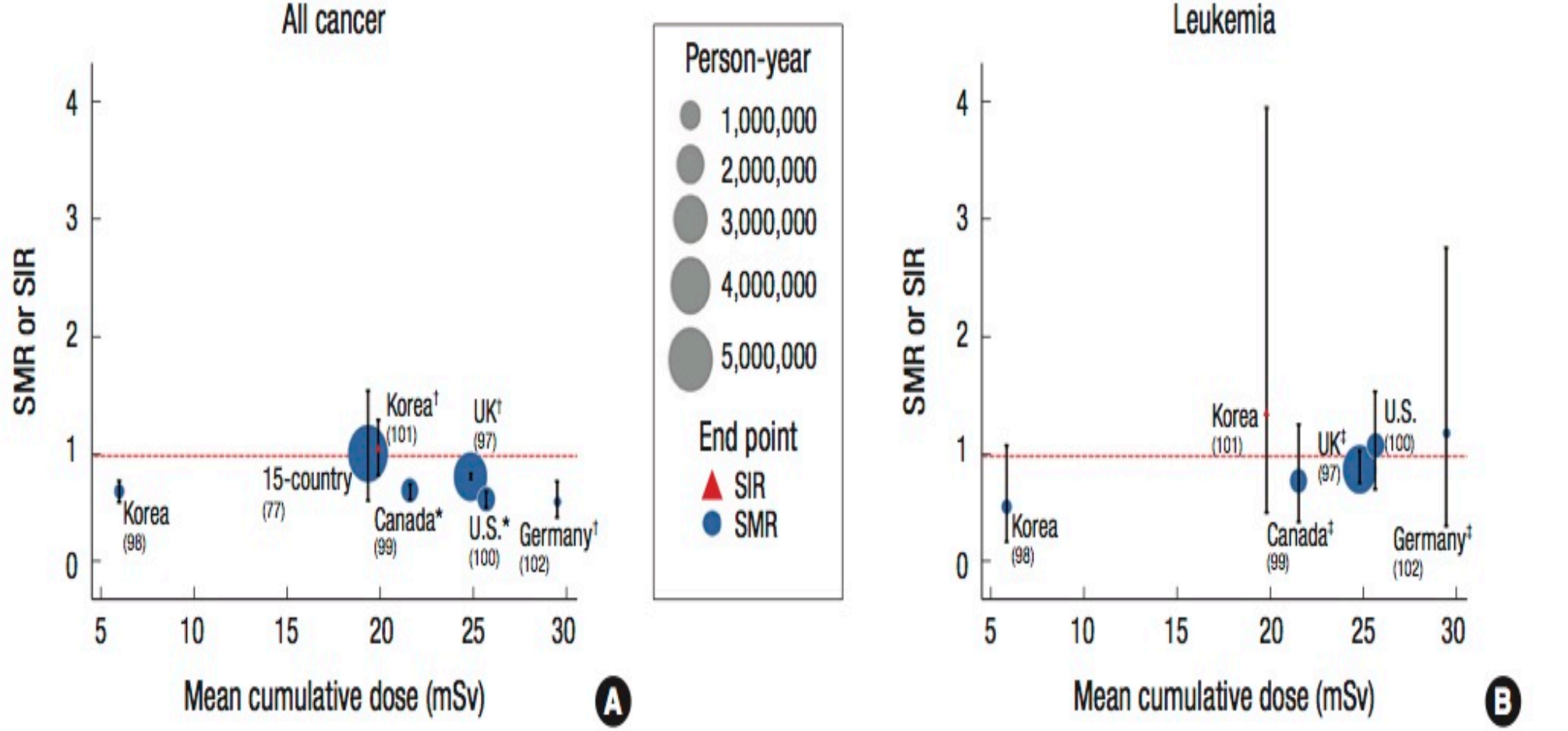


Fig. 5. Standardized mortality ratio (SMR) (or Standardized incidence ratio [SIR]) for cancer in major cohort studies of radiation workers. (**A**) All cancer; (**B**) leukemia. The mean cumulative doses are represented on the x-axis and SMRs (or SIR) for cancer are represented on the y-axis. *Solid cancer only; †All cancer excluding leukemia; ‡Leukemia excluding CLL.

SAHAR LAALPOUR

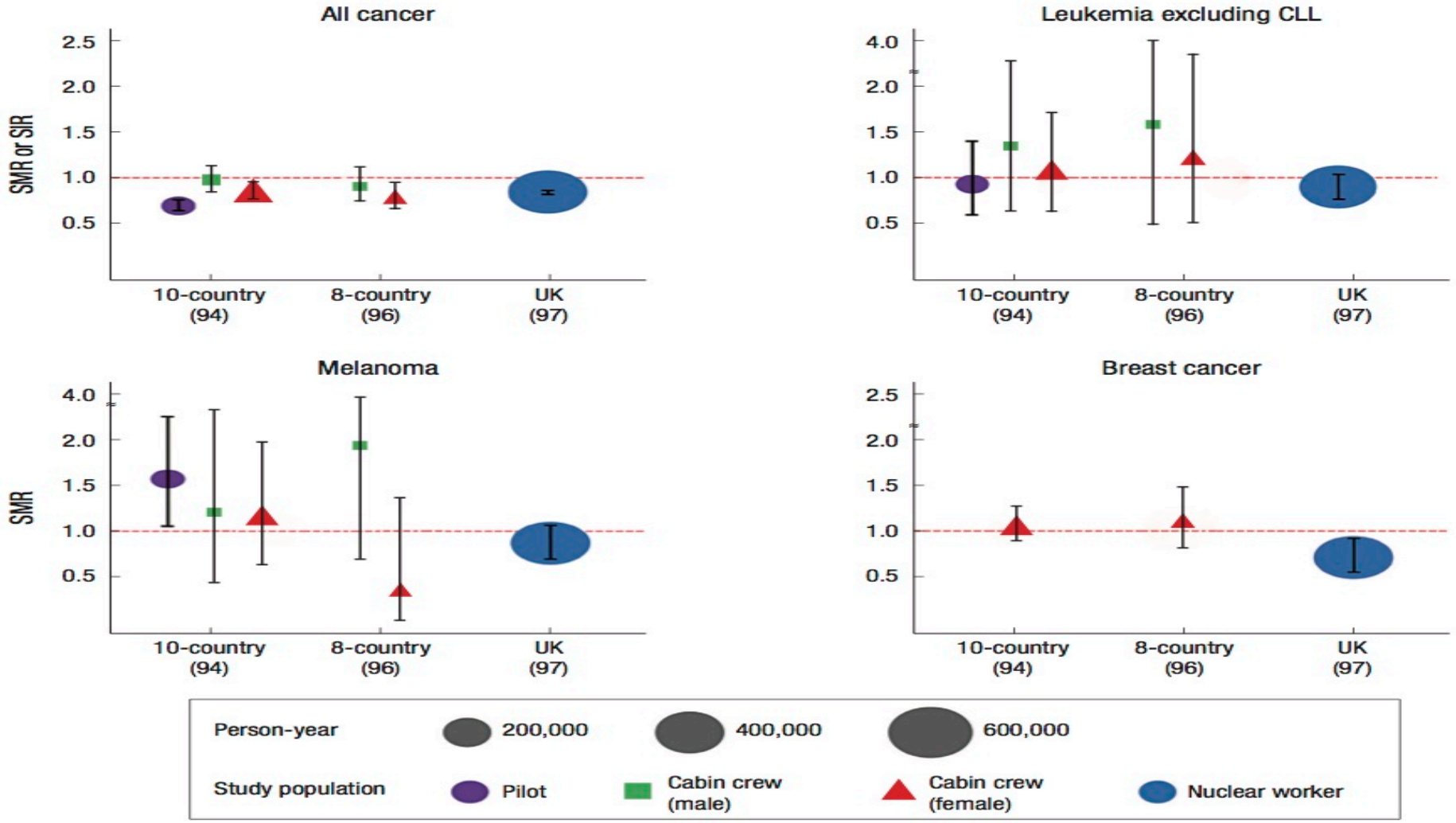


Fig. 6. SMR for cancer (all cancer, leukemia excluding chronic lymphocytic leukemia [CLL], melanoma and breast cancer) in major cohort studies of air crews and radiat workers. The names of the studies are represented on the x-axis and SMRs are represented on the y-axis.

HIGH BACKGROUND RADIATION EXPOSURE:

- average natural dose to human=2.4 mSv/year with a large variation depending on location and geology. (UNSCEAR 2000)
- HBRAS: up to 260 mSv/year (Mortazavi 2002)

The Yangjiang in China, Karunagappally in India, Guarapari in Brazil, and Ramsar in Iran

- Techa River cohort and Taiwan building residents exposed to Co^{60} : artificial (man made) radiation sources
- average effective doses ranging from 35-1/700 mSv for evacuees

HBRAS:

- Some studies that showed increased chromosomal aberration (Ghiassi nejad 2004)
- No study reported increase in cancer or lifeshortening (WEI LX 1990, Nair RR 2009)
- Techa river: elevated risks of solid cancer and leukemia
- Taiwanese residents: dose-response relationships for leukemia excluding CLL (HR, 1.19/100 mGy; 90% CI, 1.01-1.31) and breast cancer (HR, 1.12/100 mGy; 90% CI, 0.99-1.21)
- no demonstrated health effects were observed in residents of HBRAs except for the Techa River cohort exposed to artificial radiation above the low dose range.

MEDICAL EXPOSURE (DIAGNOSTIC AND THERAPEUTIC RADIATION):

- Medical exposure cohorts: demographic data, medical history, smoking and alcohol consumption
- Dose from the diagnostic radiation exposure is generally 0.1-10 mSv
- clinical benefits from the medical exposure outweigh the potential risks from radiation exposur

UNCERTAINTIES IN ESTIMATING HEALTH RISKS OF LOW DOSE RADIATION:

1) extremely large sample size is necessary to ensure statistical significance at low dose levels

- Based on the US baseline cancer risk and the radiation risk model, sample sizes of 500,000 and 2,000,000
- lifetime follow-up for exposure levels of 20 mSv and 10 mSv

(national research council committee)

CONTINUED:

2) Issues of confounding factors such as smoking, genetic variation and socioeconomic status
3) Uncertainties in radiation dosimetry cannot be avoidable
4) statistical uncertainties in selection of dose-response models, particularly great uncertainties at low dose levels
5) difference in dose-response relationships according to different types or levels of exposure
6) difference in risk according to parts of the body exposed to radiation
7) extrapolation of a dose-response relationship through risk transfer between populations with different levels of baseline risk

CONCLUSION:

- In sum, despite a variety of studies, understanding of health effects of low dose radiationless than 100 mSv, is still incomplete and difficult
- the lack of scientific knowledge about health risk of low dose radiation, the LNT approach is the most reasonable risk model at low dose levels .
- Estimated risk at low doses based on LNT hypothesis does not necessarily correspond to a real risk
- Different biological pathways between low and high dose effects are proven through sophisticated cellular and molecular studies.
- interactions between genetic susceptibility and low dose exposure
- comprehensive understanding of radiobiological mechanism
- The integration of biological and epidemiological studies along with social science research

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