

RC-1a
Epidemiology : Strengths, Limitations and
Interpretations

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Epidemiology : its Strengths, Limitations and Interpretation.

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Abstract. Radiation epidemiology has been largely developed over the large thirty years. Major analytical studies have been implemented .Large cohorts have been installed, able to register individual exposure, and to express the risk of long term diseases, by taking in account latency period, age at exposure, time since exposure and other time dependant co-factors. This paper is a support to the refresher course aiming to discuss the strenghts of these large studies, their limitations, the impact of quality of retrospectively registered individual exposure and of health indicator. Dose-response relationship is mainly considered as a strong support for a possible causal interpretation of a link between a specific disease and the dose, but major discussion comes when it is used as a tool in risk assessment, for extrapolation to low doses.

1. Context

Since the1950s, epidemiology was developed, in order to test if long term effects, like cancer mortality could be related to some “exposure indicators”. During the first period, exposure indicators were mainly of categorical nature, and the observed effects were related to two groups, or two different periods. They are still largely used, for instance when describing trends over time, with a cut point reflecting major changes in environmental exposure, or when comparing results of the period before and after an accident. This approach is of descriptive nature, able to suggest a possible increase, but not necessarily in relation with the suspected exposure. Latency period, co-factors that are not correctly taken in account, migration of populations are several of the possible factors that may contradict the evoked conclusion.

In radiation epidemiology, analytical studies were developed very soon in order to take in account more precisely the individual exposure and analyses were developed that took in account time trends of cancer mortality. The Hiroshima and Nagasaki survivors cohort is a unique example of a very large cohort installed during the 1950s, with an increasing effort of precision of the individual dose and of collection of various health indicators. It has been followed by several other cohorts focusing on workers, exposed through their occupational environment, and by large groups of patients exposed to various levels of diagnostic and therapeutic radiation. In comparison to other studies focusing on environmental factors, radiation epidemiology has the possibility to study different populations at quite different levels of exposure, with a large access to individual exposure measurements over long periods of exposure. The exposure rate effect comparing risks of populations exposed to a very short exposure with those exposed to the same total level of exposure, but protracted over several years is one of the major questions presently under study.

2. Indicators of a potential excess risk

2.1. Comparison between exposed and non exposed groups

When comparing an incidence or mortality rate between an exposed and non exposed group, results are often expressed under the expression of a relative risk (RR), it is the ratio of the incidence or mortality rate of a disease in the exposed group divided by the rate in the non exposed group. For cancer mortality, this relative risk has to be adjusted on age and calendar period, two factors that may strongly influence the increase of a rate of a specific cancer disease. A RR with value close to 1 indicates comparable rates in both groups, a RR with a value of 2 indicates a doubling of the risk in the exposed group, a value of less than 1 indicates that the exposed group has a lower risk than the

non-exposed group. A lower risk may be observed when comparing nuclear workers with general population of the same country; in this case, we consider that the workers express a healthy worker effect.

The relative risk is mainly used in cohort or descriptive studies, in the case-control studies the risk is expressed as a the “odds ratio”, which, in the case of rare diseases, can be considered as equivalent to a relative risk.

In all these situations, the concept of an excess relative risk tries to indicate the value of the potential excess risk in comparison to the risk of an unexposed or low exposed group; it is an indicator of a proportional increase, with the concept that the “background rate” or the rate of the non exposed group is adjusted indirectly on most of the confounding factors. This assumption has of course to be verified, and depends mainly of the design of the study.

It has to be pointed out that the design of a study, and its defined protocol, are a major tool for the interpretation of a possible excess of risk. In a case-control study the choice of the control group, the standardisation of the approach of the patients (cases and controls) are essential to avoid memory biases when interviewing on retrospective exposure characteristics. In retrospective cohort studies, past history of exposure may be less accurate than more recently measured individual exposures : this information with a time-dependant quality has to be documented in detail, but can be taken in account in the final analysis.

2.2.Dose-response relationship

In radiation epidemiology, any observed excess will be expressed in relation to a specific “radiation – dose”. The term of the unit of dose may vary from one study to another, mainly when distinguishing between cohorts exposed to external radiation versus those having experienced internal exposure. In some situations, cohorts may have a mixture of internal + external exposure; in this case, the best approach seems to be the calculation of a cumulated dose at organ level.

Large cohort studies are able to register all causes of death, consequently they are describing both cancer and non cancer deaths. An observed excess of lung cancer in the exposed group in comparison to the non exposed group may not necessary be linked to radiation, strong co-factors like tobacco could be responsible of this excess. The same argument may be evoked in front of an increase of cardio-vascular diseases, observed in excess in several studies. Consequently, when a study is able to demonstrate a clear dose–response relationship, the first argument is to say that in the present study the risk is increasing with increasing dose. This is a relatively strong argument proving a direct implication of the causal factor, here the “radiation dose”.

The form of this dose-response relationship is a second information, which may have large implications when trying to extrapolate to low doses or to compare results from different studies; the linear dose–response relationship, observed in many studies describing an excess of solid tumours, makes it possible to “summarize “ the observed situation by giving the value of the slope of the dose-response relationship : Excess Relative Risk (ERR) per unit of exposure.

During recent years, more performing analyses on cohort studies with large periods of follow-up were able to describe in more details the increase of the risk over time, by taking in account attained age, age at exposure.....In occupational studies, where individual exposure is protracted over various years, depending of the working period of each individual, it is possible to test the “window” of exposure that is explaining the major part of the risk. In uranium miners studies, where inhalation of radon decay products contributes to increase significantly lung cancer risk, it is now possible to show that the major contribution to this risk comes through the last twenty years of exposure, and that the risk is decreasing with time since exposure.

Increasing the follow-up in a cohort study means increasing the number of person-years and consequently the statistical power able to demonstrate the existing risk. In the Hiroshima and Nagasaki survivors cohort the results published during the last ten years indicate a better precision of the risk at low doses and give a better risk estimate for those exposed at very young ages. Indeed, in many studies, excess relative risk of solid tumours is demonstrated once the cohort has attained those age groups able to express the risk of the specific disease: in other words, by increasing attained ages of those exposed at very young ages, information of any excess is possible; if the follow-up would have been stopped earlier in time, this excess risk would have been ignored.

3. Future information expected from new or ongoing studies

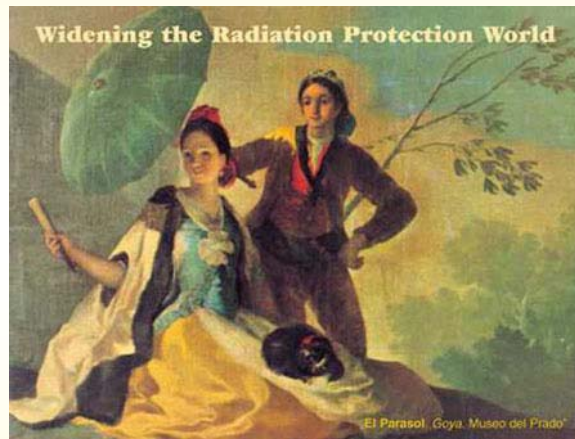
During the refresher course different examples from cohort studies will illustrate the points discussed in this chapter. Other points like exposure at very young ages, and the contribution of internal exposure need more investment in future studies..

Exposure at very young ages remains a question of major concern for radioprotection. The Chernobyl situation have shown that, at least for thyroid cancers, exposure at very young ages, when the gland is developing and rapidly growing, may induce a much higher risk than expected from studies focusing mainly on adult exposure; radioactive iodines may act differently from external exposure : most of past studies describing a thyroid cancer excess risk are in the field of external medical exposure during childhood, or from Hiroshima and Nagasaki survivors; but internal exposure may contribute to a different dose-rate exposure at organ level : the dose-rate effect is here again a major point of interest. Internal exposure of lung through inhalation of radon decay products is a situation that has been studied extensively in epidemiology, mainly through the studies on miners and on domestic exposure. They have contributed largely to the discussion of a possible inverse dose-response relationship between lung cancer risk and cumulated radon exposure. It was observed in highly exposed uranium miners studies, but also in some highly exposed animal studies. More recent results observed on relatively low exposed uranium miners studies in Europe show that this inverse dose– rate effect is not observed at low cumulated exposures. A comparison between animal experiments at low radon exposures and epidemiological results on miners was initiated during a European program (FP5) in order to exchange experience between biologists, epidemiologists and statisticians involved in mechanistic modelling of long term cancer development.

Complementary studies on nuclear workers having experienced internal exposure are necessary : the Mayak workers in Russia will largely contribute to this topic; other groups of workers in Europe or in other continents are also necessary in order to compare the results of these groups with those coming from populations with purely external exposure. The main problem of these studies is the quality of past information of individual exposure, and the relatively small number of workers per country. International efforts are necessary to implement these studies under a comparable protocol in order to be able to combine final results under a similar statistical analysis.



**International Radiation Protection Association
11th International Congress
Madrid, Spain - May 23-28, 2004**



Refresher Course : RC-1a

Epidemiology : Strengths, Limitations and Interpretations

Margot Tirmarche

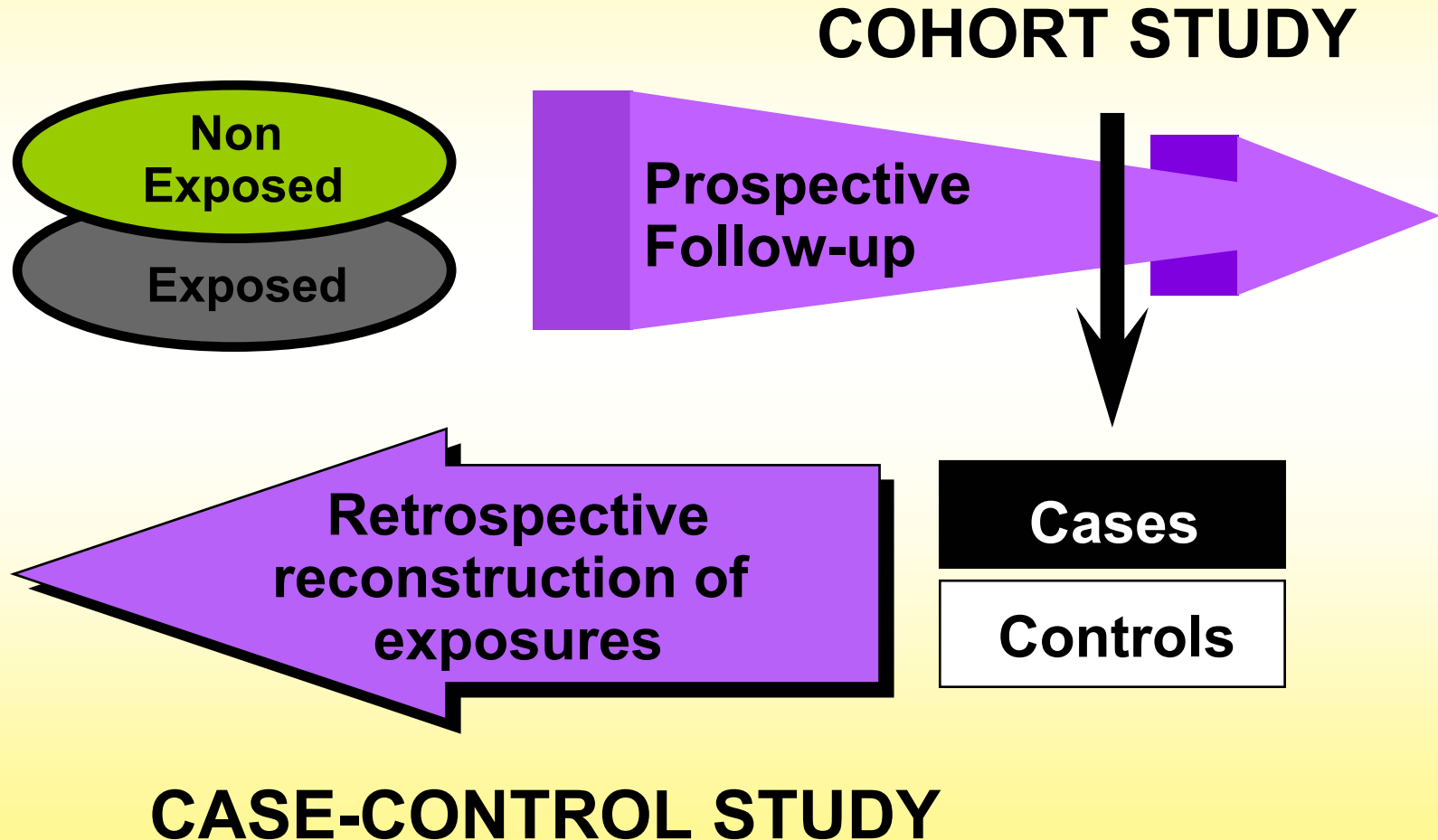
Strengths : in Field Observations on Humans

Long term follow-up in cohort studies : takes in account time-dependant variables

Adjustment on co-factors (case-control studies)

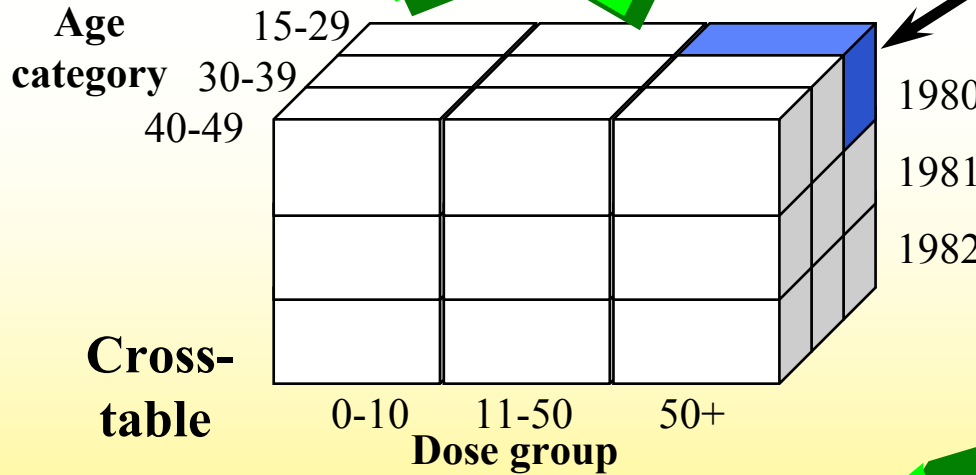
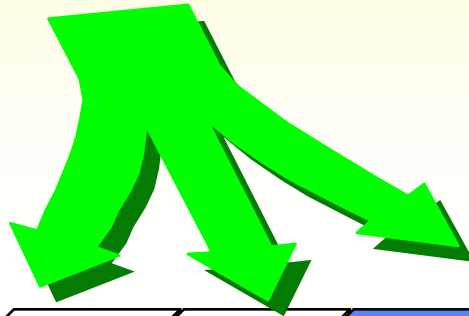
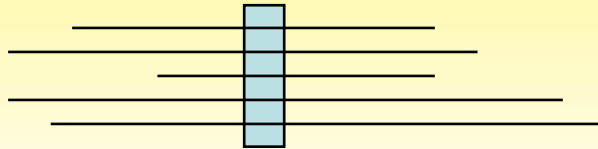
Study of potential factors that may interact in the development of a disease

Design of a Nested Case-Control Study



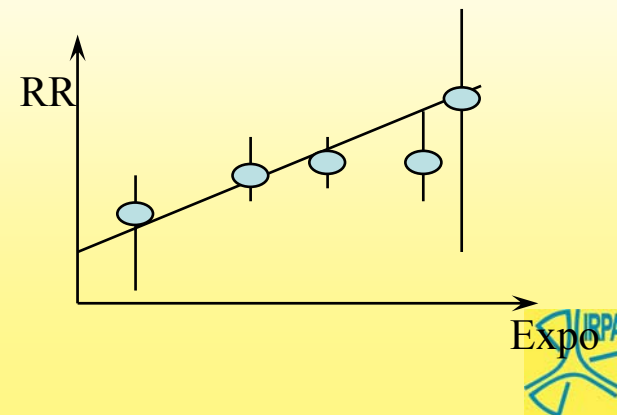
Cohort Studies

Partition in
Person-years



nb PY, Cases
cumul expo,
dose rate, ...

Regression



Limitations

- Results observed in one single study are only of indicative value; comparable results observed on a second, independent population bring more credibility to the exposure-effect conclusion
- Confounding factors may hide the relation between a disease and an exposure
- A causal hypothesis can be evoked only if the risk of a given disease is increasing with the level of exposure (excess risk per unit of exposure)

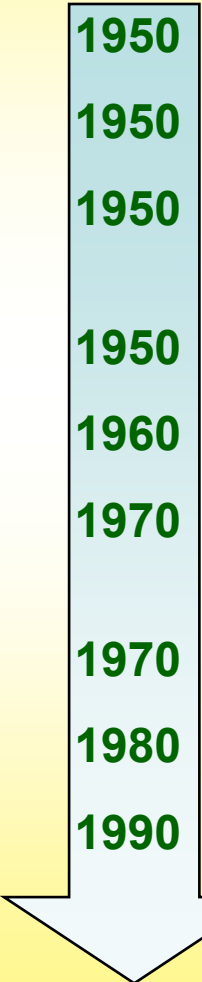
Exposure at Low Doses of Radiation

- A field of main interest for radiation protection and for comprehension of underlying mechanism (dose-rate effect, chronic versus single exposure)
- An interesting field for epidemiology as individual quantitative measurements exist over long periods (mainly through occupationally exposed populations)
- A field of controversy because different epidemiological approaches may not always bring the same results

Possible Limits in front of Low Dose Studies

- If inappropriate design of a study :
 - Limited variation of exposure in the studied population :
 - expected response : yes or no
 - Limited statistical power : negative result ?
 - Descriptive results; geographical correlations may be informative or misleading : depends of the endpoint studied
- The design (protocol) is appropriate,
 - but there may be a **bias in memory** of interveiwed persons
 - the **studied co-factor** is of major importance, but is not studied in detail: example tobacco consumption versus domestic radon exposure

History of Epidemiologic studies

- 
- 1950 Radiologists (1900-30)**
 - 1950 Radium dial painters (1910-30)**
 - 1950 Medical exposures for non malignant illnesses, diagnostic exposures (1920-40)**
 - 1950 Hiroshima-Nagasaki survivors (1945)**
 - 1960 Miners (uranium) (1940-90)**
 - 1970 Population exposed to fallout from atmospheric nuclear weapons (1950-60)**
 - 1970 Nuclear workers (1950-)**
 - 1980 Population exposed to natural background radiation**
 - 1990 Population exposed to releases from the Chernobyl accident (1986)**

Single Acute versus Chronic exposures

- Hiroshima- Nagasaki survivors :
long term follow-up of a population exposed on a specific place
(position of the individual = indicator of dose)
- Nuclear workers and uranium miners :
long term follow-up with individually registered exposure : external /
internal exposure: quality of information is time dependant
- Chernobyl studies : more complex exposure conditions, low levels
on very large populations;
 - Information from subgroups : clean-up workers, children exposed at
very young ages

Hiroshima and Nagasaki Survivors of the A Bomb

Hiroshima

300 000 inhab
06/08/45 - 15 kt
90-120 000 deaths

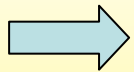
Nagasaki

330 000 inhab
09/08/45 - 21 kt
60-80 000 deaths

both sexes - all ages (and *in utero*) - high dose rate

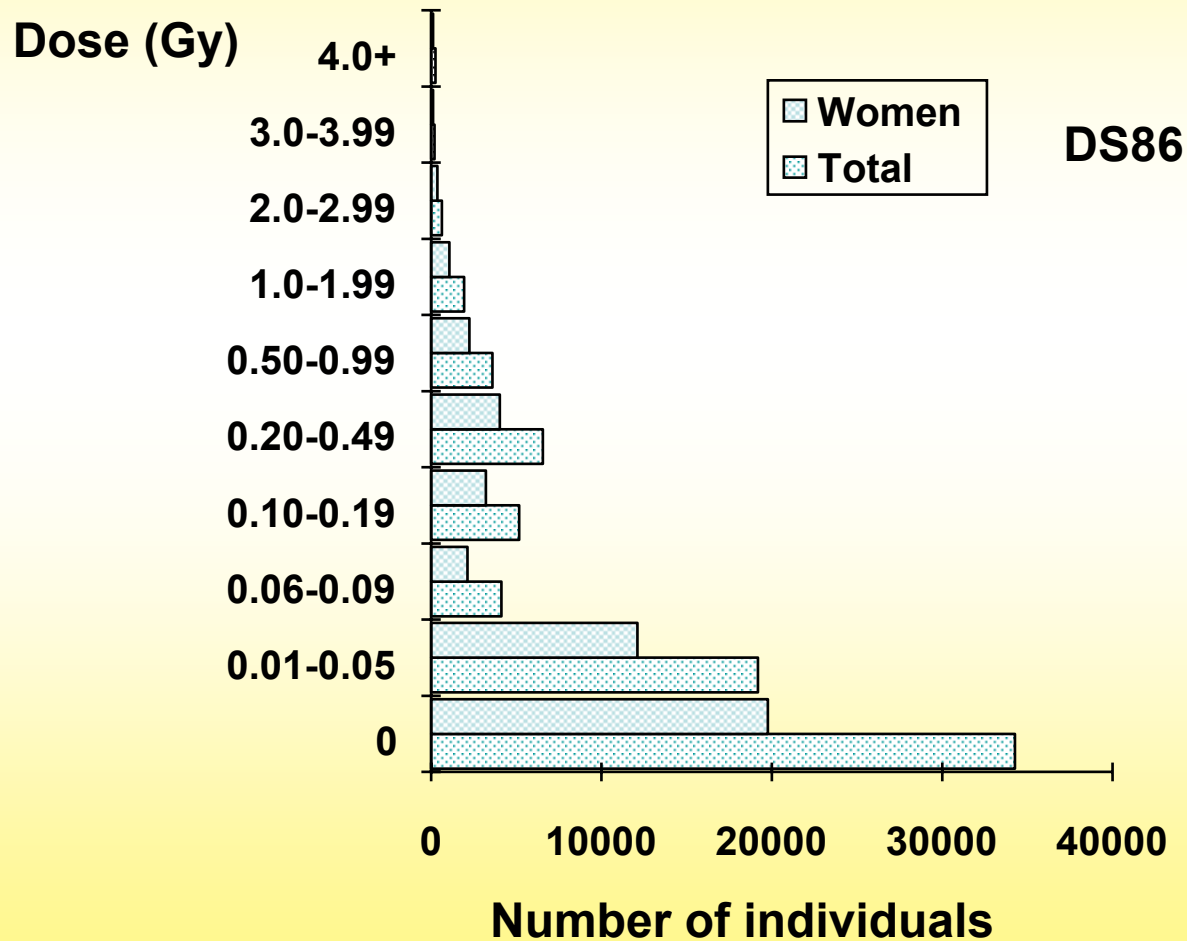
The Life Span Cohort Study (LSS)

mortality follow-up from 1950 to 1990
86 000 individuals with reconstructed dose (2/3 still alive)
44 771 deaths; 10 364 cancer deaths



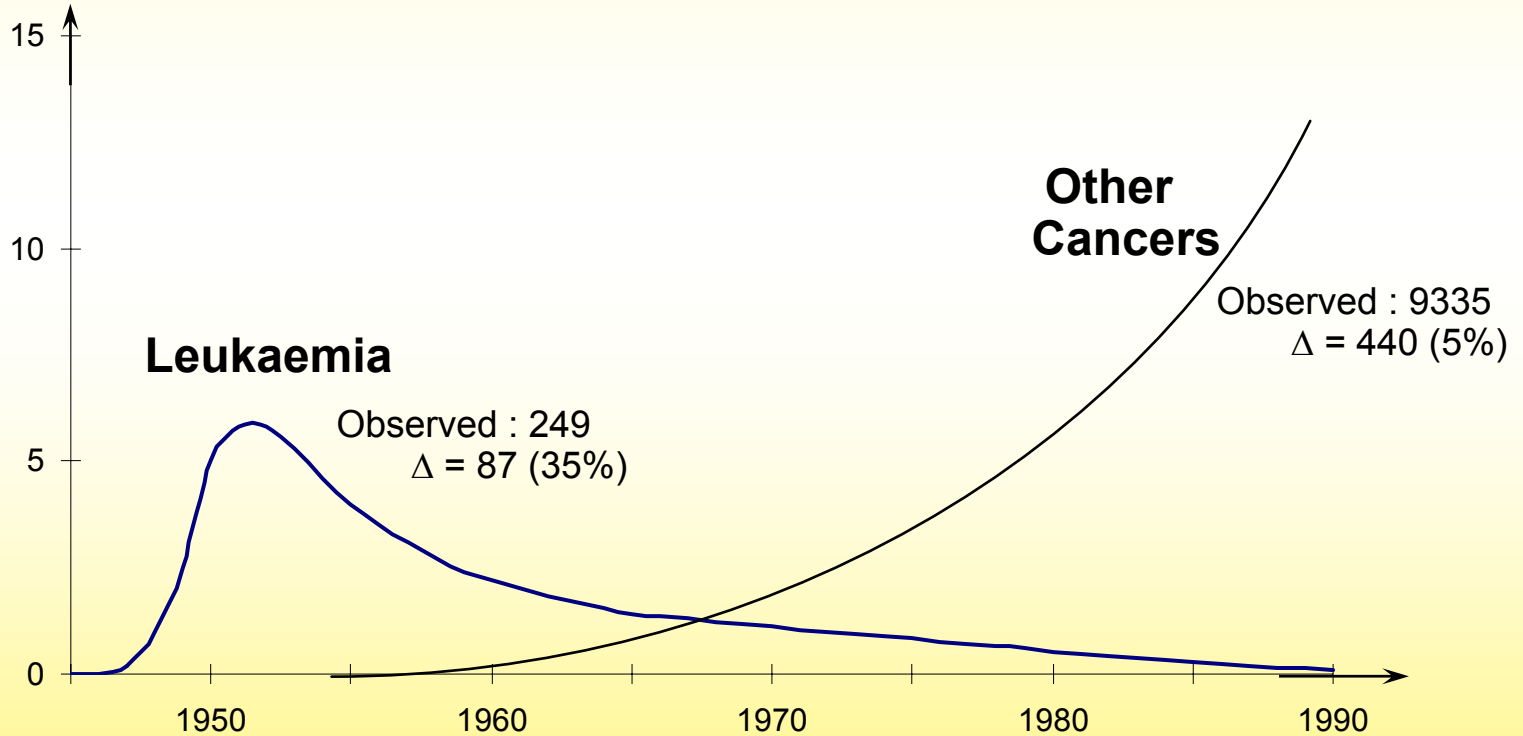
radiation induced cancers
estimate of the dose-risk relationship
latency between exposure and increased risk
effect of age at exposure

Hiroshima – Nagasaki Distribution of doses



Cancer Mortality among Hiroshima-Nagasaki Survivors

Mortality rate
/10 000

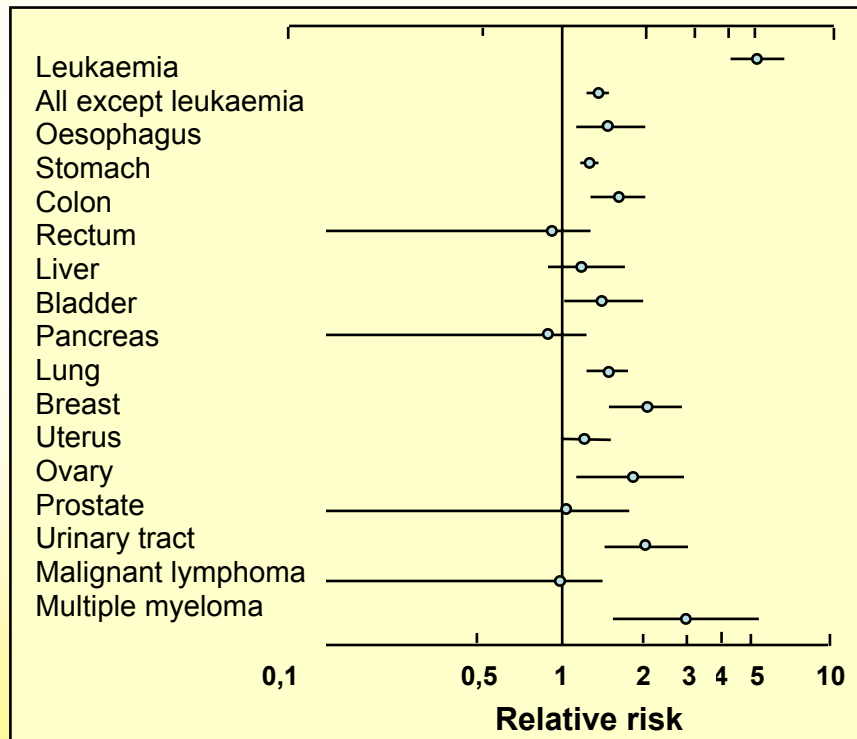


From Preston 2003, Pierce 96



Relative Risk at 1 Gy among Hiroshima-Nagasaki Survivors

**Relative risk for 1 Gy (protected kerma)
and 90% confidence interval, 1950-1985**



(from Y. Shimizu 1990)

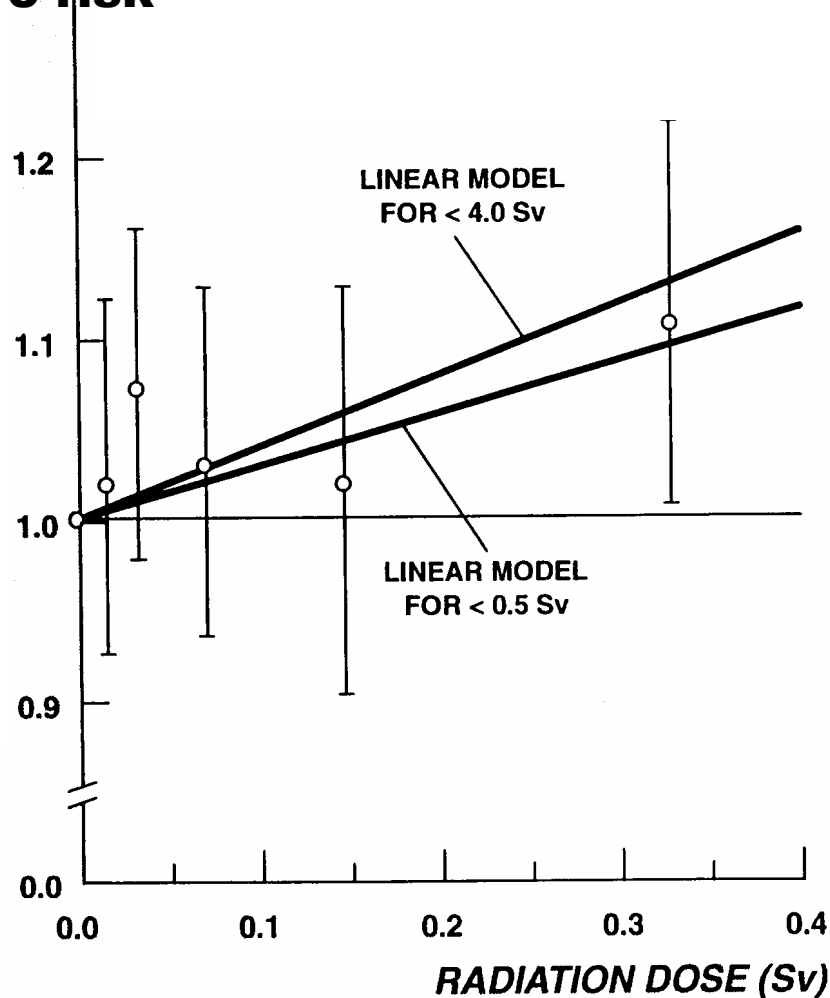
Life Span Study

Results - Solid Cancers (1950-97)

- **9335 deaths including 440 in excess (4,5 %)**
- **Latency of 15 years**
- **Excess beyond 100 mSv**
- **Excess of risk persists 50 years later**
- **Increase proportional to natural death rate by cancer**
- **Dose-effect relationship: excess of relative risk of 40% by Sievert**
- **Decrease of risk with age at exposure and with age attained**

Life Span Study Relative Risk of Solid Cancer

Relative risk

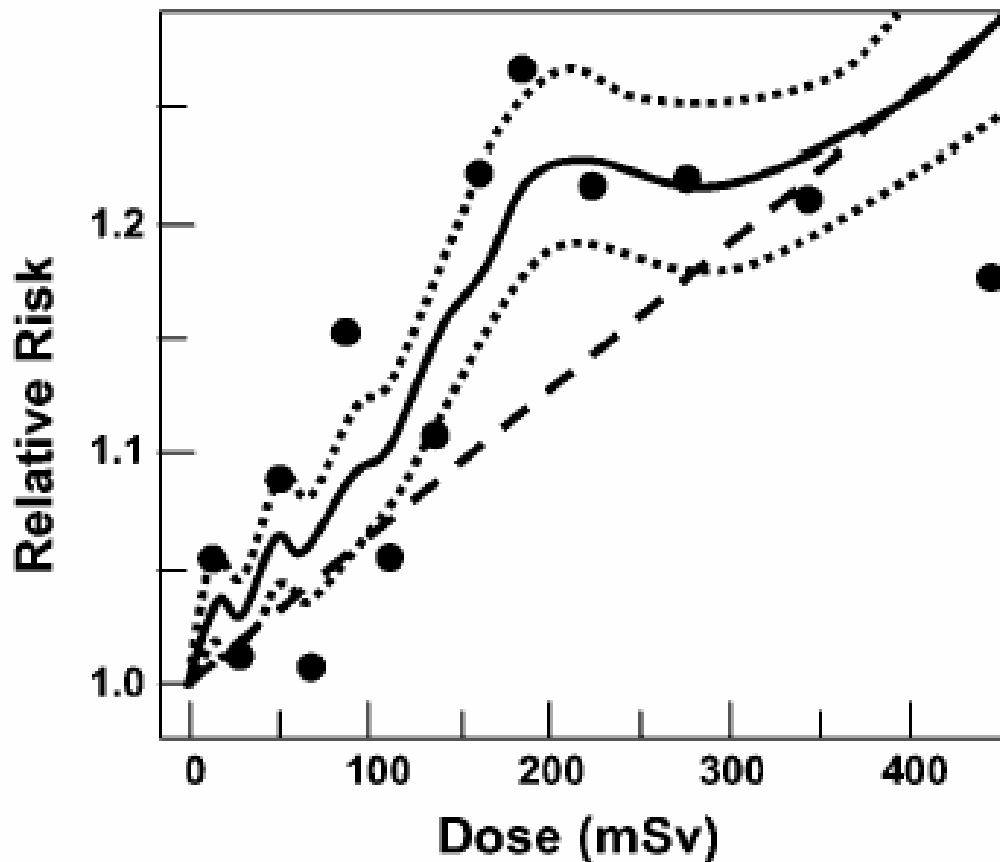


in Hiroshima-Nagasaki
survivors

from Y. Shimizu 1992

Life Span Study

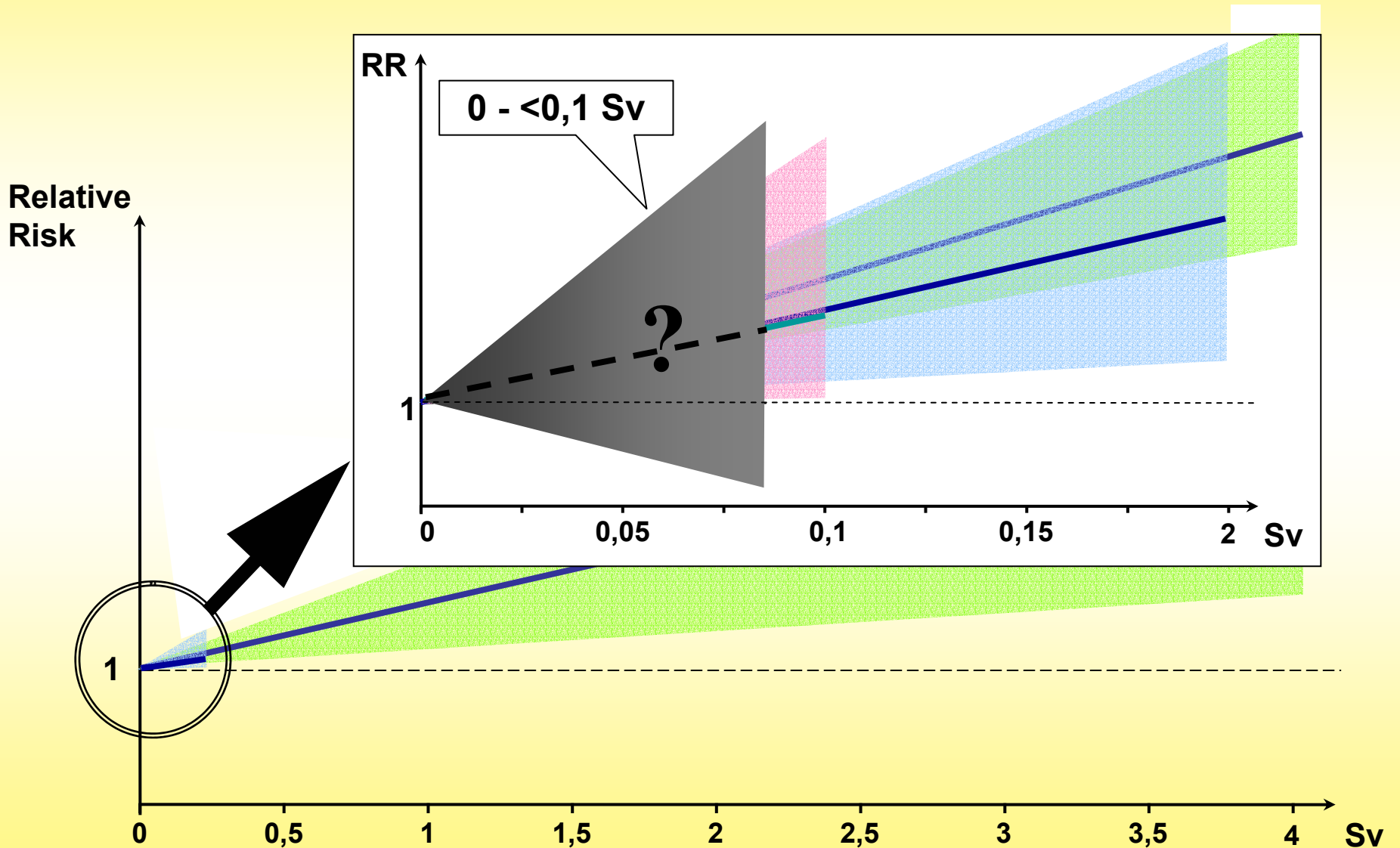
Relative Risk for Solid Tumors



(Brenner et al. 2003)

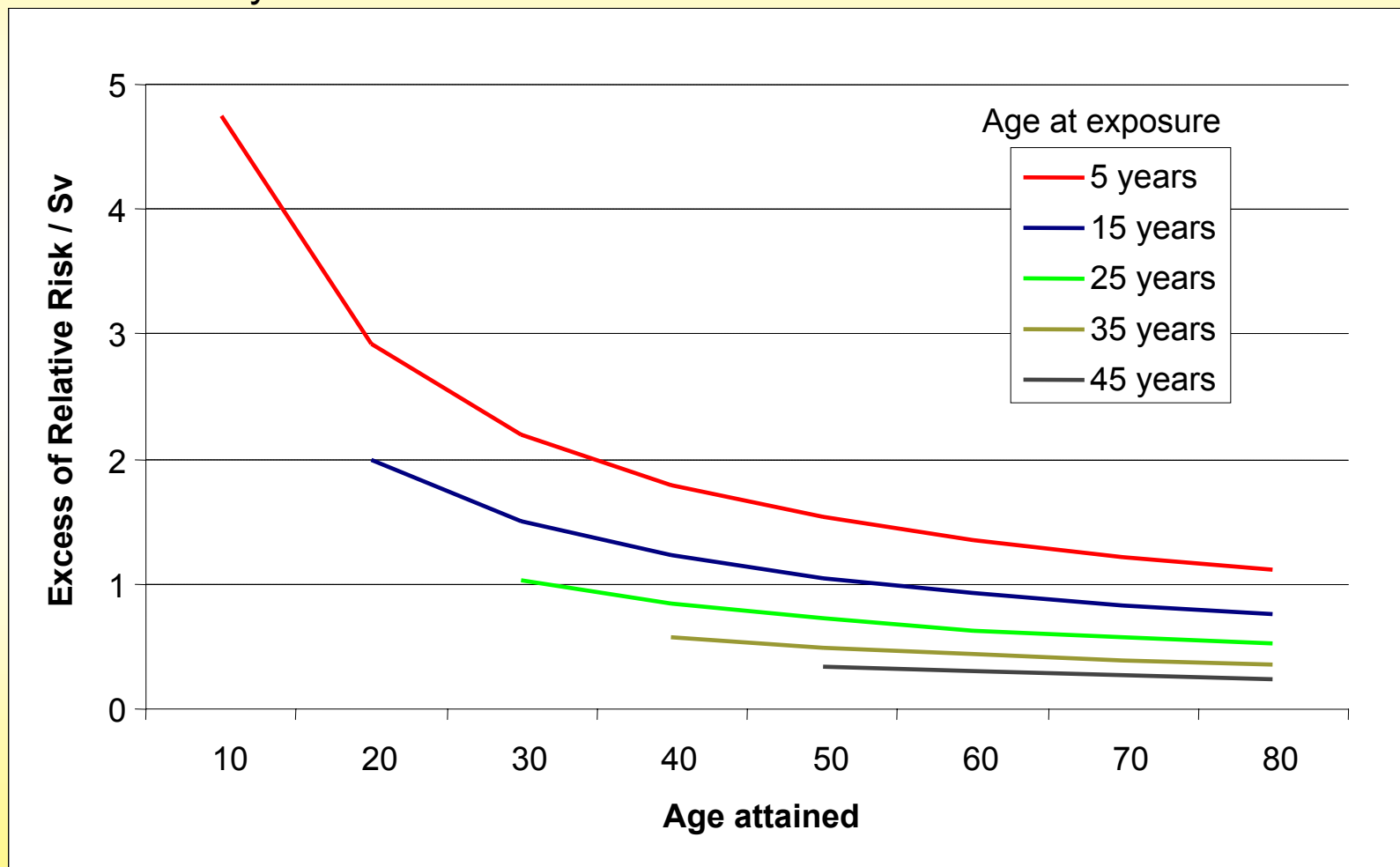
Fig. 4. Estimated risks (relative to an unexposed individual) of solid cancer in atomic bomb survivors exposed to low radiation doses (12). Data points are placed at the mean of each dose category. The solid curve represents a weighted moving average of the points shown (dotted curves: ± 1 SE), and the dashed straight line is a linear risk estimate computed from all the data in the dose range from 0 to 2,000 mSv. Age-specific cancer rates from 1958 to 1994 are used, averaged over follow-up and gender.

Hiroshima and Nagasaki : Adjustment of a Linear Model for Solid Cancer Risk at Low Doses



Life Span Study : Effect of Age at Exposure and Period since exposure

Death risk by solid cancer



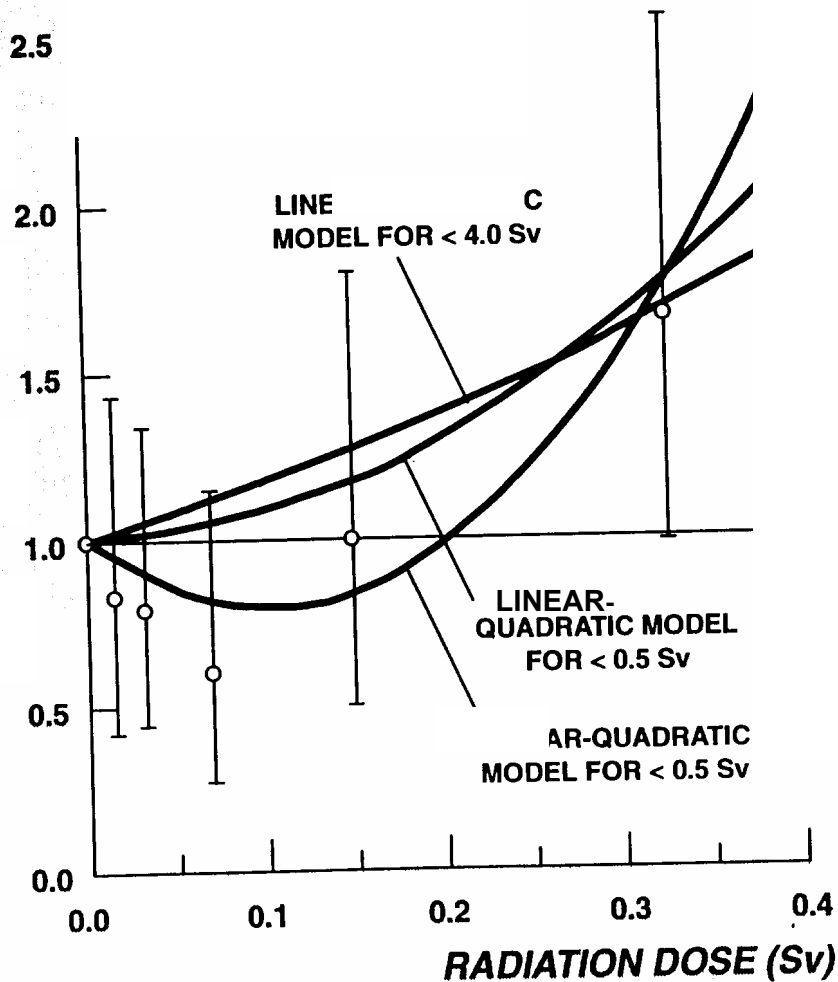
(Life Span Study, from Preston and al 2003)

Life Span Study Results – Leukaemias (1950-90)

- **249 deaths by leukemia including 87 in excess (38,1 %)**
- **latency of 3 years, peak at 6-8 years**
- **80 % observed before 1970**
- **persistence of excess of 3,5 % on 1985-1990**
- **Linear quadratic dose-effect relationship**
- **Excess relative risk of 400% by Sievert**
- **Decreasing of risk with age at exposure and with age attained**

Life Span Study Relative Risk of Leukaemias

RELATIVE RISK

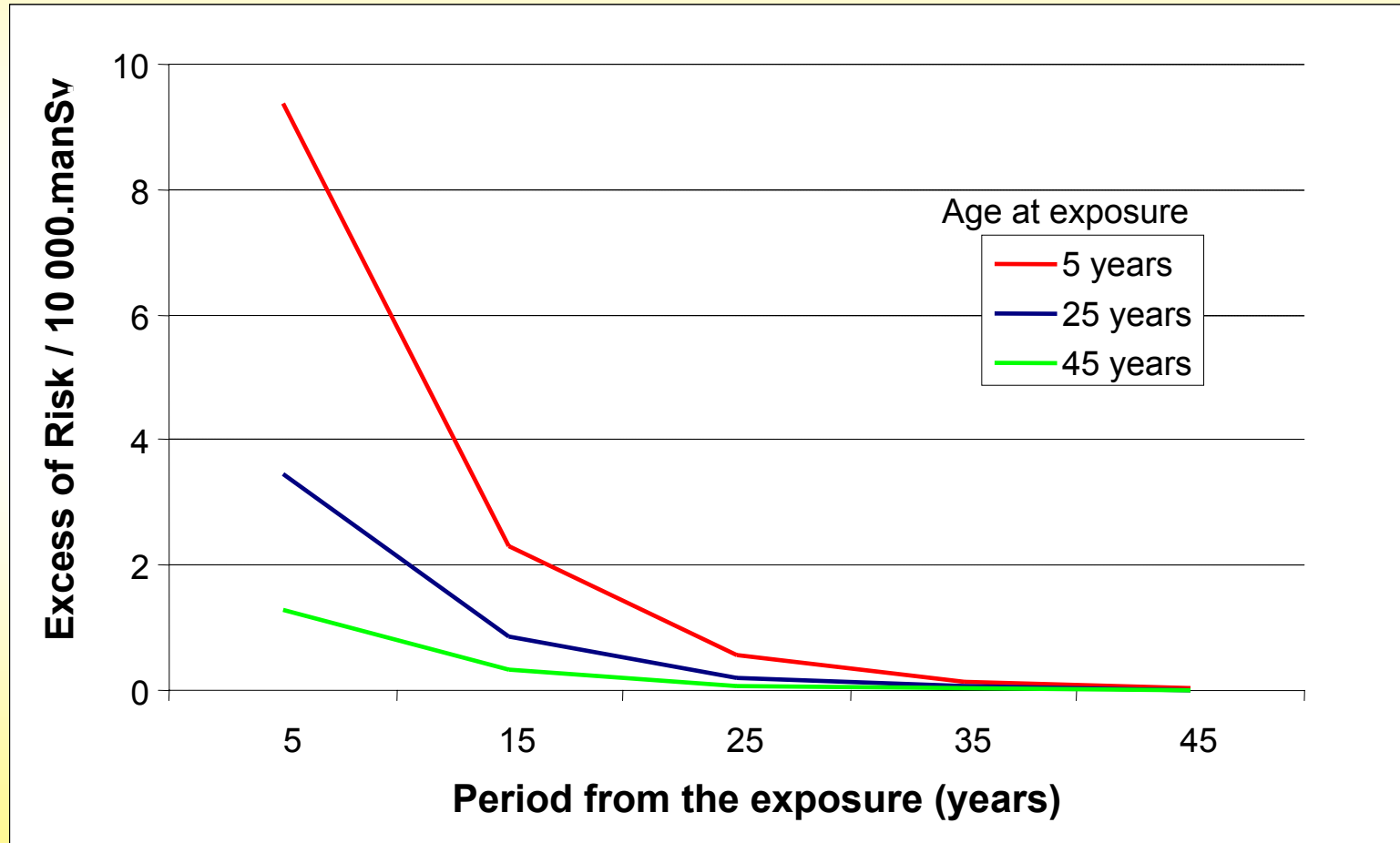


in Hiroshima-Nagasaki
survivors

from Y. Shimizu 1992

Life Span Study : Effect of Age at Exposure and Period since Exposure

Risk of acute lymphoid leukaemia



Results of the Hiroshima-Nagasaki Survivors study

- Risk of radiation induced cancer
 - recognised : **leukaemia, breast, lung, thyroid**
 - probable : **multiple myeloma, liver, digestive, bone, urinary-genital organs, brain, skin**
 - **above 100 mSv for solid cancers**
- Dose-effect relationship **compatible with a non threshold model**
 - **solid cancers : linear relative risk model**
 - **leukaemia : linear-quadratic absolute risk model**
- A basis for radiation protection
 - **need to extrapolate from high to low doses and dose -rates**

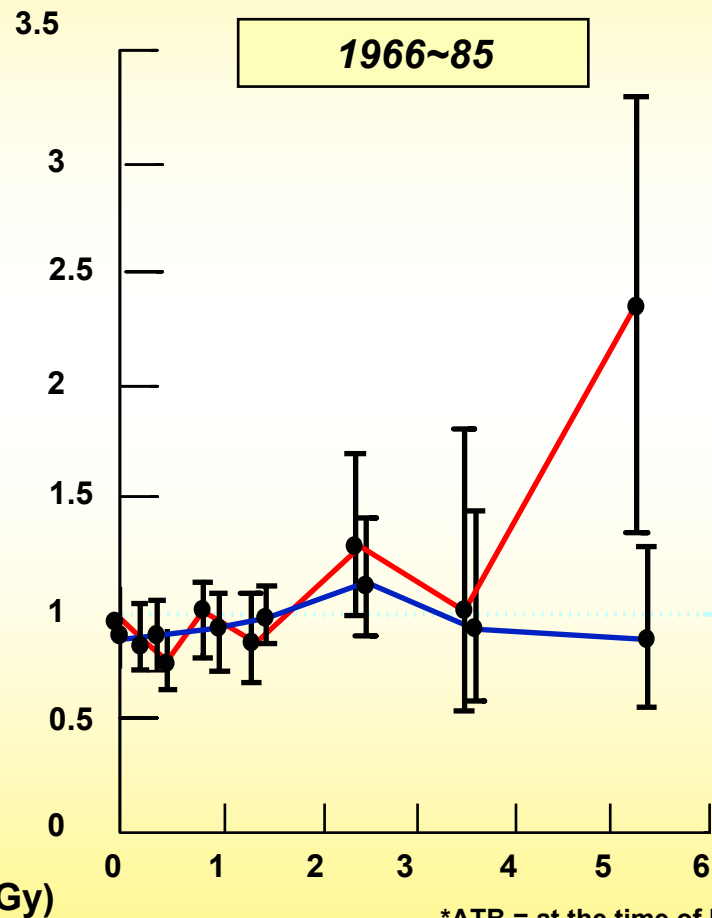
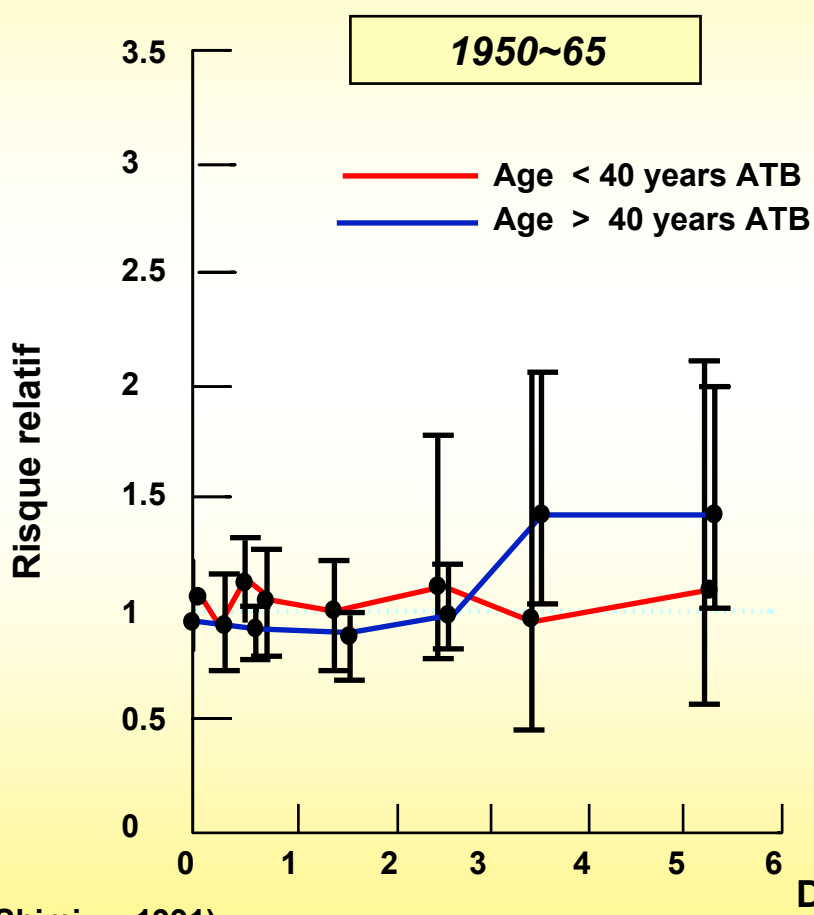
Life Span Study

Diseases other than Cancer (1950-1997)

- **31 881 deaths including 250 in excess (0,8 %)**
- **Linear dose-effect relationship: linear excess relative risk of 14% by Sievert**
- **Excess statistically significant only in recent analyses: large latency or other co-factor ?**

Hiroshima – Nagasaki : non-cancer deaths

Death by diseases other than cancer



*ATB = at the time of bombing

(Shimizu, 1991)



Hiroshima – Nagasaki : Diseases other than Cancer (1968-97)

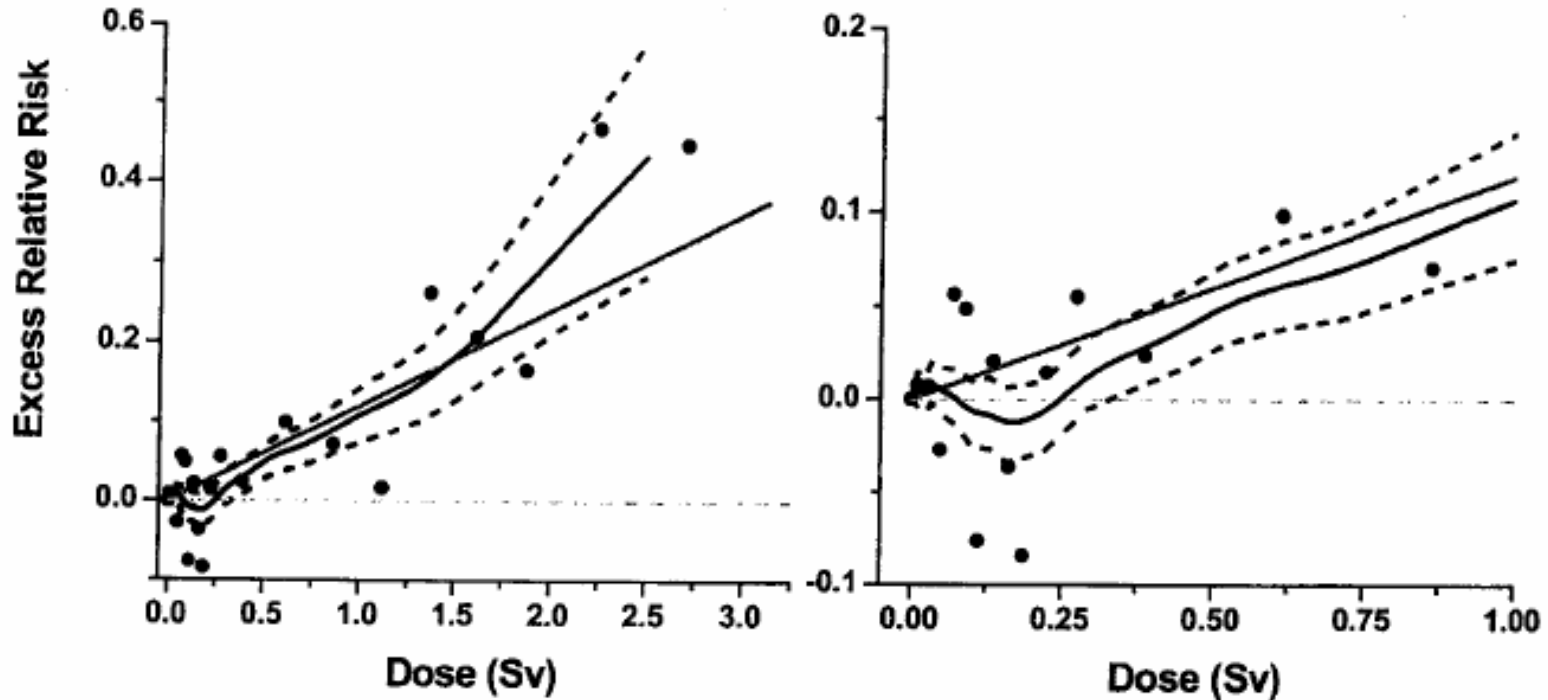


FIG. 10. Noncancer dose–response function for the period 1968–1997. The solid straight line indicates the fitted linear ERR model without any effect modification by age at exposure, sex or attained age. The points are dose category-specific ERR estimates, the solid curve is a smoothed estimate derived from the points, and the dashed lines indicate upper and lower one-standard-error bounds on the smoothed estimate. The right panel shows the low-dose portion of the dose–response function in more detail.

Hiroshima and Nagasaki

The Life Span Cohort Study (LSS) : n = 86 000

mortality follow-up from 1950 to 1990 (recent extension up to 1997)

incidence follow-up from 1950 to 1987 (recent extension up to 1995)

- Increased risk (mortality and incidence) of solid cancer and leukaemia associated with dose (Preston 94, Pierce 96, Pierce 2000)
- Dose-effect relationship for solid cancers and leukaemia varies with attained age (Preston 2002)
- Significant increase in non-cancer disease death rates with radiation dose (diseases of the circulatory, digestive, respiratory systems) (Shimizu 99)
- No reduction of life duration associated to radiation dose (Cologne 2000)

The Adult Health Study (AHS) : n = 20 000

biannual clinical examinations, medical history, life-style (nutrition, smoking ...)

- Excess risk for chronic hepatitis, liver cirrhosis, thyroid disease (Wong 93)
- No dose-response relationship for cardiovascular disease endpoints (Wong 93)

In Utero Clinical Study Sample : n = 1 600

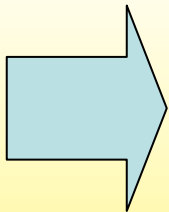
- Mental retardation linked to dose (Otake 89)
- Increased mortality risk of solid cancer associated with dose (DeLongchamp 97)

The Offspring (F1) Cohort Study : n = 31 000

- mortality follow-up of children of A bomb survivors from 1946 to 1985
- No statistically significant effect of parental radiation dose on cancer mortality (Yoshimoto 91)

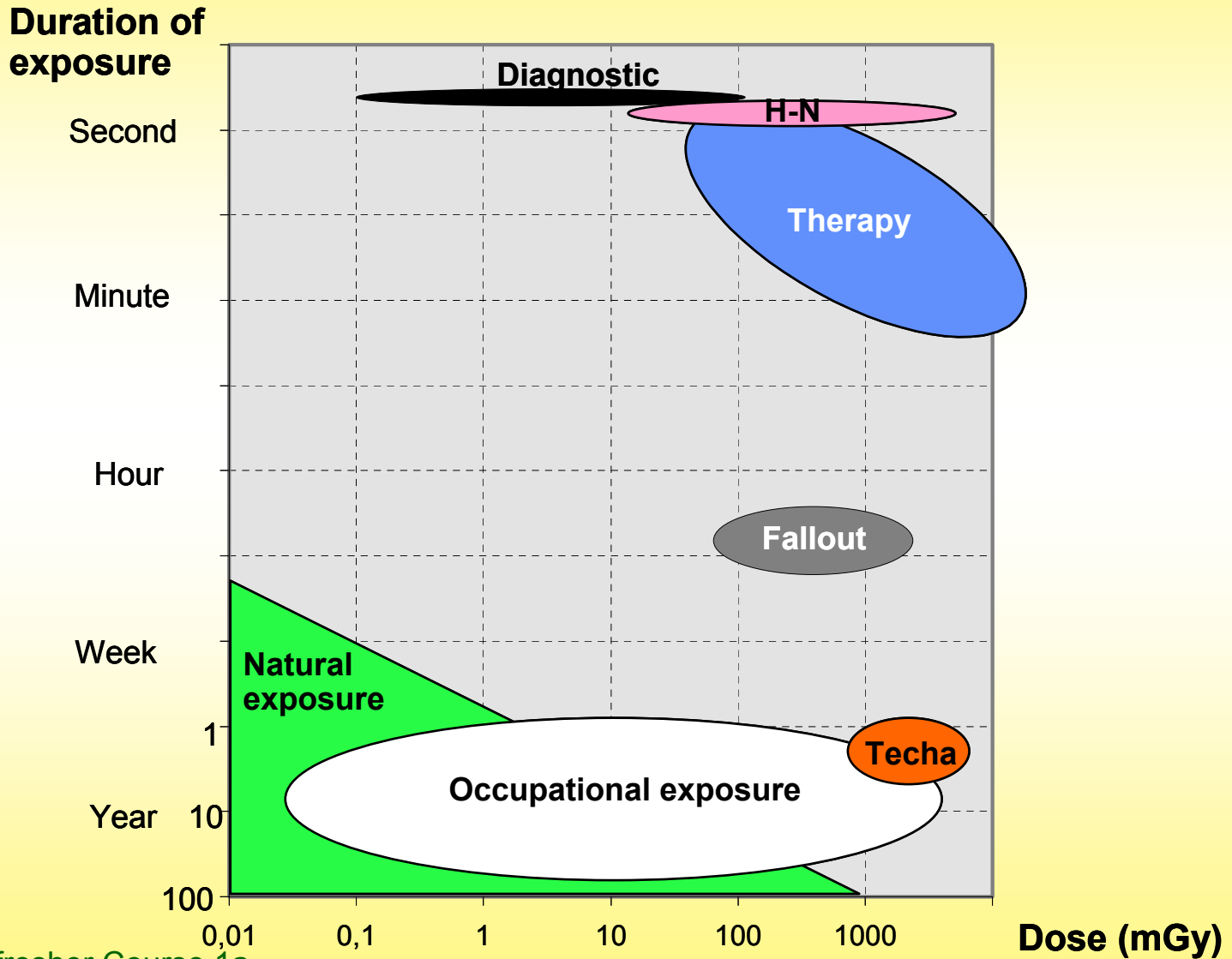
Life Span Study Limits

- **Death certificates : under-recording of cancer**
- **Particularities of Japanese population: basic rate of breast and stomach cancer (transposition problem)**
- **Exposure rate very high**
- **Only external exposure**



Studies in other populations and at various dose rates are necessary

Extrapolation Distances



Power and Epidemiological studies at low doses

Single studies are in general limited in size

→ limited statistical power

Development of **joint analyses**: analysis of data of different studies presenting similar protocols

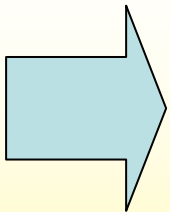
- advantage: large size (several hundred or thousands individuals)
increase of the capability to detect a small excess risk
- limits: internal variability (methods and quality of data collection, background rates,...)

International collaborations:

- joint analysis of miners cohort studies (US, NIH and Europe)
- joint analysis of indoor radon case-control studies in Europe (EC);
joint analysis of Us-Canadian + china +Europe data in near future
- joint analysis of nuclear workers cohort studies (IARC)

Occupational Studies

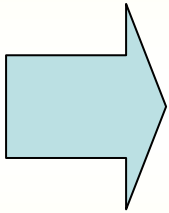
- Nuclear workers studies : external radiation at low doses and at low annual dose rates
- Uranium miners studies : inhalation of radon decay products



from risk estimation at low cumulative exposures
to general public concern

Main Contribution from Occupational Studies

- Registered individual dosimetry on annual basis
- Over long working periods (historical reconstruction)



Able to express a long-term risk , by taking in account the protection of the individual exposure over time

Nuclear Workers: Joint Analysis 1995

Data from several cohorts : (Cardis 95)

Mortality study on 95 700 workers USA, GB, Canada (15% of women)

mean duration of follow-up : 22 ans

low mean cumulated exposure : 40 mSv

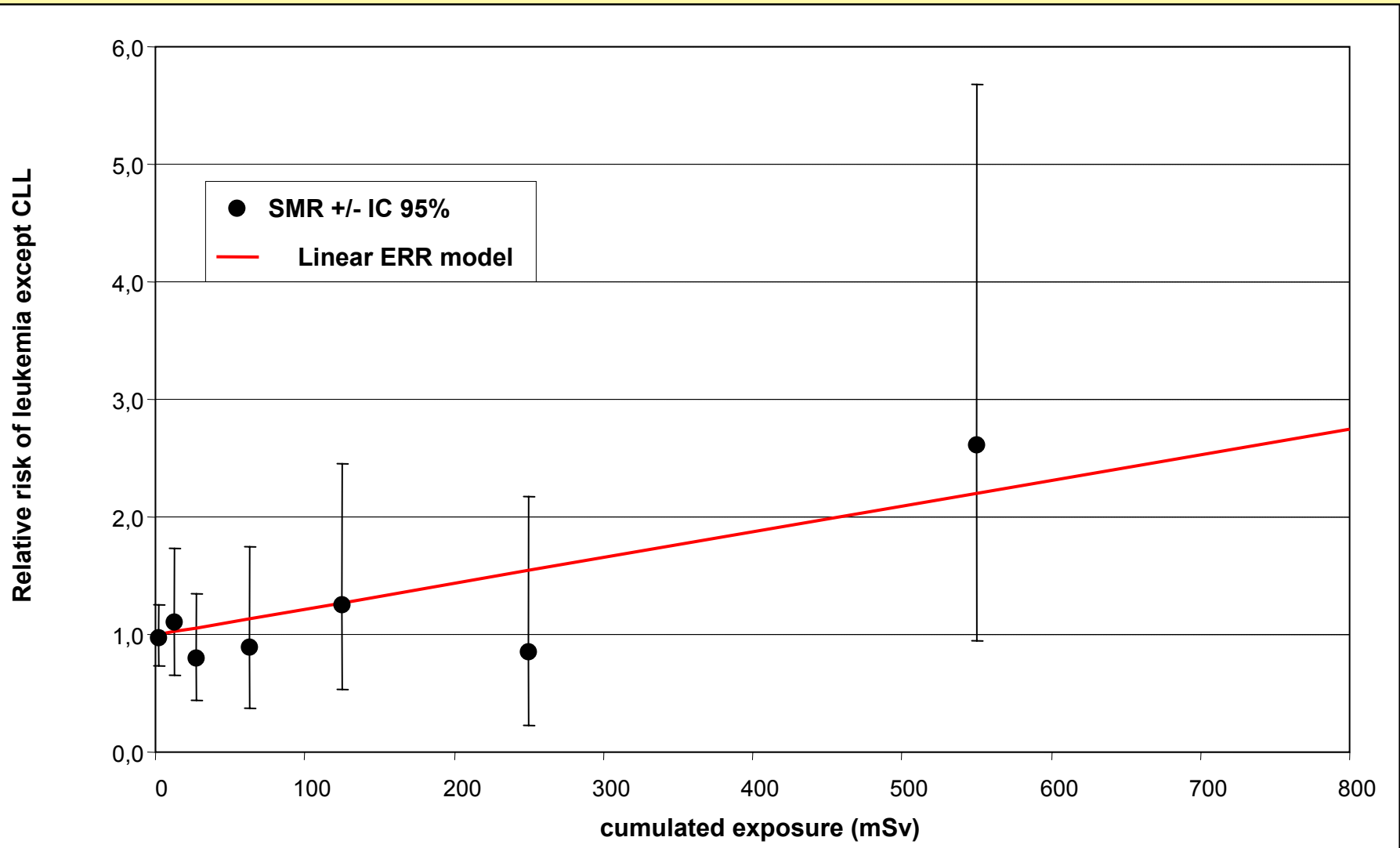
Solid tumor deaths : 3976 (expected > 4000)

leukemia deaths : 119 (expected < 90)

No dose-response relationship for solid tumors

for leukemia deaths : ERR at 1 Sv = 2.2 [0.1 – 5.7]

Nuclear Workers Study (Cardis 1995)



Cohort Study of Nuclear Workers in France (CEA-COGEMA group)

Published Results : 50 000 workers

- All causes mortality lower than in the French male general population (« Healthy worker effect »)
- No excess of mortality from leukaemia
- Elevated mortality risk observed for pleura cancer and skin melanoma (men) and breast and brain cancer (women)

Achievements in 2003:

- Integration in the international joint analysis of nuclear workers (IARC): 17 countries (Germany, Australia, Belgium, Canada, Spain, Finland, France, Hungary, Japan, Slovakia, Sweden, Switzerland, UK, USA, Russia, Lithuania, South Korea) Cohort of 400 000 individuals
- Analysis of mortality risk associated to cumulated doses : main hypothesis to be tested : potential leukemia risk increasing with exposure

Future EC program

- Analysis of mortality risk associated to multiple exposures

Cohort Study of French Uranium Miners

Objectives :

Estimation of risk of cancer death associated to cumulated radon exposure

Cohort :

- 5098 uranium miners employed in the CEA-COGEMA group between 1946 and 1990
- Reconstruction of individual annual exposure (radon, gamma, ore dust)
- Low cumulated exposure (37 WLM)
- Follow-up to December 1994 (mean duration of 26 years)
- Mortality : 1162 deaths, from which 125 lung cancer deaths

Collaborations :

- Occupational medical service of COGEMA
- European joint analysis of miners with low levels of exposure (Czech and German cohorts)

Cohort study of French Uranium Miners

Results :

- Excess risk of death from lung cancer: SMR = 1.5
- Linear dose-response relationship with cumulated radon exposure coherent with the literature : $ERR = 0.008 / WLM$
- Decrease of the risk with time since exposure (20% / 10 years)
- No dose rate effect once « time since exposure » and « exposure period » are considered

Perspectives : 6th EC program

- Extension of follow-up through end of 1999 (French+ Czech + Wismuth cohorts)
- Analysis of data collected in the frame of nested case-control studies: tobacco, other occupational factors
- Risk modelling : time dependant variables, mechanistic modelling; uncertainties linked to organ dose calculations
 - Multiple exposures : Ur + gamma + radon decay in miners

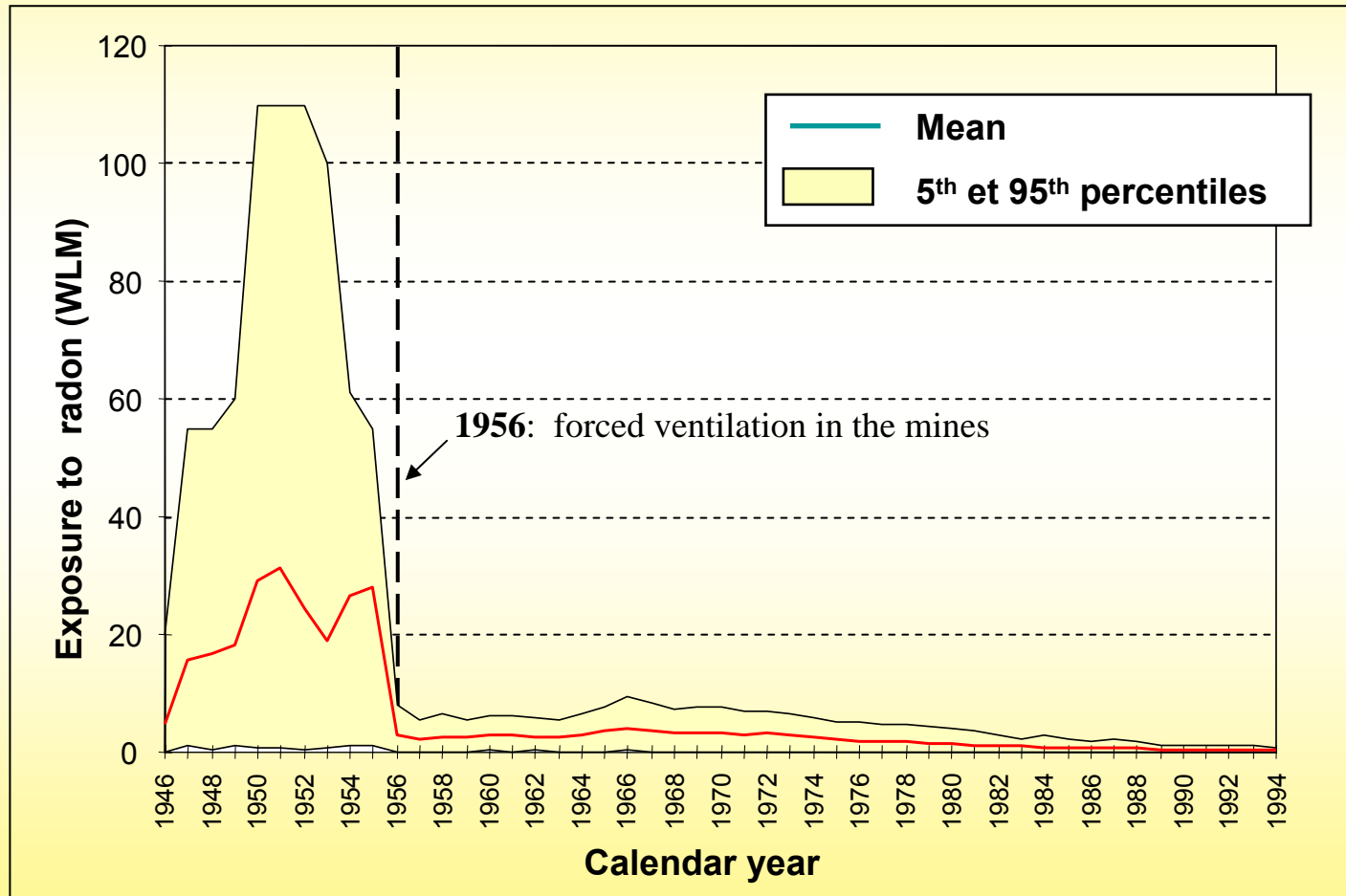
Uranium Miners Cohorts with Low Levels of Radon Exposure

	Czech Republic	France	Germany
Period	1948-95	1946-94	1946-98
Total number of miners	9960	5098	58 591
Low levels of exposure			
Number of miners	5002	5098	17 935
Duration of follow-up (y)	23	26	17
Person-years	127 400	133 500	315 500
Duration of exposure (y)	10	12	8
Cumulative exposure (WLM)	57	36	6
Number of deaths	1888	1162	690
Lung cancer deaths	448	125	21

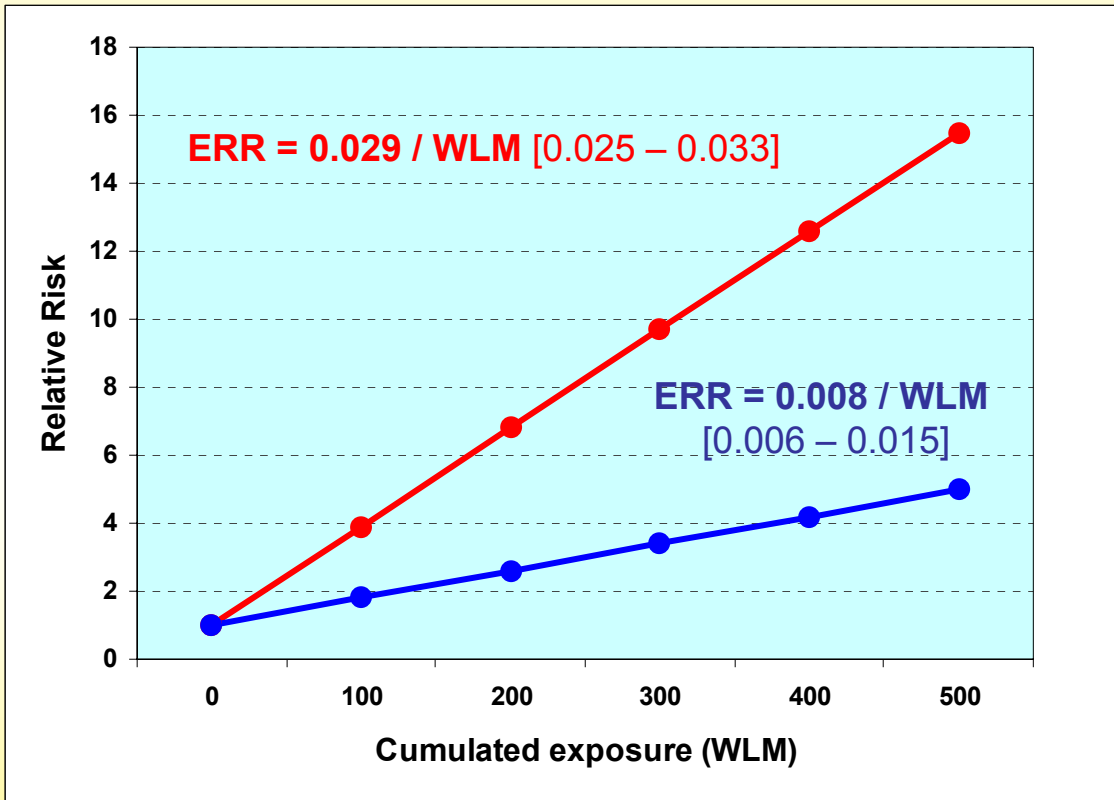
+ data on gamma, long-lived ore dust, arsenic exposures

Working Level Month (WLM): concentration in radon daughters (WL) x duration of work in months (170 h)
(1 WLM is equivalent to 3.5 mJ.h.m⁻³)

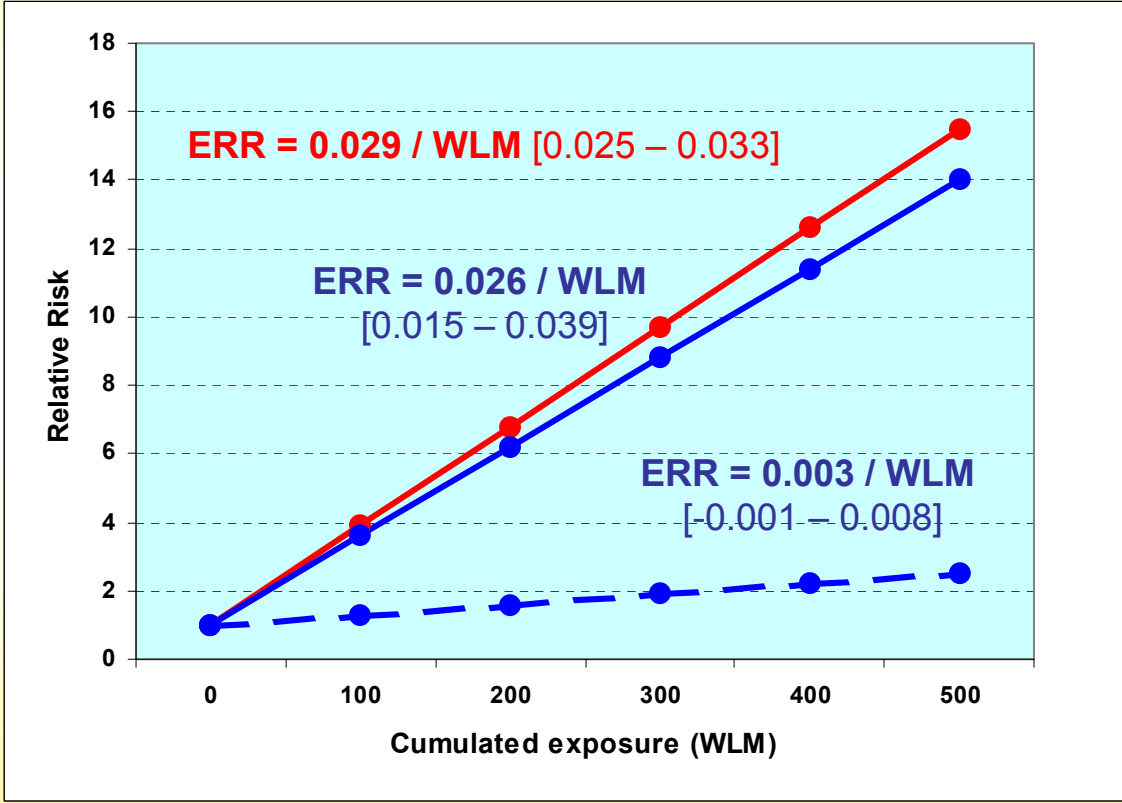
Description of Radon Exposure



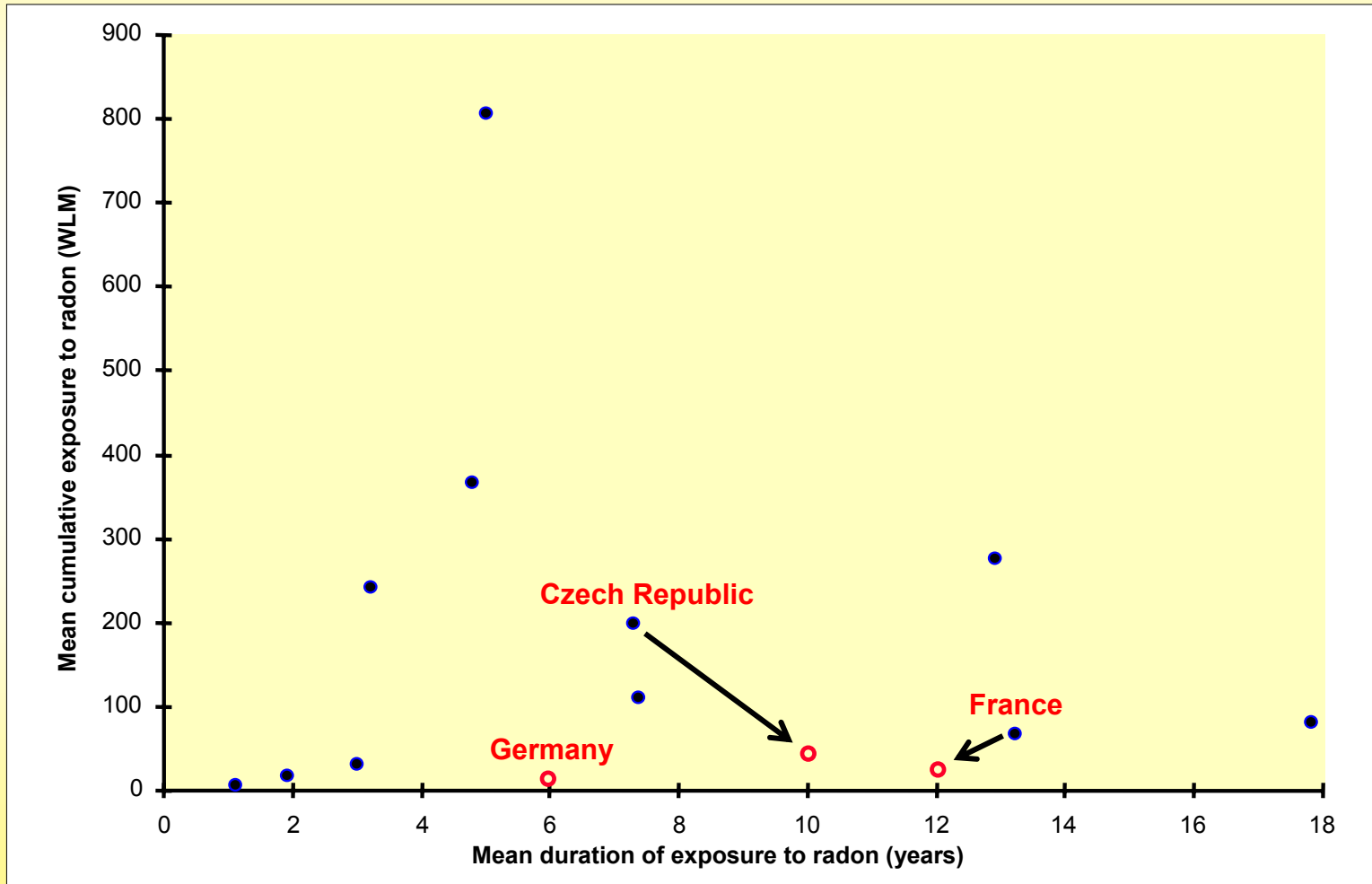
Uranium miners cohorts: Exposure-risk relationship



Uranium miners cohorts: Exposure-risk relationship

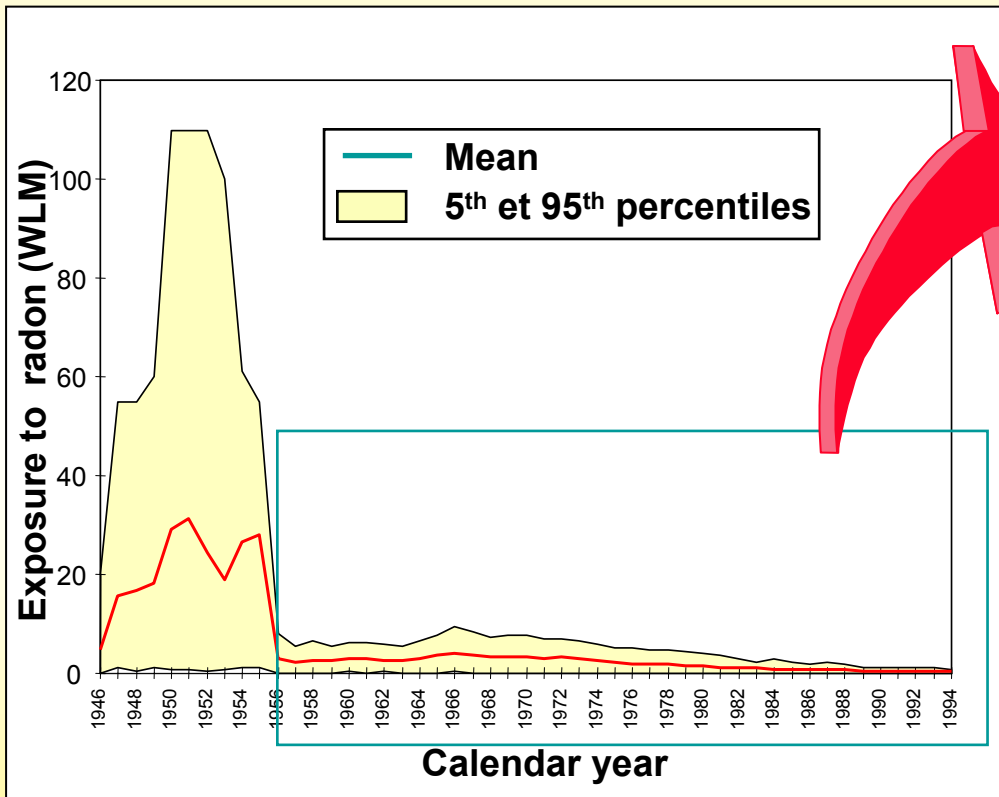


Cumulative exposure and duration of exposure to radon in miners cohorts (European program)



CZ : S52 + N studies (N=5002) Fr : extended cohort (N=5098) G : Wismut cohort C (N=17935)

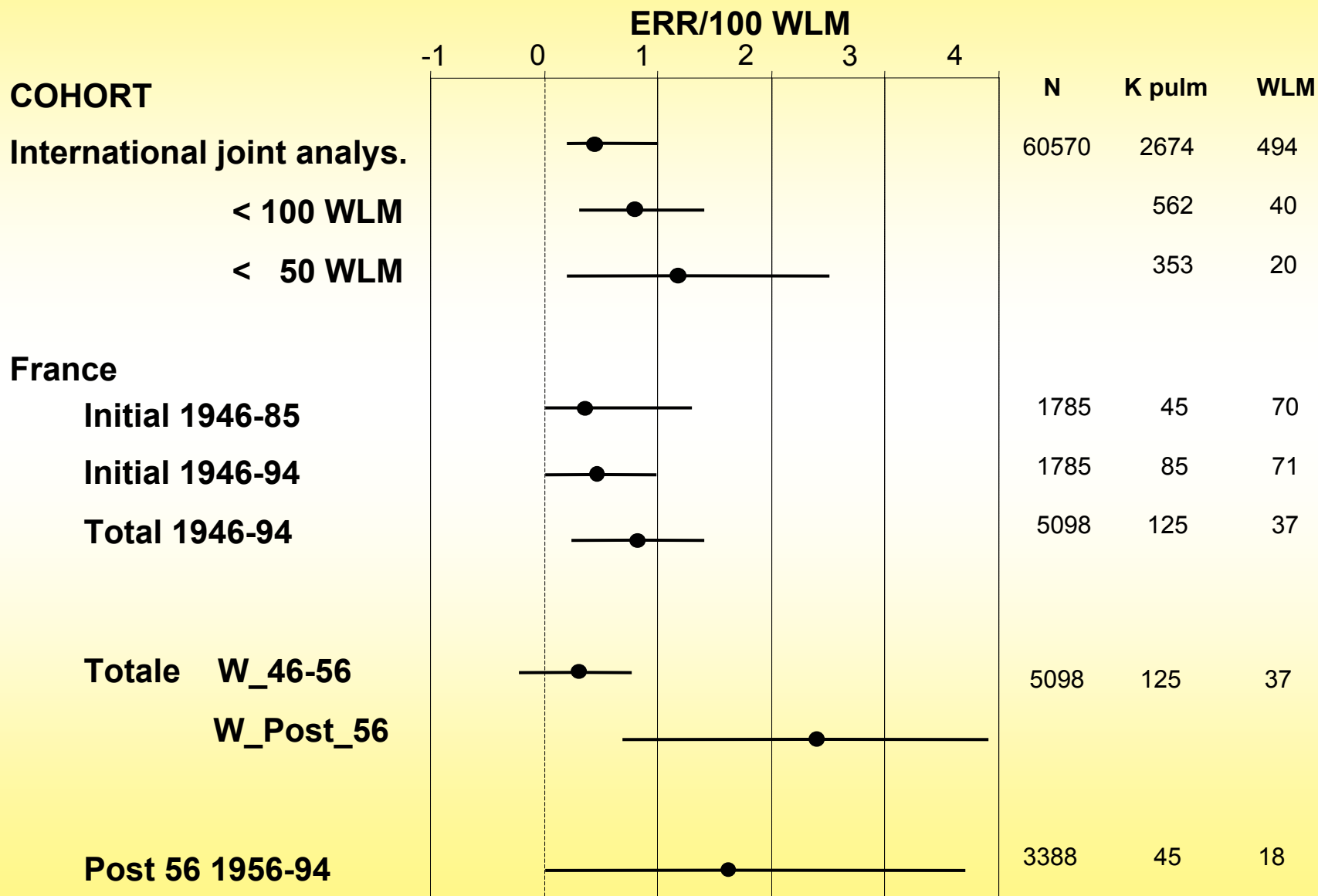
Subcohort of French Miners with low Levels of Exposure to Radon



1956: forced ventilation in the mines

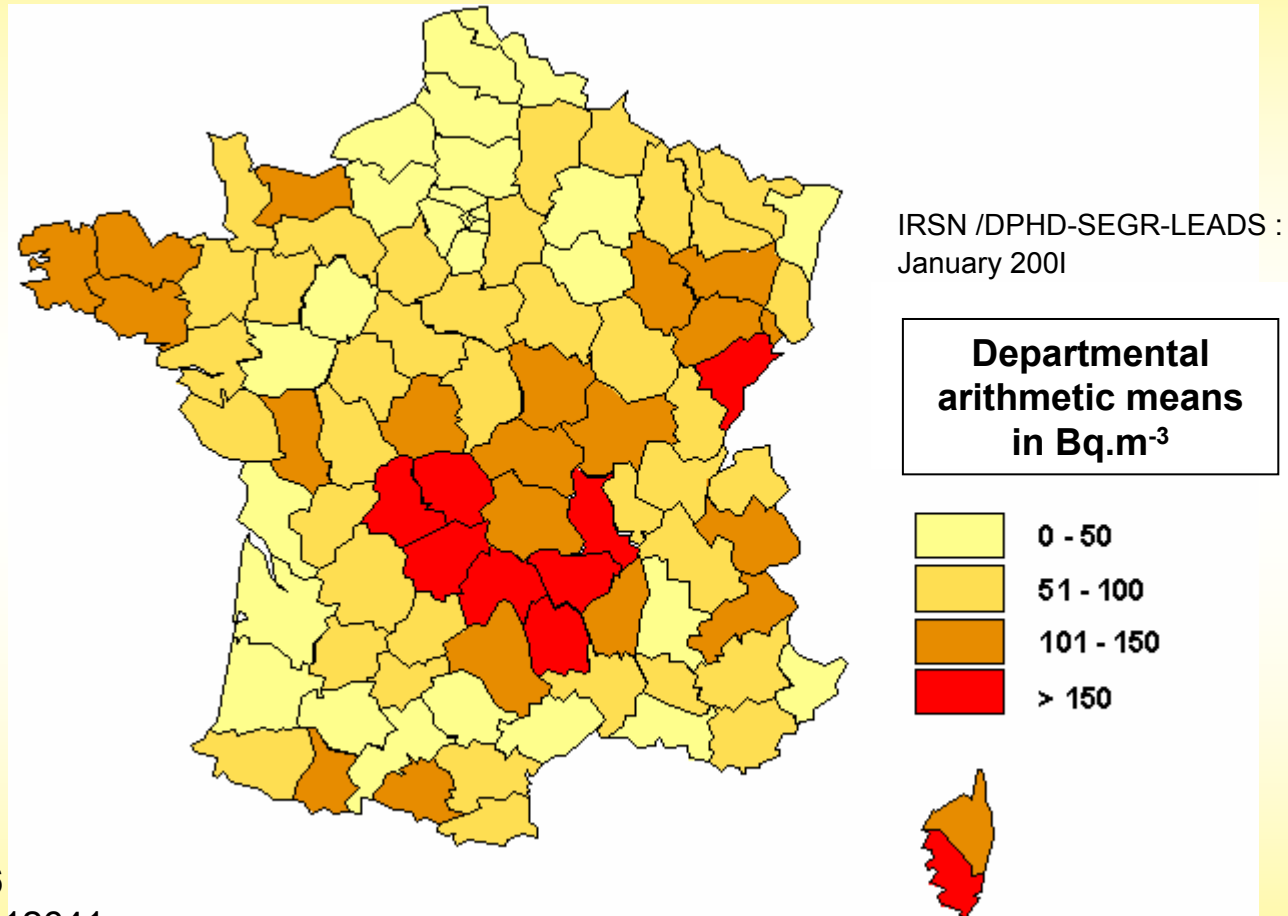
- **3,388 miners**
74,814 person-years
- precise individual records of exposure to radon
- low levels and low rates of exposure
18 WLM (over 11.5 years)
(Equivalent to 20 years of domestic exposure at 200 Bq per m³)
- measurements of gamma rays and ore dust exposure

ERR of Lung Cancer Death per Sub-cohort



Exposure of the French Population to Natural Radiation

Campaign of measurements of indoor radon concentration in France



Number of departments: 96

Number of measurements: 12641

Crude national arithmetic mean: 90 Bq,m⁻³

Population weighted national arithmetic mean: 68 Bq,m⁻³

* 1 Becquerel (Bq) = 1 disintegration per second

Case-control study of indoor radon and lung cancer in France

Objective :

to determine if lung cancer risk is associated with indoor radon exposure

Multi-center study

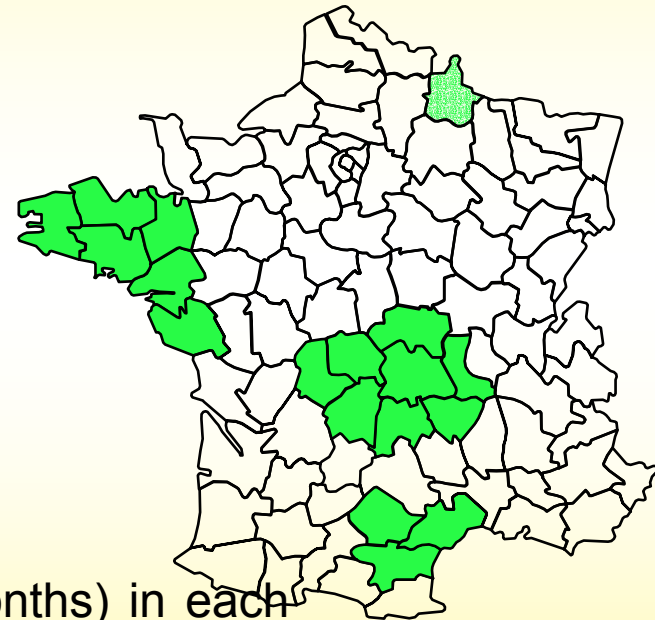
- 4 regions (+ Ardennes) : Bretagne, Limousin, Auvergne, Languedoc-Roussillon
- 10 hospitals

Subjects in the analysis

- 486 Cases (diagnosed with lung cancer)
- 984 Controls (free of respiratory disease)
- Paired (sex, age, hospital)

Risk factors :

- 2 measurements of radon concentration (6 months) in each house occupied during the last 30 years
- Questionnaire on other risk factors (occupational exposures smoking, medical history, SPC,,,))



Case-control study of indoor radon and lung cancer in France

Results :

- Past exposure to radon reconstructed over a mean duration of 20 years
- Lung cancer risk increases with exposure to radon

$$\text{RR} = 1.04 \text{ per } 100 \text{ Bq,m}^{-3} \quad \text{CI95\%} = [0.99 - 1.11]$$

(adjusted on age, sex, region, smoking and occupational exposure)

- This risk is low when compared to the risk associated to smoking
- This result is concordant with those from previous studies and with the risk extrapolated from miners studies
- Accepted for publication in Epidemiology

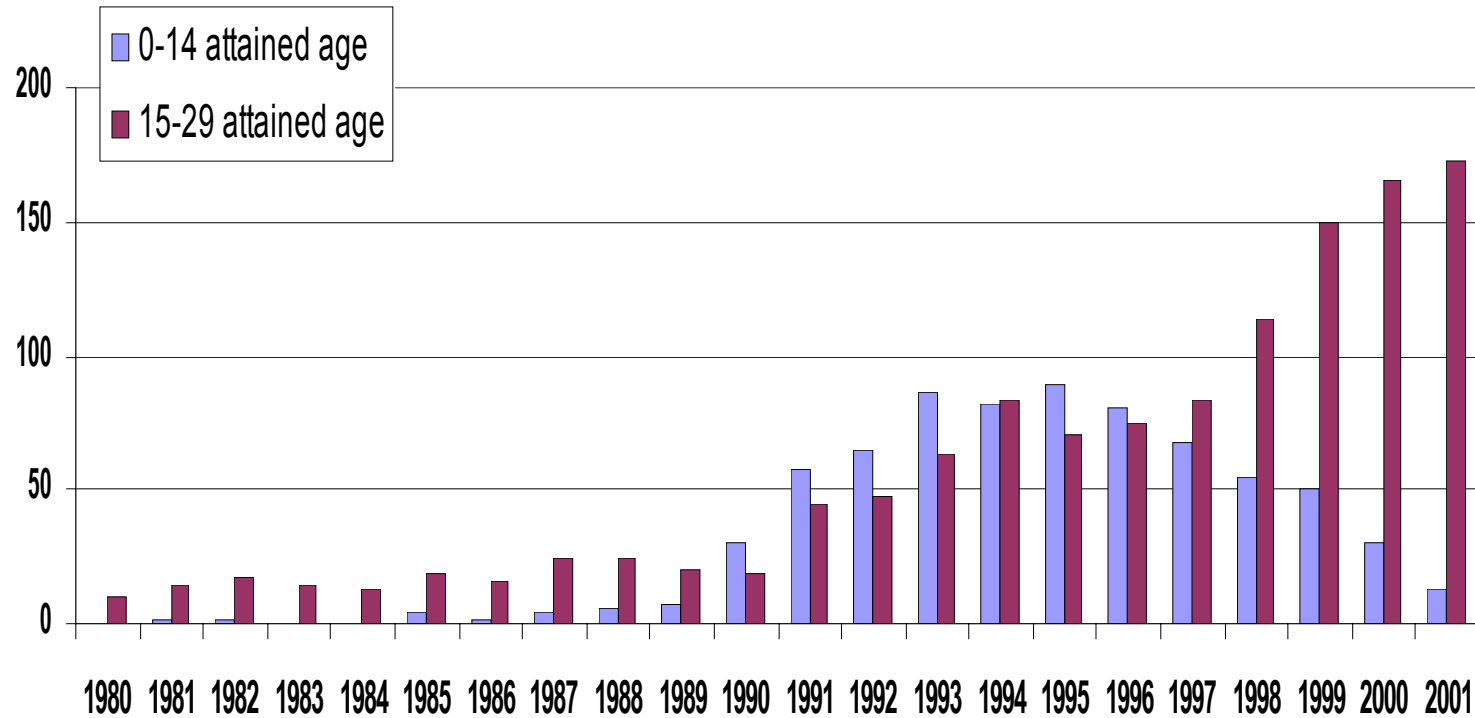
Integration in the European joint analysis (France, Belgium, Germany, UK, Sweden, Italy,,,) => about 10 000 cases : submitted for publication

Descriptive Geographical Studies

- Limits and interpretation :
 - Example : increasing incidence rate over time of childhood thyroid cancer in Belarus : comparison before / after accident
 - Example : correlation on regional level between domestic radon exposure and lung cancer : latency period too large between potential exposure and expression of risk, exposure information too sparse, migration of population, low risk in comparison to a high tobacco risk

French - German Initiative for Chernobyl (FGI)

Thyroid cancer incidence in Belarus



Conclusion

- Results of epi studies are closely related to quality of past exposure data and health indicators

Future studies have a good chance to integrate better quality of individual exposure data, of potential co-factors (occupational and others)

- Good quality of health indicator is absolutely necessary (incidence versus mortality studies)
- Collaboration with biologists is necessary in order to integrate possible new indicators of mechanisms on cellular level