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DE RADIOPROTECTION
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Faire avancer la sûreté nucléaire

The International Nuclear Worker Study (INWORKS)

Improving knowledge on cancer mortality risk
from low-dose exposure to ionizing radiation

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- The INWORKS study was approved by the IARC ethics committee
- Disclaimer: The findings and conclusions in this study are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.
- Competing financial interests: none declared

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INWORKS Context

- Protection standards for nuclear workers and public against risks associated with ionizing radiation (IR) exposure are primarily based on epidemiological studies of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945
- These studies brought out an excess of leukaemia and later an excess of solid cancer due to IR
- However, the pattern of exposure in the cohort of the survivors, *i.e. acute high dose rate exposure*, is not typical of exposure received by workers and public, *i.e. protracted low dose rate exposures*
- There remains still today a lack of precision in the estimation of health risks associated with exposure to protracted low doses of IR accrued at low dose rates

INWORKS Context

- In the 2000s, an international study pooled data from nuclear workers of 15 countries (*Cardis et al., BMJ, 2005*)
 - this study showed an excess of solid cancer associated to the dose of IR
 - the power of this study was hampered by the short length of follow-up
- A new large International Nuclear WORKer Study, INWORKS, was set out in 2011
 - large number of subjects
 - long length of time for follow-up (observation)

INWORKS Approach

- Cohort study of nuclear workers
- INWORKS consortium
 - Coordination: IARC
 - Cohort provision: IRSN (France), PHE (UK), NIOSH (US)
 - Expertise: UNC (US), CREAL (Spain)
- Protocol approved in 2011
- Data (and analyses) housed at IARC
- Analytical contributions by all partners

INWORKS Objectives

To quantify the risk of cancer and non-cancer mortality associated with low protracted IR dose

- ? What is the dose-risk relationship between external doses cumulated by nuclear workers and mortality from solid cancer and leukemia
- ? Are the dose-risk relationships observed among nuclear workers similar to those derived from the follow-up of the A-Bomb survivors
- ? What do the results bring regarding the current radiation protection system

General methods applied in INWORKS

Methods

Pooled analysis of mortality in nuclear worker cohorts assembled from three countries



National cohort

n = 59 003



UK NRRW

n = 147 866



US combined cohort

n = 101 428

Workers employed at least 1 year and monitored for external exposure to ionizing radiation (individual dosimeters)

- CEA civil
- AREVA NC
- EDF

- UK Atomic Energy Authority
- British Nuclear Fuels plc
- British Energy Generation and Magnox Electric Ltd
- Atomic Weapons Establishment
- Ministry of Defence

- Hanford Site
- Idaho National Laboratory
- Oak Ridge National Laboratory
- Portsmouth Naval Shipyard
- Savannah River Site



International Agency for Research on Cancer
Centre International de Recherche sur le Cancer

308 297 workers

Methods

Mortality follow up

- Until 2001 (UK), 2004 (Fr), and 2005 (US)
- Vital status and underlying cause of death obtained from national registries

Dosimetry

- Dose calculation methods identical in the three cohorts
- Recorded gamma doses converted into estimates of individual equivalent $H_p(10)$ doses
- Estimated organ doses (colon, lung, red bone marrow, female breast)
- Characterized uncertainty (by types of dosimeter, monitoring period...)
- Flagging of workers exposed to neutrons and internal contamination

Methods

Statistical analysis

- Regression modeling controlling for key confounders (age, sex, country...)

Estimation of mortality rate associated with cumulative dose

$$RR(dose) = 1 + \beta \times dose$$

where β is an estimate of the **excess relative rate** (ERR)

Cumulative doses were lagged to allow for an induction and latency period between exposure to IR and death: 2 or 10 years

Sensitivity analyses

- Dose-response shape, restricted dose range, country effects...

Results

Results – Characteristics of INWORKS cohort, 1943-2005

Number of workers	308 297	
Male workers	87%	
Range of year of birth	1873-1983	
Mean duration of employment (SD) in years	15	(11)
Mean age at last observation (SD) in years	58	(15)
Mean duration of follow-up (SD) in years	27	(12)
Total person years (million)	8.2	
Vital status		
Alive	236 913	(76.9%)
Deceased	66 632	(21.6%)
solid cancer	17 957	
leukemia (excluding chronic lymphocytic leukemia)	531	
circulatory diseases	27 848	
Emigrated or lost to follow-up	4 752	(1.5%)

Results – Characteristics of INWORKS cohort, 1943-2005

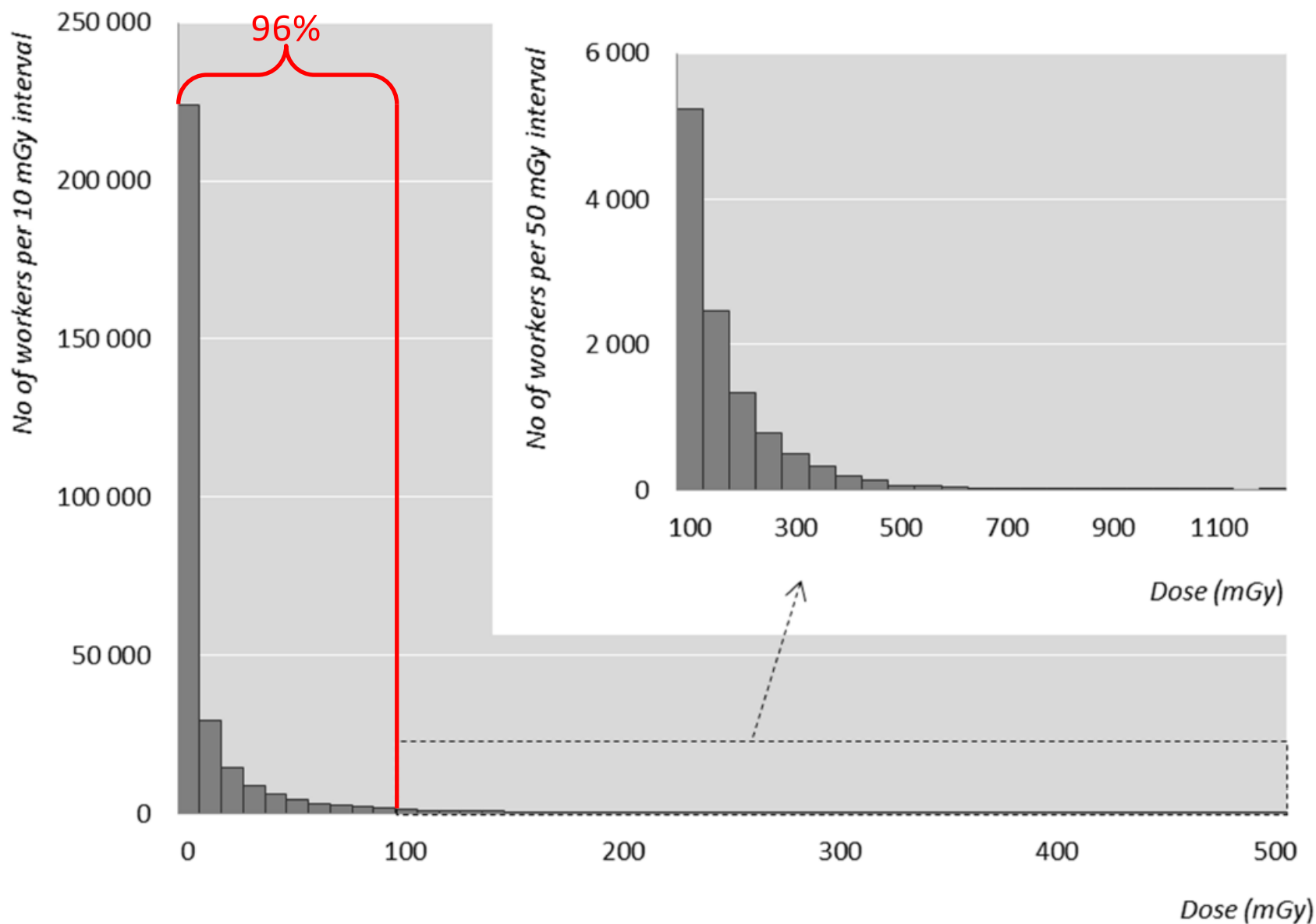
Distribution of individual doses among cohort participants

	$H_p(10)$ dose (mSv)	Colon dose (mGy)	RBM dose (mGy)
Annual doses			
Mean	1.73	1.20	1.09
Cumulative doses			
Mean (range)	25.2 (0.0, 1 932.5)	17.4 (0.0, 1 331.7)	15.9 (0.0, 1 217.5)
Median (IQR)	3.4 (0.4, 18.4)	2.3 (0.3, 12.8)	2.1 (0.3, 11.7)

Values include doses recorded as zero. RBM = red bone marrow. IQR = interquartile range (25th percentile, 75th percentile)

Results – Characteristics of INWORKS cohort, 1943-2005

Distribution of cumulative red bone marrow doses among workers



Results for lymphatic & hematopoietic cancers

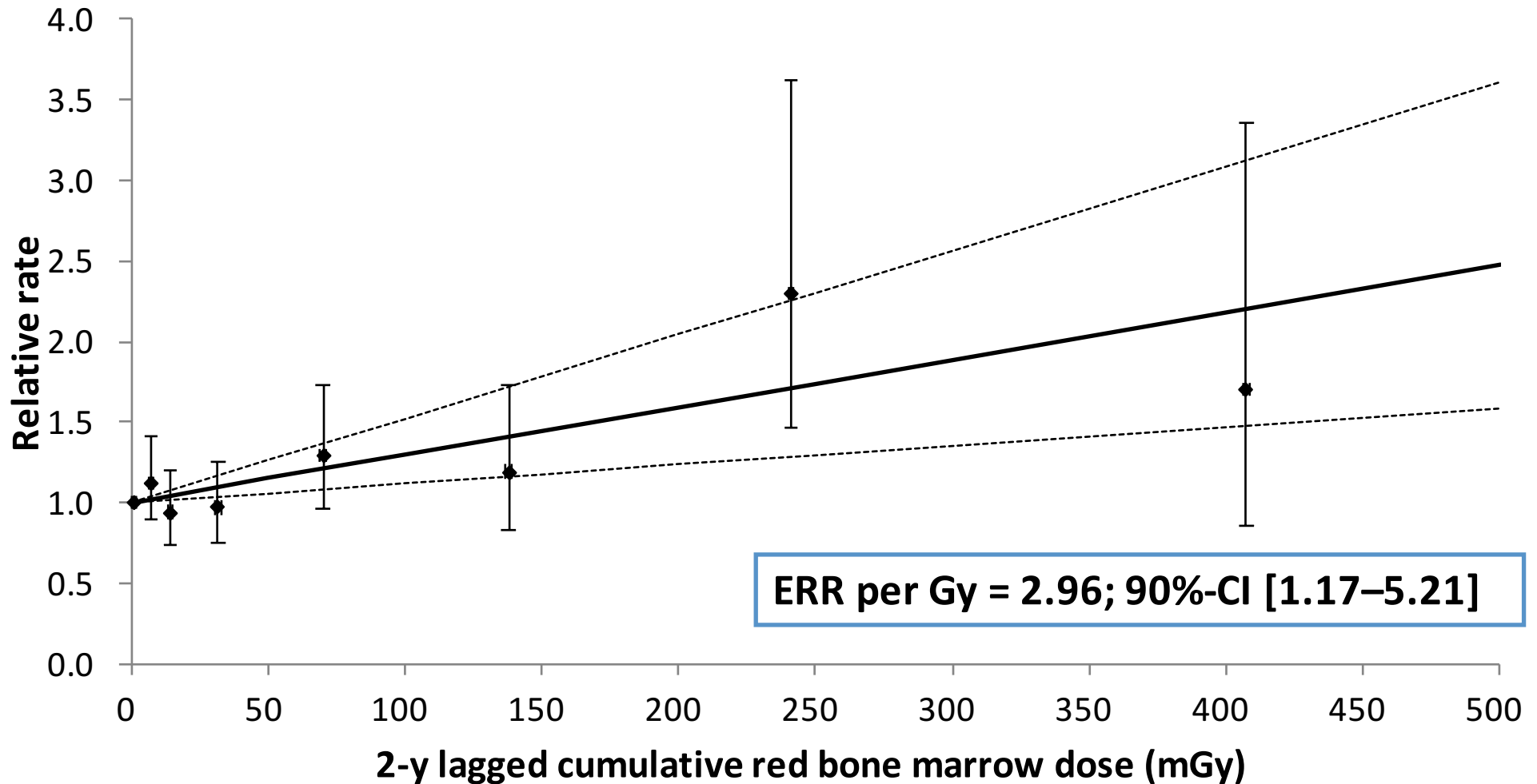
Results – Lymphatic & hematopoietic cancers

ERR per Gy of cumulative red bone marrow dose

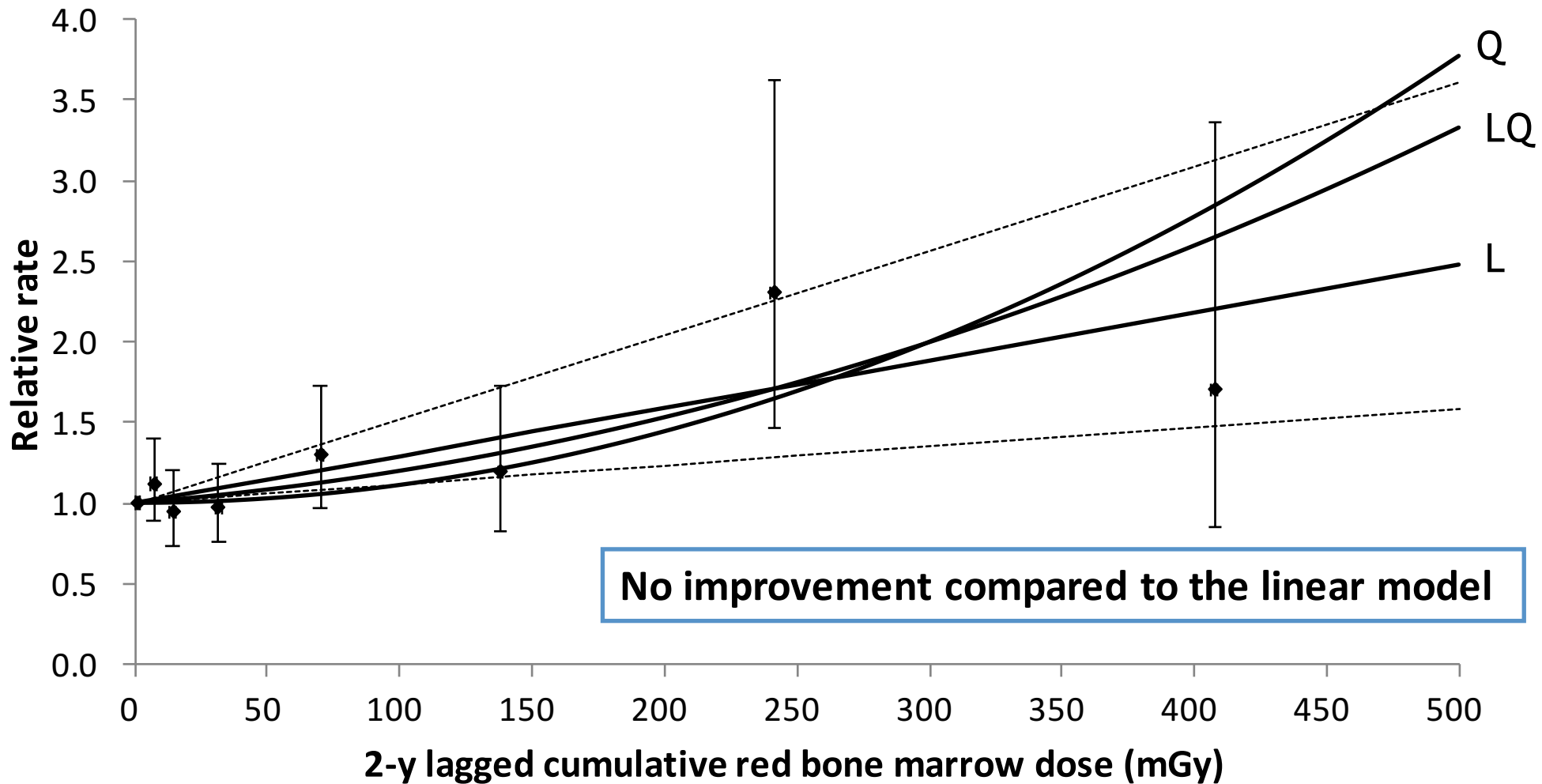
Cause of death	No of deaths	ERR per Gy	(90%-CI)
Leukemia excluding CLL*	531	2.96	(1.17–5.21)
Chronic myeloid leukemia*	100	10.45	(4.48–19.65)
Acute myeloid leukemia*	254	1.29	(-0.82–4.28)
Acute lymphoblastic leukemia*	30	5.80	(ne–31.57)
CLL*	138	-1.06	(ne–1.81)
Multiple myeloma**	293	0.84	(-0.96–3.33)
Non-Hodgkin lymphoma**	710	0.47	(-0.76–2.03)
Hodgkin's lymphoma**	104	2.94	(ne–11.49)

CLL=chronic lymphocytic leukemia. ne=not estimated. * 2-y lag assumption. ** 10-y lag assumption

Results – Risk of non-CLL leukemia and RBM dose

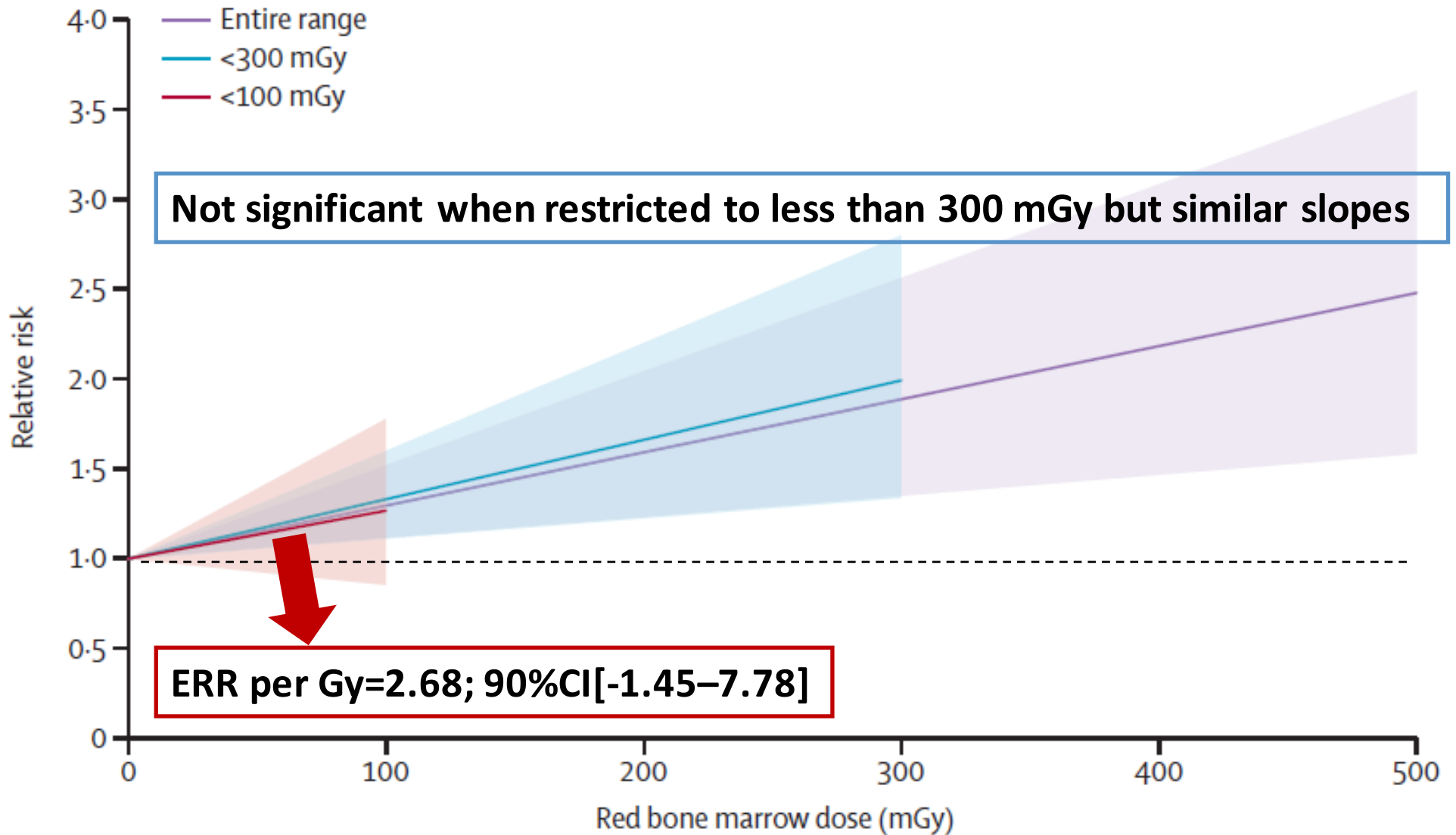


Results – Risk of non-CLL leukemia and RBM dose



No improvement compared to the linear model

Results – Risk of leukemia over restricted RBM dose ranges



Results – Sensitivity analyses for non CLL-leukemia risk

- Dose-response did not substantially improve with addition of nonlinear (quadratic) term in model
- Little between-country heterogeneity
- Alternative lag assumptions changed results little
- The ERR persisted when excluding neutron-exposed workers
 - ERR per Gy=4.19; 90%-CI [1.42–7.80]
- The ERR persisted when adjusting for internal contamination:
 - ERR per Gy=3.39; 90%-CI [1.39–5.93]

Results – Risk of leukemia, interpretation and excess deaths

Note that the ERR is expressed per Gy

- Similarly, the estimated ERR from non CLL-leukemia can be expressed per 10 mGy, a scale more representative of the average mean of the workers
- ERR per 10 mGy=0.03; 90%-CI [0.01-0.05]
- An exposure at 10 mGy multiplies the baseline cancer risk by 1.03

Estimated number of excess deaths due to non-CLL leukemia under the hypothesis of a linear ERR model

- 31 excess deaths among 531 observed deaths

Additional probability of death by leukemia attributable to exposure to IR in the studied population

- ≈ 1 death per 10 000 persons

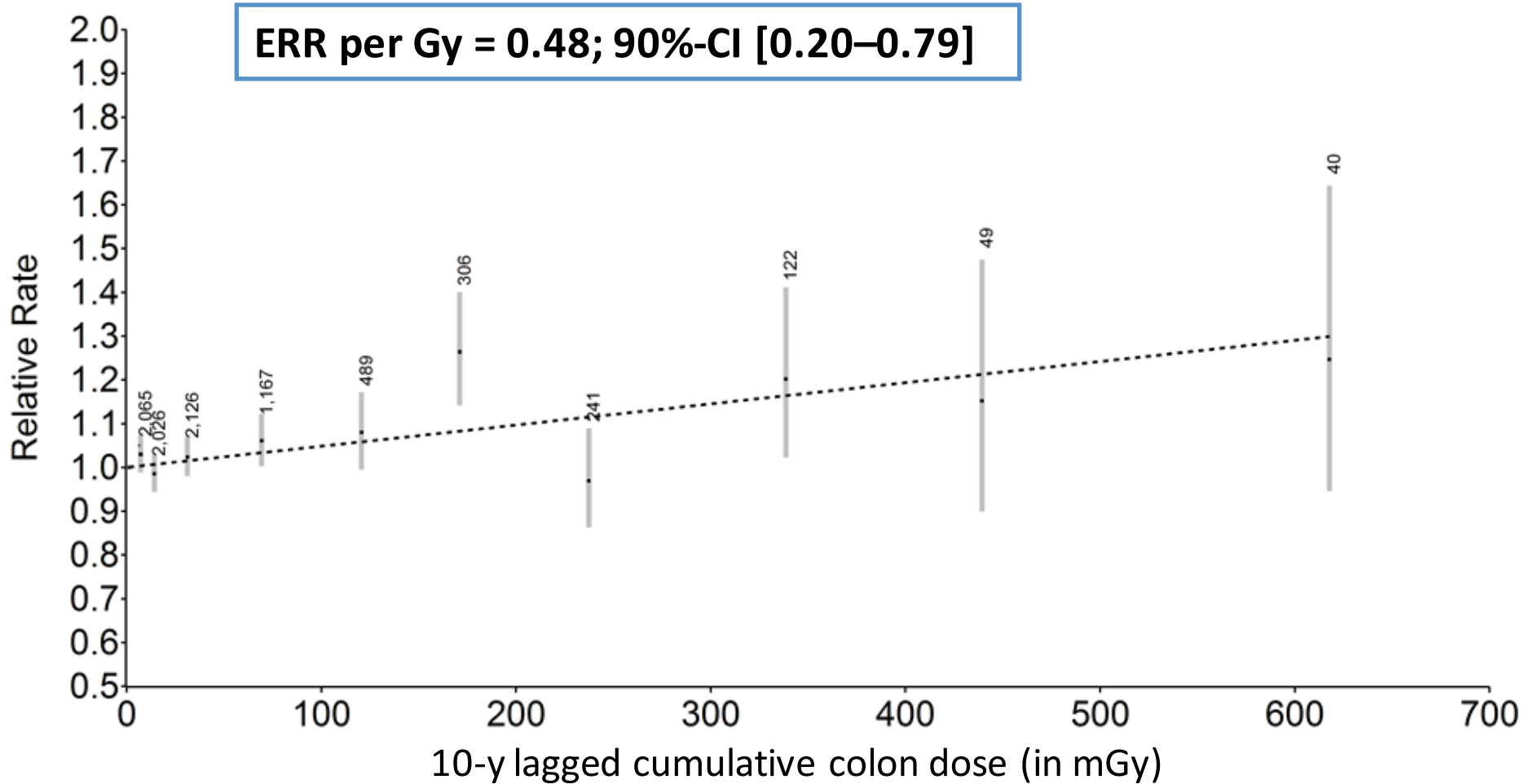
Risk of cancer other than leukemia

Results – Risk of cancer and colon dose

ERR per Gy for death due to specific cancer categories under a 10-y lag assumption

Cause of death	No of deaths	ERR per Gy (90%-CI)
All cancer	19 748	0.51 (0.23–0.82)
All cancer other than leukemia	19 064	0.48 (0.20–0.79)
Solid cancer	17 957	0.47 (0.18–0.79)
Solid cancer other than lung cancer	12 155	0.46 (0.11–0.85)

Results – Risk of cancer excluding leukemia and colon dose



Results – Risk of cancer excluding leukemia, excess deaths

10-y lagged cumulative colon dose (in mGy)	Mean dose	Person-years (thousands)	Observed	Fitted Excess
< 5	0.6	6089	10 433	5.4
5-<10	7.2	595	2 065	7.1
10-<20	14.3	545	2 026	14.3
20-<50	31.7	533	2 126	32.2
50-<100	70.1	257	1 167	37.9
100-<150	121.7	95	489	27.0
150-<200	172.1	46	306	20.3
200-<300	240.6	39	241	29.2
300-<400	341.4	14	122	16.9
400-<500	442.3	5	49	9.1
500-	630.8	4	40	9.8
Total	--	8 222	19 064	209.2

Crude attributable rate

209.2 / 308 297 \approx 7 per 10 000 persons

Results – Risk of cancer excluding leukemia over restricted colon dose ranges

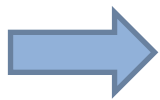
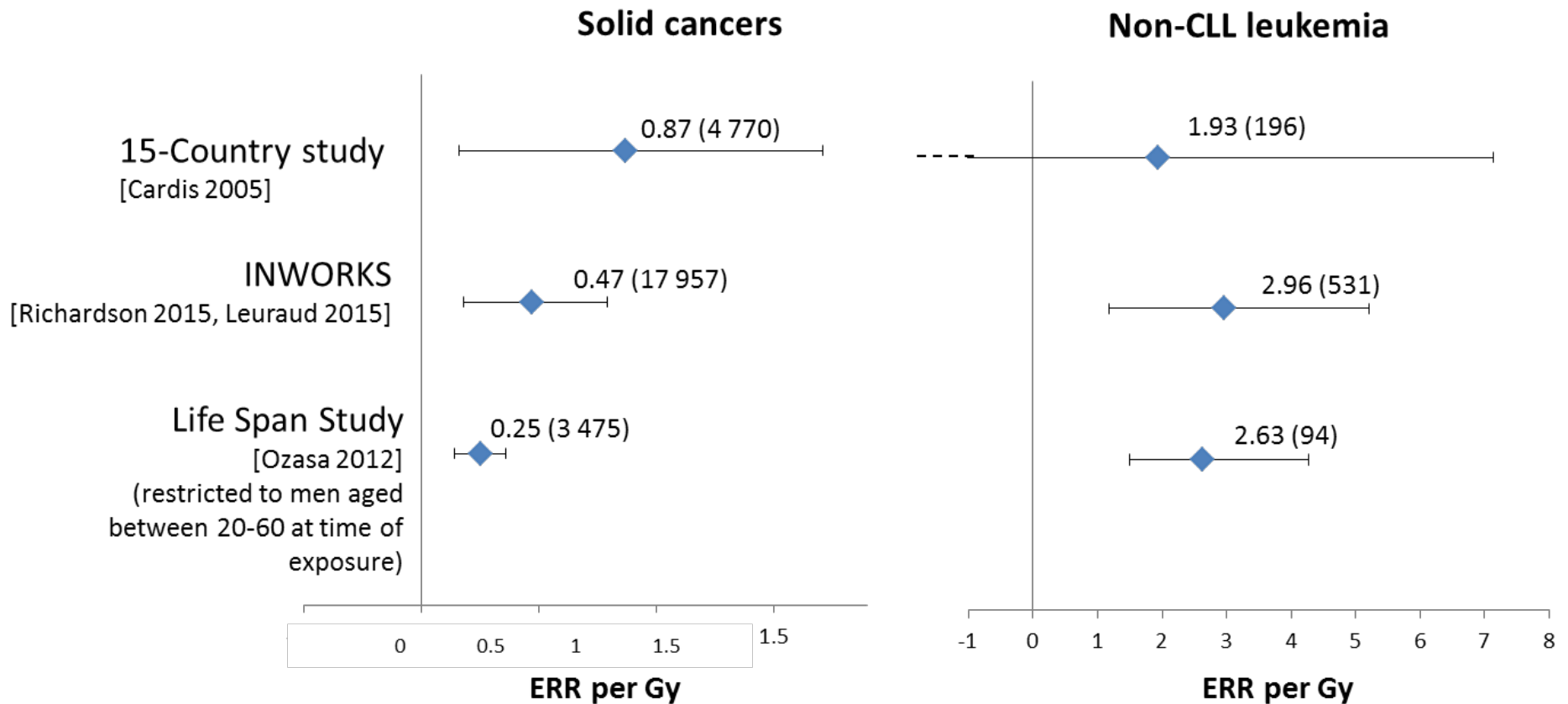
10-y lagged cumulative dose range (mGy)	ERR per Gy	90%-CI
Entire dose range	0.48	0.20–0.79
0–200	1.04	0.55–1,56
0–150	0.69	0.10–1,30
0–100	0.81	0.01–1,64

Results – Sensitivity analyses for cancer other than leukemia

- Dose-response did not substantially improve with addition of nonlinear (quadratic) term in model
- No evidence of between-country heterogeneity
- Alternative lag assumptions changed results little
- Excluding neutron-exposed workers: ERR per Gy=0.55; 90%-CI [0.17–0.95]
- Adjusting for internal contamination: ERR per Gy=0.46; 90%-CI [0.17–0.78]

Comparison with other studies

Consistency of dose-risk relationships



Estimated ERR per Gy in INWORKS close to estimates derived in the LSS

Discussion & conclusion

Strengths and limitations of INWORKS

Limitations

- Mortality study, not ideal for highly survivable cancers
- Poor precision of flags (neutron, contamination)
- Uncertainties in dose (reporting limits, measurement errors)
- No non-occupational dose information
- No information on other risk factors (e.g., benzene, smoking)
- Age at end of follow-up still limited (mean 58 years)

Strengths

- High-quality occupational dose
- Predominantly gamma dose (good confidence in organ dosimetry)
- Large pooled cohort with lengthy follow-up: ↑ power (8.2 millions person-years vs 3.3 for the total LSS)
- Standardized protocol across three countries
- Elaborated statistical analyses (recognized methodology, different partners, use of different modelling approaches, sensitivity analyses)

Conclusion

INWORKS has a large capacity to demonstrate dose-risk relationships associated with exposure to protracted low doses of external radiation

- Significant, robust dose-responses observed for cancers (solid, leukemia)
- Analyses on temporal factors effects (age at exposure, time since exposure): manuscript submitted to journal
- Analyses of non-cancer diseases: manuscript submitted to journal

Dose-risk relationships are no more significant below several tens of mGy but the risk coefficients remain similar

Derived attributable risks are small

Conclusion

- Risk coefficients in INWORKS are similar to those derived from the A-bomb survivors study
- The results are compatible with one of the main underlying hypothesis of the current radiation protection system
 - extrapolation of relationships obtained from acute high doses settings to low protracted doses settings
- These results support the rationale for radiation protection of populations exposed to low protracted doses of IR
- Results are complementary to radiobiological research

Publications

- G.B. Hamra et al. Cohort Profile: The International Nuclear Workers Study (INWORKS). *Int. J. Epidemiol.* 2015 Jul 6. pii: dyv122. doi: 10.1093/ije/dyv122.
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- D.B. Richardson et al. Solid cancer risk among Nuclear Workers in France, the United Kingdom, and the United States: The INWORKS Project. *BMJ* 2015; 351: h5359.

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