Radon and health effects other than lung cancer - PUMA, Wismut and other uranium miner studies

Michaela Kreuzer, Ph.D. (and on behalf of the PUMA study group)

Federal Office for Radiation Protection, Munich, Germany
Head of Department „Radiation effects and risks from ionizing and nonionizing radiation"
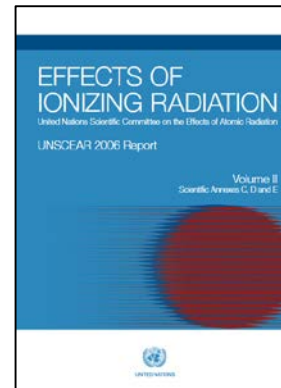**mkreuzer@bfs.de**
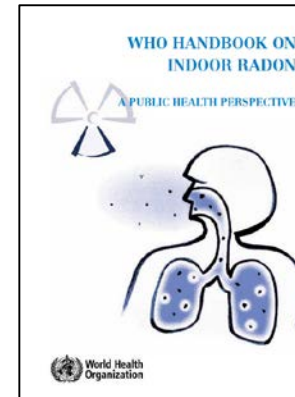
Current risk evaluation

"Radon causes no material risk for diseases other than lung cancer"

NAS, 1999

UNSCEAR, 2006

WHO, 2009

Absorbed doses from inhaled radon and its progeny to organs other than the respiratory tract are at least by a factor 100 lower [*Kendall and Smith 2002*]

Evidence from epidemiological studies

- The association between radon and non-lung cancer has been mainly investigated in **uranium miners**

- Comparisons of mortality in miners with that of the general population (so-called **SMR analyses**) show increased risks for some diseases ⇒ often inconsistent across studies; unclear what is the cause

- Detailed analyses of **exposure-response relationships are rare** and indicate little evidence for material risk.

- Due to the low absorbed doses we expect – if at all – a small excess risk, thus large studies with a wide exposure range are necessary

PUMA (Pooled uranium miner cohort study)

- Large number of deaths ($\sim$ 8,000 cancers other than lung cancer, $\sim$ 17,500 circulatory and $\sim$ 4,500 non-malignant respiratory diseases)

- Long average duration of follow-up, wide range of radon exposures $\Rightarrow$ high statistical power to detect possibly small excess risks

- SMRs elevated for cancers of the lung, stomach, larynx, liver and gallbladder [*Richardson et al. 2020*],

- Analyses on the exposure-response relationship analyses not yet available

The Wismut cohort forms about 50% of PUMA, new findings based on follow-up by end of 2013 will be shown [*work in progress, unpublished*]

Wismut cohort

Description	**n = 58,974 former employees of the Wismut company [*Kreuzer et al. 2008; 2013; 2018; 2020*]** **Mortality follow-up period: 1946-2013** **Individual data on exposure to radon and its progeny are available from a detailed job-exposure matrix**
Methods	**Internal Poisson regression** **Estimation of linear excess relative rate (ERR) per unit of cumulative exposure to radon in WLM (5-year lagged)** **Baseline stratification by age and calendar year**

Total group of cancers other than lung cancer

Published large studies	# of deaths	Person-years at risk	ERR/100 WLM 95% CI
Pooled 11 miner study *Darby et al. 1995, BEIR VI 1999*	**1,179**	**669,694**	**0.01** [-0.01; 0.02]
Wismut cohort* FU 2003, *Kreuzer et al. 2008*	**3,340**	**1,762,208**	**0.014** [0.006; 0.023]
Wismut cohort* FU 2013, *work in progress*	**5,230**	**2,334,140**	**0.012** [0.005; 0.020]

ERR/100 WLM: Excess relative risk per cumulative exposure to radon in Working Level Months (WLM)
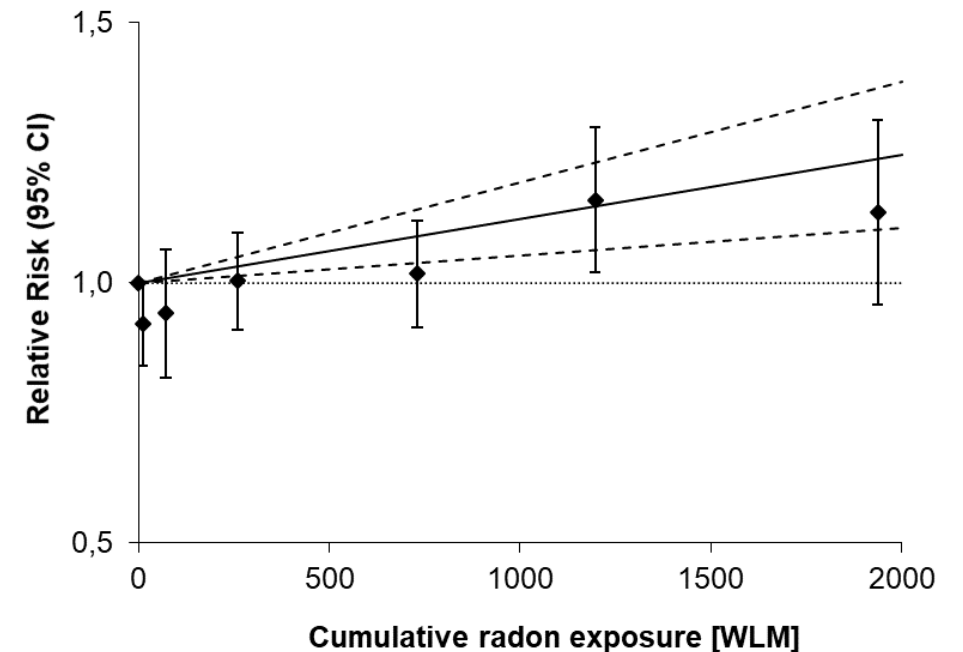* includes 4,000 millers which are excluded in PUMA

Total group of cancers other than lung cancer
Wismut cohort with end of follow-up 2013 (work in progress)

WLM	Person-ys at risk	# deaths	Relative risk	95% CI
0 .	309 846	799	1.00	
>0-50	1 031 144	1 542	0.92	0.84-1.00
50-99	145 406	326	0.94	0.82-1.06
100-499	390 890	1 147	1.00	0.91-1.09
500-999	259 623	789	1.02	0.91-1.12
1 000 -1 499	129 987	422	1.16	1.02-1.30
1 500+	67 245	205	1.14	0.96-1.31
ERR/100 WLM	2 334 140	5 230	0.012	0.005; 0.019

Individual cancer sites

Wismut cohort with end of follow-up 2013 (*work in progress*)

Bundesamt für Strahlenschutz

| Cancer site	ERR / 100 WLM (95% CI)	N	ERR
Pharynx		93	0.049
Liver		275	0.036
Colon, small intestine		482	0.026
Gallbladder		109	0.021
Non–Hodgkin lymphoma		135	0.020
Rectum		377	0.018
Tongue, mouth		72	0.017
Kidney		282	0.017
Multiple myeloma		96	0.016
Stomach		795	0.016
Hodgkin lymphoma		41	0.016
Prostate		474	0.013
Bladder		276	0.006
Leukemia		203	0.004
Larynx		109	0.001
Pancreas		357	0.000
Esophagus		200	−0.018
Melanoma		70	−0.024
Brain, CNS		166	−0.029

−0.05   0   0.05   0.1   0.15

Cancers of the respiratory tract excluding lung

Wismut cohort with end of follow-up 2013 (work in progress)

| Cancer site	# deaths	ERR/100 WLM	95% CI
Tongue/mouth	72	0.017	-0.064; 0.099
Pharynx	93	0.049	-0.041; 0.139
Nose, nose cavity	12	0.020	-0.137; 0.178
Larynx	109	0.001	-0.041; 0.043
Total	286	0.016	-0.019; 0.051
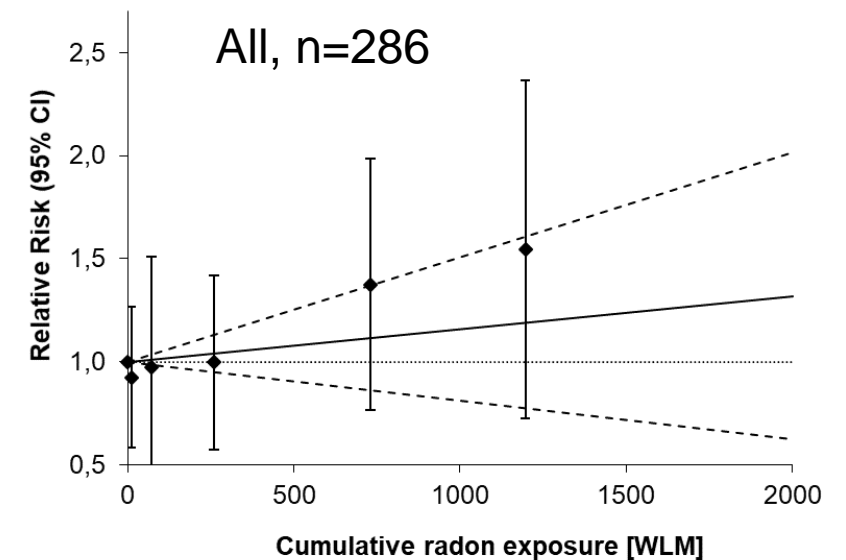
– Absorbed doses from inhalation of radon progeny very high [*Kendall and Smith 2002*]

– ERR/WLM for total group is elevated, however, not statistically significant

Liver cancer

Wismut cohort with end of follow-up 2013 (work in progress)

- SMR: Consistently elevated in many uranium miner studies and PUMA
  [*Tomasek 1993, Darby et al. 1995, Kreuzer et al. 2020, Kelly-Reif et al. 2019; Rage et al. 2019; Richardson et al. 2020*]

- **Wismut: n = 275 deaths**
  ERR/100 WLM = 0.038; 95% CI: -0.002; 0.078

- Bias? Metastases of lung cancer in the liver may have been misclassified as primary liver cancer
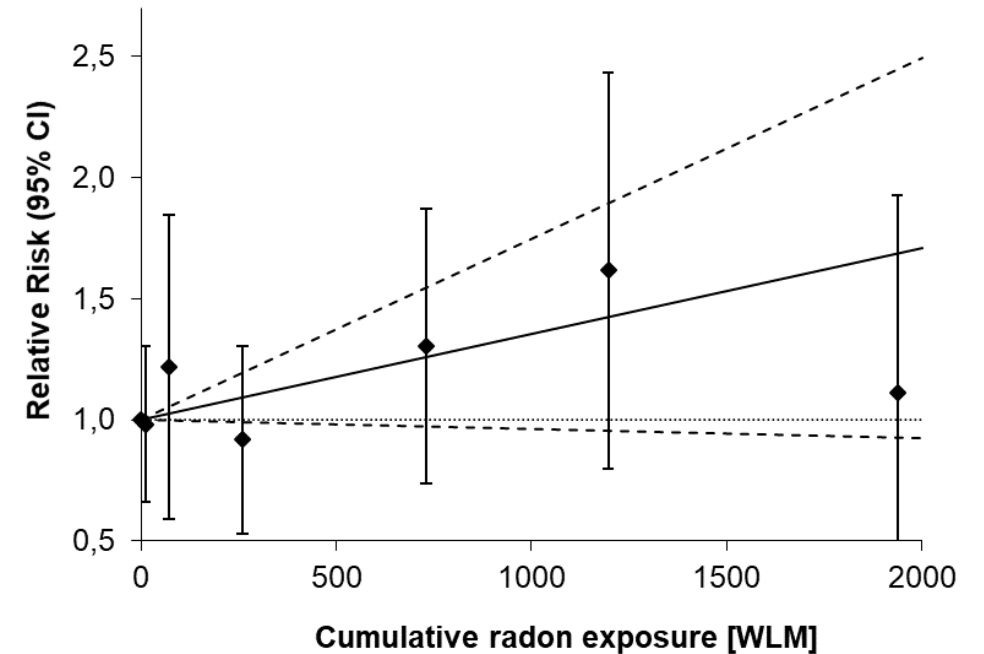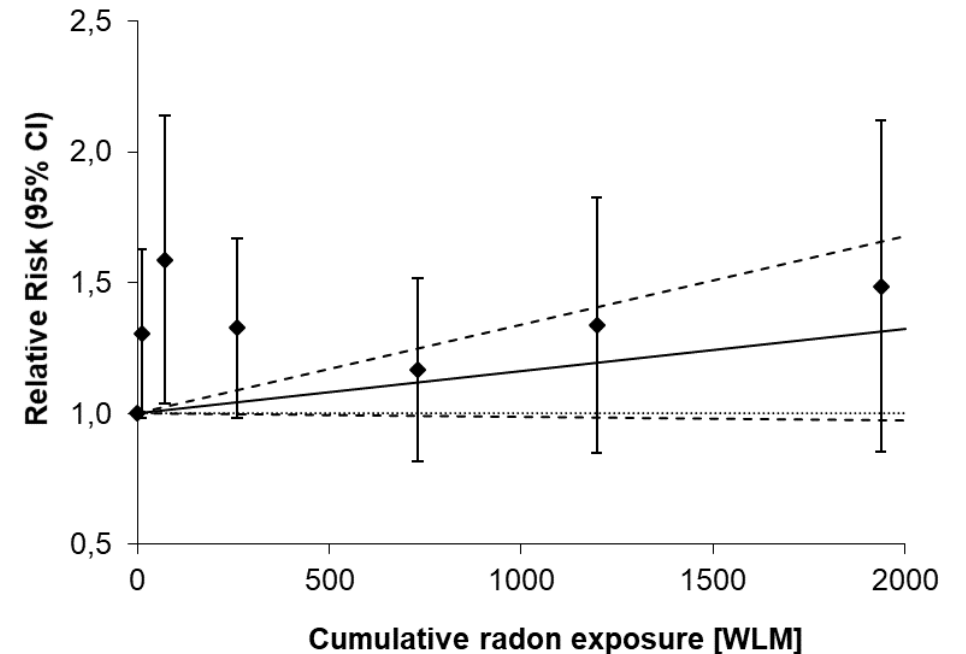
Stomach cancer

Wismut cohort with end of follow-up 2013 (*work in progress*)

— SMR: Consistently elevated SMRs in many uranium miner studies and PUMA
[*Tomasek 1993, Darby et al. 1995, Kreuzer et al. 2008; 2020, Schubauer-Berigan et al. 2009; Lane et al. 2018, Kelly-Reif et al. 2019; Rage et al. 2018, Richardson et al. 2020*]

— **Wismut: n = 795 deaths**

ERR/WLM = 0.016; 95% CI: -0.001; 0.034 no linearity!

Leukemia and its subtypes

Wismut cohort with end of follow-up 2013 (*work in progress*)

- SMR: few studies show increased SMRs, e.g. *Rericha et al. 2006*; *Kelly-Reif et al. 2019*

- Wismut: n = 203 deaths, elevated excess for myeloic leukemia $\Rightarrow$ chance?

	ICD 10	# deaths	ERR/WLM	95% CI
All	C91-C95 excl. C91.4	203	**0.004**	-0.029; 0.036
CLL	C91.1	70	**-0.016**	-0.057; 0.026
Non-CLL	C91-C95 excl. C91.1, C91.4	133	**0.021**	-0.027; 0.070
ML	C92	102	**0.059**	-0.015; 0.133

CLL: chronic lymphatic leukemia, ML: Myeloic leukemia

Circulatory diseases

Major studies		All (I00-I99)	Cerebrovascular (I60-I69)	Ischemic heart diseases (I20-I25)
Eldorado cohort *Lane et al. 2010*	Deaths ERR/100 WLM 95% CI	**n.a.**	**244** **-0.04** **n.a.**	**1,235** **-0.01** **n.a.**
French cohort *Rage et al. 2018* *Drubay et al. 2015*	Deaths ERR/100 WLM 95% CI	**446** **0.10** **[-0.04; 0.29]**	**105** **0.42** **[0.04; 1.04]**	**169** **0.09** **[n.a.; 0.39]**
Wismut cohort* FU 2008; *Kreuzer et al. 2013*	Deaths ERR/100 WLM 95% CI	**9,039** **0.002** **[-0.003; 0.006]**	**2,073** **0.000** **[-0.008; 0.009]**	**4,613** **0.006** **[-0.001; 0.012]**
Wismut cohort* FU 2013, work in progress	Deaths ERR/100 WLM 95% CI	**10,721** **0.002** **[-0.003; 0.006]**	**2,367** **-0.003** **[-0.011; 0.005]**	**5,445** **0.007** **[0.001; 0.013]**

* includes 4,000 millers which are excluded in PUMA

Non-malignant respiratory diseases

Major studies	ICD 10	All without silicosis (J00-J99 excl. J62,64,65)	COPD (J40-J44)
Wismut cohort* *Kreuzer et al. 2013*	**Deaths ERR/100 WLM 95% CI**	**1,261** **0.005** **n.s.**	**715** **0.007** **n.s.**
Wismut cohort* FU 2013, work in progress	**Deaths ERR/100 WLM 95% CI**	**1,683** **0.001** **[-0.009; 0.012]**	**903** **-0.004** **[-0.017; 0.010]**

* includes 4,000 millers which are excluded in PUMA
COPD: Chronic obstructive pulmonary disease

Summary – Wismut findings

Group of non-lung cancers

— Significant exposure-response relationship

— Excess risk is low, particularly compared to lung cancer

  (1.2% vs. 19% per 100 WLM)

— No material risk below 1,000 WLM

Individual cancer sites

— Majority of ERR coefficients are positive (15 out of 19)

— Largest ERR coefficients estimated for pharynx, liver, …

Other diseases than cancer

—Little evidence for excess risk

Discussion

Potential limitations

— Confounding: No adjustment for e.g. alcohol, smoking, other risk factors

— Chance findings, particularly for individual cancer sites

— Bias due to uncertainty in exposure assessment, particularly in early years

— Validity of causes of deaths

— Lack of data on cancer incidence

Comparison with other studies

— Other studies: Few and inconsistent results → wait for PUMA

Relevance, if an excess would be present

— Compensation claims of former and current workers

— Radon dose conversion factor, regulation at homes and at work