Academies' Gilbert W. Beebe Symposium 2016

Late Health Effects in Cleanup Workers Following the Chornobyl Accident

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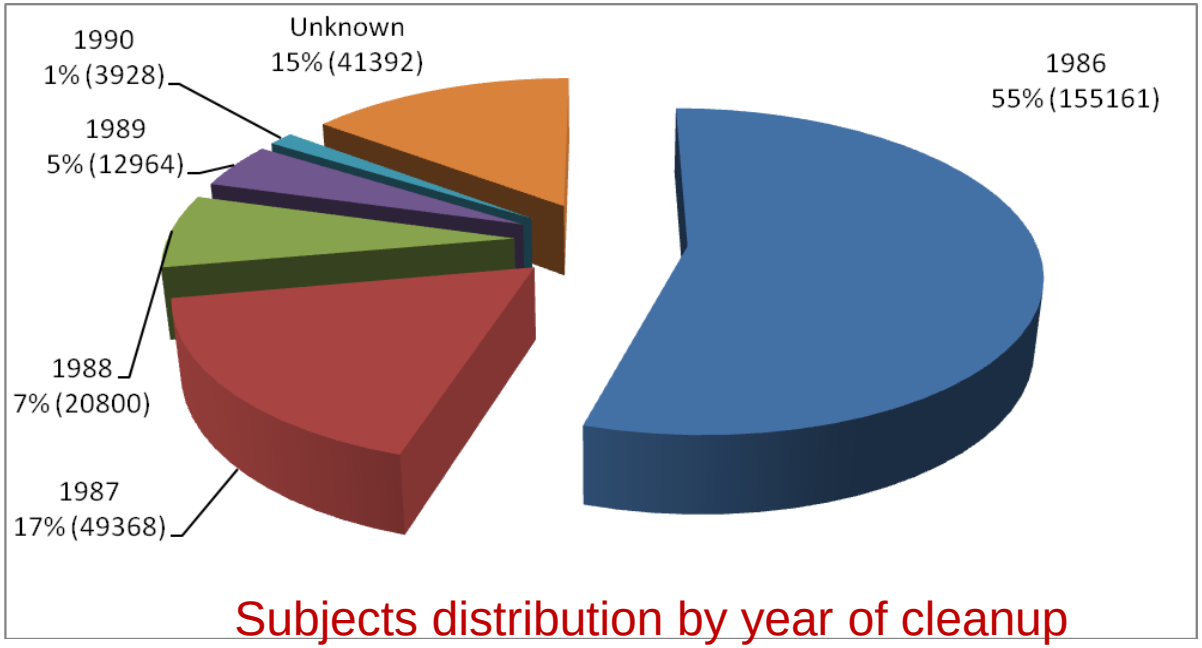
Ukrainian Clean-up Workers Cohort

Category	Number
Registered cleanup workers	308,694
From them: cleanup workers of 1986/87	207,436
From them: Deterministic effects: ARS (800 - 8,000 mSv)	134



Subjects distribution by year of cleanup

Health of the exposed population 20 years after the Chornobyl accident, Volume I. 2007. Kyiv, Ministry of Health Care of Ukraine, 177p

National system of registration of radiation effects – a source for scientific analysis

- State Chornobyl registry of radiation exposed
  - **Covers all territory of Ukraine**
  - **2,251,584 exposed including 305,639 cleanup workers**
  - **Annual health information for 1988 - 2015**
- National Cancer registry (since 1996)
  - **Covers all territory of Ukraine & used for linkage with the Chornobyl registry**
- Local registries of exposed professionally
  - NPPs, nuclear industry,
  - Research Center for Radiation Medicine (Clinical and Epidemiological registry) **– used for the State Chornobyl registry validation**

Late health effects

- Effects after high dose exposure in Acute radiation syndrome (ARS) survivors
- Cancer effects after low-dose exposure in cleanup workers:
  - Leukemia
  - Multiple myeloma
  - Thyroid cancer
  - Breast cancer
  - Other solid cancers
- Non-cancer diseases
  - Cardio- and cerebrovascular (incidence, mortality),
  - Cognitive deficit
  - Radiation cataracts

Studies of Chornobyl NPP staff and first responders: RCRM performs follow-up of survivors since 1986

Total number of diagnosed with ARS – 237 (1986). In 1989 after re-evaluation diagnosis of ARS 1-3 was confirmed in **134**; not confirmed in **103** (ARS-NC). From them the RCRM performs a long-term follow-up of both groups: **(ARS1-3 – 91; ARS-NC – 99**).

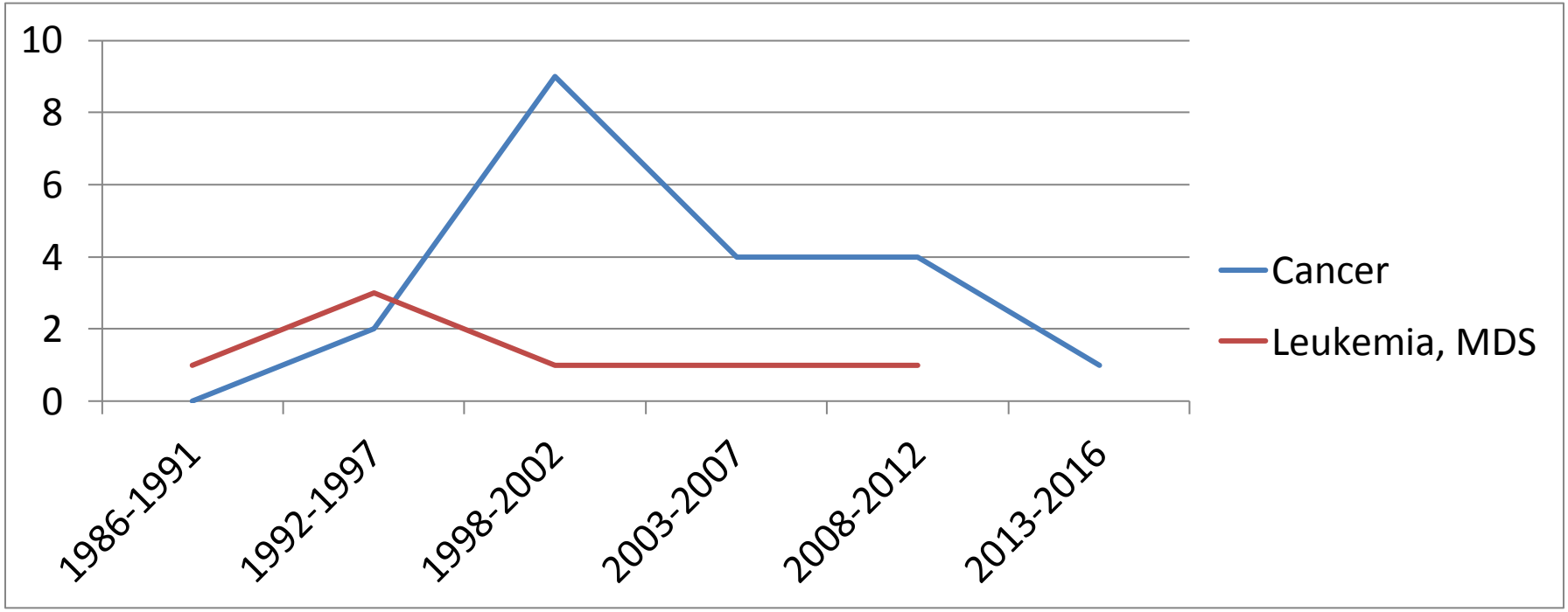
Age-gender and dosimetric characteristics of ARS survivors and ARS NC patients

Indices	ARS NC	ARS grade 1	ARS grade 2	ARS grade 3	ARS grade 1–3
Gender: f / m	10/89	2/36	1/40	0/12	3/88
Age at irradiation, years					
M ± SD[a]	35.9 ± 10.3	33.2 ± 8.2	38.5 ± 13.9	40.9 ± 16.5	36.6 ± 12.5
min – max	18.4–60.3	17.6–56.3	17.9–79.3	20.4–72.6	17.6–79.3
95% CI[b]	33.8–38.2	30.5–35.8	34.1–42.9	30.4–51.3	34.0–39.2
Absorbed radiation dose, Gy	n[c] = 15	n = 30	n = 37	n = 11	n = 78
M ± SD	0.4 ± 0.3	1.0 ± 0.6	2.4 ± 0.9	4.5 ± 1.4	2.2 ± 1.5
min – max	0.1–1.0	0.1–3.3	0.5–4.9	2.9–7.1	0.1–7.1
95% CI	0.2–0.5	0.8–1.3	2.1–2.7	3.6–5.5	1.9–2.5

Notes. [a] – mean ± standard deviation; [b] – confidence interval; [c] – number of patients for whom the adsorbed radiation dose was determined.

IAEA Director-General Mr. H.Blix with ARS survivors and RCRM staff (1988)

Distribution of cancer, leukemia and CVD cases in first responders with ARS by year of diagnosis

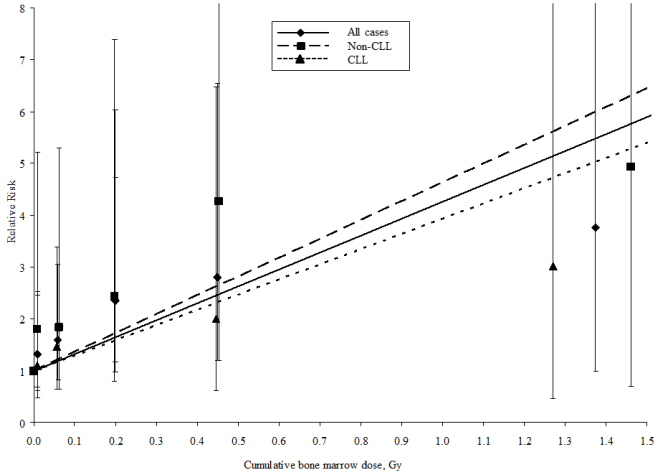


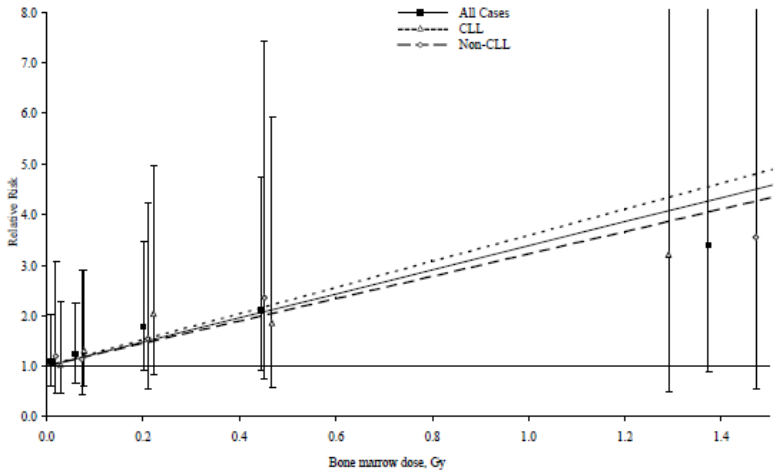
Radiogenic effects were the main causes of late deaths **(52; ARS1-3 -30; ARS-NC-22):**

Cancers and leukemia – **18;** Cardiovascular – **20;**
Other other somatic and neurological diseases **– 7**
(including tuberculosis **- 3**); trauma & accidents – **7**

Leukemia: the RCRM-NCI case-control study among Chornobyl cleanup workers from Ukraine

Cohort - 110,645 male cleanup workers from 6 regions of Ukraine
160 confirmed cases. Case control = 1:5
RADRUE doses in 137 cases
Mean bone marrow radiation doses:
- Cases -132.3 mGy (SD 342.6)
- Controls - 81.8 mGy (SD 193.7)





First **15 years**: ERR/Gy is **3,44** (95% CI 0,47; 9,78; p<0,01)

Romanenko A., et al., Rad.Res., (2008)

20 years: ERR/Gy is **2,38** (95% CI 0,49; 5,87; p<0,004)

Zablotska et al., EHP (2013)

NCI-RCRM joint study: International Leukemia hematological review headed by Dr. S. Finch

RCRM-NCI data on leukemia risks (ERR/Gy) in clean-up workers in comparison with other studies

Cohort	Period	Excess Relative Risk (ERR / Gy)	95% CI
Chornobyl clean-up workers, Ukraine, 1986-2000 (A.Romanenko, et al., 2008)	1986-2000	3,44	0,47 - 9,78; p<0.01
1986-2006 (L. Zablotska, et al., 2013)	1986-2006	2,38	0,49 –5,87; p<0.04
Chornobyl clean-up workers, Russia 1986 - 1997 (V.Ivanov, et al., 2012)	1986-1997	4,98**	0,59 – 14,47#
	1998-2007	-1,64**	-2,55 – 0,57#
Life Span Study cohort, Japan (W.L.Hsu, et al., 2013)	1950-2001	4,7**	3,3 – 6,5
Chornobyl clean-up workers, Russia, Belarus, Baltic countries (A.Kesmniene, 2008)	1990-2000	5.0**	-3.8 – 57#

** excluding chronic lymphocytic leukemia (CLL); # 90% confident interval

Risks by type of leukemia

Doses	Case number	Mean dose, mGy
1986-2000	72	150
CLL	40	114
not CLL	32	195
2001-2006	65	121
CLL	39	102
not CLL	26	144

Effects:	ERR/Gy (95% CI)
1986-2000	
CLL	2.58 (0.02, 8.43)
not CLL	2.21 (0.05, 7.61)

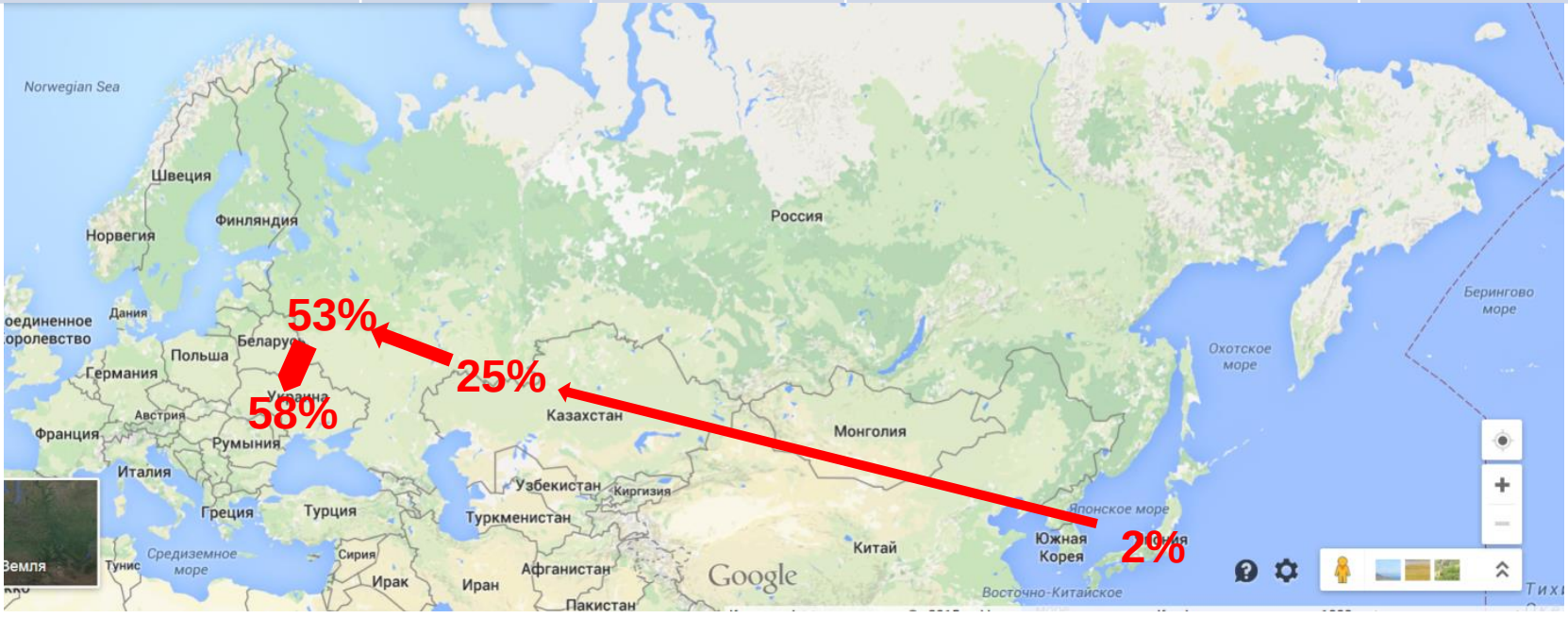
- The higher is dose, the earlier non-CLL leukemia is induced
- CLL seems to be induced at lower doses

Standardized CLL incidence ratio in the Cohort of male clean-up workers in 1987 - 2012

Study Period	Person-years	Cases number		Crude rate per 105	SIR (95 % CI)
		observed	expected		
1987-1996	543,289.5	30,0	8.3	5.52	**3.61 (2.32;4.91)**
1997-2006	907,385.6	59.0	42.7	6.50	**1.38 (1.03;1.73)**
Subtotal, 1987-2006	1,450,675	89.0	51.0	6,13	**1.75 (1.38;2.11)**
2007-2012	610,552.6	57.0	50.24	9,34	**1.13 (0.84;1.43)**
Total, 1987-2012	2,061,227.6	146.0	101.24	7,08	**1.44 (1.21;1.68)**

CLL rates in other cohorts

Cohort (number of subjects)	A-bomb Survivors (87,000; 50 yrs)	Techa (30,000; 52 yrs)	Belarus, Russia & Baltic	Ukraine (110.640; 20 yrs}	15-country (400,000; 7 yrs)
Number of CLL cases (%)	6 (2%)	23 (25%)	21 (53%)	79 (58 %)	47 (17%)
Average cumulative recorded dose, mGy	300	300	-	91.3	9.4
Reference	Preston et al. 2004	Krestinina et al. 2010	Kesminiene et al. 2008	Zablotska et al. 2013	Cardis et al. 2007



Cancer studies

Several studies are performed in an updated cohort of 152,520 male cleanup workers 22–26 years after exposure:

- a significant excess was registered by descriptive studies in incidence of:
  - multiple myeloma (SIR 1.61, 95% CI 1.01; 2.21) and
  - thyroid cancer(TC) (SIR 3.50, 95% CI 3.04; 4.03).
- Cases were identified by linkage of Chornobyl Registry with the National Cancer Registry of Ukraine

Case-control

- The RCRM-NCI case-control study based on 150 cases, 458 controls and updated ROCKVILLE reconstructive dosimetry is ongoing to confirm radiation risks in male adults

Thyroid cancer in exposed as adults: Chornobyl cleanup workers

Based on individual case data from the RCRM- U.S. NCI case-control study

Thyroid cancers, person-years and SIRs by year of mission in the Chernobyl zone

Year of mission	Mean age at exposure, yrs	Person-years	Thyroid cancer number		Crude rate per 10^5	SIR, 95%CI
			Observed	Expected		
1986	33.5	1233836	135	35.0	10.94	3.86 3.26 – 4.57
1987	32.4	365599	28	9.6	7.66	2.91 2.01 – 4.21
1988+	35.0	288844	15	8.1	5.19	1.84 1.11 – 3.06
Unknown	*unknown*	*95217*	18	*3.3*	18.90	*5.48* *3.45 – 8.69*
Total	**33.5**	**1983496**	**196**	**56.0**	**9.88**	3.50 3.04 – 4.03

RCRM-NCI study: Ostroumova et al., Eur J Epidemiol. 2014.

Standardized MM incidence ratios in the Cohort of male cleanup workers in 1996 – 2013

Time period	Person-years	Number of cases		Crude rate/ 10^5	SIR/ 10^5 (95% CI)
		Observed	Expected		
1996-2001	823,198	13	13.2	1.58	0.98 (0.45; 1.52)
2002-2007	707,428	17	15.7	2.4	1.08 (0.57; 1.60)
2008-2013	593,309	39	21.0	6.6	1.86 (1.27; 2.44)
1996-2013	2,123,324	69	49.9	3.24	1.38 (1.06; 1.71)
Age at diagnosis					
< 50	983,091	10	9.7	1.02	1.03 (0.39; 1.67)
>= 50	1,140,843	59	37.9	5.17	1.56 (1.16; 1.95)

Updated Cohort: 152,520 cleanup workers.
0-year lag period for analysis
RADRUE doses are reconstructed (now -36 cases).
RBM dose due to external irradiation is in the range of 0.12–2920 mGy

In press, 2016

Comparison of thyroid cancer (C73) incidence studies

Cohort	Time period	Risks
	ERR	
A-bomb survivors (Preston et al., 2007)	1958 - 1998	ERR/Gy = **0.47 (90% CI 0.24 – 1.10)**
Cleanup workers, case/control (107/423) (Kesminieme et al., 2012)	Russia: 1993–1998; Belarus: 1993–2000; Baltic: 1990–2000.	**ERR per 100mGy = 0.38** (95% CI 0.10 – 1.09)
	SIR	
Cleanup workers of 86/87; Cohort: 95.0 thousand (Prysyazhnyuk et al., 2014)	1994-2011	SIR = 4,77 (95% CI 4,27 – 5,Cl27)
Cleanup workers; Cohort: 150,813; (E Ostroumova, 2014).	1986-2010	SIR = 4,26 (3.73 – 4.79)

Cancer incidence rates in Chornobyl recovery operation workers of 1986-1987 (follow-up period 1994-2013).

Site of tumors (ICD10 codes)	Actual No of cases	Expected No of cases	Standardized incidence ratio SIR, %, (95% CI)
All cancers (C00-C96)	**11,116**	**10,373.1**	**107.5 (105.4 – 109.6)**
Thyroid cancer (C73)	**374**	**86.6**	**431.9 (388.1 – 475.6)**
Female breast cancer (C50)	**336**	**212.8**	**157.8 (141.0 – 174.7)**
Leukemia and lymphoma (C81-C96)	**687**	**474.0**	**144.9 (131.1 – 155.8)**

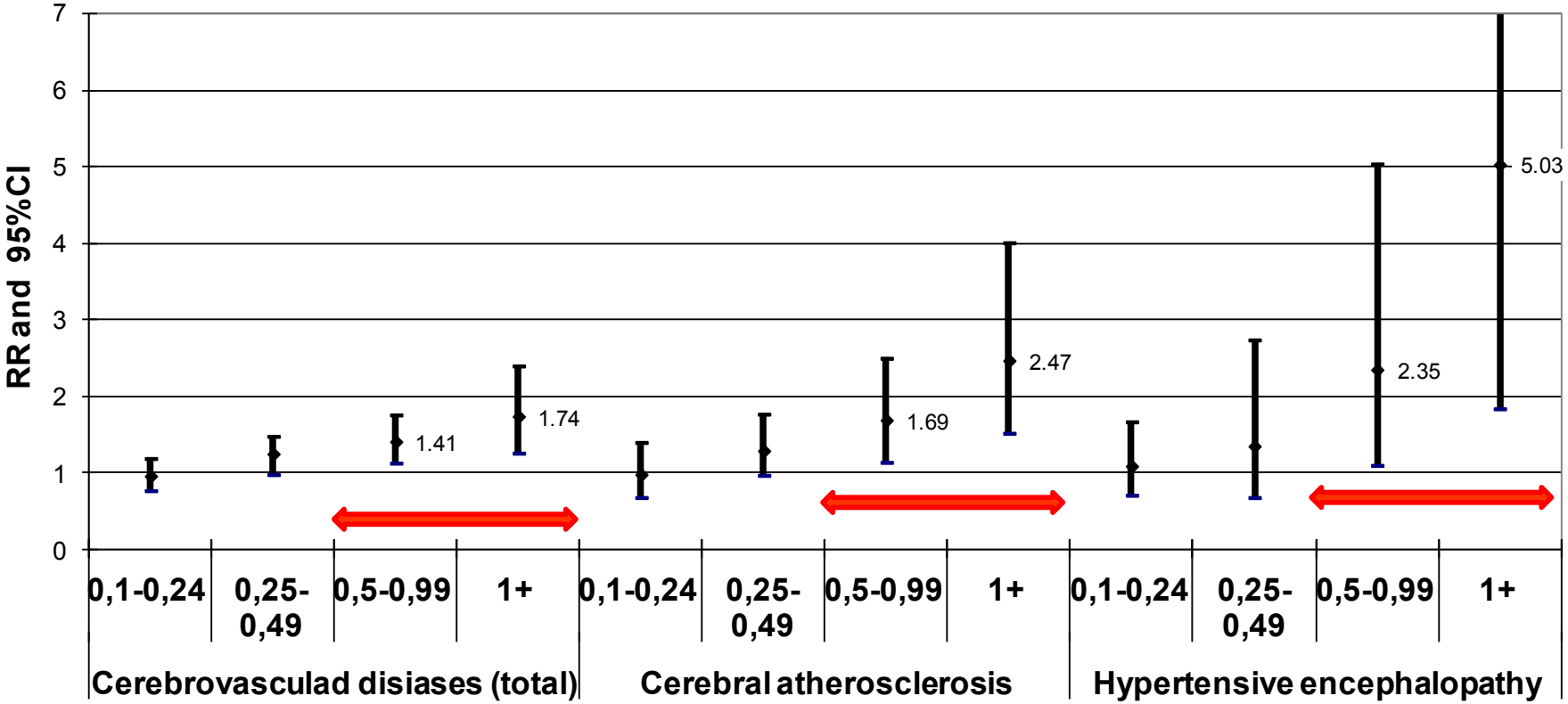
Comparison of cancer studies in the Chornobyl cleanup workers

Study group, reference	Time period	The results
ALL cancers (ICD10: C00-C80)		
Ukrainian cleanup workers of 1986-1987 [Prysyazhnyuk, 2007, 2016]	1994-2012	SIR 107.5 (95% CI:105.4 – 109.6)
A-bomb survivors (Preston et al., 2007)	1959-1998	ERR/Gy: 0.47 (90% CI: 0.40-0.54)
Female breast cancer (C50)		
Ukrainian cleanup workers of 1986-1987 [Prysyazhnyuk, 2007, 2016].	1994-2012.	SIR 1.57 (95% CI 1.47 – 1.75)
Russian cleanup workers [AR Islamova, 2004]		SIR 1.84 (95% CI 1.23 – 2.45)
A-bomb survivors (Preston et al., 2007)	1959-1998	**ERR/Gy 0.87** (90% CI: 0.55– 1.30)

Non-cancer effects

- Late non-cancer effects other than radiation cataracts are disputable
- 8-country meta-analysis demonstrated increase of cardiovascular mortality in cleanup workers (Little et al., 2013)
- Previous data have shown effects after exposure to doses over 500 mGy
- New approaches demonstrate effects at low dose range:
  - Coronary heart disease at 150+ mGy:
  - Cognitive deficit at 100+ mGy (EU CEREBRAD study, 2015)
- Additional studies are in need

Cerebrovascular disease relative risks in cleanup workers of 1986-87 subjects of the Clinical-Epidemiological Registry of the RCRM



RCRM: L.Krasnikova, V.Buzunov, 2008

Excess relative and excess absolute radiation risks of coronary heart disease in Chornobyl cleanup workers of 1986–1987 (cases of cerebrovascular disease excluded from the analysis)

Significant excess is demonstrated at doses over 150 mGy

Доза, Гр / Dose, Gy < 0,05 (контроль/control)	Когорта в цілому Cohort as a whole		Опромінені у віці до 40 років Exposed at the age under 40					
	RRY (95 % CI)	p ≤	ARY#	ATRY#	RRY (95 % CI)	p ≤	ERR $Гр^{-1}$ / Gy^{-1}	EAR##
0,05-0,09	1,1 (0,5; 2,2) *1,2 (0,8; 1,8)*		18,3	4,5	1,3 (0,5; 3,9)		4,7	
0,1-0,14	1,02 (0,8; 1,2) *1,4 (0,8; 2,2)*		18,3	4,5	1,3 (0,7; 2,5)		2,7 (0,3; 25,5)	
0,15-0,25	1,1 (0,8; 1,4) *1,5 (1,03; 2,2)**	*0,05**	26,3	12,5	1,9 (1,2; 3,1)	0,05	4,6 (1,5; 14,9)	64,2
0,25-0,99	1,6 (0,9; 1,6) *1,34 (1,0; 1,8)*	*0,05**	24,8	11,0	1,8 (1,1; 2,9)	0,05	1,8 (1,1; 3,0)	25,3
1+	1,8 (1,1; 3,0) *2,1 (1,2; 3,8)*	0,05 *0,05**	44,4	30,6	3,2 (1,3; 7,8)	0,05	1,4 (1,1; 1,9)	19,8

Примітка, # – на 1000 люд.-років
– на 1000 люд-років, $Гр^{-1}$

Note, # – per 1000 PY
– per 1000 PY, Gy^{-1}

RCRM: 2013

Cognitive function studies of cleanup workers in CEREBRAD project (Loganovsky et al., 2015)

Changes registered by the general psychoneurological (BPRS, EDSS), self-estimation (SDS, GHQ-28) and psychometric tests (Wechsler) were significant **at doses over 100 mSv**

GHQ-28 total scores by group (general health)

Groups	M	±SD
1. Cleanup workers, <20 mSv (n-38) (internal control)	24,18	15,27
2. Cleanup workers, 20-100 mSv (n-65)	25,46	12,06
3 Cleanup workers, 100- 250 mSv (n-83)	32,72*	16,84
4. Cleanup workers, 250-500 mSv (n-53)	30,45 *	13,16
5. Cleanup workers, >500 mSv (n-28)	36,00*	15,22

* - p<0,05 compared with internal control group

Biomarkers of exposure and of late effects at doses below 500 mSv studied at the RCRM

Type of biomarker	Range of use
Cytogenetics – DCA, FISH	Official doses testing
TCR variant cells	At late period an increase in workers exposed over 2 Gy
Telomere length (RTL)	Biomarker at low-dose and low dose rates Late period – marker of dose and CVD/cognitive function
Gamma-H2AX	Early period – up to 14 days Late period – increase in doses over 500 mSv
Gene expression	Early period – TRF1, TRF2 Late period – CCND1

24

Future direction of the studies in cleanup workers

- Expected effects for the next period include:
  - increased rates of thyroid, breast and lung cancers; multiple myeloma,
  - reduction of radiation risks of leukemia to population levels,
  - increased morbidity and mortality of cleanup workers from non-cancer diseases, in the first place – cardio- and cerebrovascular pathology and related cognitive dysfunction.
- Analytical cohort and case-control studies are in need using molecular epidemiology approach:
  - circulation pathology,
  - late high dose effects,
  - specific types of radiogenic cancers,
  - second cancers after leukemia

Acknowledgements

RCRM:
Romanenko A.
Prysyazhniuk A.
Klimenko V.
Gudzenko N.
Chumak V.
Sushko V.,
Likhtarev I.,
Bebeshko V.,
Lyashenko L.
Shvayko L.
Loganovsky K.
Pilinska M.
Dibsky S.
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Chumak A.
Dyagil I.
Belyi D.
Buzunov V.
Krasnikova L.
US NCI:
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