Cancer risks associated with protracted versus acute exposures to ionizing radiation: results from INWORKS and the Life Span Study

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Context & aim

- The findings from the Life Span Study (LSS) constitute a major basis for the assessment of radiation detriment in the current system of radiation protection
    - ICRP

- However, the members of the LSS were exposed to ionizing radiation (IR) in the form of photons and neutrons at a high dose rate, whereas contemporary occupational and environmental exposure situations often involve protracted exposures to IR at relatively low dose rates

- The appropriate use of results from acute exposure settings for elaborating radiation protection guidelines in settings of protracted low dose-rate exposures remains an open issue

Context & aim

- Recently, an international study of nuclear workers, INWORKS, provided direct estimates of associations between low dose rate external radiation exposure (primary gamma radiation and x-rays) and mortality from leukemia and solid cancer

- Aim: to compare cancer risk estimates (ERR, EAR) derived under two different settings of exposures to IR
  - acute exposures to A-bomb radiation: the LSS
  - protracted low-dose exposures at work: INWORKS

Methods

- LSS
  - publicly-available tabulation of persons, person-time, and deaths due to solid cancers and leukemia provided by the RERF (Ozasa et al. 2012)
  - 86,611 survivors, follow-up 1950-2003
  - weighted photon and neutron doses to the colon and bone marrow in gray (Gy): DS02

- INWORKS
  - pooled cohort of nuclear workers from USA, UK, France: 308,297 adults
  - monitored for external radiation: personal dosimeters
  - recorded doses converted to colon absorbed doses in Gy: photon

- Restrictions were made so that the two study populations are similar with respect to ages and periods of exposure
  - exposed in 1945 and after
  - age at exposure: 20-59 years
  - born after 1885

Methods

- Outcome: solid cancer and leukemia
- Poisson regression
  - Cross-classification of person-years at risk, events, and mean dose by city/country, sex, age, year of birth, calendar time, colon dose categories
- $\lambda_0(c,s,b,a)[1 + ERR(d,s,a)]$
- $\lambda_0(c,s,b,a) + EAR(d,s,a)$
- Linear and linear-quadratic radiation dose-response functions
- Analyses on restricted dose ranges
- Reported risk estimates are sex-averaged for the LSS (12% for women)

Results

Characteristics of the LSS and INWORKS subsets used for comparison

	Life Span Study N = 45,625	INWORKS N = 259,350
Period of follow-up	1950-2003	1950-2005
Period exposure	1945	1945-2005
Percentage of males	36%	88%
Age at exposure[a] (years), mean [range]	37.3 [20.1; 59.9]	37.7 [19.4; 71.5]
Attained age (years) , mean [range]	65.9 [27.6; 112.1]	60.0 [25.5; 112.3]
Colon dose[b] (mGy), mean [range]	115.7 [0.0; 2,905.2]	19.2 [0.0; 1,237.1]
Red bone marrow dose[b] (mGy), mean [range]	134.3 [0.0; 3,630.0]	17.6 [0.0; 1,131.5]
Person-years (millions)	1.48	6.18
Causes of deaths		
All causes, *n* (%)	37,943 (83.2%)	59,118 (22.8%)
Solid cancer, *n* (% of total deaths)	7,982 (21.0%)	16,279 (27.5%)
Leukemia,[c] *n* (% of total deaths)	196 (0.5%)	464 (0.8%)

[a] age at atomic bombings in the LSS; age at mid-period of radiation monitoring in INWORKS, [b] cumulative dose in INWORKS, [c] excluding chronic lymphocytic leukemia in INWORKS.

Results

		Life Span Study			INWORKS		
		Coefficient	90% CI	P_{1df}	Coefficient	90% CI	P_{1df}
ERR model (per Gy)							
$ERR(d)=\beta_1 d$	β_1: linear	0.28	0.18; 0.38		0.29	0.07; 0.53	
$ERR(d)=\beta_1 d+\beta_2 d^2$	β_1: linear	0.23	0.10; 0.40	0.548	0.27	-0.14; 0.68	0.909
	β_2: quadratic	0.03	-0.05; 0.10		0.06	-0.78; 1.04	
$ERR(d,a)=\beta_1 d \exp(\upsilon a)$				0.147			0.307
ERR/Gy at attained age <60 years		0.35	0.19; 0.57		0.35	-0.26; 1.04	
ERR/Gy at attained age 60-<80 years		0.31	0.20; 0.43		0.19	-0.05; 0.46	
ERR/Gy at attained age 80+ years		0.16	0.06; 0.29		0.86	0.20; 1.61	
EAR model (per 10,000 person-years, per Gy)							
$EAR(d)=\beta_1 d$	β_1: linear	8.03	3.74; 13.07		1.68	<0; 7.55	
$EAR(d,a)=\beta_1 d \exp(\upsilon a)$				<0.001			0.029
EAR/Gy at attained age <60 years		5.84	3.07; 9.50		0.42	<0; 6.10	
EAR/Gy at attained age 60-<80 years		20.79	11.56; 31.55		13.86	-4.34; 33.16	
EAR/Gy at attained age 80+ years		33.27	13.85; 60.23		190.40	58.67; 334.9	

Leukemia

Results

		Life Span Study			INWORKS		
		Coefficient	90% CI	P_{1df}	Coefficient	90% CI	P_{1df}
ERR model (per Gy)							
$ERR(d)=\beta_1 d$	β_1: linear	2.75	1.73; 4.21		3.15	1.12; 5.72	
$ERR(d)=\beta_1 d+\beta_2 d^2$	β_1: linear	0.10	-1.03; 1.49	<0.001	-	-	
	β_2: quadratic	1.61	0.81; 2.68		-	-	
$ERR(d,a)=\beta_1 d \exp(\upsilon a)$				0.111			0.472
ERR/Gy at attained age <60 years		4.57	2.41; 8.45		-0.04	<0; 5.21	
ERR/Gy at attained age 60-<80 years		2.48	1.32; 4.29		3.71	1.15; 7.15	
ERR/Gy at attained age 80+ years		1.21	0.25; 3.15		5.07	-0.19; 15.07	
EAR model (per 10,000 person-years, per Gy)							
$EAR(d)=\beta_1 d$	β_1: linear	3.54	2.30; 5.05		2.03	0.36; 4.07	
$EAR(d,a)=\beta_1 d \exp(\upsilon a)$				0.564			0.104
EAR/Gy at attained age <60 years		2.98	1.74; 4.67		1.11	<0; 3.18	
EAR/Gy at attained age 60-<80 years		4.15	2.46; 6.37		4.80	1.12; 9.23	
EAR/Gy at attained age 80+ years		4.53	1.28; 10.00		27.01	1.80; 63.22	

Solid cancer

Results

	Colon dose ranges (mGy)					
	0–100	0–200	0–300	0–500	0–1,000	Whole
Life Span Study						
Mean colon dose	14.2	25.2	34.4	50.2	77.0	115.7
Person-years	1,158,870	1,266,440	1,320,560	1,382,440	1,442,100	1,480,340
Observed deaths	6,069	6,664	6,973	7,315	7,686	7,982
ERR/Gy	0.38	0.50	0.45	0.25	0.24	0.28
90% CI	-0.27; 1.07	0.17; 0.86	0.21; 0.70	0.11; 0.41	0.15; 0.34	0.18; 0.38
P (*vs*. null model)	0.343	0.011	0.001	0.004	<0.001	<0.001
INWORKS						
Mean colon dose	9.4	12.8	14.5	15.9	16.3	16.4
Person-years	5,943,550	6,104,410	6,150,100	6,173,470	6,178,150	6,178,320
Observed deaths	15,094	15,832	16,079	16,235	16,278	16,279
ERR/Gy	0.49	0.63	0.32	0.26	0.31	0.29
90% CI	-0.21; 1.23	0.21; 1.07	0.01; 0.65	0.01; 0.52	0.09; 0.54	0.07; 0.53
P (*vs*. null model)	0.253	0.012	0.092	0.091	0.021	0.026

Discussion

- A set of parallel analyses of cancer mortality for A-bomb survivors included in the LSS and nuclear workers included in INWORKS were conducted, focusing on a comparison of the coherence of results in the two populations

- For solid cancer mortality,
  - the magnitude of the estimated ERR/Gy was similar in the two populations
  - absence of support for a linear-quadratic radiation dose-response function
  - no evidence for a reduction of risk at low doses
  - EAR estimates quite different between the two cohorts: depend on attained age
    - questions the use of relative risk transport

- For leukemia,
  - the magnitude of the estimated ERR/Gy was similar in the two populations
  - upward curvature in the DR function in the LSS
  - EAR higher in the LSS

Discussion

- Further attention to neutron dose estimation and internal contamination in nuclear worker cohorts remains an important goal

- Nuclear worker studies provide a useful complement to the LSS
  - in the LSS, few men exposed to IR at typical working ages: challenging when using the LSS data to elaborate radiation protection for occupational exposures
  - acute/protracted low dose exposures

- Nuclear worker studies help improving our understanding of radiation risks at low doses and offers insights into the transport of radiation risk estimates between populations

- This work illustrate the potential benefit of examining different study populations as sources of information for risk estimates used in radiation protection