Low Dose/Low Dose Rate Environmental Exposures Studies

Beebe Symposium on the Future of Low-Dose Radiation Research in the United States

National Academies
May 8, 2019

Dale L. Preston
Hirosoft International

Overview

- Introductory remarks
- Studies of environmentally-exposed populations (a fly-over view)
- Issues in the design, analysis, and interpretation of studies of radiation health effects in (environmentally) exposed populations

Nuclear Power Plant Accidents

Study	Type	Cancer	Cases	Cohort size /Controls	Mean/Median Dose (mGy)	ERR @ 100mGy	95% CI
Three Mile Island	Cohort	Solid Inc	1,643	21,494	0	-1	(-1; 30)
Chornobyl-Ukraine	Cohort	Thyroid	65	12,415	650/200	0.19	(0.04; 0.63)
	Case-Control	Thyroid	66	835	cases 44 controls 16	4.9	(0.5; 12)
Chornobyl-Belarus	Cohort	Thyroid	23	12,504	770	0.21	(0.03; 1.0)
	Cohort (prevalence)	Thyroid	87	11,970	560/230	0.21	(0.08; 0.54)
Chernobyl Bel,Ukr, Rus	Case-Control	Leukemia	421	824	11/0.9 (cases) 4/0.7 (controls)	3.2	(0.9; 8.4)

Weapons Production and Testing

Study	Type	Cancer	Cases	Cohort size /Controls	Mean/Median Dose (mGy)	ERR @ 100mGy	95% CI
Techa River	Cohort	Solid Inc	1,933	17,435	52/15	0.08	(0.01; 0.15)
	Cohort	Solid Mort	2,303	29,730	35	0.06	(0.004; 0.13)
	Cohort	Leukemia	72	28,233	250/410	0.22	(0.08; 0.54)
Hanford I131	Cohort (prevalence)	Thyroid	19	3,191	174/97	0.07	(-0.03; 0.6)
Utah Fallout	Case-Control	Leukemia	939	4,302	2.9 cases 2.7 controls	4.5	(-0.4; 14)

Natural and Unnatural Background Radiation

Study	Type	Cancer	Cases	Cohort size /Controls	Mean/Median Dose (mGy)	ERR @ 100mGy	95% CI
UK	Case-Control	Leukemia	27,447	36,793		12	(3; 22)
Yiangjing, China	Cohort	Solid	941	31,604	85 High 22 Low	-0.1	(-0.25; 0.3)
Switerzland	Cohort	Cancer	1,782	2,093,660	9	3	(1; 5)
	Cohort	Leukemia	530			4	(0; 8)
	Cohort	Lymphoma	328			1	(-4; 5)
Finland	Case-Control	Leukemia	1,093	3,027	1.96 cases 1.90 controls	-1	(-1; 6)
India, Kerala	Cohort	Solid cancer	1,349	69,958	110	-0.01	(-0.06; 0.05)
Taiwan Buildings	Cohort	Cancer	117	6,242	48	0.19	(0.01; 0.31)

Issues – Design

- Power is not the only (or in many cases the primary) consideration
- Seek identifiable populations with different levels of exposure
  - Oversample higher dose groups
  - Consider impact of screening
  - Case-cohort designs should be considered (especially with biospecimens or complex dosimetry)
- Consider dosimetry (and uncertainty) in the design phase
    - Focus on (broadly) shared multiplicative errors
    - Seek to keep study-participant data-provision burden reasonable and practical
- Follow-up
  - Identify sources and methods to determine vital status and migration
  - Linkage to cause of death , cancer diagnosis info

Issues -- Confounding

- Not all risk factors are confounders
- Confounding more likely to impact exposed-unexposed comparisons than dose response analyses
- Vague suggestions of confounding are often baseless
- Ascertainment bias can distort risk estimates
  - Stratification can often (but not always) help deal with this

Issues – Dose Uncertainty

- Dose uncertainty unlikely to induce a spurious dose response
- Good, practical methods to adjust for measurement error exists
  - Should be incorporated into the dosimetry system
  - Tend to increase risk estimates and their standard error to the same extent
- Shared multiplicative error (bias) is the most important source of error
  - Adjustment possible but not trivial
    - Increases width of confidence intervals mainly by increasing the upper bound
  - Shared error has essentially no effect on tests of the null hypothesis

References for Specific Studies (1)

Han YY, Youk AO, Sasser H, Talbott EO. Cancer incidence among residents of the Three Mile Island accident area: 1982-1995. Environ Res. 2011;111(8):1230-5.

Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. Br J Cancer. 2011;104(1):181-7.

Brenner AV, Tronko MD, Hatch M, Bogdanova TI, Oliynik VA, Lubin JH, et al. I-131 dose response for incident thyroid cancers in Ukraine related to the Chornobyl accident. Environ Health Perspect. 2011;119(7):933-9.

Kopecky KJ, Stepanenko V, Rivkind N, Voilleque P, Onstad L, Shakhtarin V, et al. Childhood thyroid cancer, radiation dose from Chernobyl, and dose uncertainties in Bryansk Oblast, Russia: a population-based case-control study. Radiat Res. 2006;166(2):367-74.

Davis FG, Krestinina LY, Preston D, Epifanova S, Degteva M, Akleyev AV. Solid Cancer Incidence in the Techa River Incidence Cohort: 1956-2007. Radiat Res. 2015;184(1):56-65.

Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL. Solid cancer mortality in the Techa River cohort (1950-2007). Radiat Res. 2013;179(2):183-9.

Krestinina LY, Davis FG, Schonfeld S, Preston DL, Degteva M, Epifanova S, et al. Leukaemia incidence in the Techa River Cohort: 1953-2007. Br J Cancer. 2013;109(11):2886-93.

Davis S, Kopecky KJ, Hamilton TE, Onstad L. Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the Hanford nuclear site. JAMA. 2004;292(21):2600-13.

References for Specific Studies (2)

Stevens W, Thomas DC, Lyon JL, Till JE, Kerber RA, Simon SL, et al. Leukemia in Utah and radioactive fallout from the Nevada test site. A case-control study. JAMA. 1990;264(5):585-91. Epub 1990/08/01. PubMed PMID: 2366297.

Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JC, Vincent TJ, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. Leukemia. 2012.

Tao Z, Akiba S, Zha Y, Sun Q, Zou J, Li J, et al. Cancer and non-cancer mortality among Inhabitants in the high background radiation area of Yangjiang, China (1979-1998). Health Phys. 2012;102(2):173-81.

Spycher BD, Lupatsch JE, Zwahlen M, Roosli M, Niggli F, Grotzer MA, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect. 2015;123(6):622-8.

Nikkila A, Erme S, Arvela H, Holmgren O, Raitanen J, Lohi O, et al. Background radiation and childhood leukemia: A nationwide register-based case-control study. Int J Cancer. 2016;139(9):1975-82.

Nair RR, Rajan B, Akiba S, Jayalekshmi P, Nair MK, Gangadharan P, et al. Background radiation and cancer incidence in Kerala, India-Karanagappally cohort study. Health Phys. 2009;96(1):55-66.

Hwang SL, Hwang JS, Yang YT, Hsieh WA, Chang TC, Guo HR, et al. Estimates of relative risks for cancers in a population after prolonged low-dose-rate radiation exposure: a follow-up assessment from 1983 to 2005. Radiat Res. 2008;170(2):143-8.

Dose uncertainty issues and methods

Stram DO, Kopecky KJ. Power and uncertainty analysis of epidemiological studies of radiation-related disease risk in which dose estimates are based on a complex dosimetry system: some observations. Radiat Res. 2003;160(4):408-17. PubMed PMID: 12968933.

Stram DO, Preston DL, Sokolnikov M, Napier B, Kopecky KJ, Boice J, et al. Shared dosimetry error in epidemiological dose-response analyses. PLoS One. 2015;10(3):e0119418.

Zhang Z, Preston DL, Sokolnikov M, Napier BA, Degteva M, Moroz B, et al. Correction of confidence intervals in excess relative risk models using Monte Carlo dosimetry systems with shared errors. PLoS One. 2017;12(4):e0174641

Kwon D, Hoffman FO, Moroz BE, Simon SL. Bayesian dose-response analysis for epidemiological studies with complex uncertainty in dose estimation. Stat Med. 2016;35(3):399-423