Risk of leukemia at low radiation doses: the NIOSH Multisite Leukemia Case-Control Study

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Background

Ionizing radiation and leukemia

- High-dose studies (patients exposed during therapy, atomic bomb survivors) show increased risk at 30-600 rad
- Moderate-dose studies (Mayak workers, Techa River residents in former Soviet Union) show effects at 10-100 rad
- Low dose studies among nuclear workers at 1-30 rad are inconsistent

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NIOSH multisite leukemia case-control study (LCCS) purpose

- Is exposure to external ionizing radiation related to risk of leukemia among nuclear workers?
- Do lower doses and dose rates reduce risk per unit of dose?
- Does exposure to chemicals that cause leukemia (benzene and carbon tetrachloride) affect leukemia risk from low-dose radiation?

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NIOSH LCCS Study Principles

- Include workers of either gender and all races and ethnicities
- Pool existing cohorts (study populations) and apply consistent methods
- Use consistent criteria to select study cohorts
  - Large, previously studied cohorts (at least 10 cases)
  - Good external dosimetry
  - Minimal exposures to internal radiation
- Use nested case-control design to improve chemical & radiation exposure assessment
  - All workers with leukemia (cases) and randomly picked four workers without leukemia (controls) per case, matched on age
- Account for all work-related radiation exposures

US Nuclear Facilities Initially Evaluated

Did not meet criteria

Substantial Plutonium

Mound, Rocky Flats

Substantial Uranium

Fernald

K25, Y12 & TEC

Too small

Linde

Mallinckrodt & Pantex

No cohort available

Idaho National Laboratory

Met criteria

Hanford

Los Alamos National Laboratory

Oak Ridge National Laboratory

Portsmouth Naval Shipyard

Savannah River Site

Zia Company (at LANL)

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Cohort assembly methods

- Electronic roster & dosimetry data from previous investigators for six cohorts
- Used cohorts that were previously followed-up
- Follow-up extended to 1994 for SRS and Hanford, to 1996 for PNS
- Merged cohorts together
- Applied study inclusion criteria for base cohort
  - Included in previous study (generally, early workers)
  - Worked at least 30 days at one of included sites
  - Ever-monitored for external radiation exposure

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Description of selected cohorts

Site	Year of hire eligibility	Year of last follow up	Cohort size	Percent Deceased	No. total leukemia cases	Non-CLL cases
Hanford	1944-1978	1994	36,384	31%	94	77
ORNL	1944-1978	1990	19,815	26%	49	37
SRS	1952-1974	1994	12,886	31%	44	33
LANL	1943-1977	1990	12,179	14%	23	32
Zia	1946-1978	1990	5686	27%	14	
PNS	1952-1977	1996	9662	38%	33	27
Total cohort	--	--	94,517		257	206

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Methods: Radiation exposure assessment

Dosimetry record sources

- Electronic dose-of-record (gamma and neutron)
  - Hanford, LANL/Zia
- Original site dosimetry records (gamma, neutron, Pu)
  - ORNL, PNS, SRS
- Medical records
  - Medical X rays at Hanford
  - Incident reports, some dosimetry at LANL (e.g., early badge readings, test shot doses)
- Site log books (tritium & neutron at SRS)

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Methods: Radiation exposure assessment

Absorbed dose to bone marrow from

- High-energy gamma
- Neutron
- Tritium
- X-rays
  - Work-required medical
  - Resulting from plutonium source exposures
- Plutonium
  - Grouped workers according to urine monitoring levels
  - Bone marrow dose was calculated for workers with urine levels $\geq$1.7 mBq per day

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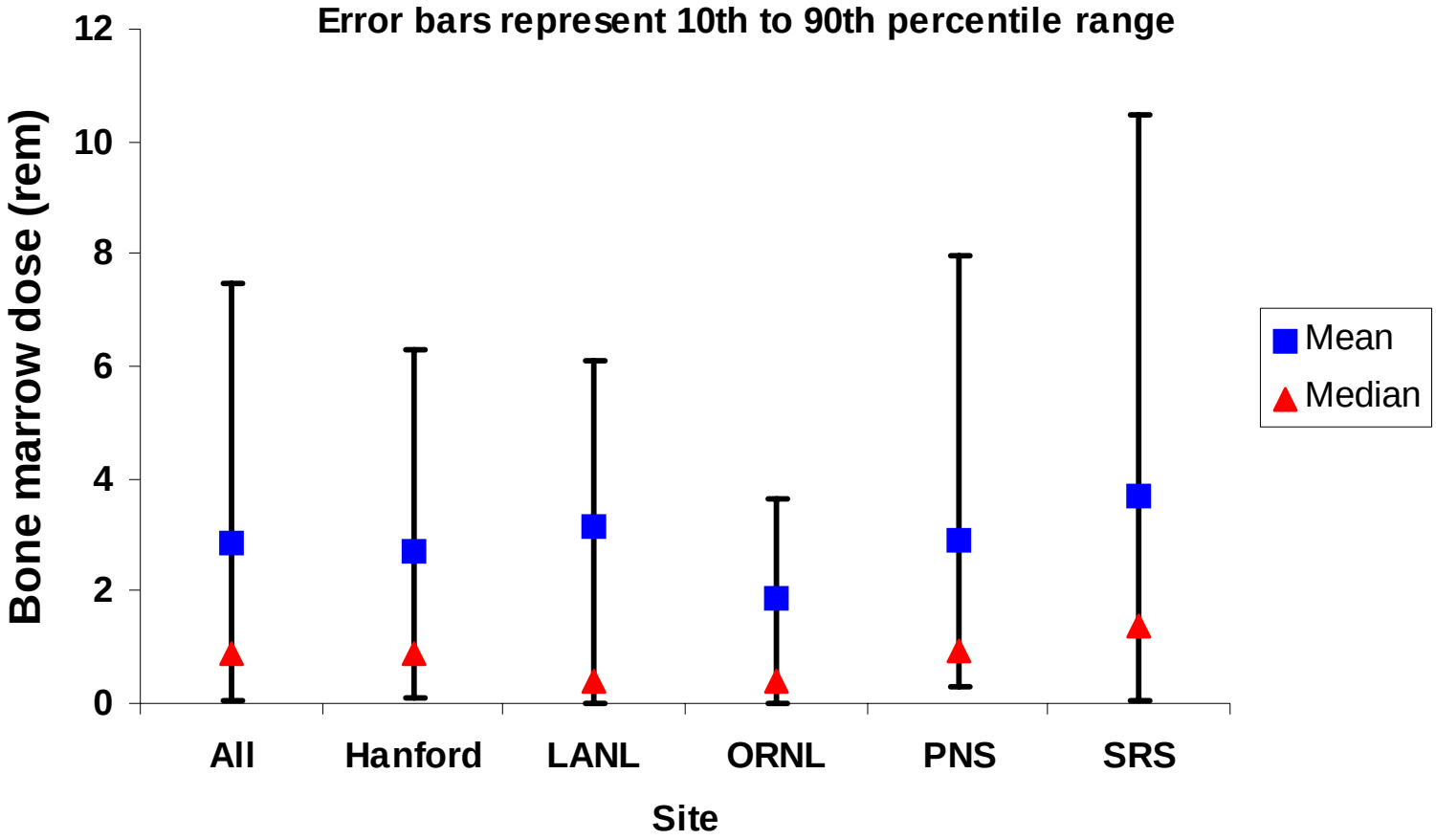
Average cumulative dose by site



Other information

- Cigarette smoking was available from medical records for half the workers
- Benzene & carbon tetrachloride job-exposure matrix put together from
  - Work history information placing each worker in job and area at a point in time
  - Information on sources of chemicals at each site
    - Industrial hygiene monitoring data (limited)
    - Historical operations and facility design descriptions
    - Health and safety documents
    - Environmental remediation documents
    - General job- and time-specific industry information

Radiation dose-response analysis

- Because other studies have found radiation risk varies by leukemia subtype, we looked separately at
  - Leukemia excluding chronic and unspecified lymphocytic
  - Chronic lymphocytic leukemia (CLL)
- Used conditional logistic regression to analyze data
- Included factors that changed the leukemia risk estimates from radiation (confounders)
- Looked at how leukemia risk from radiation changed by level of year of birth, hire year, gender, race, solvent exposure, smoking

Basic definitions of risk

Relative risk = RR

- The rate of death from leukemia in an exposed population divided by the rate of death from leukemia in an unexposed population

Excess relative risk = ERR

- Relative risk minus one
- Important because it is used to compare risk per rem to other epidemiology studies of radiation

Non-CLL Results (adjusted only for age)

	Category	Relative risk (95% CI)
Benzene exposure	Unexposed (79%) Exposed <200 (11%) Exposed ≥ 200 (10%)	1.0 1.3 (0.77, 2.0) 1.8 (1.1, 2.9)
Plutonium category	Unmonitored (57%) <1.7 mBq/d (34%) 1.7 to <17 mBq/d (6%) ≥17 mBq/d (3%)	1.0 1.1 (0.75, 1.5) 1.6 (0.84, 2.8) 1.4 (0.59, 3.1)
External dose	<0.1 rem (17%) 0.1 to <1 rem (41%) 1 to <5 rem (29%) 5 to <10 rem (7%) ≥10 rem (6%)	1.0 1.0 (0.65, 1.7) 1.6 (0.98, 2.7) 1.9 (0.94, 3.7) 2.1 (1.0, 2.6)

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Radiation risk estimates for non-CLL leukemia

Adjusted for:	ERR % per rem (95% CI)
Age	4.0 (-0.47, 12)
Age and gender	2.4 (-1.0, 9.4)
Age, gender & benzene	1.4 (<-1.0, 7.6)

- No other variables changed radiation risk estimates very much

Relative risk for non-CLL leukemia

- After adjusting for age, gender and benzene, the group of workers whose lifetime dose was greater than one rem (their average dose was much higher at 5.9 rem) had a significantly higher risk of death from leukemia than workers with lifetime doses of less than one rem
- RR = 1.45 (95% CI: 1.04,2.01)

Other findings for non-CLL leukemia

All these analyses were adjusted for age, gender and benzene

Removing 22 leukemias of uncertain subtype increased the risk estimates

- ERR (% per rem) = 2.6 (95% CI: <-1.0,10)

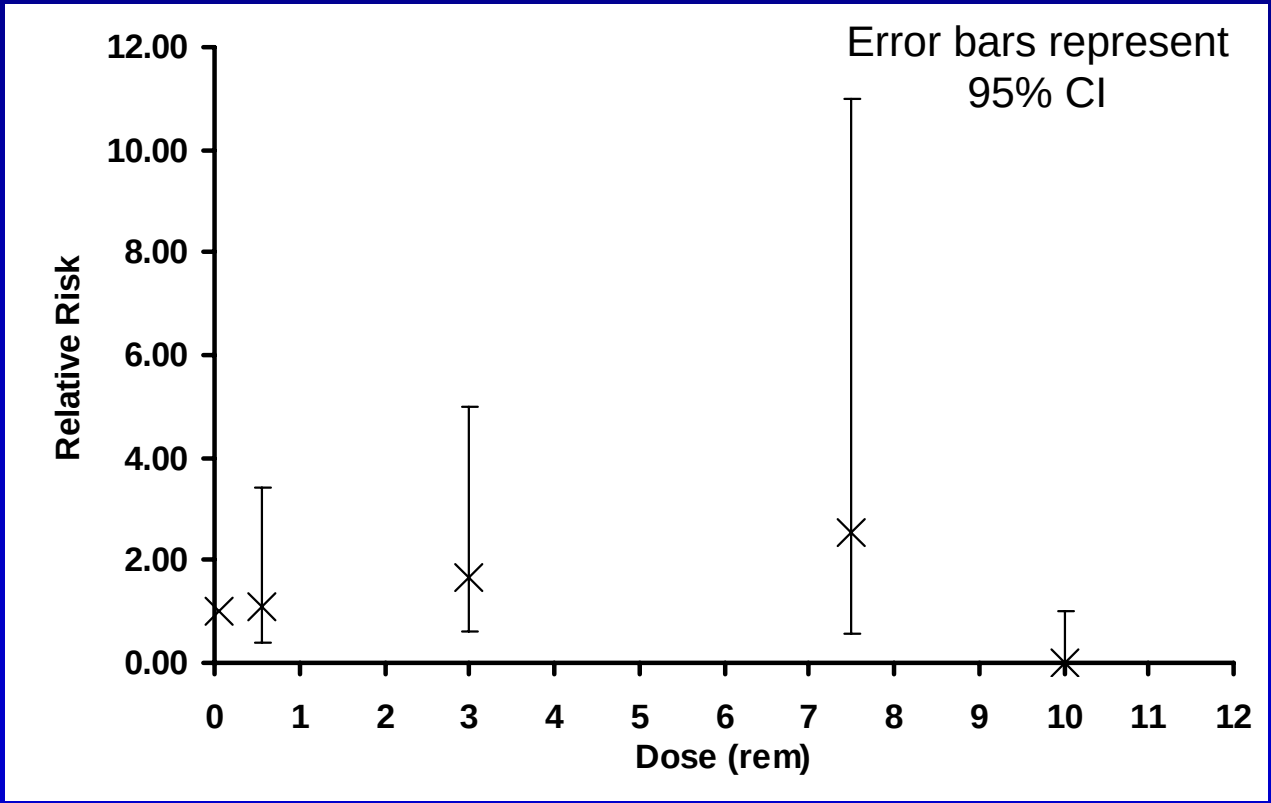
Excluding higher-dose workers (more than 10 rem) increased the risk estimates

- ERR (% per rem) = 6.8 (95% CI: -2.9, 24)

Results for chronic lymphocytic leukemia

Adjusted for smoking, workers with ≥ 1 rem had a non-significantly higher risk compared to workers with lower dose

RR=1.36 (95% CI: 0.69, 2.70)



Conclusions

- Acute and chronic myeloid leukemia (non-CLL)
  - The group of workers whose lifetime dose was greater than one rem (their average dose was much higher at 5.9 rem) had a significantly higher risk of death from leukemia than workers with lifetime doses of less than one rem
  - The estimated increased risk per rem
    - is similar to that found in other studies
    - was not statistically significant for all workers combined
    - was statistically significant among workers hired after 1952
  - Increased risk per rem is not driven by higher-dose workers
  - Workers exposed to both benzene and radiation had higher risk of leukemia than workers exposed just to benzene or radiation
- Chronic lymphocytic leukemia
  - CLL was not statistically significantly elevated in our study

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Conclusions

Putting increased risk per rem into context

- Excluding CLL and unspecified types of leukemia, we found an excess relative risk of 2.6% per rem (95% confidence interval: -1% to 10%)

- What does this mean?
  - With no radiation exposure
    - The lifetime chance of dying from leukemia (other than CLL) is estimated as 71 men out of 10,000
  - With 3 rems of radiation exposure (the average exposure for the men with leukemia in our study)
    - We estimate the lifetime chance of dying from leukemia (other than CLL) is 77 men out of 10,000 (95% confidence interval: <71 men out of 10,000 to 92 men out of 10,000)

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Study strengths and limitations

- Strengths
  - Large population
  - Dose range studied is relevant for current workers
  - Adjustment for benzene
  - Detailed adjustments for dosimetry biases and some sources of missed dose
- Limitations
  - Low power
  - Highly skewed doses, with few workers >10 rem
  - Dose uncertainties
    - early doses are less certain than later doses, when monitoring methods improved
    - lack of original dose records at LANL and Hanford

Comments and questions

- Radiation dosimetry: Doug Daniels, rtd2@cdc.gov
- Benzene and carbon tetrachloride exposure: Don Fleming, dmf9@cdc.gov
- Epidemiologic analyses: Mary Schubauer-Berigan, zcg3@cdc.gov

Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear naval shipyard. Radiat Res 167:222-232, 2007.

Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. Br J Haematol 139:799-808, 2007.