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FOR SCIENCE AND EDUCATION

Shaping the Future of Science

The Intersection of Epidemiology, Dosimetry & Biostatistics:

Optimal approaches in the Million Person Study

Presented at the USTUR SAC

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Intersection of Epidemiology, Dosimetry & Biostatistics



- Team approach
- Goal of MPS –
Develop & implement optimal methods
 - Careful epidemiologic considerations
 - Exclusion criteria, vital status/tracing
 - Novel, refined dose estimates
 - Organ doses from all sources, newest approaches
 - Rigorous statistical models
 - Appropriate models, covariates, sensitivity analyses



Epidemiology considerations

- Build from prior studies
- Consistent vital status & cause of death ascertainment
 - Michael T. Mumma, Sarah S. Cohen, Jennifer L. Sirko, Elizabeth D. Ellis & John D. Boice Jr. (2018): Obtaining vital status and cause of death on a million persons, International Journal of Radiation Biology, DOI: 10.1080/09553002.2018.1539884
- Exclusion criteria
 - Insufficient identifier information for tracing
 - Worked at least 30 days
 - Other site specific issues

Mallinckrodt Chemical Works (MCW)

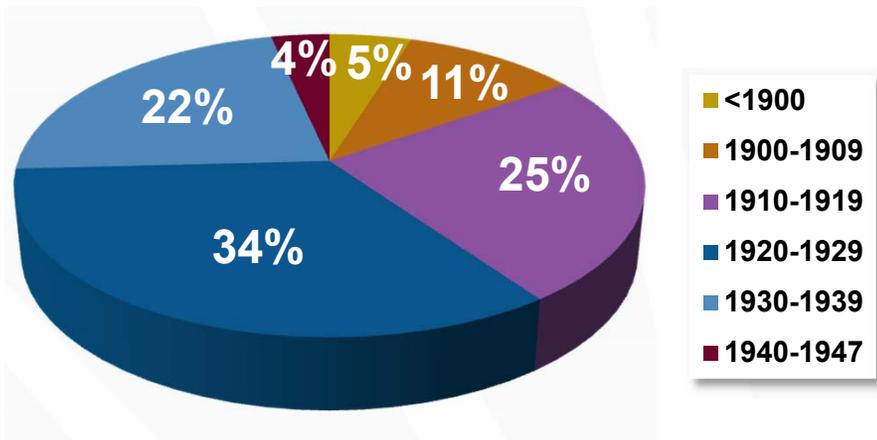
- Refined large amounts uranium ore (Belgian Congo)
 - St. Louis & Weldon Springs, MO
 - Began July 1942
- Workers exposed to
 - Internal and external radiation
 - Pitchblende dust
 - Radon
- Previous Study (Dupree 2000)
 - Considered external radiation



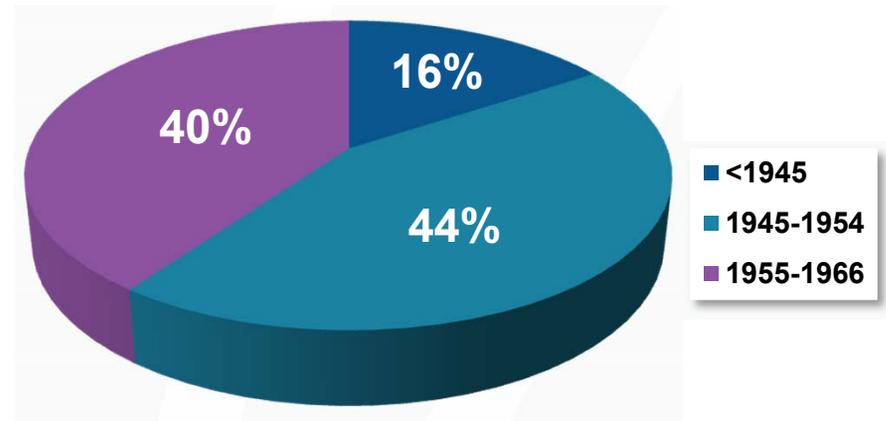
MCW Cohort

2,514 white males employed on or after January 1, 1942 in the MCW Uranium Division

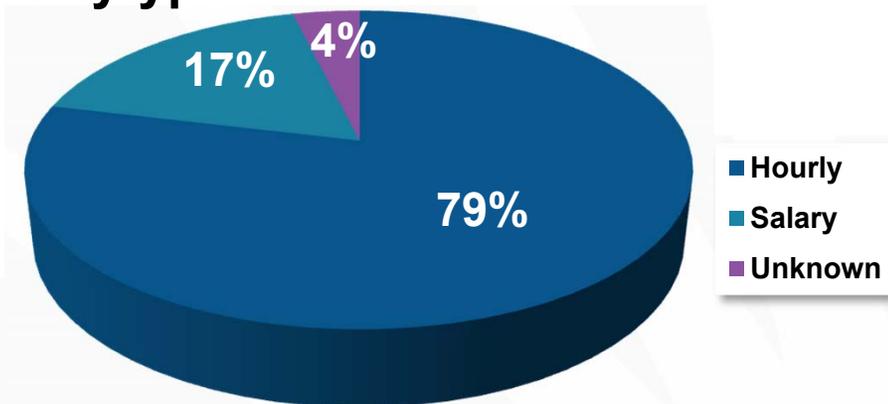
Year of Birth



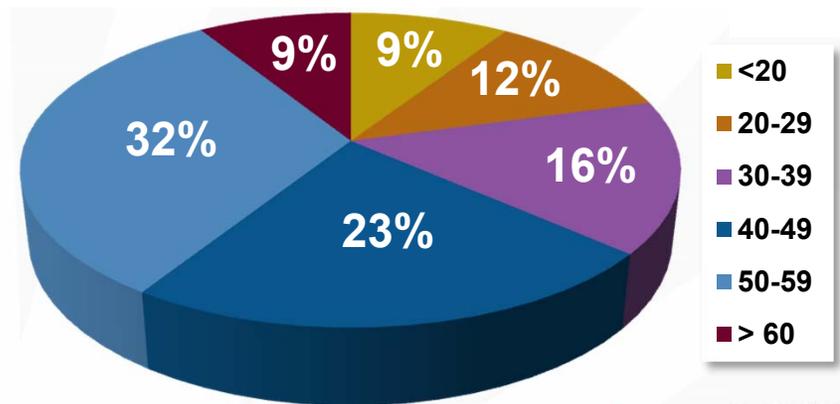
Year of Hire



Paytype



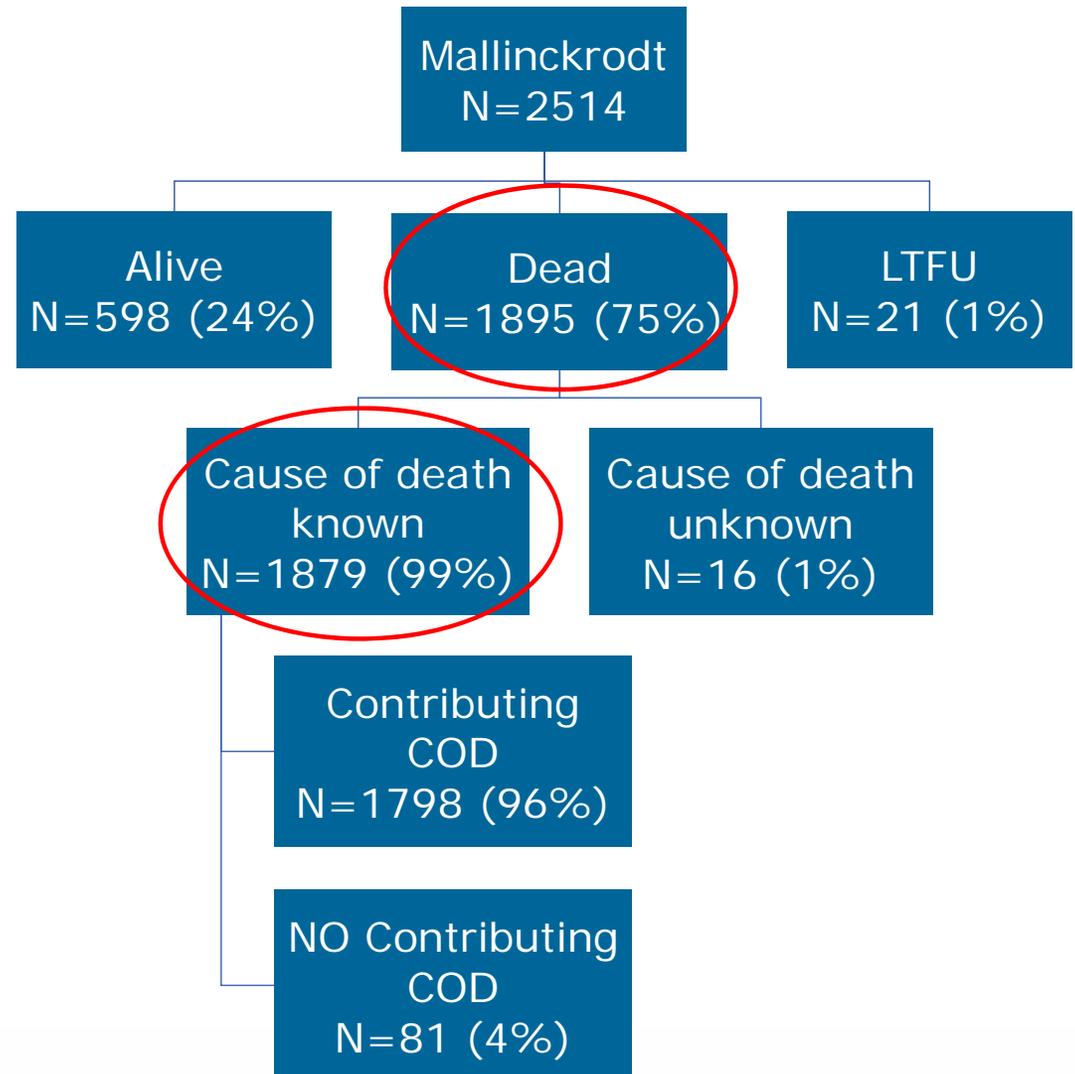
Years of Followup



Methods – Vital Status

- Tracing methods:
 - SSA, PBI, and NDI
 - LinkPlus program
- Serious renal disease identified by linkage with
 - U.S. Renal Data System, 1977-2008 (USRDS 2011)
- COD coded to revision at time of death
- Included contributing causes for outcomes with small numbers

Through Dec. 31, 2012



MPS Dosimetry methods

- Recommendations from NCRP Report 178
 - Annual, absorbed doses to the organ/tissue of interest
- Data needed
 - Detailed process description
 - Site documents, NIOSH TBD, Former workers
 - Radiation monitoring data
 - Film badge, chest x-rays, urinalysis, fecal, radon breath, etc.
 - Work histories
 - Job start/stop dates, job titles, building locations
- Consider all sources
 - Combine internal and external organ doses

MCW Radiation Monitoring Data

Type	# records	# workers	Years covered	Imputed (Y/N)
MCW Film Badge	12,686	2,024	1945-1966	Y
Occupational Chest X-rays	31,297	1,995	1942-1966	Y
Non-MCW Film Badge/TLD	210	43	1944-2008	N
Uranium Urinalysis	39,451	1,925	1948-1966	N
Breath Radon	2,341	500	1948-1959	N
Uranium Dust Exposure Worksheets	6,300	1,091	1942-1952	Y
Ambient Radon Exposure	6,846	1,392	1944-1955	Y



MCW Dosimetry methods – 7 sources

- Organs of interest: lung, red bone marrow, kidney, brain, heart, colon, liver, thoracic lymph nodes
- Organ dose from external exposure
 - Film badge: photon energy, organ dose conversion, orientation, ICRP 116
 - Chest x-ray: organ doses considering air kerma & view, ICRP 34
 - Other data: DOE REMS, NRC REIRS, Legacy DOE, Atomic Veterans
- Organ dose from internal exposure
 - Uranium urinalysis – ICRP 68 models
 - Breath radon: ^{226}Ra in the body
 - ICRP 68 and Srivastava et al. (1986)
 - Ambient radon: job history, air monitoring, ICRP 137
- Dust exposure - $\text{mg}/\text{m}^3\text{-year}$
 - Time-weighted job-specific dust measurements



Estimated Radiation Doses

Type of dose (mGy)	Mean	Median	Max
External - occupational			
Lung	36.0	11.2	724
Brain	33.0	10.7	738
Heart	35.6	11.0	711
Kidney	27.9	8.9	604
Colon	35.6	11.0	712
Red Bone Marrow	32.9	10.3	676
Thoracic Lymph Nodes	32.9	10.3	676
External - Medical x-ray (chest)			
Lung	10.7	7.2	54
Brain	4.2	3.0	20
Heart	11.8	8.0	59
Kidney	10.7	7.2	54
Colon	2.3	1.8	12
Red Bone Marrow	2.2	1.8	11
Thoracic Lymph Nodes	10.0	6.7	50

Type of dose (mGy)	Mean	Median	Max
Internal doses > 0			
Lung	27.1	11.2	416
Brain	0.08	0.04	1
Heart	0.09	0.04	1
Kidney	0.73	0.41	12
Colon	0.13	0.058	3
Red Bone Marrow	0.57	0.18	10
Thoracic Lymph Nodes	2.57	1.08	44
Total dose (external + internal)			
Lung	69.9	33.1	885
Brain	37.2	15.2	750
Heart	47.5	23.3	738
Kidney	39.2	20.2	637
Colon	38.0	13.4	714
Red Bone Marrow	35.6	12.9	683
Thoracic Lymph Nodes	45.1	21.8	708

- Average doses 35-70 mGy
- Largest doses from external
- Lung = Max dose

- Some high outliers
- SMR—All Causes = 0.94
- Healthy worker effect

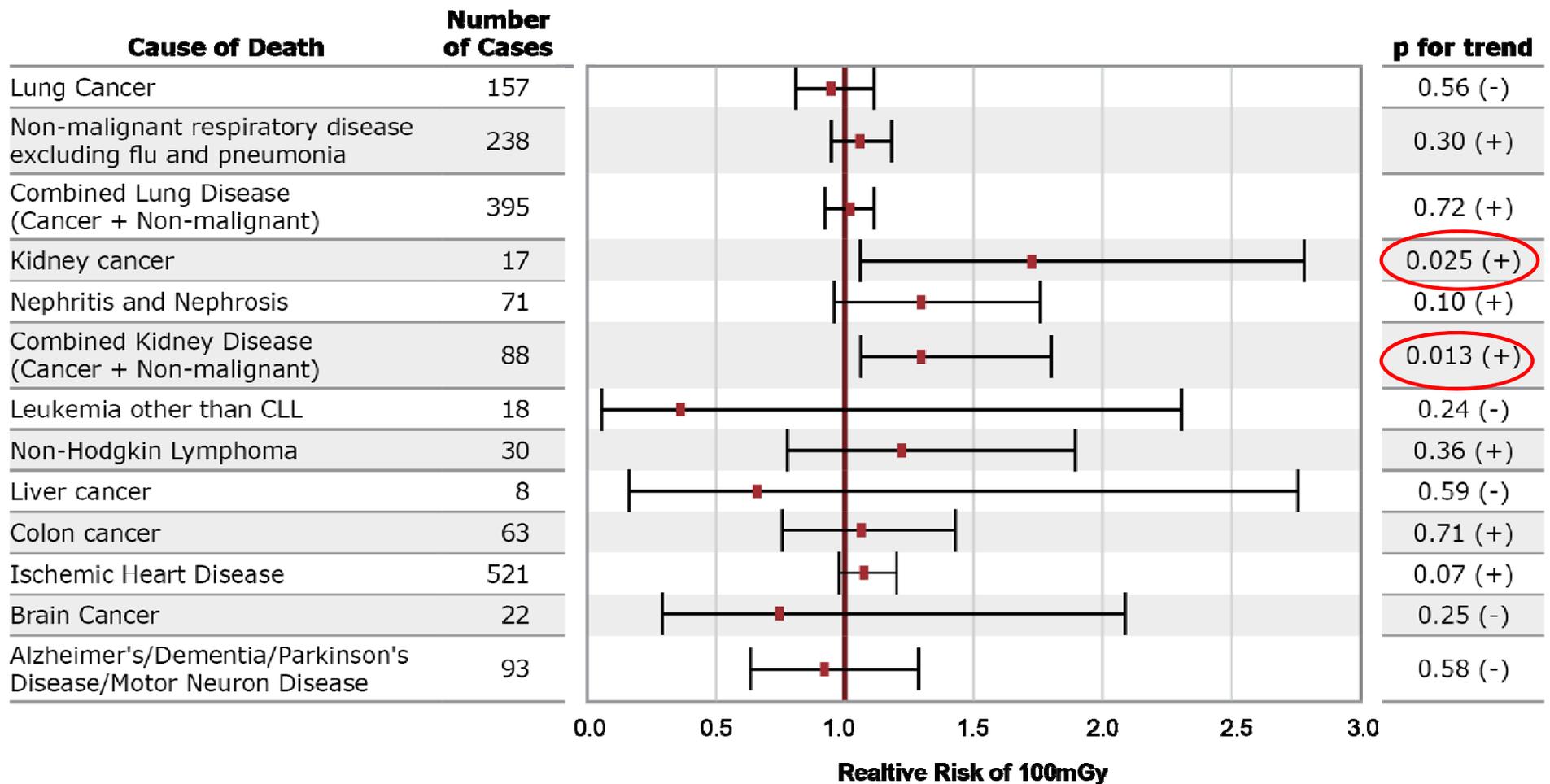
MPS Biostatistical Considerations

- Time dependent dose-response model choice
 - Poisson vs. Cox proportional hazards
 - Golden, Cohen, Chen, Ellis & Boice Jr. (2018): Evaluation of statistical modeling approaches for epidemiologic studies of low-dose radiation health effects, International Journal of Radiation Biology, DOI:10.1080/09553002.2018.1554924
- Measures of effect
 - Relative risk (RR) = Risk in “exposed”/Risk in “unexposed”
 - RR = 1, no relationship
 - If CI for a RR includes 1, then there is no increased risk
 - Cox model gives Hazard ration (HR) ~ relative risk
 - Excess relative risk (ERR) = RR – 1
 - Excess risk of occurrence associated with exposure
 - ERR = 0, no relationship
 - If CI includes 0, then there is no significant excess risk

MPS Biostatistical Considerations

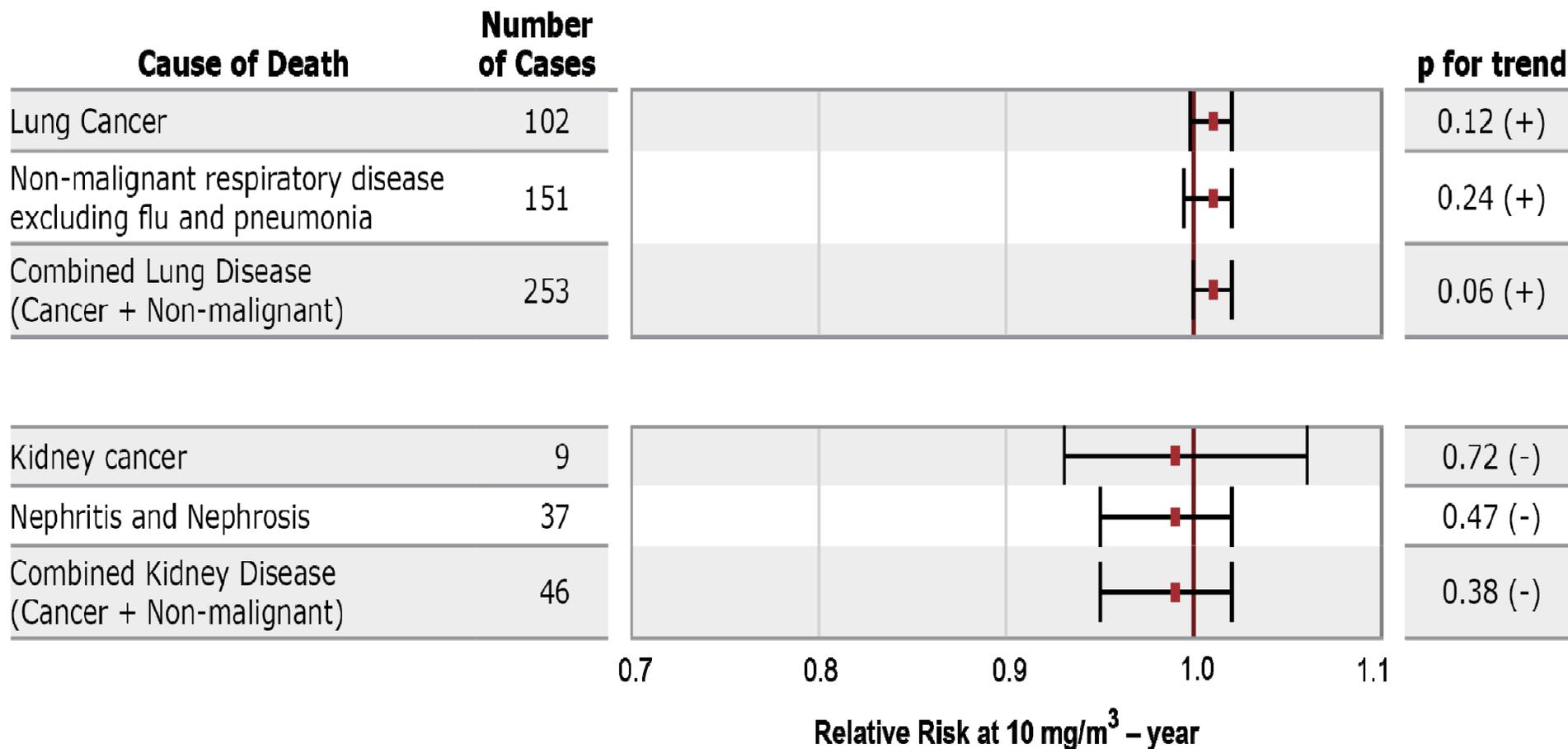
- Cause-specific dose-response analyses
 - Includes both underlying and contributory cause of death
- Cox proportional hazards model
 - SAS – hazards ratio (relative risk model)
 - Epicure – ERR model (using Peanuts module)
 - Continuous (linear, linear-quadratic) & categorical models
 - Referent group was workers with <10 mGy
- Model specifications
 - Doses lagged: 10 years-solid cancers, 2 years-leukemia
 - Underlying timescale: attained age
 - Covariate adjustments: year of birth, paycode
- Sensitivity analyses
 - RBE of 10 & 20 for alpha particle doses (mSv)
 - Consideration of categories for categorical estimates
 - Covariates: duration of employment, year of hire

MCW Relative Risks - Radiation



- Cox proportional hazards, age=time scale, adjusted for paycode & year of birth, doses lagged
- Dose weighting factors 10 & 20 = some change to estimates, but did not affect significance
- No important changes observed when adjusted for dust exposures

MCW Relative Risks - Dust



- 1230 workers, at MCW 1942-1952
- Average dust exposure 15.08 mg/m³-year (range: 0-400.3)
- No statistically significant associations
- Adjusting for radiation resulted in some change to estimates, but not significance

Summary of MCW study

- Only significant association was kidney cancer (RR at 100 mGy 1.73)
 - Nephritis and Nephrosis: trending at 1.30
 - Possible confounding by non-radiogenic properties of uranium dust
- Golden, Ellis, Cohen, et al. (2019): Updated mortality analysis of the Mallinckrodt uranium processing workers, 1942–2012, International Journal of Radiation Biology, DOI: 10.1080/09553002.2019.1569773
- Unique and sophisticated analyses
 - High quality follow-up
 - Robust dosimetry approach
 - Optimal statistical methods
- Future direction: pool cohorts for \uparrow power
 - MCW, Middlesex, Fernald, Port Hope
 - International pooled study of uranium processors



The Future.....

- After completing individual cohorts/DOE sites with
 - Consistent methods for vital status/tracing, dosimetry, and biostatistics models
- Pool all MPS cohorts into one analysis
 - Potential challenges
 - Accounting for cohort effects
 - Uncertainties in dosimetry models
 - Harmonization of covariates
 - Overlap between cohorts
- Largest, high-quality study for US radiation workers = greatest precision in risk estimates (including low dose)

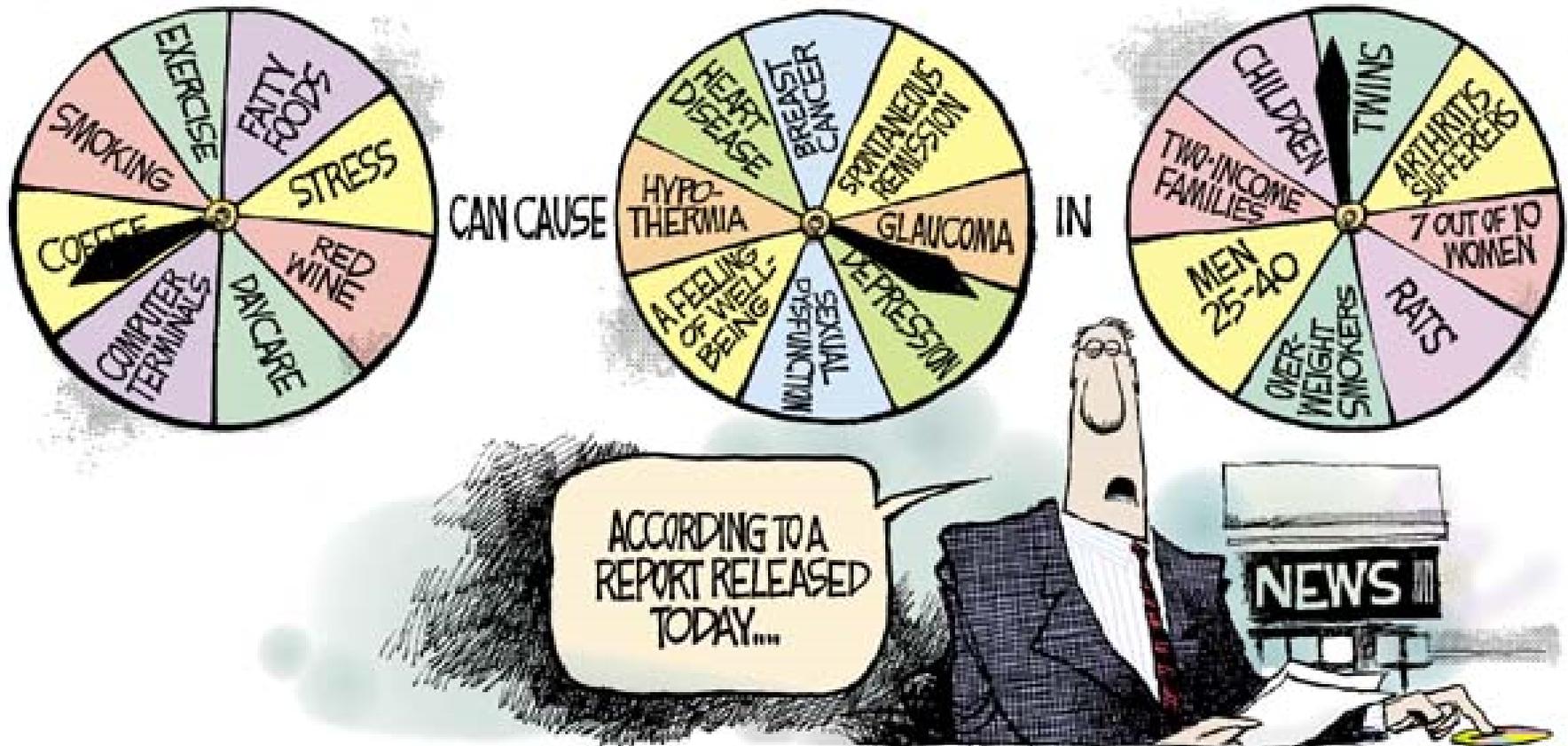


Questions?

Today's Random Medical News

from the New England Journal of Panic-Inducing Gobbledygook

JIM BORGMAN



Cartoon by Jim Borgman, first published by the Cincinnati Inquirer and King Features Syndicate 1997 Apr 27; Forum section: 1 and reprinted in the New York Times, 27 April 1997, E4.