Occupational Cancer: Knowledge and Needs

AARON BLAIR, PhD, MPH

Occupational Cancer Research Centre,
Toronto, ON
and the
Occupational and Environmental Epidemiology Branch
National Cancer Institute,
Bethesda, MD

INSTITUTE FOR WORKERS HEALTH
TORONTO, ON
NOVEMBER 4, 2009

Occupational Cancer

- What do we know about occupational cancer?
- What are we doing now?
- What are the important methodologic issues?
- Has prevention been successful?

References on Occupational Causes of Cancer

- Tomatis L, Huff J, Hertz-Picciotto I, Sandler DP, Bucher J, Boffetta P, Axelson O, Blair A, Taylor J, Stayner L, Barrett JC. Avoided and avoidable risks of cancer. Carcinogenesis 18:97-105, 1997.
- Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, Rousseau M, Boffetta P. Listing of occupational carcinogens. Environ Health Perspect 112:1447-1459, 2004.

Some Well-Established Occupational Causes of Cancer

Cancer Site	Exposure	Cancer Site	Exposure
Bladder	Bendizine	**Mesothelioma**	Asbestos
	Coal tars	**Bone**	Radium
	2-Naphthylamine	**Larynx**	Sulfuric acid mist
	4-Aminobiphenyl	**Liver**	Arsenic
Lung	Arsenic		Vinyl chloride
	Asbestos	**Nasal cavity/sinuses**	Nickel
	Beryllium		Radium
	Chloromethyl ether		Chromium
	Chromium	**Skin**	Arsenic
	Coal tar pitch volatiles		Coal tars
	Radon	**Lukemia**	Benzene
	Silica	**Nasopharynx**	Formaldehyde Leukemia
	Mustard gas		

Partial List of Chemicals Causing Cancer in Animals, but With No Adequate Epidemiologic Data

(From IARC, Supplement 7)

- Chlordecone
- Chloro-ortho-toluidine
- Dichloroethane
- Ethylhexyl phthalate
- Diethylhydrazine
- Ethyl acrylate
- Methylene dianiline
- Mirex
- Nitropropane
- Potassium bromate
- Safrole
- Styrene oxide
- Sulfallate
- Thioacetamide
- Toluene diisocyanate
- Vinyl bromide

New Epidemiologic Leads: Suggested Associations Requiring Further Evaluation (adapted from Monson, 1996)

Substance	Cancer	Substance	Cancer
Asbestos	Gastrointestinal	**Butadiene**	Leukemia
	Kidney		Lymphoma
	Larynx, Lung	**Selected herbicides**	Non-Hodgkin's lymphoma
Cadmium	Prostate		Lung
Cutting oils	Lung	**Diesel fumes**	Bladder
	Skin		Stomach
Formaldehyde	Nasal sinuses	**Dust**	Lung
	Hodgkin disease	**Man-made mineral fibres**	Lymphoma
Silica	Stomach		Lung
Talc	Lung	**Selected pesticides**	Lung
	Ovary		Leukemia
Vinyl chloride	Brain		Prostate
	Ovary		

New Epidemiologic Leads: Occupations Associated with Cancer Where Agent Has Not Been Clearly Identified

(adapted from Monson, 1996)

Occup Group	Cancer Site	Occup Group	Cancer Site
Farmers	Leukemia	**Dry cleaners**	Bladder
	NHL		Esophagus
	Lung		Kidney
	Prostate		Liver
	Lip		Cervix
	Stomach	**Embalmers**	Leukemia
	Brain	**Petrochemical workers**	Leukemia
	Myeloma		Brain
Chemists	Various sites		Kidney
Pattern makers	Colon		NHL
Welders	Lung	**Rubber workers**	Leukemia
			Lung

New Epidemiologic Leads: Occupations Associated with Cancer Where Agent Has Not Been Clearly Identified

(adapted from Monson, 1996)

Occup Group	Cancer Site	Occup Group	Cancer Site
Veterinarians	Leukemia	**Lead workers**	Lung
Waiters	Lung		Brain
Artists	Bladder	**Meat workers**	Lung
Bakers	Lung		Leukemia
Cement workers	Lung	**Painters and paint manufacturers**	Lung
	Stomach		Bladder
Coal miners	Stomach		Myeloma
	Leukemia	**Plumbers**	Lung
Coke plant workers	Pancreas		Leukemia
	Colon	**Truck drivers**	Bladder
Beauticians	Leukemia		Lung

Proportion of Cancer Due to Various Factors

(from Doll and Peto, 1981 and Lichtenstein et al., 2000)

Factor	%
Genes	20-40
Diet	35
Tobacco	30
Infections	10
Reproductive/sexual behavior	7
Occupation	4
Geophysical factors	3
Alcohol	3
Pollution	2
Medicines	1

Issues Regarding Estimation of the Cancer Burden

- Two groupings of causal factors
  - **Major** – diet,tobacco, and genes
  - **Minor** - environment, occupation, infections, alcohol, pollution, reproductive/sexual behavior, medicines
- Strength of evidence for various risk factors varies
- Contributions vary in subpopulations, i.e., occupational contribution among blue-collar workers may approach 25%, not 4%
- Occupational and environmental exposures typically not voluntary

Occupational Carcinogens from IARC Monographs

- IARC evaluations through 2003
  - 89 Sufficient; 28 occupational carcinogens
  - 64 Probable; 27 occupational carcinogens
  - 264 Possible; 110 occupational carcinogens
- 18 Industries/occupations as 1, 2A, or 2B
- Percent Occupational
  - Sufficient - 31%
  - Probable - 42%
  - Possible - 42%

From: Siemiatycki et al. Environ Health Perspect 2004;112:1447-1459.

Number of Occupational Associations by Cancer

Cancer	Strong Associations	Suggestive Associations
Lung	18	16
Bladder	8	15
Skin	8	3
Nasal cavities/sinus	7	3
Leukemia	3	4
Larynx	3	2
Liver	2	2

From: Siemiatycki et al. Environ Health Perspect 2004;112:1447-1459.

Cancer and Occupational Exposures

- Airway sites prominent
- Bladder and skin frequent
- Leukemia and liver occurs
- Digestive and reproductive systems largely absent
- Leads for blood/lymph, digestive, and reproduction systems

Growth in Understanding about Occupational Carcinogens

	2003 IARC Rating	1987 IARC Rating	1964 WHO Rating
1	28	19	14
2A	27	22	9 (2A & 2B)
2B	110	70	

From: Siemiatycki et al. Environ Health Perspect 2004;112:1447-1459.

What Are We Doing Now

Survey of issues of Am J Industr Med from 01/2007 to 05/2009

- **256 research articles**
- **31 research articles on cancer (12%)**

<u>Gender</u>	**<u>Design</u>**
- 24 white men	**- 11 cohort**
- 12 women	**- 13 case-control**
- 3 minorities	**- 7 other**

<u>Country Location</u>	**<u>Exposure Assessment</u>**
- 27 developed	**- 18 occupation/industry**
- 4 developing	**- 4 JEM**
	- 1 quantitative estimates
	- 9 other

How is Research on Occupational Cancer Faring?

- Funding? Decrease
- Number of occupational research projects? Decrease
- Number of occupational cancer sessions at scientific meetings? Decrease
- Number of published papers? Probably a decrease

Why the Reduction in Occupational Research

Perceptions:

- Not an important contributor to the cancer burden
  - Contributes as much as any factor, except diet and tobacco use
- No new leads
  - Many leads from epidemiological and experimental studies
- Occupational exposures well controlled
  - Some are, most are not
- Not scientifically important
  - Provided much of what we know about carcinogenesis. Can be even more important in the "omics" era
- Political decisions
  - The major impediment

What Don't We Know About Occupational Carcinogens

- Women and minorities seldom studied
  - Survey of 1233 occupational cancer reports (Zahm, 1994)
    - Only 14% with any analyses of women
    - Only 7% with more than 5 risk estimates
- Workers in small businesses rarely studied
- Most studies in developed countries
- Some sites studies more than others

IARC and NORA Evaluation of 2A and 2B Carcinogens: Needs and Gaps

Criteria to be placed on the list:

- Widespread occupational exposure
- Other reasons for public health importance
- Preference for single agents

Other considerations:

- Associations with cancers with increasing rates
- Caution against an overemphasis on molecular research

2A and 2B Carcinogens Selected for IARC Needs and Gaps Meeting

Selected

Shiftwork
Diesel exhaust
Styrene-7,8 oxide
Tetrachloroethylene
Trichloroethylene
Cobalt with tungsten carbide
Indium phosphide
Refractory ceramic fibers
Carbon black
Styrene
Propylene oxide
Chloroform
Dichloromethane
Welding fumes
Atrazine
Ethylhexyl phthalate
Formaldehyde
PCBs
Lead and lead compounds

Considered But Not Selected

Toluenes and benzoyl chloride
Acrylamide
Epichlorohydrin
Naphthalene
Acrylonitrile
Chloroprene
Ethyl acrylate
Toluene diisocyanates
Carbon tetrachloride
Methylenedianiline
Nitrobenzene
1,4-Dioxane
Hydrazine
Ethylene dibromide
Vinyl fluoride and vinyl bromide

Methodologic Needs for Future Studies

- More studies of women, minorities, and in developing countries
- Enhanced use of quantitative exposure assessment
- Collection of information on non-occupational risk factors
- Assess mechanisms of action and evaluate gene-exposure interactions
- More frequent use of cross-sectional, case-control, and prospective designs than in the past

Type of Exposure Assessment in Occupational Studies of Cancer

Type of Exposure Assessment	Number of Studies	%
Occupation or Industry only	23	32
Occupation/Industry and duration	19	26
Ever/never for specific exposures	7	10
Qualitative estimates	15	21
Quantitative estimates	8	11
Total	72	100

From articles on occupational cancer published in the Scand. J. Work Environ. Health and the Amer. J. Industr. Med. over a two year period.

Issues in Occupational Epidemiology of Cancer

- Confounding
- Exposure Misclassification
- Prevention

Control for Smoking Confounding in a Case-Control Study of Lung Cancer and Occupation

Occupational Category	Unadjusted OR	Smoking/Age Adjusted OR
Professionals/technicians	0.9	1.1
Office/related personnel	1.0	1.1
Agric/forestry/fishery workers	1.4	1.5
Metal smelting and treatment	1.2	1.1
Chemical workers	1.6	1.4
Textile workers	0.7	0.7
Food/beverage workers	0.9	1.0
Printers	1.2	1.5
Pipe fitters/welders	0.9	0.9
Painters	1.6	1.4
Transportation equipment	1.1	1.1
Construction workers	1.6	1.4

From: Levin et al. Br J Ind Med 1988;450-458.

Control for Smoking and Asbestos Confounding in a Case-Control Study of Lung Cancer and Occupation

Industry	Age Adj OR	Age/Smk Adj OR	Age/Smk/Asbestos Adj OR
Agric/forestry/fishing	1.3	1.3	1.3
Energy/mining	1.7	1.5	1.4
Chemical/oil	1. 2	1.2	1.2
Stone/glass/pottery	1.8	1.6	1.5
Metal production	1.4	1.4	1.3
Electrical/sheet metal	0.9	0.9	0.9
Leather/textile	1.0	1.0	1.0
Construction	1.6	1.4	1.3
Financing/insurance	0.8	0.8	0.8
Restaurants/hotels	1.4	1.0	1.1

From: Bruske-Hohlfeld et al. Am J Epid 2000;151:384-395.

Relative Risks (# Exposed Deaths) for Lung Cancer by Cumulative Exposure to Acrylonitrile

	Quintile of Estimated Exposure					
Analysis Group	**Lowest**	**2nd**	**3rd**	**4th**	**Highest**	**P for Trend**
% Ever Smoked Cigarettes	62%	64%	68%	72%	75%	
Entire Cohort	1.1 (27)	1.3 (26)	1.2 (28)	1.0 (27)	1.5 (26)	0.65
Entire Smoking Subcohort (Not Adj. for Smoking)	0.8 (27)	1.1 (26)	1.0 (28)	0.9 (27)	1.5 (26)	0.70
Smoking Subcohort with Smoking Data (Not Adj.)	0.3 (5)	0.9 (6)	1.0 (7)	1.0 (13)	1.7 (9)	0.80
Smoking Subcohort Adj. for Ever Used Cigarettes	0.3 (5)	0.8 (6)	1.0 (7)	0.9 (13)	1.6 (9)	0.99

From: Blair et al. Scand J Work Environ Health 1998;24:suppl 2:25-41.

Summary of Comparisons of Unadjusted and Adjusted RRs from Six Recent Am. J. Epidemiology Issues

- Four of 92 comparisons differed by >0.3
- Four of 92 might result in a different conclusion using adjusted RR
  - Two with a change in magnitude
  - Two with a change to no effect

Conclusions About Confounding

- My Conclusion:
  - Confounding is rare – only 5% occurrence in this sample
  - Should not discount findings based on a suggestion of confounding without some evidence that it actually occurs
- Confounding – What if you cannot adjust directly?
  - Are requirements for confounding evident?
  - Are other effects of confounding apparent?
  - Has this confounding occurred in other studies?
  - Estimate possible effect (Axelson method for smoking)

Misclassification of Exposure in Epidemiologic Studies

The major limitation in epidemiology because:

- Direct biologic measures extremely rare
- Air measurements clustered in recent years
- Quantitative estimates desirable, but fraught with error

Exposure and Disease Misclassification: Bias towards the Null

True Exposure Classification

	Exposed: Yes	Exposed: No	
Case	150	350	500
Control	50	450	500
	200	800	

OR=3.9

With 20% Non-differential Misclassification of Exposure

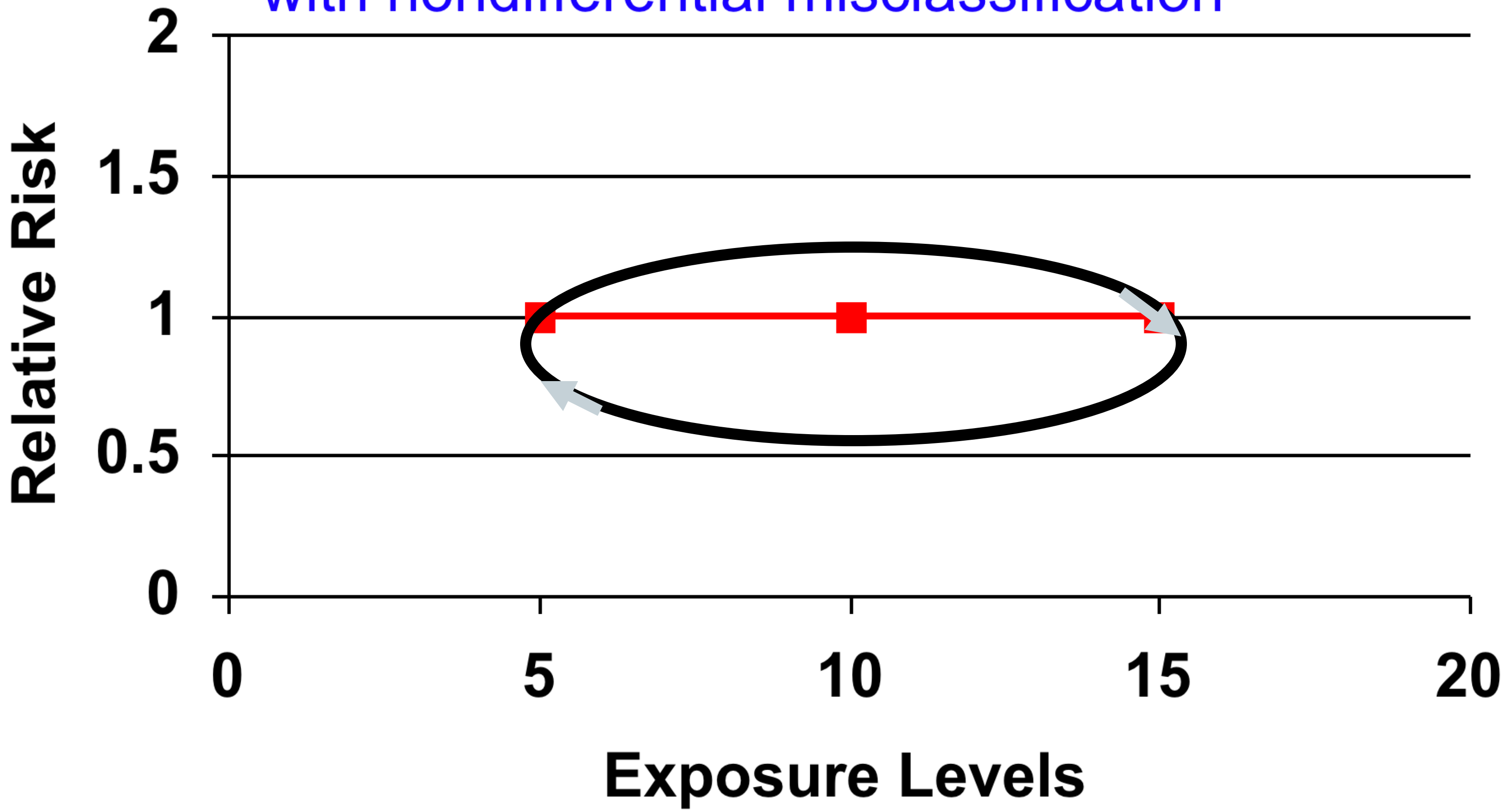
	Exposed: Yes	Exposed: No	
Case	190	310	500
Control	130	370	500
	320	680	

OR=3.9 ▶ OR=1.7

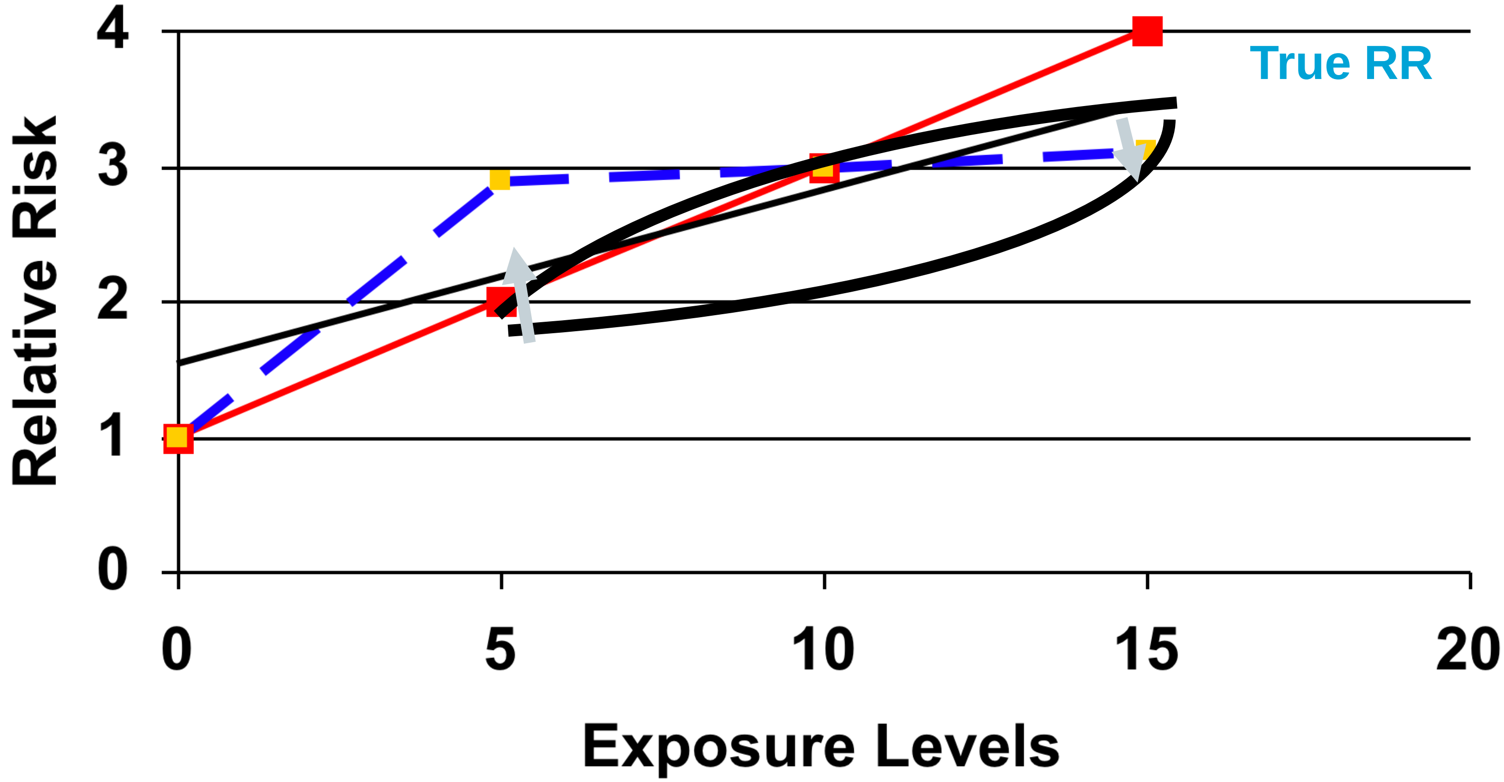
In this example, the observed OR is attenuated by 56% when 20% of exposed cases (n=30) and controls (n=10) are misclassified as non-exposed, and 20% of non-exposed cases (n=70) and controls (n=90) are misclassified as exposed.

Misclassification of Exposure: True Association

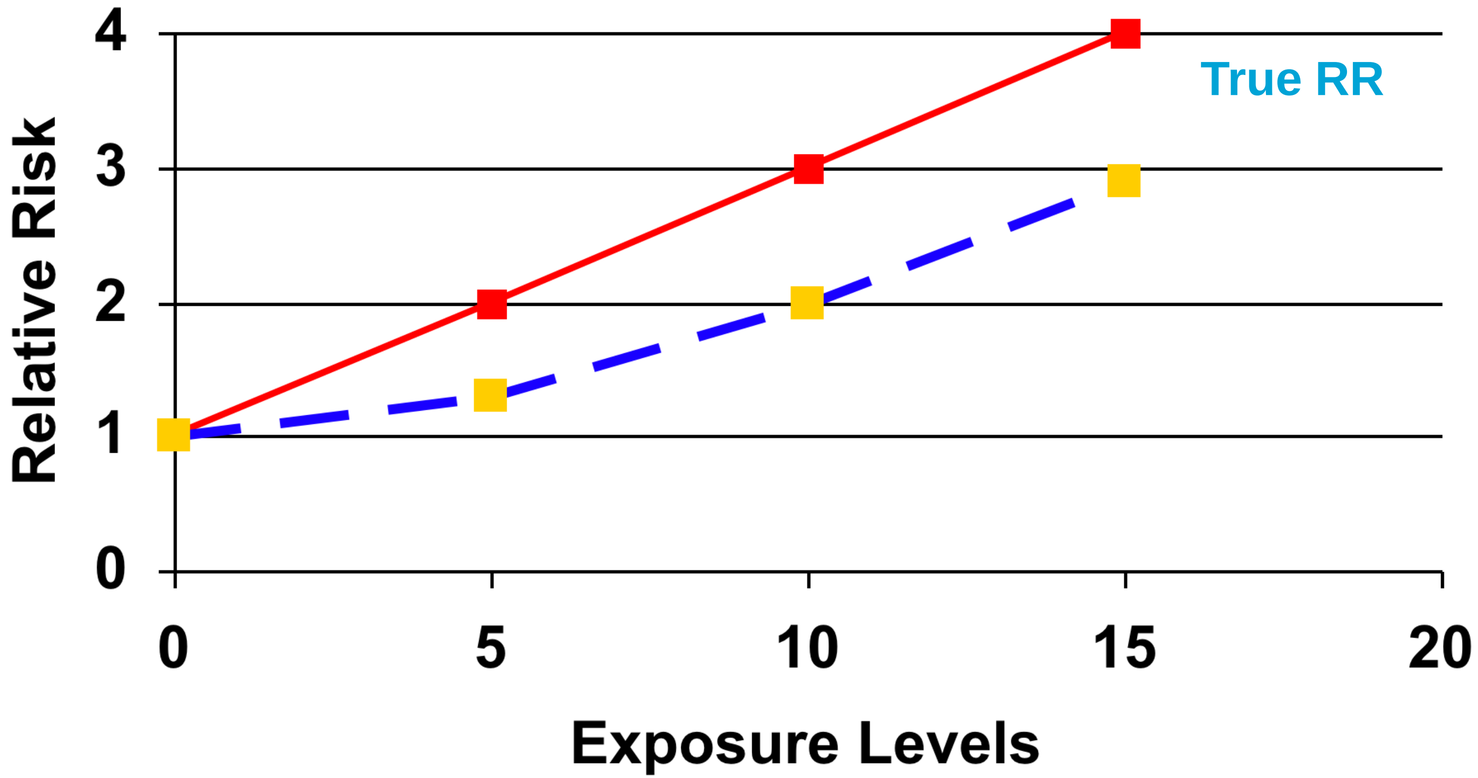
with nondifferential misclassification



Misclassification of Exposure: True Association



Misclassification of Exposure: True Association



Levels of Misclassification in Occupational Studies

- Acrylonitrile – Measurements/estimates, r = 0.6
- Dioxin – Serum levels/estimates, r = 0.70
- Coal tar volatiles – Measurements/estimates, r = 0.42
- Formaldehyde – Different estimates, r = -0.1 to 0.7
- Jobs – Reported/recorded jobs, 83% agreement
- Welding fumes- Measurements/experts, r = 0.42
- Asbestos – Supplementary Qx/JEM, Kappa = 0.39
- 2,4-D – PK Model/urinary measurements, r = 0.65

Misclassification of Exposure

- Conclusion
  - Misclassification is the major weakness
  - Not well considered in data interpretation
  - Ignoring it creates false negative impressions
- Must consider impact of misclassification
  - Evaluation degree of misclassification
  - Scour literature for relevant data and examples
  - Perform sensitivity analyses to estimate effects
  - Assess magnitude of misclassification in relation to other study biases and problems

Prevention of Occupational Cancer

- Cancer incidence and mortality has not declined as rapidly as other major causes of death
- 50% of cancers might be prevented
- Disagreement on the proportion attributable to various risk factors
- Estimates of attributable risks largely based on unverified assumptions
- Effect primary prevention could be achieved by number of exposures and reduction in level of exposure
- Not much direct evidence on effectiveness of occupational exposure intervention
- Epidemiology criteria for establishing causality are stringent and demanding
  - Protect against false positives
  - May have allowed false negatives and impeded adoption of public health measures
- Important remaining issues:
  - Shape of the dose-response and the question of a threshold
  - Complex mixtures and multiple exposures

Tomatis L, Huff J, Hertz-Picciotto I, Sandler DP, Bucher J, Boffetta P, Axelson O, Blair A, Taylor J, Stayner L, Barrett JC. Avoided and avoidable risks of cancer. Carcinogenesis 18:97-105, 1997.

Preventive Approaches

Type of Action	Example
Direct Action	Changing processes or raw ingredients
Regulation	Restricting or banning use in industry
Commerce	Requiring radon assessment
Education	Publicity about the risks from exposure from asbestos

Evidence Indicating That Prevention Works for Occupational Exposures

- Decreased risk when individuals leave an exposure area
- Changes in risks in a cohort as exposure levels decrease
- Lower risks among those entering a workforce when exposures were lower

From: Tomatis et al. Carcinogenesis 1997;18(1):97-105

Cancer Risk After Cessation of Asbestos Exposure Among Cement Workers

(Individuals leave exposure area, i.e., the workplace)

Years since last Exposure	Number	Relative Risk
Lung		
<3	21	0.38
3-15	125	1.00 (referent)
15-30	89	0.70
30+	23	0.56
Pleura		
<3	13	0.67
3-15	55	1.00 (referent)
15-30	55	0.90
30+	16	0.65

From: Magnani et al. Occup Environ Med 2007;65:164-170

Stove Improvement and Lung Cancer in Cohort in China

(Reduction in exposure for the cohort)

Stove Improvement

	None	0-10 Years Later	10-19 Years Later	20+ Years Later
Men	1.0	1.79	0.25	0.07
Women	1.0	1.41	0.24	0.17

All RR are statistically significant

From: Lan et al. J Natl Cancer Inst 2002;94:826-835

Risk of Nasal Adenocarcinoma by Calendar Year of First Exposure to Wood Dusts

(Lower risk among those first exposed at lower levels)

Year of first exposure	# Cases	# Controls	Odds Ratio
Before 1930	7	8	22.9
1930-1941	10	3	86.0
After 1941	0	6	0

From: Hayes et al. Am J Epid 1986;124-569-577

Why So Few Clear Examples of Preventive Successes for Environmental Exposures

- Public tends to view intervention as the final step in the prevention process
- Funding more difficult for studies to characterize preventive effectiveness than to identify etiology
- For chronic diseases a consider time lapse is required before disease rates change

From: Tomatis et al. Carcinogenesis 1997;18(1):97-105

Thanks

QUESTIONS?

Why Preventive Approaches Should Work for Occupational Exposures

- Natural experiments
  - Rates for some cancers go down among migrants
- Toxicologic principle
  - Rates rise with increasing exposure, so they should decline with decreasing exposure
- Empirical evidence
  - Worked for tobacco

Odds Ratios for N-Acetylation, Benzidine, and Bladder Cancer

	Fast Acetylators	Slow Acetylators
Phenotype	1.0	0.3 (0.1-1.3)
Genotype	1.0	0.5 (0.1-1.8)

From: Hayes R, et al. Carcinogenesis 14:675-8, 1993

Explanation of N-acetylation, Benzidine, and Bladder Cancer Results

- Slow acetylation not associated with increased bladder cancer risk among benzidine exposed workers
- Biologic effects of N-acetylation are chemical specific
- Exposure assessment is critical
- Exposure assessment can often be performed more accurately in the workplace than elsewhere