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STONY BROOK CANCER CENTER

Perspectives in Occupational Cancer

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IMPORTANCE OF OCCUPATIONAL CANCER RESEARCH

- Occupation remains an important cause of cancer, especially in men
- It is likely that occupational causes of cancer are yet to be identified
- Once causal associations are identified, control measures are feasible
- The discovery of occupational carcinogens of disease has implications for the general environment
- It provides information relevant to the understanding of disease mechanisms
- It has greatly contributed to methodological research

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OCCUPATIONAL EPIDEMIOLOGY RESEARCH

- Surveillance of exposed workers
- Etiological research
- Special exposure circumstances

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OCCUPATIONAL EPIDEMIOLOGY RESEARCH

- Surveillance of exposed workers
- Etiological research
- Contribution to mechanistic studies

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SURVEILLANCE OF EXPOSED WORKERS

- Burden of occupational cancer
- Shape of the risk function after cessation of exposure
- Risk in workers hired after technological changes
- Risk outside ‘traditional’ industries

NUMBER OF CANCER DEATHS ATTRIBUTABLE TO OCCUPATIONAL EXPOSURES – FRENCH MEN, 2000

- IARC Group 1 agents
- Estimates of exposure prevalence from nationwide survey
- Relative risks from meta-analyses of large studies

Agent	Cancer	P(exp)%	RR	AF%	N deaths
Silica	Lung cancer	2.35	1.20	0.5	96
Radon	Lung cancer	-	-	0.1	23
Wood dust	Sinonasal cancer	-	-	19.2	19
Leather dust	Sinonasal cancer	2.70	1.92	2.4	2
Benzene	Leukemia	1.68	3.30	3.7	100
Asbestos	Lung cancer	9.10	1.48	5.4	1116
	Mesothelioma	-	-	83.2	504
Chromium(VI)	Sinonasal cancer	1.16	5.18	4.6	5
	Lung cancer	1.16	3.10	2.4	489
Cadmium	Lung cancer	0.22	1.17	0.04	8

Boffetta et al., 2010

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NUMBER OF CANCER DEATHS ATTRIBUTABLE TO OCCUPATIONAL EXPOSURES – FRENCH MEN, 2000

Agent	Cancer	P(exp)%	RR	AF%	N deaths
PAH	Larynx cancer	8.36	1.38	3.1	53
	Lung cancer	8.36	1.37	3.0	619
	Bladder cancer	8.36	1.40	3.2	104
Untreated mineral oils	Skin SCC	5.00	1.46	2.2	5
Aromatic amines	Bladder cancer	0.61	1.60	0.4	12
Butadiene	Leukemia	0.25	1.16	0.04	1
SHS (never smokers)	Lung cancer	56.7	1.12	6.4	54
Painters	Lung cancer	2.00	1.29	0.6	119
	Bladder cancer	2.00	1.23	0.5	15
Rubber industry	Bladder cancer	1.10	2.40	1.5	49
	Leukemia	1.10	1.30	0.3	9
Total				4.0	3440

FRACTION OF CANCERS ATTRIBUTABLE TO OCCUPATIONAL EXPOSURES IN MEN

Reference	Population	Method	I/M	All ca AF	Lung ca AF
Doll & Peto, 1981	USA	Review	M	7%	15%
Dreyer et al., 1997	Nordic c.	RR, exp	I	3%	13%
Boffetta et al., 2010	France	RR, exp	M	4%	10%
Parkin et al., 2011	UK	RR, exp	I	5%	20%
GBD, 2020	Global	RR, exp	M	4%	18%

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BURDEN OF OCCUPATIONAL CANCER

- Targeting interventions
- Identifying gaps in knowledge and priorities for future research

- Methodological issues
  - Interactions
  - Evolving exposure circumstances

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SURVEILLANCE OF EXPOSED WORKERS

- Burden of occupational cancer
- Risk after cessation of exposure
- Risk in workers hired after technological changes
- Risk outside ‘traditional’ industries

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STUDYING THE EFFECT OF CESSATION OF EXPOSURE

- Need for long-term follow-up
- Assumption of no temporal changes in other determinants of the disease

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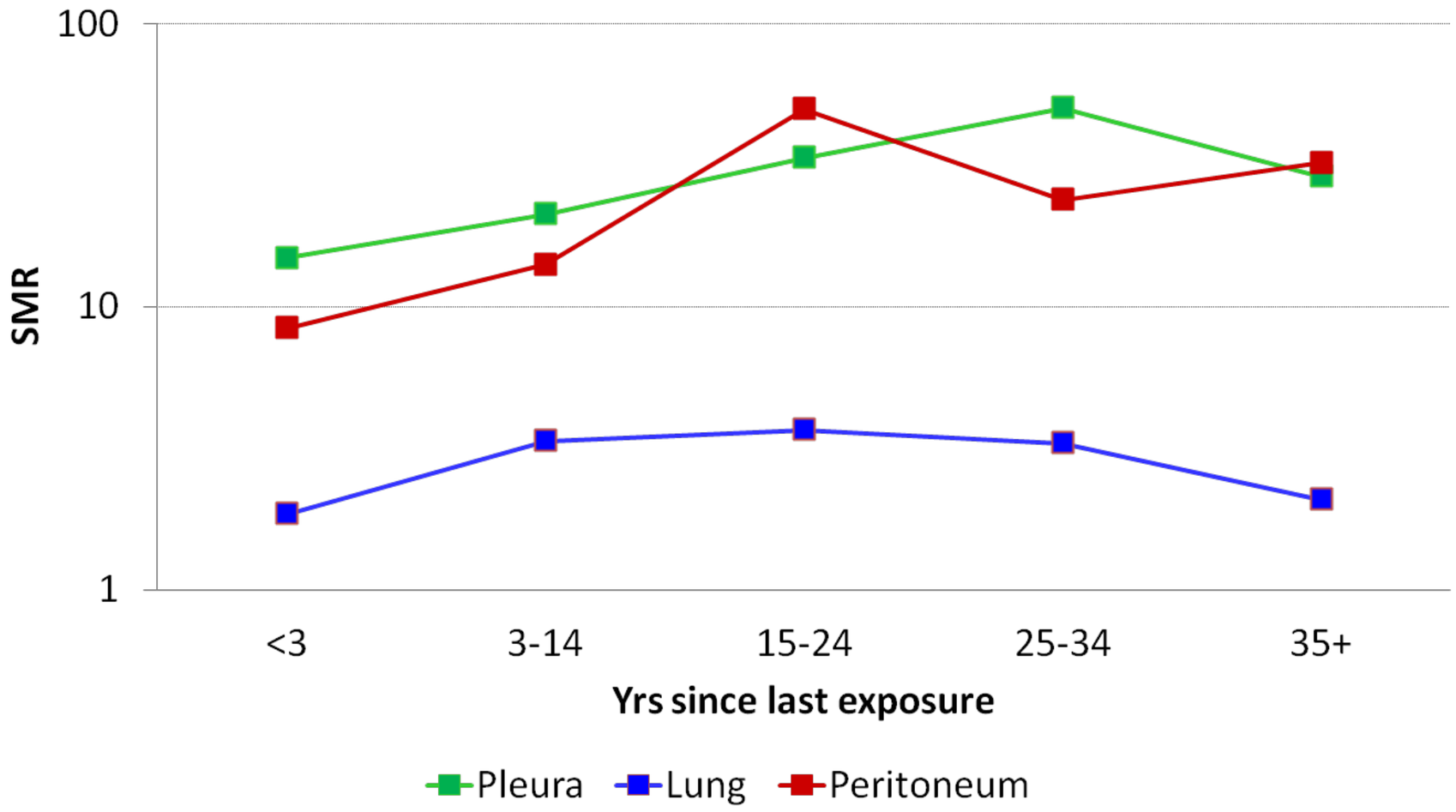
MORTALITY IN ASBESTOS TEXTILE WORKERS BY YEARS SINCE LAST EXPOSURE



Pira et al., 2016

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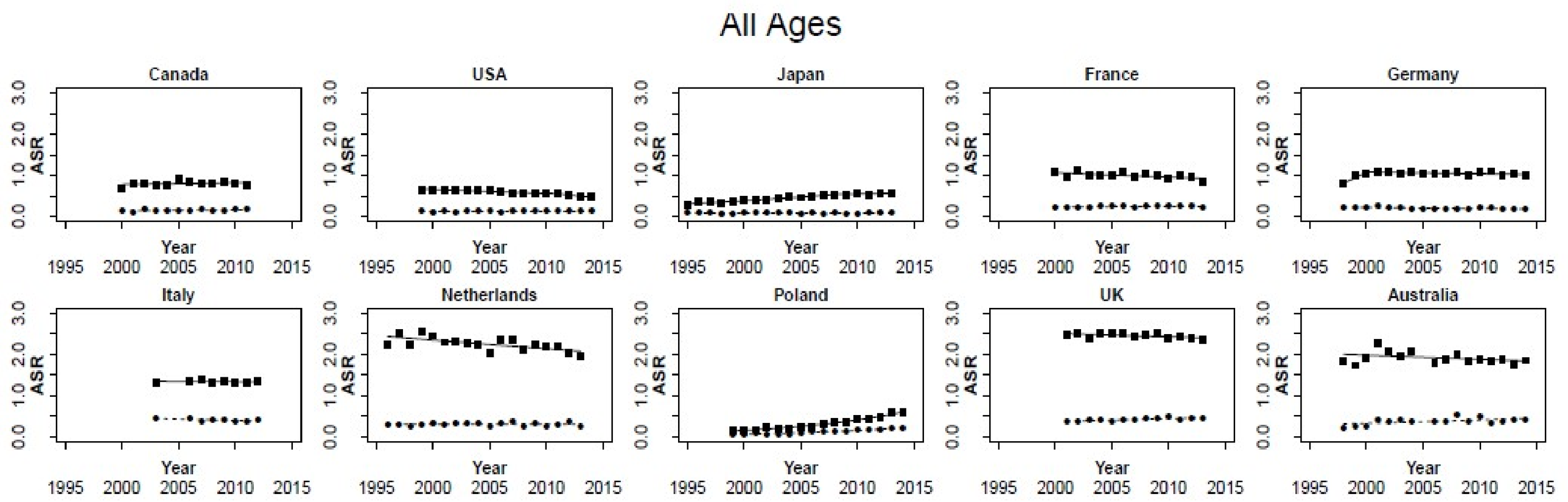
TEMPORAL TRENDS IN MESOTHELIOMA MORTALITY IN SELECTED COUNTRIES



■ men ♦ women

Boffetta et al., 2018

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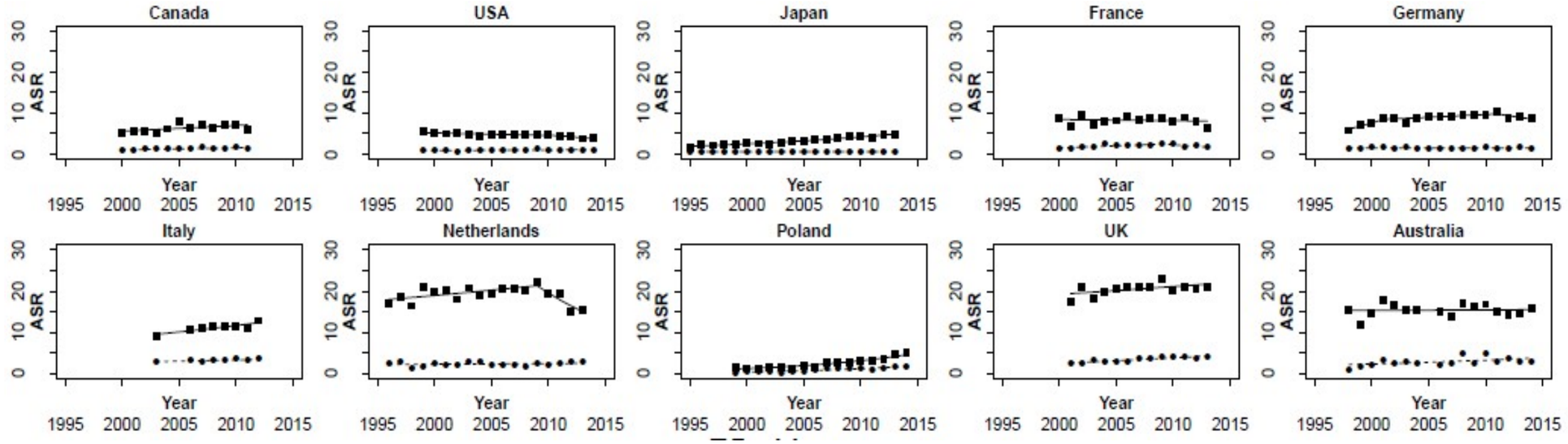
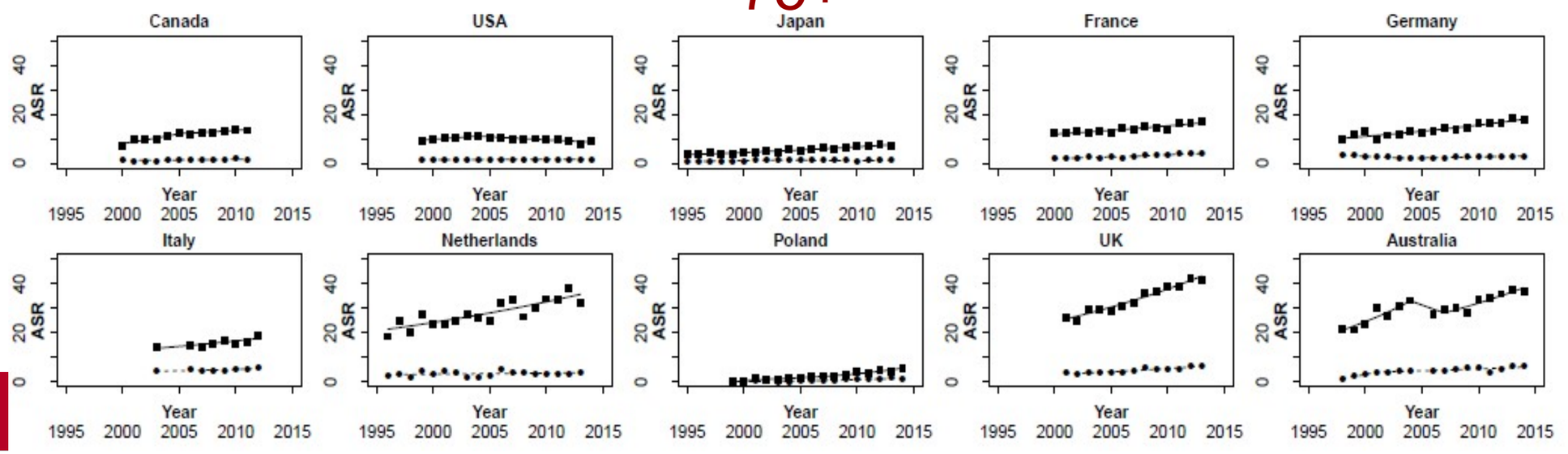
TEMPORAL TRENDS IN MESOTHELIOMA MORTALITY – AGE 65+

65-74



75+



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STUDYING THE EFFECT OF CESSATION OF EXPOSURE

- Detailed information on risk functions
- Implications for surveillance and compensation
- Information on disease mechanisms

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SURVEILLANCE OF EXPOSED WORKERS

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- Risk in workers hired after technological changes
- Risk outside ‘traditional’ industries

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STUDYING THE EFFECT OF CHANGES IN EXPOSURE CIRCUMSTANCES

- Evidence of risk reduction from many industries
- Evidence at ecological level

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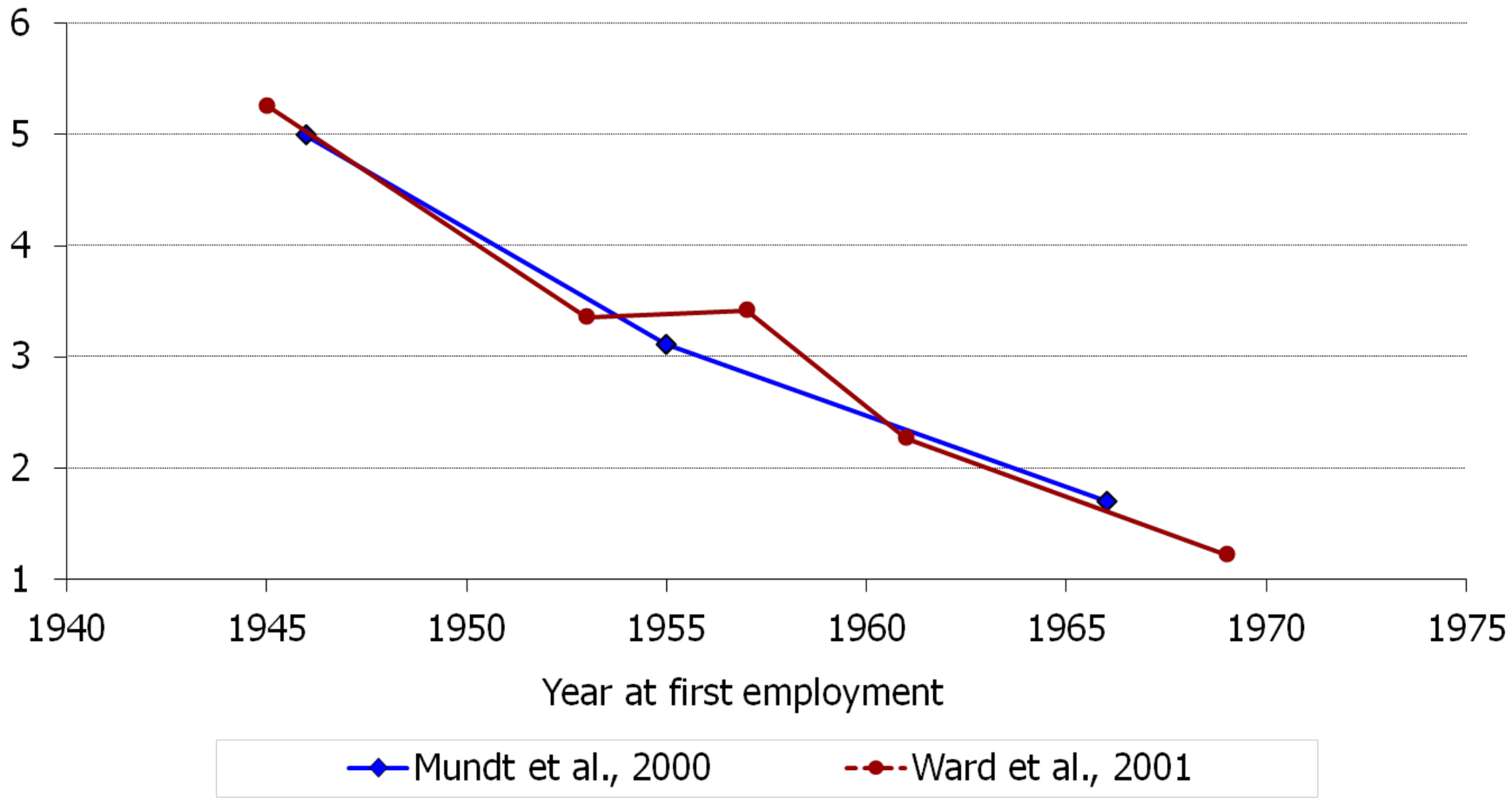
SMR OF LIVER CANCER IN TWO COHORTS OF VINYL CHLORIDE WORKERS



Boffetta et al., 2003

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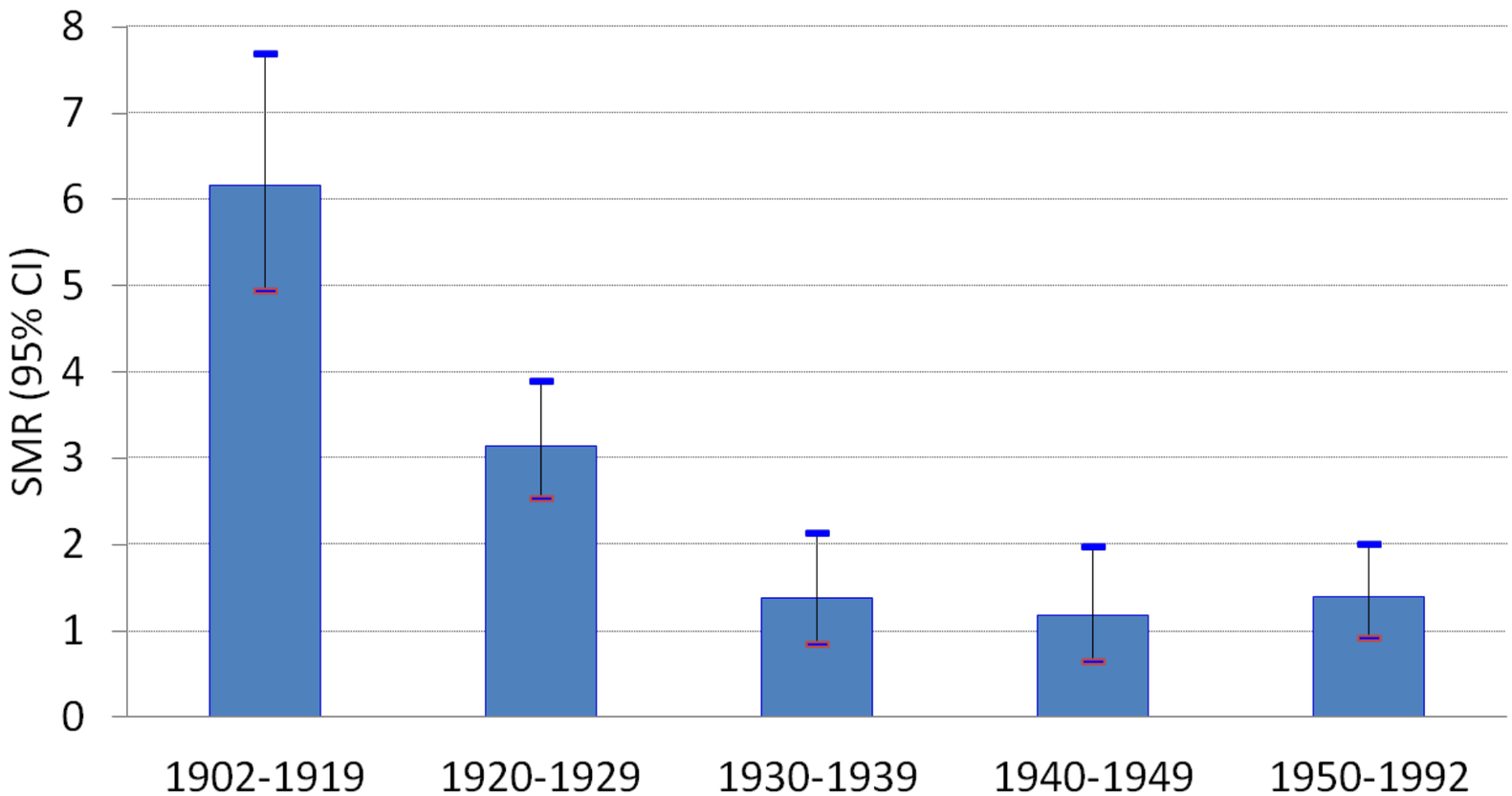
SMR OF LUNG CANCER IN WELSH NICKEL WORKERS BY YEAR OF FIRST EMPLOYMENT



Grimsrud & Peto, 2006

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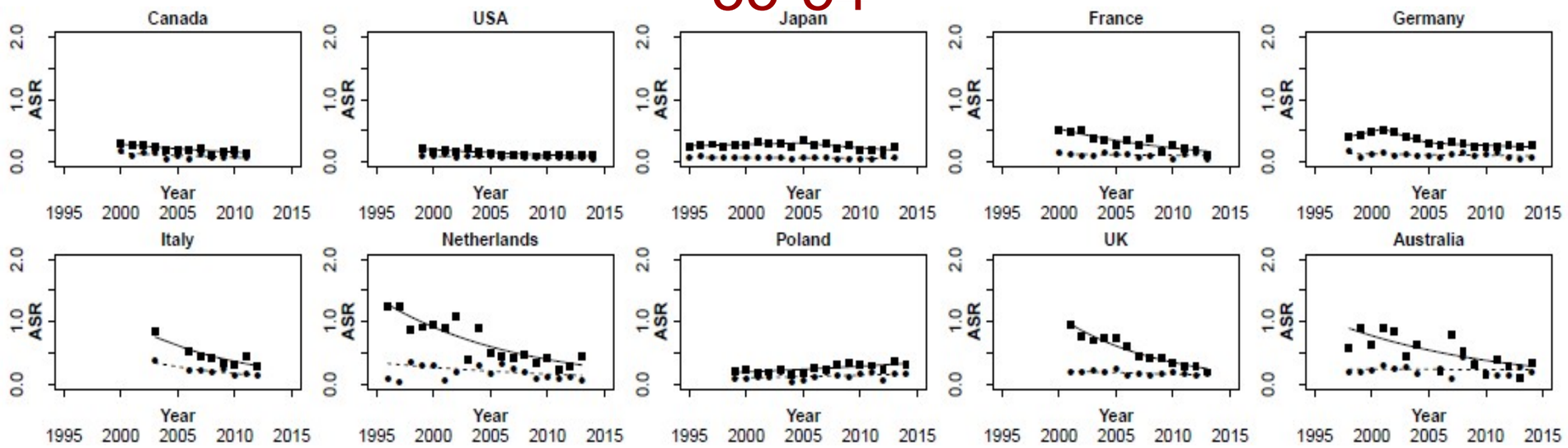
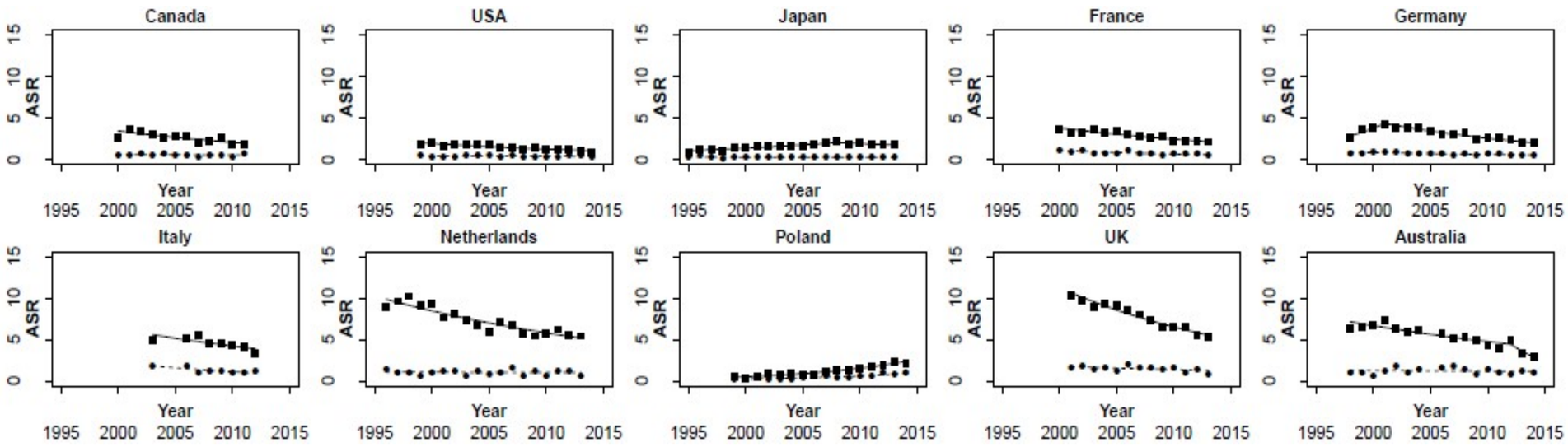
TEMPORAL TRENDS IN MESOTHELIOMA MORTALITY – AGE <65

35-54



55-64



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STUDYING THE EFFECT OF CHANGES IN EXPOSURE CIRCUMSTANCES

- Effectiveness of preventive measures
- Information on disease mechanisms

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RISK OF MESOTHELIOMA IN DIFFERENT OCCUPATIONAL GROUPS

Occupational category	Cases	Controls	OR (95% CIs)
Non-construction high risk			
Any non-construction high-risk job	102	78	16.8 (9.6, 29.3)
Construction			
Carpenter	93	36	36.0 (19.2, 67.3)
Plumber, electrician, painter or decorator	115	96	14.6 (8.8, 24.4)
Other construction	81	120	7.9 (4.7, 13.3)
Medium-risk industrial			
Any medium-risk industrial job	157	331	5.2 (3.3, 8.2)
Low-risk industrial			
Any low-risk industrial job	153	406	4.1 (2.6, 6.4)
Reference group[a]	25	278	1.0 (ref)

Rake et al., 2009

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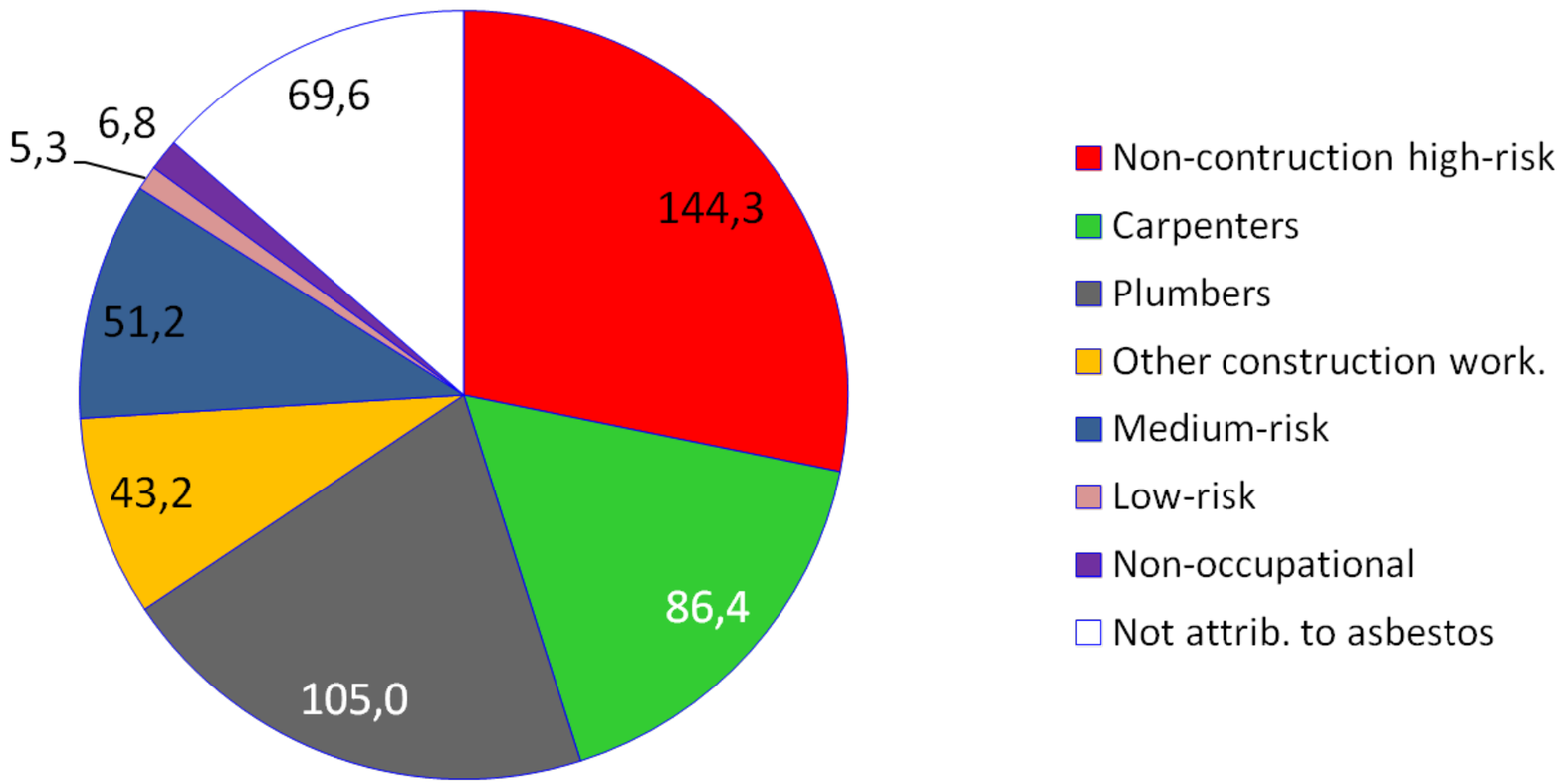
NUMBER OF CASES ATTRIBUTABLE TO DIFFERENT SOURCES OF ASBESTOS EXPOSURE



Rake et al., 2009

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OCCUPATIONAL EPIDEMIOLOGY RESEARCH

- Surveillance of exposed workers
- Etiological research
- Information on disease mechanisms

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ETIOLOGICAL RESEARCH

- Identification of causal associations
- Interactions
- Indirect effects of occupation on disease risk
- Special exposure circumstances

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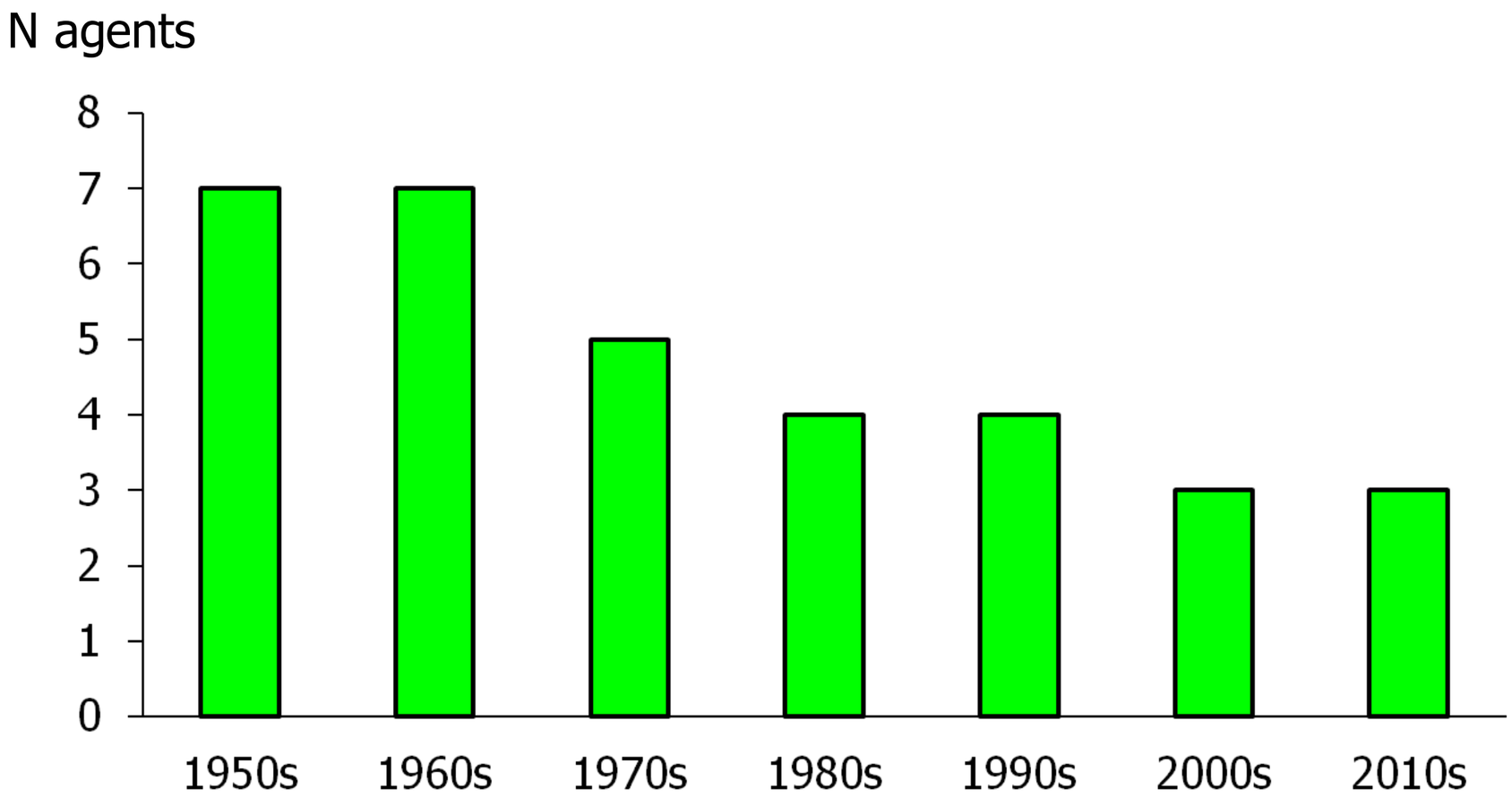
DECADE OF PUBLICATION OF KEY RESULTS FOR IARC GROUP 1 EVALUATION (N=32)



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EVOLUTION OF CLASSIFICATION OF IARC GROUP 1 CARCINOGENS (N=32)

	In earlier years		
Rating	IARC 1987	IARC 1979	WHO 1964[(1)]
1	19	16	13
2A	5	3	3
2B	1	2	N/A
3	1	1	N/A
Unrated	6	10	16

(1) WHO. Prevention of cancer. Report of an Expert Panel. No 276, Geneva, 1964.

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‘HISTORICAL’ AND ‘NEW’ OCCUPATIONAL CARCINOGENS

	Historical carcinogens	*New carcinogens*
Potency	High	Low
Exposure levels	High	Low
Co-exposures	Few	Many
Target tumour	Rare	Common

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CARCINOGENS INCLUDED IN FIRST WHO LIST

Agent	Target organ	RR
Sunlight	Skin	4
Tobacco chewing	Oral cavity	4
Tobacco smoking	Lung	15
Alcohol drinking	Oral cavity	5
Aromatic amines	Bladder	8
Asbestos	Lung	5

WHO, 1964

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EXAMPLES OF 'NEW' CARCINOGENS

Agent	Target organ	Year	RR
Tobacco smoking	Liver	2004	1.6
Involuntary smk	Lung	2004	1.25
Formaldehyde	NPC	2007	1.3
Alcohol drinking	Breast	2007	~1.2
1,3 Butadiene	Lymphohem.	2008	1.15

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THE EXAMPLE OF THE SEMI-CONDUCTOR INDUSTRY

- Suspected toxic reproductive effects
- Exposure to experimental carcinogens
  - indium phosphide, gallium arsenide
- Rapidly evolving technology
- Unstable workforce
- Migration of industry to low- and medium-resource countries

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ETIOLOGICAL RESEARCH

- Identification of new causal association
  - new target organs
- Interactions
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INTERACTIONS

- Risk from exposure A depends on presence of exposure B (and vice-versa)
- Risk from joint exposure to A and B (or any two factors) differs from what would be expected based on the separate effects
  - Requires knowing what we should expect for joint effects

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INTERACTION BETWEEN NAT2 POLYMORPHISM AND EXPOSURE TO AROMATIC AMINES

	Unexposed	Exposed	Marginal effect
NAT2 rapid	1.0 (Ref.)	2.19 (1.35, 3.56)	2.19
NAT2 slow	1.24 (0.90, 1.71)	3.20 (2.12, 4.82)	2.58
Marginal effect	1,24	1.46	

Vineis et al., 2001

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STUDYING INTERACTIONS

- Rationale for studying interactions
  - Stronger effects
  - Subgroups at higher risk
  - Information on mechanisms of disease
- Models of interaction
  - Additive model: $RR_{AB} \neq (RR_A - 1) + (RR_B - 1) + 1$
  - Multiplicative model: $RR_{AB} \neq RR_A \times RR_B$
  - Lack of power to discriminate between models

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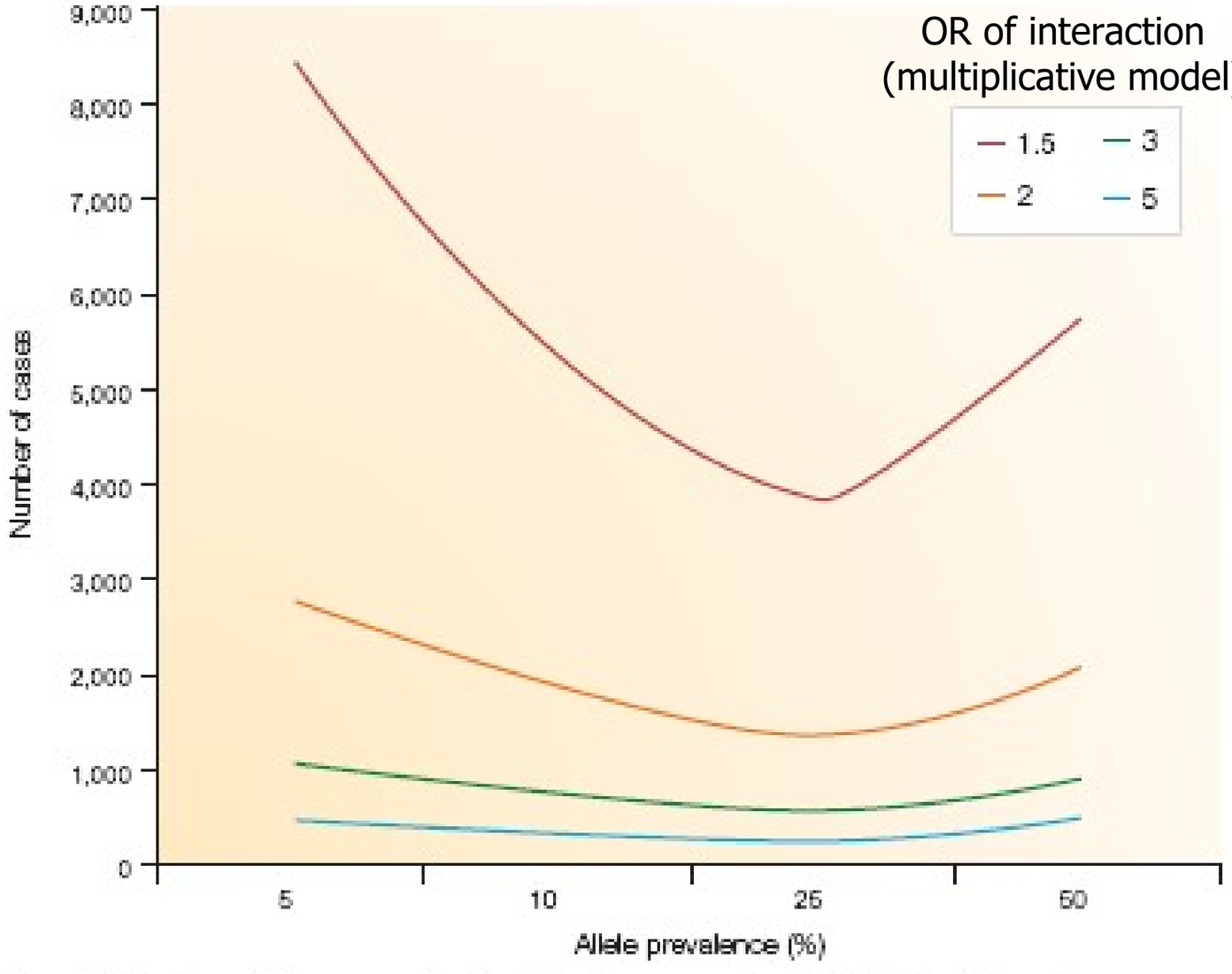
SAMPLE SIZE REQUIREMENT FOR GXE INTERACTIONS



OR_G = 1.5
OR_{eE}= 1.5
p(exp) = 0.1
α = 0.05
1 – β = 0.8
ca/co ratio = 1

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INTERACTION BETWEEN NAT2 POLYMORPHISM AND EXPOSURE TO AROMATIC AMINES

	Unexposed	Exposed
NAT2 rapid	1.0	2.19
NAT2 slow	1.24	3.20

Additive model: (2.19 – 1) + (1.24 – 1) + 1 = 2.43
Multiplicative model: 2.19 x 1.24 = 2.72

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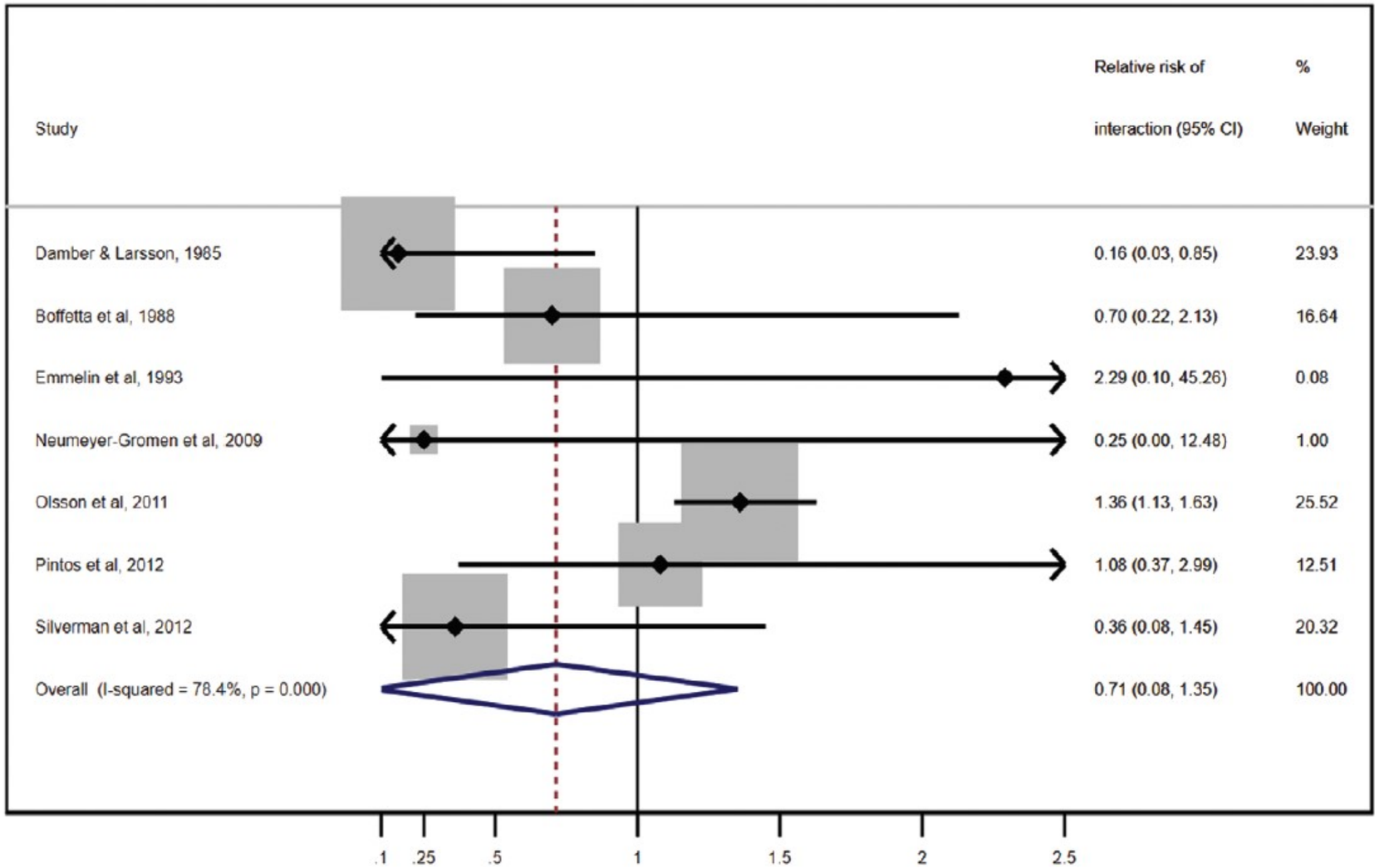
INTERACTION BETWEEN DIESEL EXHAUST AND TOBACCO SMOKING IN LUNG CANCER



Rizzello et al., 2021

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ETIOLOGICAL RESEARCH

- Identification of new causal association
  - new target organs
- Interactions
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INDIRECT EFFECTS OF OCCUPATION ON DISEASE RISK

- A large proportion of cancers are due to lifestyle factors, which might be influenced by occupation
  - delayed age at first pregancy, reduced duration of breastfeeding → breast cancer
  - reduced physical activity → colon cancer
- Poorly studied relationships
- Impact possibly larger than traditional carcinogens

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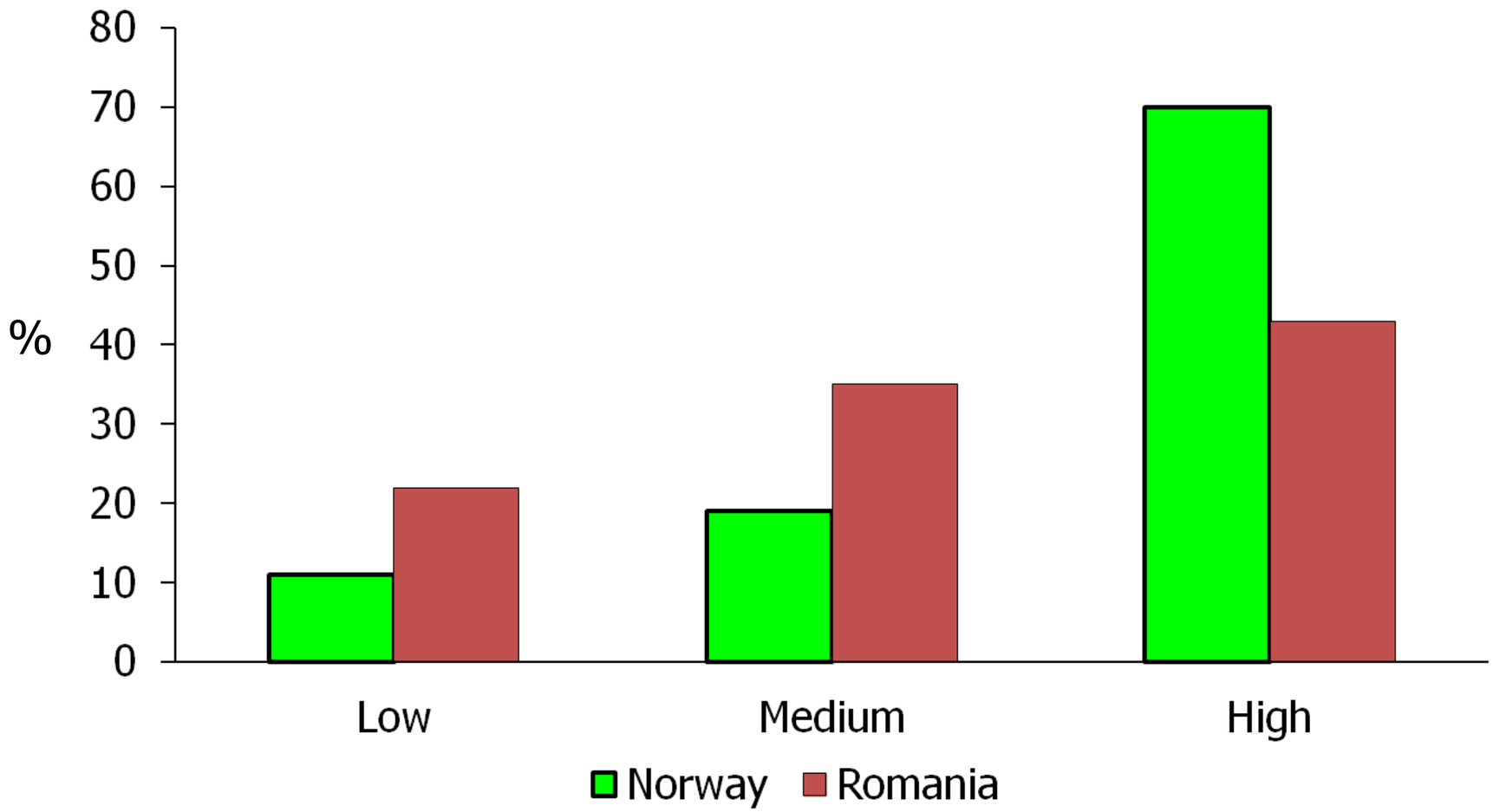
% OF LIVE BIRTHS IN MOTHERS 35+ YRS BY EDUCATION LEVEL, 2017



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ETIOLOGICAL RESEARCH

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OCCUPATIONAL CANCER IN LOW- AND MEDIUM INCOME COUNTRIES

- Exposure circumstances
  - Lack of data for most industries and countries
  - Obsolete technology
  - Lack of workers' training
  - Informal sector
- Limited evidence from analytical studies
  - short latency
  - poor exposure characterization
- Susceptibility
  - childhood exposure
  - infections

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PREVALENCE OF EXPOSURE TO OCCUPATIONAL CARCINOGENS IN BRAZIL

	Norte			Nordeste			Sudeste		
	Total	Masc	Fem	Total	Masc	Fem	Total	Masc	Fem
Asbesto	1,36	1,50	1,22	2,08	2,33	1,84	4,41	4,95	3,89
Benzeno	3,09	3,40	2,78	4,44	4,98	3,92	9,93	11,15	8,76
Benzopireno	0,91	1,00	0,82	0,36	0,40	0,32	0,13	0,15	0,11
Borracha	0,10	0,11	0,09	0,12	0,13	0,11	0,24	0,27	0,21
Diesel	2,56	2,82	2,30	2,45	2,75	2,16	1,14	1,28	1,01
Formaldeído	1,11	1,22	1,00	1,94	2,18	1,71	4,34	4,87	3,83
Fundição de aço e ferro	1,14	1,25	1,03	2,23	2,50	1,97	3,79	4,25	3,34
Níquel	0,96	1,06	0,86	0,40	0,45	0,35	0,16	0,18	0,14
Pintor	0,88	0,97	0,79	1,44	1,62	1,27	3,91	4,39	3,45
Poeira de couro	0,71	0,78	0,64	1,13	1,27	1,00	1,97	2,21	1,74
Poeira de madeira	3,81	4,19	3,43	4,19	4,70	3,70	1,70	1,91	1,50
Radiação Gama	0,04	0,04	0,04	0,04	0,04	0,04	0,15	0,17	0,13
Radiação Solar	3,87	4,26	3,48	5,35	6,01	4,72	1,74	1,95	1,54
Radônio	1,06	1,17	0,95	1,44	1,62	1,27	3,02	3,39	2,66
Sílica	1,57	1,73	1,41	2,11	2,37	1,86	5,83	6,54	5,14

Legenda: Masc – Masculino; Fem – Feminino

Azevedo e Silva et al., 2014

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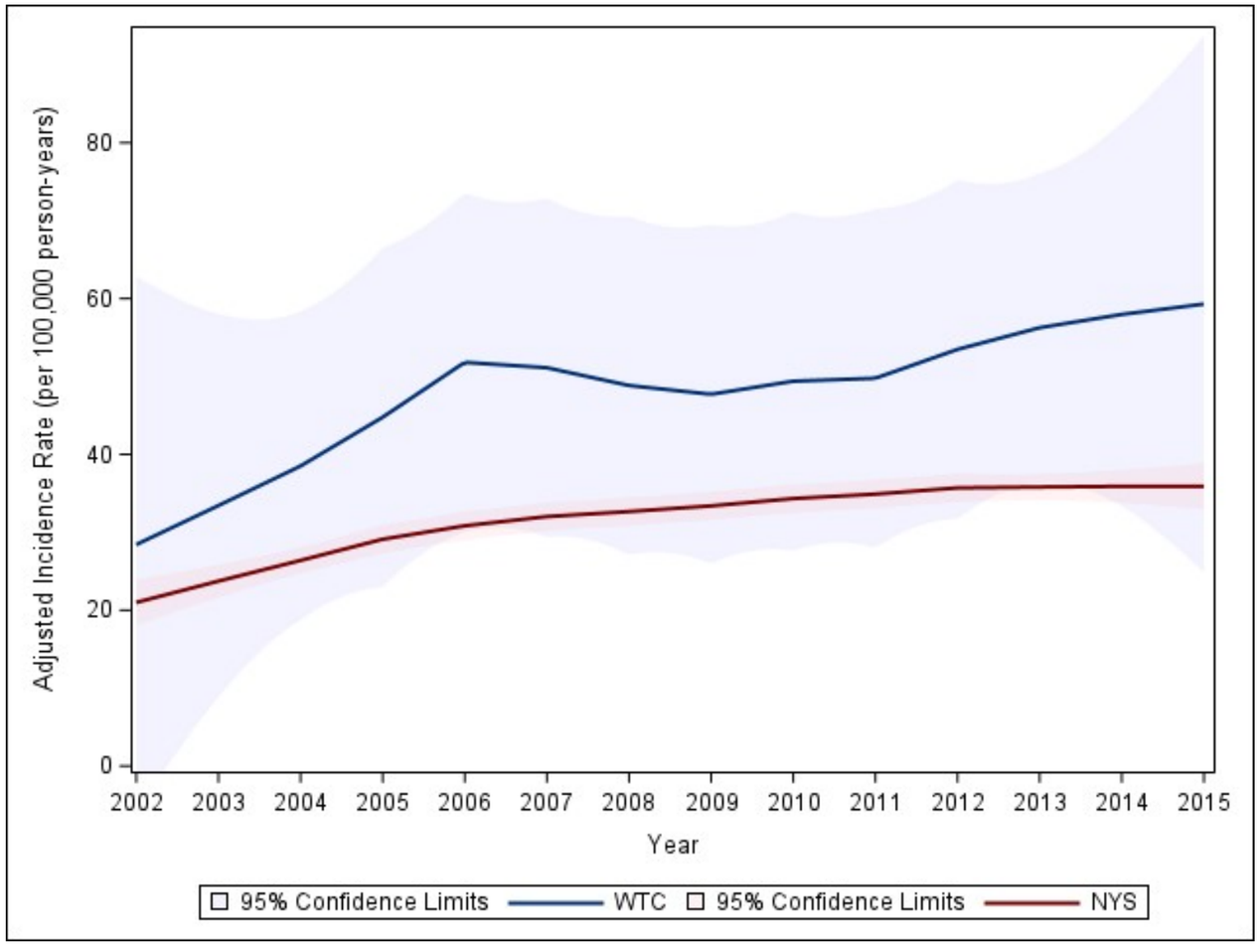
INCIDENCE OF MELANOMA AMONG WORLD TRADE CENTER RESPONDERS

- 58,000 WTC rescue and recovery workers
- Firefighters, police officers, EMS workers, construction workers
- On-going follow-up
- Comparisons
  - NYS population
  - Other occupational cohorts
  - Internal analyses



Boffetta et al., 2021

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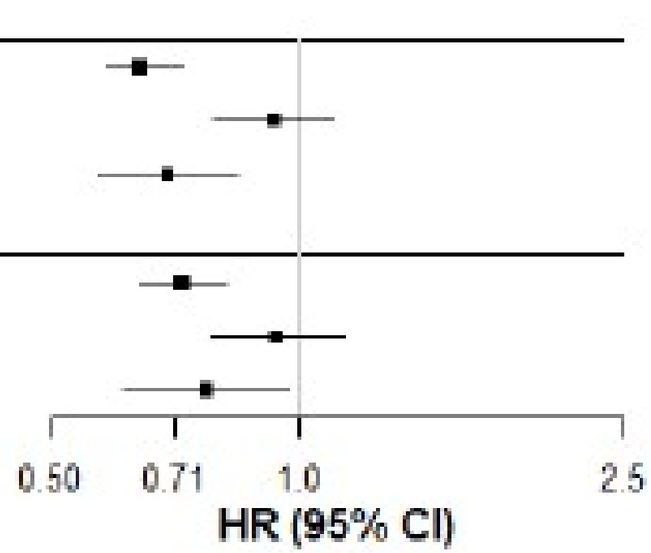
MORTALITY AMONG WTC RESPONDERS DIAGNOSED WITH CANCER, 2005-2015

- 2037 cases among WTC responders enrolled in medical monitoring and treatment program
- 564 cases among WTC responders not enrolled in the program
- Comparison with 11 Southern NYS counties

	HR (95% CI)
All-cause mortality	
WTC-MMTP vs. NYS-non-responders	0.64 (0.58, 0.72)
WTC-non-MMTP vs. NYS-non-responders	0.93 (0.79, 1.10)
WTC-MMTP vs. WTC-non-MMTP	0.69 (0.57, 0.84)
Cancer-specific mortality	
WTC-MMTP vs. NYS-non-responders	0.72 (0.64, 0.82)
WTC-non-MMTP vs. NYS-non-responders	0.94 (0.78, 1.14)
WTC-MMTP vs. WTC-non-MMTP	0.77 (0.61, 0.97)



Boffetta et al., 2021

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OCCUPATIONAL EPIDEMIOLOGY RESEARCH

- Surveillance of exposed workers
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- Information on disease mechanisms

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CONTRIBUTION OF OCCUPATIONAL EPIDEMIOLOGY TO MECHANISTIC RESEARCH

- Direct
  - molecular cancer epidemiology
- Indirect
  - interpretation of descriptive and analytical studies

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EPIDEMIOLOGICAL STUDIES OF LHN IN WORKERS EXPOSED TO ETHYLENE OXIDE

Industry	N studies	N cases	RR	95% CI
Chemical	6	32	1.3	0.9-1.8
Sterilization	3	41	1.1	0.8-1.5

Dose-response in US cohort of sterilization workers
RR for 45 ppm-yrs: 1.2 (95% CI 1.1-1.4)

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ETHYLENE OXIDE HB ADDUCTS

- *N*-2(hydroxyethyl) adducts at N-terminal of His and Val
- Studies of exposed workers from Netherlands, Sweden, US, Mexico
- Same adducts found in exposed rats and mice, with dose-response

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AGENTS CLASSIFIED IN GROUP 1
IARC MONOGRAPHS VOLUMES 1-100

Type of evidence	N
Evidence from traditional epidemiology	85
Evidence from molecular epidemiology	11*
Mechanistic evidence	10
Evidence from other relevant data	1
Total	107

* 9 biological agents

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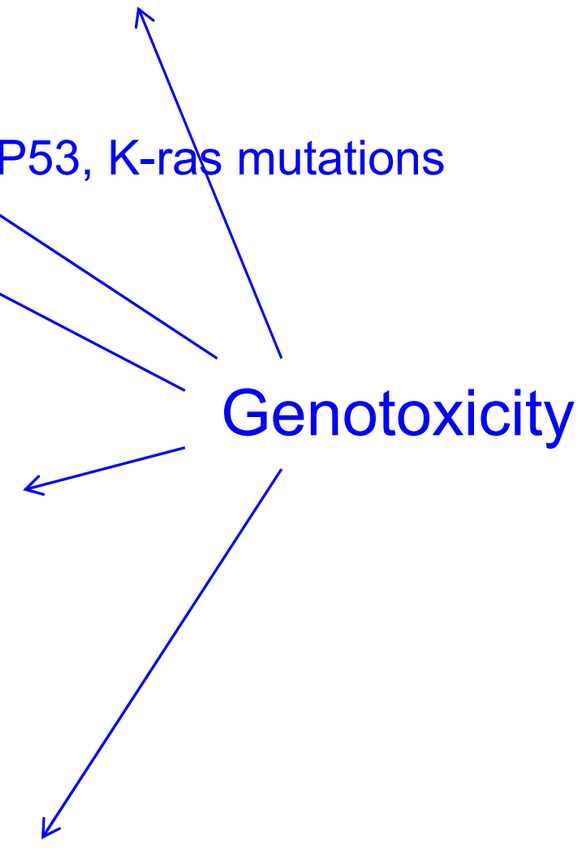
MECHANISTIC EVIDENCE CRITICAL TO HAZARD IDENTIFICATION

Agent	Mechanisms
Aristolochic acid	DNA adducts; TP53 mutations
NNN, NNK	DNA adducts
BaP	DNA, protein adducts; TP53, K-ras mutations
Dyes metabolized to benzidine	Metabolism
Ethylene oxide	Protein adducts
MOCA	DNA adducts; SCE, MN
Etoposide	MLL translocations
PCB-126	AhR receptor
PCDBF	AhR receptor
Phenacetin	Genotoxicity; cell proliferation



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INDIRECT CONTRIBUTION OF EPIDEMIOLOGY

- Analytical studies
  - tobacco smoking and lung cancer
  - asbestos and mesothelioma
  - hormones/nutrition and breast cancer
- Descriptive epidemiology
  - general model of carcinogenesis
  - asbestos and mesothelioma

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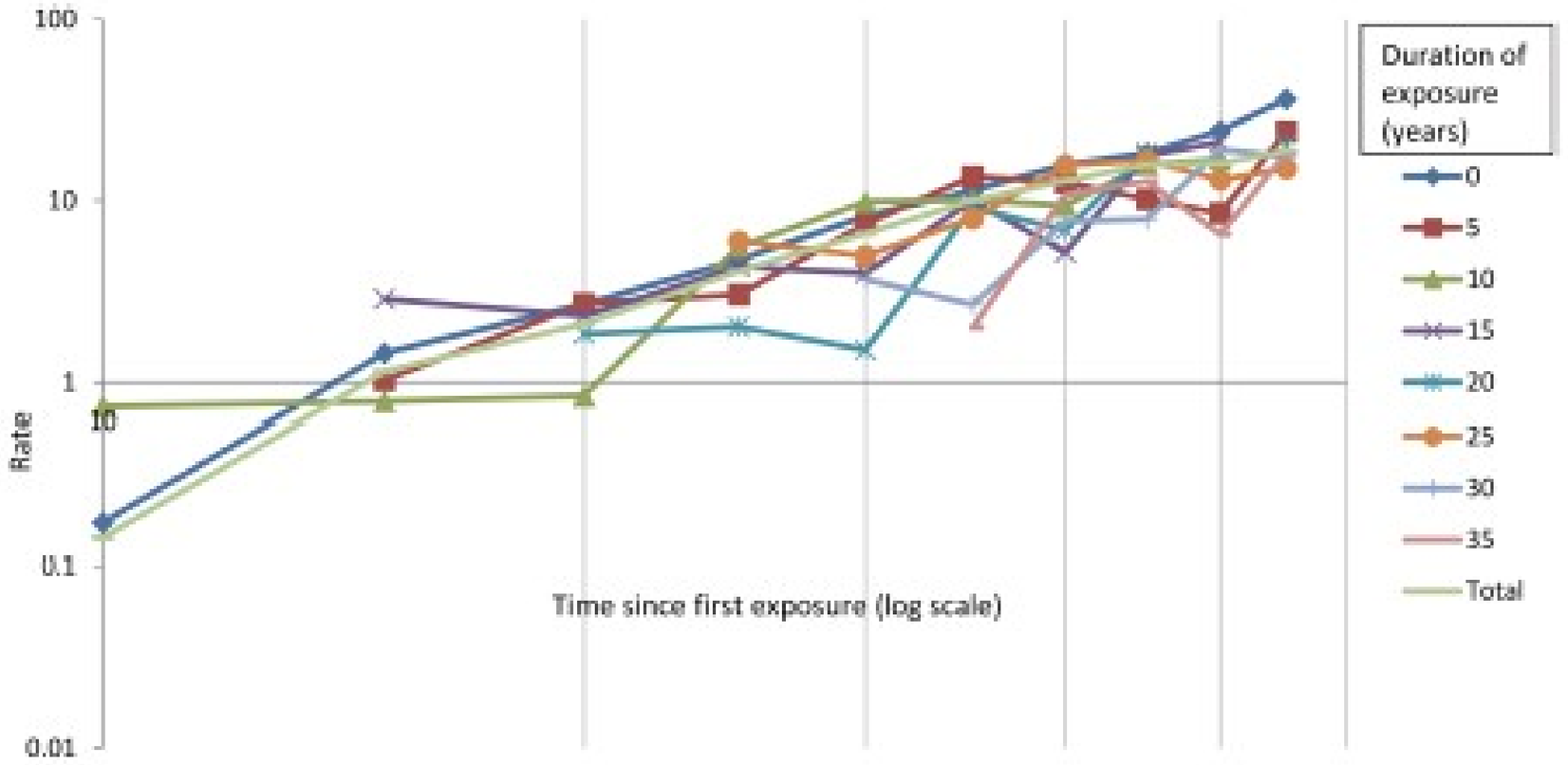
EFFECT OF TIME SINCE FIRST EXPOSURE
NO EFFECT OF DURATION OF EXPOSURE



Pleural mesothelioma rate by time since first exposure and duration of exposure
Pooled analysis of 8 cohorts

Reid et al., 2014

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MESOTHELIOMA TREND ANALYSIS INTERPRETATION

- Strong association with time since first exposure
- No association with duration of exposure
- Limited/no effect of cessation of exposure
- Consistent with an effect on the early stages of carcinogenesis
- Role of biopersistence of fibers in the pleura

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CONCLUSIONS

- Occupational cancer in high-resource country is a success story in cancer control
- Efforts should be made to investigate and control occupational cancer in medium- and low-income countries
- Occupational cancer has implications for cancer research and control in general

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