Occupational case studies and case-control studies

Michelle Turner

March 29, 2022

OMEGA-NET

Objectives

- Define case reports and case series
- Describe their strengths and limitations
- Examples of case reports and case series and how they may contibute to epidemiological understanding

Case Report

Dictionary of Epidemiology, 6th Ed.

“Detailed descriptions of a few patients or clinical cases (frequently, just one sick person) with an unusual disease or complication, uncommon combination of diseases, an ususual or misleading semiology, case, or outcome (maybe a surprising recovery). They are often preliminary observations that are later refuted. They cannot estimate disease frequency or risk (e.g., for lack of a valid denominator)…”

National Cancer Institute

“A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin).”

Case Series

Dictionary of Epidemiology, 6th Ed.

“A collection of subjects (usually, patients) with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, exposure, or diagnostic procedure.”

National Cancer Institute

“A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment.”

Example 1 – First report of a possible association between asbestos and mesothelioma (outbreak of mesothelioma in crocidolite mining region). Most cases had worked in the mines (23/33), some did not (10/33) .

DIFFUSE PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE IN THE NORTH WESTERN CAPE PROVINCE

BY

J. C. WAGNER, C. A. SLEGGS, and PAUL MARCHAND

From the Pathology Division, Pneumoconiosis Research Unit of the Council for Scientific and Industrial Research, Johannesburg, West End Hospital, Kimberley, and the Department of Thoracic Surgery, University of the Witwatersrand and Johannesburg General Hospital

(RECEIVED FOR PUBLICATION APRIL 24, 1960)

Primary malignant tumours of the pleura are uncommon. Thirty-three cases (22 males, 11 females, ages 31 to 68) of diffuse pleural mesothelioma are described; all but one have a probable exposure to crocidolite asbestos (Cape blue). In a majority this exposure was in the Asbestos Hills which lie to the west of Kimberley in the north west of Cape Province. The tumour is rarely seen elsewhere in South Africa.

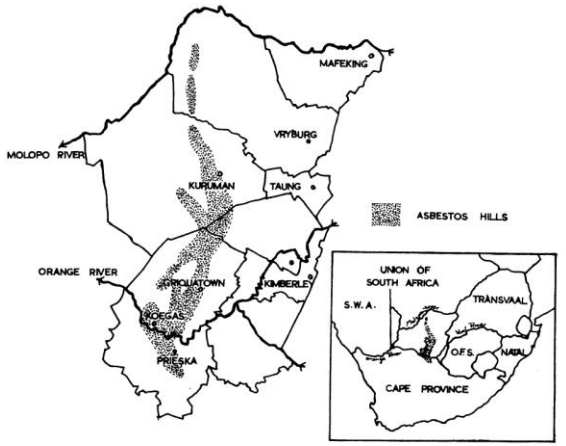

FIG. 1.—Map of Griqualand West asbestos fields.

TABLE 3

DIFFUSE PLEURAL MESOTHELIOMA: ASSOCIATION WITH ASBESTOS

(1) Case No.	(2) Year of Birth	(3) Age at Diagnosis	(4) Race	(5) Sex	(6) Born on Asbestos Fields	(7) Asbestos Exposure	(8) Diagnosed on Biopsy	(9) Necropsy	(10) Histological Evidence of Asbestosis	(11) Survival from Initial Symptoms (in months)
1	1920	36	B	M	+	Other history unknown until came to the Witwatersrand at the age of 23	−	+	+	8
2	±1913	±42	MXD	M	+	Mined asbestos from 1930-33; left area at the age of 27	−	+*	−	29
3	1902	53	B	F	+	Lived whole life in a location near an asbestos mill	+	−	−	11
4	1896	58	W	F	+	Lived on asbestos fields until the age of 5; worked in asbestos warehouse 1916-20	+	−	−	30
5	1925	31	B	M	+	Spent all his working life in the vicinity of mines	−	+*	−	11
6	1903	53	W	F	+	Lived all her life in the vicinity of mines	+	−	−	15
7	1920	36	W	M	+	Lived all his life in the vicinity of mines; worked as a miner	+	−	+	24
8	1894	63	MXD	F	+	From the age of 24 lived in a village serving local mines; often visited mines; watched cobbing outside houses	+	−	−	5
9	1905	52	MXD	M	+	Whole life spent near mines, digging wells	+	−	−	5
10	1909	49	W	M	+	Lived at the mine from age 7-17 years; played on dumps and in mine as a boy; returned to assist from age 21-25	+	−	−	13

Case Histories

The following eight case histories illustrate various aspects of the disease and the different types of exposure to asbestos dust.

Case 1.—B.P., a Bantu male, 36 years of age (born 1920), was a mine labourer, and was the first case diagnosed as a mesothelioma with evidence of asbestosis. He was born in the Kuruman district but it is not known whether he worked in the asbestos mines. He was employed on the Witwatersrand gold-mines underground for two years and in the change rooms for a further 11 years.

A radiograph taken at a mine hospital on August 18, 1955 showed a massive right-sided pleural effusion, and 3,000 ml. of fluid was withdrawn. He was admitted to the Witwatersrand Native Labour Association Hospital on August 24, 1955, and two days later aspiration yielded 1,000 ml. of thick gelatinous pus "which could be pulled out in threads". He was treated with frequent aspirations and instillation of varidase but without improvement, and he died on February 15, 1956 (Martiny, 1956).

At autopsy the right thoracic cavity was occupied by a large gelatinous tumour which displaced the mediastinum and compressed the left lung. The tumour had infiltrated the pericardium. The right lung was completely compressed by neoplastic tissue (Fig. 2) but the right bronchial tree did not show any evidence of a primary bronchogenic carcinoma. Histological sections of the pleural growth showed a papillary mesothelioma (Fig. 3). There was evidence of asbestosis in both lungs (Fig. 4).

IARC 2012

Example 1 – First report of a possible association between asbestos and mesothelioma (outbreak of mesothelioma in crocidolite mining region). Most cases had worked in the mines (23/33), some did not (10/33) .

- Very rare cancers
- Few known risk factors
- Initial case reports were thus credible
- Association confirmed in large number of subsequent cohort and case–control studies
- Causal association has now been well established

IARC 2012, 2021

Example 2 – Bladder cancer in *ortho*-anisidine exposed workers

An epidemic of bladder cancer: ten cases of bladder cancer in male Japanese workers exposed to *ortho*-toluidine

Makiko Nakano[1], Kazuyuki Omae[1], Toru Takebayashi[1], Shigeru Tanaka[2] and Shigeki Koda[3]

Table 1. Surrogate exposure levels and urinary tract abnormalities in BCa cases.

Case	1	2	3*	4*	5	6	7*	8	9*	10
Surrogate level of exposure										
OT	440	395	380	370	310	258	215	160	105	100
MX	121	315	190	192	155	282	202	80	110	-
AN	256	122	237	175	142	470	155	107	115	-
OA	-	-	-	-	-	65	-	-	60	180
OCA	-	-	-	38	-	-	-	-	75	-
PT	-	-	-	-	-	-	-	-	-	195
Smoking status Pack-years	32	36	0	33	15	39	29.3	10	45	0
Past histories of urinary tract diseases, signs or symptoms: Years before the BCa diagnosis:										
Cystitis	5	11	-	-	21	-	-	11–2 (5 times)	-	-
Interstitial cystitis	-	-	-	-	-	-	-	-	-	2
Gross hematuria	0	0	1	1	12, 7, 2	0	-	2	-	0
Microscopic hematuria	-	-	-	22–1	-	-	-	-	-	-
Incomplete emptying of the bladder	-	11	-	1–0	21	-	-	2–0	-	2–0
Dysuria	12, 5	11	17–1	1–0	21	-	-	-	-	0
Ureteral stones	-	24#	-	22	-	-	-	-	-	-
Subjective symptom at BCa diagnosis										
Hematuria	+	+	+	+	+	+	–	–	–	+
Incomplete emptying of the bladder	–	–	–	–	–	–	–	+	–	+
Dysuria	–	–	+	–	–	–	–	–	–	+

Cases are ordered based on the surrogate level of OT exposure. The surrogate level of exposure to each aromatic amine was calculated as the total job-weight/month for each process for each job-year. Job-weight/month was allocated as follows: 0 (none), 1 (1–2 days per month), 5 (3–9 days per month), and 10 (more than 10 days per month). OT: *ortho*-toluidine, AN: aniline, MX: 2,4-xylidine, PT: *para*-toluidine, OA: *ortho*-anisidine, OCA: *ortho*-chloroaniline

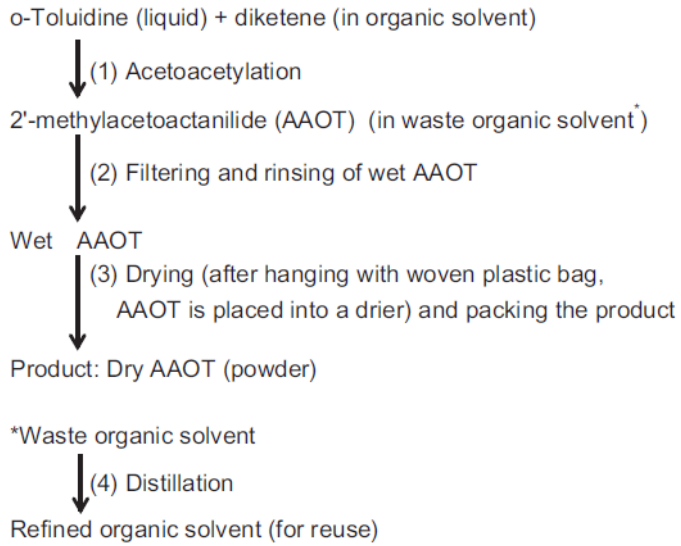

Fig. 1. Flow diagram of the materials and procedures used by the workers

- 10 affected workers hired from 1987-1997 and primarily engaged in drying and packing organic dye and pigment intermediates made from *ortho*-toluidine at two plants
- Of these 10 cases, 3 were also exposed to *ortho*-anisidine
- Surrogate levels of exposure to six aromatic amines were calculated based on number of years and proportion of time spent on each of four production processes each month

IARC, 2021

Example 2 – Bladder cancer in male Japanese workers

- All 3 *ortho*-anisidine-exposed cases were in workers co-exposed to *ortho*-toluidine (Group 1 with *sufficient evidence* in humans for bladder cancer)
- 2 of the 3 ortho-anisidine-exposed cases were also tobacco smokers (Group 1 with *sufficient evidence* in humans for bladder cancer)

IARC, 2021

International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

PREAMBLE

2. Studies of cancer in humans

(a) Types of study considered

"Several types of epidemiological studies contribute to the assessment of carcinogenicity in humans; they typically include **cohort studies** (including variants such as case–cohort and nested case–control studies), **case–control studies**, **ecological studies**, and **intervention studies**. Rarely, results from randomized trials may be available.

Exceptionally, case reports and case series of cancer in humans may also be reviewed."

IARC, 2019

IARC Preamble

"Exceptionally, case reports and case series may provide compelling evidence about the carcinogenicity of an agent. In fact, many of the early discoveries of occupational cancer hazards came about because of observations by workers and their clinicians, who noted a high frequency of cancer in workers who share a common occupation or exposure.

Such observations may be the starting point for more structured investigations, but in exceptional circumstances, when the risk is high enough, the case series may in itself provide compelling evidence. This would be especially warranted in situations where the exposure circumstance is fairly unusual, as it was in the example of plants containing aristolochic acid (IARC, 2012a)."

IARC, 2019

Example 3 – Aristolochic acid nephropathy

- Chinese-herb nephropathy, progressive form of renal fibrosis, develops in some taking weight-loss pills containing Chinese herbs.
- Due to a manufacturing error, one of the herbs in the pills was inadvertently replaced by *Aristolochia fangchi,* which is nephrotoxic and carcinogenic (animal studies).

THE LANCET
Volume 344, Issue 8916, 16 July 1994, Page 188

Letters to the Editor

Urothelial malignancy in nephropathy due to Chinese herbs

Jean-Pierre Cosyns, Michel Jadoul, Jean-Paul Squifflet, Paul-Joseph Van Cangh, Charles van Ypersele de Strihou

The New England Journal of Medicine

VOLUME 342 JUNE 8, 2000 NUMBER 23

UROTHELIAL CARCINOMA ASSOCIATED WITH THE USE OF A CHINESE HERB (*ARISTOLOCHIA FANGCHI*)

JOËLLE L. NORTIER, M.D., PH.D., MARIE-CARMEN MUNIZ MARTINEZ, M.D., HEINZ H. SCHMEISER, PH.D., VOLKER M. ARLT, CHRISTIAN A. BIELER, PH.D., MICHEL PETEIN, M.D., PH.D., MICHEL F. DEPIERREUX, M.D., LUC DE PAUW, M.D., DANIEL ABRAMOWICZ, M.D., PH.D., PIERRE VEREERSTRAETEN, M.D., PH.D., AND JEAN-LOUIS VANHERWEGHEM, M.D., PH.D.

- Among 19 kidneys and ureters removed prophylactically from 10 patients (mean age 40 years) multifocal high-grade carcinoma *in situ* observed in four patients (40%)

- Among 39 patients who agreed to undergo prophylactic surgery (end stage renal failure), there were 18 cases of urothelial carcinoma : 17 cases of carcinoma of the ureter, renal pelvis, or both and 1 papillary bladder tumor (mean age 54 years)

IARC 2012

Example 3 – Aristolochic acid nephropathy

- No control groups for either study

- However,
- Use of Chinese herbs by all women
- Absence of other common exposure
- Presumed low prevalence of malignant disease in this age group compared to high prevalence observed
- Strong temporal association

- **IARC Working Group: causal association between use of the herb and nephropathy/urothelial cancer**

IARC 2012

Example 4 – Bladder cancer and aniline exposure

- Four cohort studies and four case–control studies
- 17 case reports or series, 16 on bladder tumours and one on lung cancer published from 1895-2018

IARC, 2021

Example 4 – Bladder canacer and aniline exposure

An epidemic of bladder cancer: ten cases of bladder cancer in male Japanese workers exposed to *ortho*-toluidine

Makiko Nakano[1], Kazuyuki Omae[1], Toru Takebayashi[1], Shigeru Tanaka[2] and Shigeki Koda[3]

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OCA		-	-	-	38	-	-	-	-	75	-
PT		-	-	-	-	-	-	-	-	-	195
Smoking status	Pack-years	32	36	0	33	15	39	29.3	10	45	0
Past histories of urinary tract diseases, signs or symptoms: Years before the BCa diagnosis:											
Cystitis		5	11	-	-	21	-	-	11–2 (5 times)	-	-
Interstitial cystitis		-	-	-	-	-	-	-	-	-	2
Gross hematuria		0	0	1	1	12, 7, 2	0	-	2	-	0
Microscopic hematuria		-	-	-	22–1	-	-	-	-	-	-
Incomplete emptying of the bladder		-	11	-	1–0	21	-	-	2–0	-	2–0
Dysuria		12, 5	11	17–1	1–0	21	-	-	-	-	0
Ureteral stones		-	24#	-	22	-	-	-	-	-	-
Subjective symptom at BCa diagnosis											
Hematuria		+	+	+	+	+	+	–	–	–	+
Incomplete emptying of the bladder		–	–	–	–	–	–	–	+	–	+
Dysuria		–	–	+	–	–	–	–	–	–	+

Cases are ordered based on the surrogate level of OT exposure. The surrogate level of exposure to each aromatic amine was calculated as the total job-weight/month for each process for each job-year. Job-weight/month was allocated as follows: 0 (none), 1 (l–2 days per month), 5 (3–9 days per month), and 10 (more than 10 days per month). OT: *ortho*-toluidine, AN: aniline, MX: 2,4-xylidine, PT: *para*-toluidine, OA: *ortho*-anisidine, OCA: *ortho*-chloroaniline

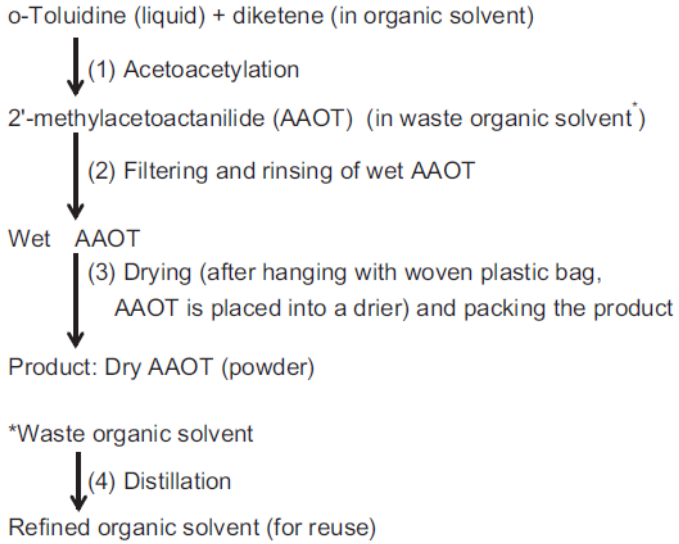

Fig. 1. Flow diagram of the materials and procedures used by the workers

- Of these 10 cases, 9 were exposed to *aniline*
- All 9 aniline workers were co-exposed to ortho-toluidine
- Eight of the 9 aniline workers were also tobacco smokers.

IARC, 2021

Example 4 – Bladder cancer and aniline exposure

- 17 case reports or series, 16 on bladder tumours and one on lung cancer published from 1895-2018

- Conclusion: These case series and reports provided historical perspective but were mostly uninformative
  - Co-exposures occupational bladder carcinogens and/or tobacco smoking
  - Limited information provided in report

IARC, 2021

Positives	Negatives
First identification of a concern/new diseases	No denominator/comparison group
Establish a hypothesis/new ideas	Cannot estimate disease frequency or risk
Stimulate further analytical research	Selection biases, convenience sampling
Progress science, stimulate eduation	Confounding
Together with findings from other analytical studies, may support causal assessments	Severly limited/usually inadequate for making statements regarding causal infrence by themselves

Vandenbroucke et al, 2001

ELSEVIER
CrossMark
Journal of Clinical Epidemiology 89 (2017) 218–235
Journal of Clinical Epidemiology

CARE guidelines for case reports: explanation and elaboration document

David S. Riley[a,*], Melissa S. Barber[b], Gunver S. Kienle[c], Jeffrey K. Aronson[d], Tido von Schoen-Angerer[e], Peter Tugwell[f], Helmut Kiene[g], Mark Helfand[h], Douglas G. Altman[i], Harold Sox[j], Paul G. Werthmann[g], David Moher[k], Richard A. Rison[l], Larissa Shamseer[k], Christian A. Koch[m], Gordon H. Sun[n], Patrick Hanaway[o], Nancy L. Sudak[p], Marietta Kaszkin-Bettag[q], James E. Carpenter[r], Joel J. Gagnier[s,t]

The narrative: A case report tells a story in a narrative format that includes the presenting concerns, clinical findings, diagnoses, interventions, outcomes (including adverse events), and follow-up. The narrative should include a discussion of the rationale for any conclusions and any take-away messages.

Section	Item number	Item description
Title	1	The words "case report" (or "case study") should be in the title along with phenomenon of greatest interest (e.g., symptom, diagnosis, test, intervention)
Keywords	2	The key elements of this case in 2–5 words.
Abstract	3	a) Introduction—What does this case add? b) Case presentation: – The main symptoms of the patient – The main clinical findings – The main diagnoses and interventions – The main outcomes c) Conclusion—What were the main "take-away" lessons from this case?
Introduction	4	Brief background summary of the case referencing the relevant medical literature.
Patient information	5	a) Demographic information of the patient (age, gender, ethnicity, occupation) b) Main symptoms of the patient (his or her chief complaints) c) Medical, family, and psychosocial history —including diet, lifestyle, and genetic information whenever possible and details about relevant comorbidities and past interventions and their outcomes
Clinical findings	6	Describe the relevant physical examination (PE) findings
Timeline	7	Depict important dates and times in the case (table or figure)
Diagnostic assessment	8	a) Diagnostic methods (e.g., PE, laboratory testing, imaging, questionnaires) b) Diagnostic challenges (e.g., financial, language/cultural) c) Diagnostic reasoning including other diagnoses considered d) Prognostic characteristics (e.g., staging) where applicable
Therapeutic interventions	9	a) Types of intervention (e.g., pharmacologic, surgical, preventive, self-care) b) Administration (e.g., dosage, strength, duration) c) Changes in intervention (with rationale)
Follow-up and outcomes	10	a) Clinician and patient-assessed outcomes b) Important follow-up test results (positive or negative) c) Intervention adherence and tolerability (and how this was assessed) d) Adverse and unanticipated events
Discussion	11	a) Strengths and limitations of the management of this case b) Relevant medical literature c) Rationale for conclusions (including assessments of cause and effect) d) Main "take-away" lessons of this case report
Patient perspective	12	The patient should share their perspective or experience whenever possible.
Informed consent	13	Did the patient give informed consent? Please provide if requested.

Case-control studies

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Case-Control Studies

- Comparing past exposure histories of persons with the condition of interest (cases) with those of persons who were free of the index condition at the times the cases occurred (controls)
- Originally developed as a convenient alternative to prospective cohort studies of chronic diseases
- Cost efficient by limiting exposure assessment to selected persons who already developed the condition of interest
- Useful in occupational epidemiology, for collection of detailed job and exposure history information
- Particularly for diseases that are rare or have a long induction time

Checkoway, Pearce, Kriebel 2004

ORIGINAL ARTICLE

Occupational exposure to chlorinated solvents and kidney cancer: a case–control study

Mark P Purdue,[1] Patricia A Stewart,[2] Melissa C Friesen,[1] Joanne S Colt,[1] Sarah J Locke,[1] Misty J Hein,[3] Martha A Waters,[4] Barry I Graubard,[1] Faith Davis,[5] Julie Ruterbusch,[6] Kendra Schwartz,[6] Wong-Ho Chow,[7] Nathaniel Rothman,[1] Jonathan N Hofmann[1]

Participants:

- were mailed a work history calendar, list each job held for at least 12 months since the age of 16, and the employer
- during a subsequent home visit, a trained interviewer administered a computer-assisted personal interview (CAPI) to capture additional information on each job, usual number of hours worked per week, type of business or service, tasks, and a description of chemicals/materials and equipment used
- for selected occupations, 1 of 39 job-specific or industry-specific interview modules on the solvent(s) used, average frequency of solvent-related tasks, work practices (job location (indoors, outdoors, both), local exhaust ventilation (effective, ineffective, absent), mechanism of solvent release (evaporation, aerosolised, other active), proximity (near, far, both) and process temperature (room temperature, elevated, both), and potential for dermal exposure
- five modules maximum to minimise participant burden

Case Ascertainment - Definition

- It is necessary to define criteria for identifying a patient as a case.
- These criteria may not coincide with those used for clinical diagnoses.
- It is advisable to evaluate definitions used in previous studies.
- In some diseases, cases can be easily defined, e.g. lung cancer.
- In other, diagnosis may be complex e.g. asthma, general symptoms of malaise, burnout.
- Different disease phenotypes may be associated with different disease risks.

Wacholder et al. 1992a

INTERPHONE/INTEROCC Case Definition

	Topography and behaviour		Topography	Morphology codes	
	ICD-9	ICD-10	ICD-O2, ICD-O3	ICD-O2, ICD-O3	
				Benign or suspected malignant	Malignant
Glioma					
High grade	191.0-191.9	D33.0, D43.0 - D43.9, C71.0 - C71.9	C71.0 - C71.9	9442/1*	9380/3, 9381/3, 9382/3, 9390/3**, 9392/3, 9401/3, 9423/3^{+}, 9440/3, 9441/3, 9442/3, 9451/3, 9460/3***, 9505/3
Low grade	225.0, 237.5, 191.0-191.9	D33.0, D43.0 - D43.9, C71.0 - C71.9	C71.0 - C71.9	9383/1, 9384/1, 9394/1, 9421/1^{+++}, 9444/1, 9505/1	9391/3, 9393/3^{++}, 9400/3, 9410/3, 9411/3, 9420/3, 9424/3**, 9450/3
Unassigned	191.0-191.9	C71.0 - C71.9	C71.0 - C71.9	9390/0, 9390/1*	9430/3, 9480/3
Meningioma	225.2, 237.6, 192.1	D32.0, D32.9, D42.0, D42.9, C70.0, C70.9	C70.0, C70.9	9530/0, 9530/1, 9531/0, 9532/0, 9533/0, 9534/0, 9535/0, 9537/0, 9538/1, 9539/1*	9530/3, 9538/3, 9539/3
Acoustic neurinoma	225.1	D33.3	C72.4	9560/0	
Parotid gland tumour	210.2, 235.0, 142.0, 142.9	D11.0, D11.9, D37.0, C07.9	C07.9	8010/0, 8010/2, 8147/0, 8149/0**, 8190/0, 8200/0, 8211/0, 8290/0, 8310/0, 8410/0, 8430/1**, 8450/0, 8503/0, 8550/0, 8550/1, 8561/0, 8940/0, 8982/0	8010/3, 8020/3, 8021/3, 8041/3, 8050/3, 8070/3, 8082/3, 8140/3, 8147/3**, 8190/3, 8200/3, 8290/3, 8310/3, 8410/3, 8430/3, 8440/3, 8450/3, 8480/3, 8500/3, 8550/3, 8560/3, 8562/3**, 8940/3, 8941/3, 8980/3, 8982/3

Cardis et al. 2007

Sources for the Identification of Cases

- All incident cases appearing in the “registry” during a specified time period
- From a population-based registry (ie. cancer or disease registry)
- Records collected for other purposes (ie. hospital admission records, insurance claims, disability pension records)
- Complete case ascertainment may not be achieved but will not produce bias unless case identification is associated with exposure (ie. if more exposed workers have more medical screening and are more likely to have non-fatal diseases diagnosed)
- Complimentary sources are especially valuable for studying diseases with low case fatality rates (ie. death certificates and cancer registry data)

Checkoway, Pearce, Kriebel 2004

Control Selection

Controls should originate from the same population as cases.

Controls have to be selected independent of their exposure status.

The time during which a subject is eligible to become a case is also the time for a subject to be selected as a control.

Wacholder et al. 1992a

Principles in the Selection of Cases and Controls

1.**Study base principle**: cases and controls should originate from the same population, "*representative of the same base experience*"

2. **Deconfounding**: potential confounding factors should be controlled either in the design or in the analysis.

3. **Accuracy**: Exposures of interest should be measured with the same accuracy in both cases and controls.

4. **Efficiency**: information per unit cost.

Wacholder et al. 1992a

1.Study base principle. Description of Source of Cases

Study centre	Source population	Source of cases (primary and secondary)
Australia	People with a right to vote who reside in the study regions at the time of diagnosis as a case or of selection as a control, and capable of participating in a face-to-face interview in English.	Pathology laboratories servicing all neurosurgical units (for both brain tumours and acoustic neurinomas), surgeons specialising in treatment of acoustic neurinomas (for acoustic neurinomas), population-based cancer registries for parotid gland cancers and as back-up for malignant brain tumours (both Sydney and Melbourne) and for benign brain tumours and acoustic neurinomas (Melbourne only).
Canada: Montreal	Citizens who reside in the study region at the time of diagnosis as a case or of selection as a control	Pathology and radiology departments, as well as medical archives in the following hospitals: McGill University Hospital Center, Centre Hospitalier de l'Université de Montréal, Jewish General Hospital, Hôpital du Sacré-Coeur de Montréal, Hôpital Charles Lemoyne, Cité de la Santé de Laval, St-Mary's Hospital, Hôpital Maisonneuve-Rosemont, Montreal Neurological Institute
Canada: Ottawa	Residents of the study region at the time of diagnosis as a case or of selection as a control	Departments of neurosurgery, neuroradiology, neuropathology, and medical archives in the Ottawa Hospital, where treatment and diagnosis for the region is centralised (brain). Acoustic neurinoma and parotid gland cases were recruited through all ENT specialists in the Ottawa area.

Cardis et al. 2007

1.Study base principle. Description of Source of Controls

Study centre	Source population	Source of controls
Australia	People with a right to vote who reside in the study regions at the time of diagnosis as a case or of selection as a control, and capable of participating in a face-to-face interview in English.	Controls were randomly selected from the electoral rolls covering the statistical divisions of Melbourne and Sydney. Only subjects actually resident in those divisions at the time of selection were included.
Canada: Montreal	Citizens who reside in the study region at the time of diagnosis as a case or of selection as a control	Electoral lists. In Quebec, the electoral lists are continually updated, from multiple sources of information available to the provincial government, such as drivers' permits and medical insurance cards.
Canada: Ottawa	Residents of the study region at the time of diagnosis as a case or of selection as a control	Random digit dialing

Cardis et al. 2007

The Study-Base Principle

***Primary base*:** defined by the population experience that the investigator wishes to target, ie. population-based studies, population experience is defined geographically and temporally.

Cases: Incident cases were rapidly recruited from major treatment centers, or nationwide, with completeness verified through secondary sources between the years 2000 and 2004.

Controls: Population controls were selected from electoral lists, population-based registries, patient lists, or random digit dialing according to study center.

Challenge: Complete case identification in the base.

Wacholder et al. 1992a

The Study-Base Principle

Secondary base: when ascertainment of all cases in a primary base is difficult of impractical, defined by the case-series, cases are defined before the base is defined.

Cases: All patients newly diagnosed with the study disease at one hospital.

Controls: Patients diagnosed with unrelated diseases from the same hospital as the cases.

Secondary base, all subjects who would be diagnosed at that hospital had they developed the disease.

Challenge: Definition of the study base.

Wacholder et al. 1992a

Trends in participation rates in case–control studies of occupational risk factors 1991–2017

Jeavana Sritharan ,[1] Yang Luo,[2] M Anne Harris[1,2,3]

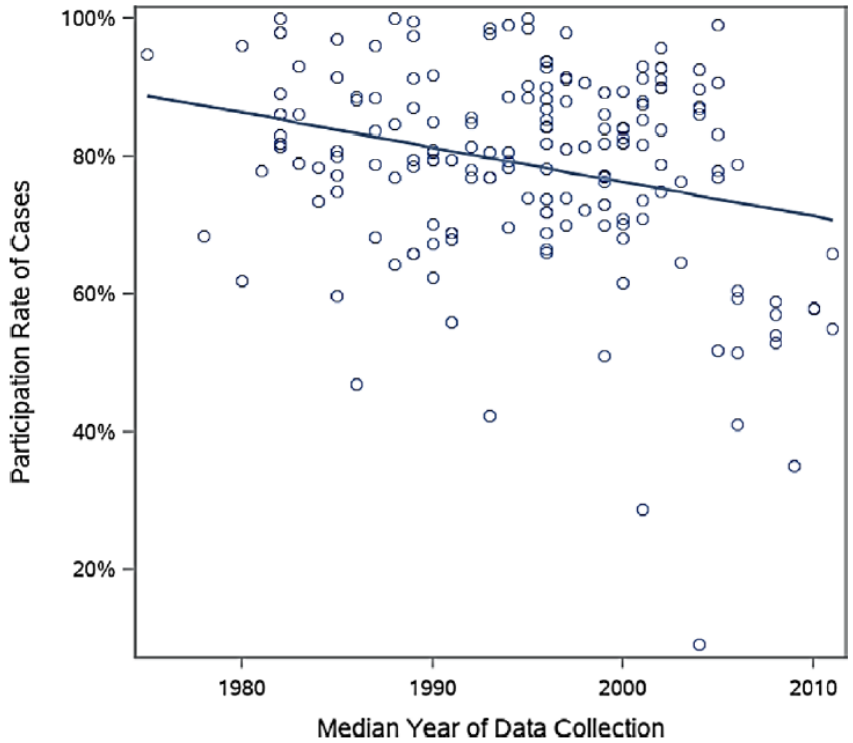


Figure 2 Reported participation among cases in 189 case–control studies by median year of data collection.

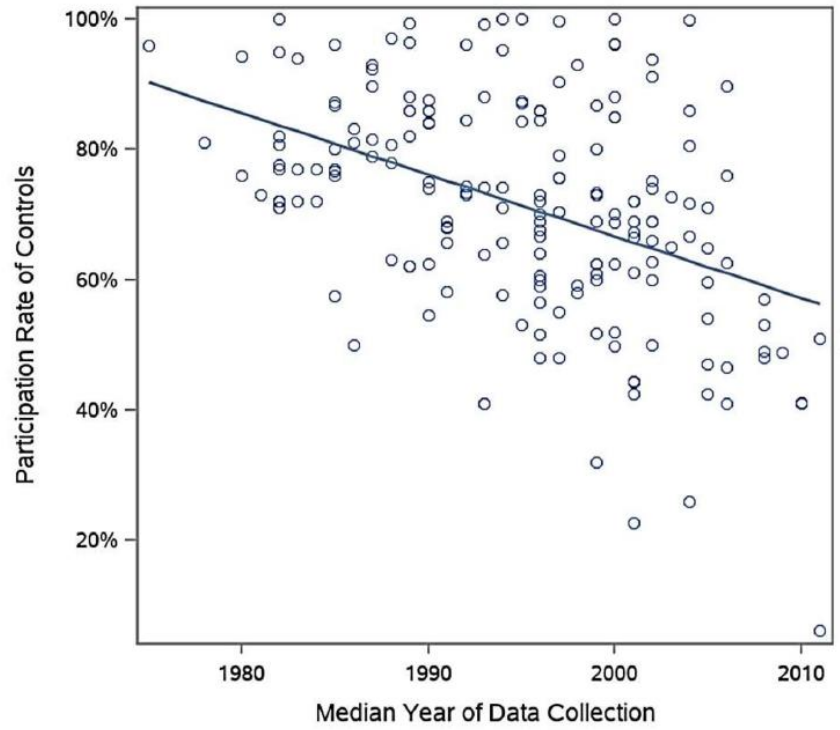


Figure 3 Reported participation among controls in 189 case–control studies by median year of data collection.

Systematic review

Trends in participation rates in case–control studies of occupational risk factors 1991–2017

Jeavana Sritharan ,[1] Yang Luo,[2] M Anne Harris[1,2,3]

- Declining trend in participation in occupational case-control studies from 1975 to 2011 (did not separate population vs hospital controls)
- Participation is important indicator of study quality, even small biases introduced by differential participation can distort study findings
- Occupational case–control studies may be particularly demanding to research participants because of detailed work and exposure histories
- Low participation could hinder future research into occupational risk factors
- Consider nested case–control designs if source cohort is already a voluntary subgroup with high willingness to participate

- In a case-control study of occupational risk factors using population controls, investigators considered excluding cases diagnosed at smaller hospitals in the catchment region for logistic reasons

- Possible problem: If these hospitals serve rural communities, urban occupations may be overrepresented among the cases

Wacholder et al. 1992b

2. Deconfounding

- Few established risk factors
- Individually or frequency matched to cases according to age (5-year groups), sex and study centre

3. Accuracy

Table 2 Distribution of delays between diagnosis and interview—glioma cases only

Study Centre	Number of cases	Delay between diagnosis and interview (months)				
		Median	Percentage of cases			
			–1 to 1	1 to 3	3 to 6	More than 6
Australia	301	4	1	41	30	29
Canada						
Montreal	65	7	0	3	37	60
Ottawa	25	8	8	16	8	68
Vancouver	80	5	0	1	60	39
Denmark	181	2	15	50	19	16
Finland	178	0	75	16	4	4
France	94	2	32	30	14	24
Germany	256	0	69	6	5	20
Israel	180	3	19	27	18	36
Italy	118	6	15	15	19	50
Japan	60	1	42	40	12	7
New Zealand	84	4	0	27	58	14
Norway	180	14	16	2	7	75
Sweden	227	3	13	42	30	15
UK						
North	429	2	5	62	20	13
South	307	4	2	27	34	37
Total	2,765	3	19	31	22	27

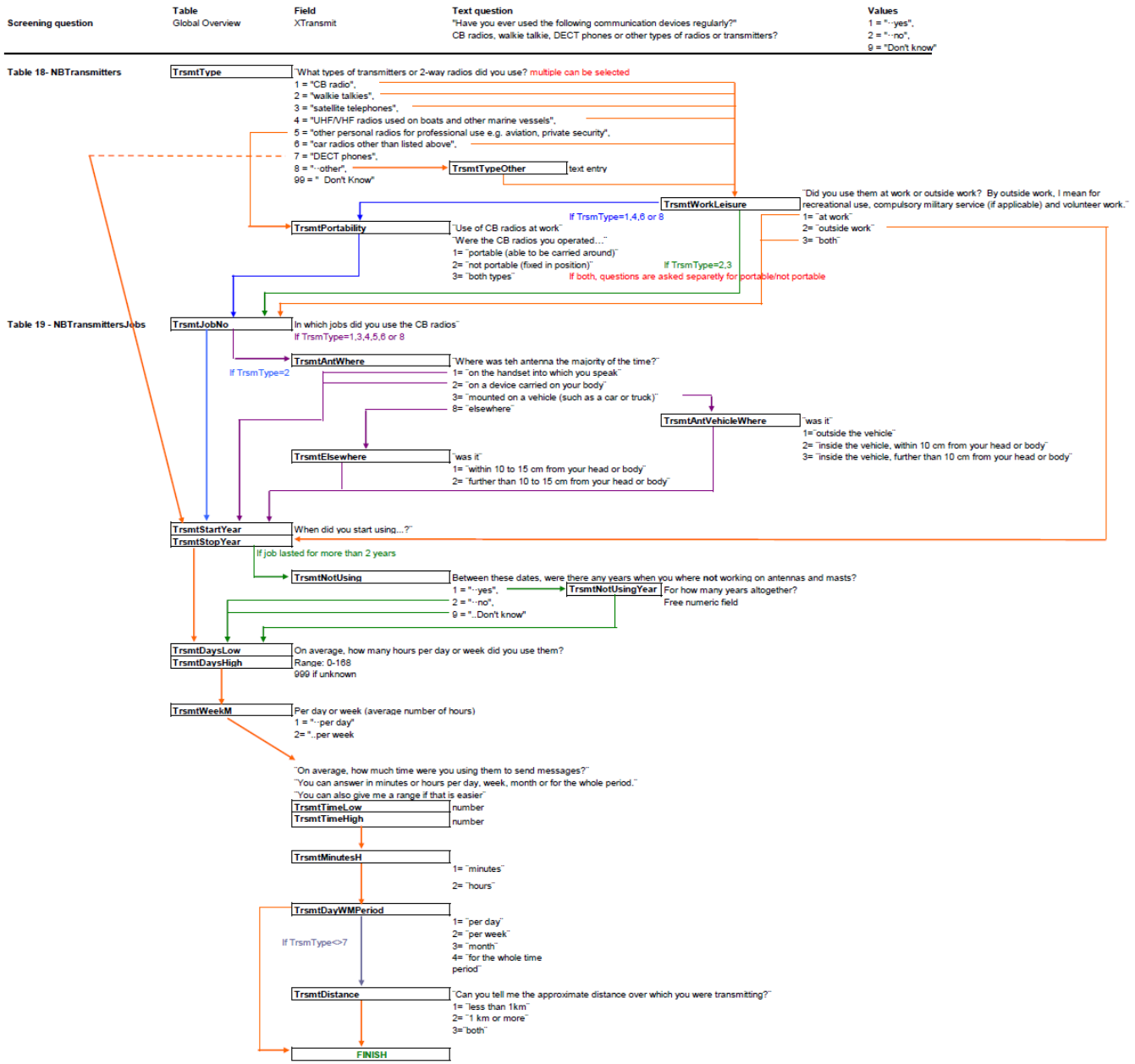
3. Accuracy

Table 6 Distributions of interviews by mode of interview and interviewee, for glioma cases and all controls

Study centre	Total number of interviews		Percentage of interviews that were							
			Mode of interview				Interviewee			
			Face-to-face		Telephone		Subject alone or with another person		Proxy	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Australia	301	669	99	98	1	2	86	100	14	0
Canada										
Montreal	65	234	95	94	5	6	63	98	37	2
Ottawa	25	180	92	100	8	0	84	100	16	0
Vancouver	80	239	100	100	0	0	98	100	3	0
Denmark	181	662	100	100	0	0	94	100	6	0
Finland	178	559	99	99	1	1	97	100	3	0
France	94	472	97	88	3	12	89	100	11	0
Germany	256	1190	100	100	0	0	90	100	10	0
Israel	180	599	99	99	1	1	81	100	19	0
Italy	118	340	61	35	39	65	56	95	44	5
Japan	60	287	100	100	0	0	98	100	2	0
New Zealand	84	172	100	100	0	0	79	88	20	12
Norway	180	278	52	54	48	46	69	100	31	0
Sweden	227	407	94	94	6	6	93	100	7	0
UK										
North	429	788	100	100	0	0	92	100	8	0
South	307	582	100	100	0	0	95	100	5	0
Total	2,765	7,658	94	95	6	5	87	99	13	1

4. Efficiency

- Diagnosis and treatment
- Electric utility
- Electrician
- Electric motors
- Electric transport
- Heating food and medical-dental
- Industrial heating
- Semiconductors
- Telecommunication antennas
- Transmitters
- Aviation
- Construction, repair, maintenance
- Radar
- Ionising radiation



Population Controls

Advantages

- Controls are selected from the same base as cases.
- Extrapolation of results to the base is straightforward.
- Can examine range of occupational exposures

Disadvantages

- If a population registry is not available, difficult to ensure all have the same chance of selection, use other method
- The quality of information retrieved may not be similar in cases and controls.
- Complicated and more expensive than hospital-based.
- Response rates may be lower.

Wacholder et al. 1992b

Occupational solvent exposure and risk of glioma in the INTEROCC study

Geza Benke*[,1], Michelle C Turner[2,3,4,5], Sarah Fleming[6], Jordi Figuerola[2,3,4], Laurel Kincl[7], Lesley Richardson[8], Maria Blettner[9], Martine Hours[10], Daniel Krewski[5,11], David McLean[12], Marie-Elise Parent[13], Siegal Sadetzki[14,15], Klaus Schlaefer[16], Brigitte Schlehofer[16], Jack Siemiatycki[8], Martie van Tongeren[17,18] and Elisabeth Cardis[2,3,4]

	Controls											
	All				Men				Women			
Agent	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed
Any solvent	5119	7.6	—	—	2213	14.7	—	—	2906	2.2	—	—
Aliphatic and alicyclic hydrocarbons	4869	2.9	7262	10.9	1990	5.2	9078	13.4	2879	1.3	2065	3.7
Aromatic hydrocarbons	5081	6.9	10 585	11	2193	14.0	11 430	12.0	2888	1.6	4840	4.4
Benzene	4796	1.4	1054	4.7	1929	2.2	1428	5.7	2867	0.8	399	3.0
Chlorinated hydrocarbons	4743	0.3	4614	7.6	1895	0.4	6276	9.8	2848	0.2	1954	4.0
Gasoline	4755	0.5	169	4.2	1900	0.7	247	5.7	2855	0.4	83	2.7
Methylene chloride	4730	0	—	—	1887	0	—	—	2843	0	—	—
Other organics	4819	1.8	7167	13.4	1964	3.9	7799	14.9	2855	0.4	3115	4.2
Perchloroethylene	4730	0	—	—	1887	0	—	—	2843	0	—	—
1,1,1-Trichloroethane	4733	0.1	458	3.7	1889	0.1	344	2.8	2844	0	688	5.5
Toluene	4858	2.6	10 742	10.6	1990	5.2	12 744	12.4	2868	0.9	2493	3.5
Trichloroethylene	4741	0.2	3521	6.1	1894	0.4	4704	7.8	2847	0.1	1450	3.3

Hospital Controls

- If the hospitals (or other health care centres) providing the cases only treat a part of the population in the geographic area, or
- if the study base cannot be well identified, then
- referrals patterns to the hospital are important when sampling controls.
- A list of diagnoses (preferably more than one diagnosis) should be defined among diseases that were not previously associated with the exposure(s) under study.

Wacholder et al. 1992b

Example. Mobikids

Active identification of eligible cases is performed through contact with neurosurgery, radiology, and oncology units with periodic review of cancer registry and/or hospital discharge records (where available).

Hospital controls were selected among patients who underwent an appendectomy for suspected diagnosis of appendicitis during the study period, matched by age, sex, date of surgery/interview and residence.

Difficulty to recruit representative controls (prevent selection biases)

Much higher participation rates among hospital-controls

Common disease among subjects in the age range of the study unrelated to mobile phone use or socioeconomic status

Sadetzki et al. 2014

Advantages

- Depending on study base from which cases originated, hospital controls may be the only alternative.
- The quality of information retrieved is similar in cases and controls.
- Response rates are usually higher, particularly when collecting biological samples.
- Convenient and cheaper.

Disadvantages

- Controls may not have the same referral patterns as cases.
- Distribution of exposure under study may not be the same as in the base that produced the cases. May not be selected independently of exposure in the source population.

Wacholder et al. 1992b

Imitation Disease

- Subjects with a disease with outward manifestations identical to those of the disease of interest
- Those diagnosed with the disease of interest become cases and those with the imitation disease become controls
- Appropriate if imitation disease is unrelated to the exposure of interest

Wacholder et al. 1992b

A Case-Control Study of the Relationship Between the Risk of Colon Cancer in Men and Exposures to Occupational Agents

Mark S. Goldberg, PhD,[1,2*] Marie-Élise Parent, PhD,[3] Jack Siemiatycki, PhD,[3]
Marie Désy, MSc,[3] Louise Nadon, PhD,[3] Lesley Richardson, MSc,[3]
Ramzan Lakhani, MSc,[3] Benoit Latreille, MSc,[3] and Marie-France Valois, MSc[1]

- 497 male colon cancer cases, 1,514 controls with cancer at 18 other sites, 533 population-based controls
- Job histories translated by chemists/industrial hygienists into occupational exposures including into 175 occupational and industrial categories and 300 occupational agents
- Cancer control group
  - Excluding subjects who had cancers of the lung and peritoneum (recognized strong associations with workplace exposure)
  - Excluding subjects with cancers of the esophagus, stomach, small intestine, rectum, liver, gall bladder, pancreas (which might share common risk factors with colon cancer)
- Population control group
- Generally similar results using either control group

Key Points

- A major advantage of case-control studies is that they save time and expense relative to cohort studies
- A variety of case-control studies designs have been described
- Careful selection of case and control participants is required

Discussion