Surgery and Risk of Sporadic Creutzfeldt-Jakob Disease in Denmark and Sweden: Registry-Based Case-Control Studies

Ignacio Mahillo-Fernandez^a Jesús de Pedro-Cuesta^a Maria José Bleda^a
Mabel Cruz^b Kåre Mølbak^c Henning Laursen^d Gerhard Falkenhorst^c
Pablo Martínez-Martín^a Åke Siden^b
on behalf of the EUROSURGYCJD Research Group

^aDepartment of Applied Epidemiology, National Center for Epidemiology, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Carlos III Institute of Health, Madrid, Spain; ^bDepartment of Clinical Neurosciences, Neurology Division, Karolinska Institutet, Stockholm, Sweden; ^cDepartment of Epidemiology, Statens Serum Institute, and ^dNeuropathology Laboratory, Rigshospitalet, Copenhagen, Denmark

Key Words

Creutzfeldt-Jakob disease, case-control studies ·
Creutzfeldt-Jakob disease, risk assessment · Denmark,
prion diseases · Sweden, prion diseases

Abstract

Background: Epidemiologic evidence of surgical transmission of sporadic Creutzfeldt-Jakob disease (sCJD) remains controversial. **Methods:** From Danish and Swedish registries we selected 167 definite and probable sCJD cases (with onset between 1987 and 2003) and 3,059 controls (835 age-, sex-, and residence-matched, and 2,224 unmatched). Independent of case/control status, surgical histories were obtained from National Hospital Discharge Registries. Surgical procedures were categorized by body system group and lag time to onset of sCJD. Exposure frequencies were compared using logistic regression. **Results:** A history of any major surgery, conducted ≥ 20 years before sCJD onset, was more common in cases than both matched (OR = 2.44, 95% CI =

1.46–4.07) and unmatched controls (OR = 2.25, 95% CI = 1.48–3.44). This observation was corroborated by a linear increase in risk per surgical discharge (OR = 1.57, 95% CI = 1.13–2.18; OR = 1.50, 95% CI = 1.18–1.91). Surgery of various body systems, including peripheral vessels, digestive system and spleen, and female genital organs, was significantly associated with increased sCJD risk. **Conclusions:** A variety of major surgical procedures constitute a risk factor for sCJD following an incubation period of many years. A considerable number of sCJD cases may originate from health care-related accidental transmission.

Copyright © 2008 S. Karger AG, Basel

EUROSURGYCJD group members: Danish team: Gerhard Falkenhorst, Henning Laursen and Kåre Mølbak; Finnish team: Jussi Kovanen; Swedish team: Mabel Cruz and Åke Siden; Spanish team: Javier Almazán, María J. Bleda, Miguel Calero, Ignacio Mahillo Fernandez, Pablo Martínez Martín, Jesús de Pedro Cuesta (coordinator) and Alberto Rábano.

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disease with deposition of a pathologic isoform (termed PrPSc) of the normal cellular prion protein (PrPC). CJD exists in various forms, namely, inherited, caused by mutations in the gene encoding PrPC, acquired (variant and iatrogenic), and sporadic. Most cases are classified as sporadic (sCJD), the etiology of which remains unknown [1]. A history of neurosurgery can be a risk factor for CJD. In addition, CJD might be transmitted during other major surgical interventions by infectious PrPSc surface-bound to reused instruments, despite repeated cleaning and sterilization [2].

Seven case-control studies [3–10] and one meta-analysis [11] investigated surgical history as a risk factor for sCJD with partially inconsistent results. Several of these epidemiologic studies had important limitations, due to potentially underlying case selection and/or recall bias [3–10], or bias conferred by the use of clinical controls [3–6], surrogate informants solely for cases [3, 4, 7, 9] and different time intervals for operations [7, 9]. Hence, there is a clear call for studies that can overcome these limitations [10]. This need has been underscored by additional evidence of blood-related iatrogenic transmission of variant CJD (vCJD) [12–15], a human transmissible encephalopathy with a considerable accumulation of PrPSc in lymphoreticular tissues [16], and by evidence from experimental models demonstrating a significant probability of successful transmission among animals exposed to infective tissue by different, surgically relevant routes [17, 18]. Experimental work suggests that lower inocula of prion protein correlate with a long incubation period [19], which may indicate that the sCJD incubation period from the time of surgery may be long.

The aim of this registry-based case-control study was to identify associations between history of surgery and risk of sCJD in the national populations of Denmark (approx. 5 million) and Sweden (approx. 9 million). For both cases and controls, information on surgical history was retrieved from national hospital discharge registries, thereby ensuring an unbiased ascertainment of exposures.

Methods

The study was designed as a case-control study with two control groups: one matched and the other unmatched. We selected two control groups in order to improve the reproducibility of the study, the robustness, and allow for comparison with previous

published work which included both matched and unmatched reference groups. The base study population was the resident population of Sweden in 1987–2002 and Denmark in 1994–2003, aged 40 years and over. Both countries maintain continuously updated centralized population registries.

Case Selection

A case was defined as a person from the base study population who fulfilled the established EUROCJD diagnostic criteria for sCJD [20]. Potential cases, 212 Swedish and 78 Danish, were identified from three sources: National Hospital Discharge and Cause-of-Death registers, with diagnoses at discharge or death coded as 046.1 or 331.5 according to the 9th revision of the International Classification of Diseases (ICD-9) or A81.0 as per ICD-10 in Sweden, and A81.0 or F021 as per ICD-10 in Denmark; the third source was the mandatory notification system for suspected CJD cases, introduced in both countries in 1997. Diagnosis of probable or definite sCJD, and the date of clinical onset and death were validated for each potential case. To this end, CJD surveillance personnel and board-certified neurologists (including the authors G.F., H.L., K.M., M.C., and Å.S.) used information from case notifications, medical records, death records, and autopsy reports. All validated probable and definite sCJD cases, with onset in the study period, were included. The vital status of cases was verified in 2003 using national population registries and direct contact.

Control Selection

Controls were randomly sampled from national population registries. Five matched controls (MCs) per case were sampled, matched by sex, year and month of birth, and municipality of residence on December 31 of the case's year of death. For 3 cases who were not found registered as dead, the year of the latest hospital discharge was used instead. Unmatched controls (UMCs) were sampled from the resident general population aged ≥ 40 years at a rate of 20 per million in Sweden and 30 per million in Denmark. This sampling procedure was repeated for each year in which cases from the respective country were recruited.

Exposure Ascertainment

For cases and controls alike, data on past hospital discharges [diagnoses, surgical procedures (SPs) and dates of admission and discharge] were obtained from the National Hospital Discharge Registers in Sweden and Denmark by the authors Å.S. and K.M. Personal identifiers and case status indication were removed before the authors J.P.C. and I.M. analyzed the data with respect to exposure to SPs. Reported SP codes were identified and categorized according to Swedish, Danish and Nordic (NOMESCO-NCSP) classifications of SPs [21–23]. Codes describing procedures that were not properly surgical, such as delivery, and nonspecific codes, e.g. 'investigative procedures connected with surgery', were omitted from further analysis.

The remaining SPs were categorized into two major groups: 'main surgical procedures' and 'subsidiary procedures'. Main SPs were further subdivided into 15 body system groups (fig. 1) as defined in the 1.7 edition of NOMESCO-NCSP (http://www.nordclass.uu.se/verksam/Ncsp1_7.pdf). 'Subsidiary procedures' is a heterogeneous category that includes minor surgery (punctures, needle aspiration or biopsy, superficial incision), other nonsurgical, potentially invasive procedures, such as transluminal endoscopies (with or without biopsy), and blood transfusion.

Fig. 1. Percentage distribution of 5,990 codes (regardless of repetition) for SPs and blood transfusion, 341 for cases and 5,649 for controls, associated with registered discharges predating operational date of clinical onset or ID-2 by ≥ 1 year (time windows 1–3).

Definition of Time Windows of Exposure

We defined *a priori* five time windows of exposure [24], based on biologic knowledge, clinical management, and study size (fig. 2). For cases and their MCs, index date 1 (ID-1) is the date of the cases' death (or the last hospital discharge if a patient was still alive at the date of time window definition – 2 cases only). Index date 2 (ID-2) is the operational date of the cases' symptom onset. For UMCs, ID-1 was defined as December 31 of the year from which the UMCs originated, and ID-2 as ID-1 minus 159 days (until 1996) or 151 days (after 1996). These periods are the observed mean disease durations from onset to death in cases until and after 1996. We decided to calculate them separately, because we expected that CJD with a short duration, i.e. among the elderly, would be better diagnosed after the first report of vCJD in 1996 due to a higher awareness of clinicians.

The earliest limit of individuals' time window 1 was opened. It corresponded to early national discharge registry coverage, which was fairly comprehensive in Denmark in 1974 and had been progressive in Sweden since 1973, reaching 78% of the somatic care hospital population by 1977 (www.sos.se/epc; www.scb.se/databaser). The earliest-in-life registered surgical discharge of a case occurred at age 23 in 1979.

Statistical Analysis

An individual was classified as exposed to a specific category of surgery or procedure in a specific time window, when at least one discharge associated with at least one code of such surgery or procedure had taken place at a date within the limits of the designated time window; surgical history in other windows was disregarded. In core analyses, only individuals who underwent no kind of main surgical or subsidiary procedure during the window under study were considered unexposed. The independent effect of main surgical and subsidiary procedures was quantified in complementary analyses by including the two exposure variables in

the same regression model. Multiple exposures were defined by the number of surgical discharges.

Conditional logistic regression was used for comparisons with MCs, and logistic regression with adjustment for age, sex, and country of residence at ID-1 for comparisons with UMCs. Only exposures during time windows 1–3, i.e., predating ID-2 by ≥ 1 year, were considered relevant for the present study and included in the analyses.

The study was notified to the Danish Data Protection Agency (record No. 2003-41-3104) and approved by the Karolinska Institute's Ethics Committee (South; report No. 452/02).

Results

In total, 167 sCJD cases (113 definite and 54 probable), 835 MCs and 2,224 UMCs were included in the study (table 1). Recorded mean and median disease duration were 154 and 92 days (range: 3–963), with 2 Swedish and 1 Danish probable sCJD cases being alive at the end of case finding. Mean and median ages at clinical onset or ID-2 were 67 and 68 years (range: 40–88) for cases and MCs, and 60 and 58 years (range: 40–99) for UMCs. The annual number of cases was higher in Sweden than in Denmark (which has a smaller population). Due to the sampling procedures, the annual number of UMCs was similar for both countries (table 1). Time at risk of surgery covered by each window was the same in cases and controls by design. Duration of registered domestic residence in Sweden from January 1, 1969 to clinical onset or

Fig. 2. Schematic illustration of the study design and methodologic details. **a** Annual (calendar year X) national study population with: (1) selected illustrative cases; (2) MCs, and (3) UMCs. **b** Time windows included in the present study were those covering surgical history >1 year prior to clinical onset/ID-2, namely, windows 1, 2 and 3.

Table 1. Cases and controls included in the study

Population study year or year of clinical onset	sCJD cases					Controls		
	all	definite/ probable	male/ female	Swedish/ Danish	average age at clinical onset years	matched	unmatched	
							all	Swedish/Danish
1987	3	1/2	3/0	3/0	59	15	79	79/0
1988	4	2/2	2/2	4/0	68	20	80	80/0
1989	6	2/4	4/2	6/0	67	30	80	80/0
1990	6	4/2	5/1	6/0	59	30	81	81/0
1991	3	1/2	2/1	3/0	61	15	82	82/0
1992	4	3/1	2/2	4/0	66	20	83	83/0
1993	6	4/2	1/5	6/0	70	30	83	83/0
1994	13	5/8	6/7	9/4	70	65	179	84/95
1995	8	4/4	5/3	7/1	70	40	171	84/87
1996	7	4/3	1/6	2/5	68	35	172	85/87
1997	19	17/2	7/12	11/8	63	95	172	85/87
1998	16	12/4	7/9	11/5	68	80	178	86/92
1999	17	13/4	10/7	11/6	66	85	176	86/90
2000	14	12/2	4/10	10/4	69	70	172	87/85
2001	17	12/5	9/8	11/6	68	85	180	87/93
2002	14	12/2	6/8	4/10	65	70	183	88/95
2003	10	5/5	4/6	0/10	68	50	73	0/73
All	167	113/54	78/89	108/59	67	835	2,224	1,340/884

Surveillance diagnostic criteria for definite or probable sCJD were used. Definite cases were neuropathologically/immunochemically confirmed. Probable sCJD cases fulfilled reported clinical criteria (rapidly progressive dementia and specific symptoms) and laboratory criteria (typical EEG, or duration <2 years + positive 14-3-3 protein test in cerebrospinal fluid), <http://www.cjd.ed.ac.uk/criteria.htm>. One probable sCJD case was excluded from the study due to unclear onset date within the limits of the study period.

ID-2 accounted for 100, 99, and 96% of lifetime during that period for cases, MCs, and UMCs, respectively. The combined surgical experience of cases and controls corresponded to 1,445 distinct SP codes related to 3,876 hospital discharges during time windows 1–3 (fig. 1).

In the time window ≥ 20 years prior to CJD onset/ID-2, cases had an increased risk of major surgery compared to both MCs [odds ratio (OR) = 2.44, 95% confidence interval (CI) = 1.46–4.07], and UMCs (OR = 2.25, 95% CI = 1.48–3.44) (table 2). There was a significant dose-response effect with a linear increase per surgical discharge (OR = 1.57, 95% CI = 1.13–2.18). There was also a tendency towards increased risk of major surgery in time window 2 (10–19 years prior to disease onset), but no indication of excess risk in window 3 (1–9 years prior to disease onset) (table 2).

We conducted subgroup analyses by country, study period, gender, age of onset, and case classification (table 3). A statistically significant excess risk for main SPs carried out at least 20 years before onset of sCJD was pres-

ent in most of these analyses, and the point estimates remained stable.

Table 4 shows results for major surgery of specific body systems, as well as statistically significant findings for procedures carried out in other time windows. The number of procedures performed in window 1 varied substantially between groups. Statistically significant excess risk, sometimes based on sparse data, was registered for gastrointestinal surgery, gynecologic surgery (compared with UMCs only), surgery of peripheral vessels and lymphatic system, and thorax surgery. The most frequent SPs undergone by cases, for which excess risk was observed, were distributed as follows: of 14 gastrointestinal procedures, 3 were appendectomy, 3 explorative laparotomy, and 2 hemorrhoidectomy; of 26 gynecologic procedures, 10 were uterus curettage and 9 were cervix conization, excision or curettage; all 6 vascular procedures were varicose vein surgery. In addition, in comparison with UMCs, we observed an excess number of operations on heart and major thoracic vessels in cases, predating clin-

Table 2. Associations for main surgical and subsidiary procedures for specific periods predating onset or ID-2

Time window	Surgery under study	Subject	Unexposed ¹ , n	Surgery under study		Other surgery ² , n
				n	OR	
Time window 1 (≥20 years)	main surgical procedures	case	134 (80.2)	32 (19.2)		1 (0.6)
		MC	745 (89.2)	89 (10.7)	2.44 (1.46–4.07) ³	1 (0.1)
		UMC	1,985 (89.3)	230 (10.3)	2.25 (1.48–3.44) ⁴	9 (0.4)
	subsidiary procedures	case	134 (80.2)	3 (1.8)		30 (18.0)
		MC	745 (89.2)	13 (1.6)	1.64 (0.43–6.42)	77 (9.2)
		UMC	1,985 (89.3)	34 (1.5)	1.25 (0.36–4.36)	205 (9.2)
Time window 2 (10–19 years)	main surgical procedures	case	110 (65.9)	57 (34.1)		0 (0.0)
		MC	603 (72.2)	223 (26.7)	1.44 (1.01–2.04)	9 (1.1)
		UMC	1,569 (70.5)	623 (28.0)	1.40 (0.99–1.98)	32 (1.4)
	subsidiary procedures	case	110 (65.9)	11 (6.6)		46 (27.5)
		MC	603 (72.2)	50 (6.0)	1.24 (0.64–2.38)	182 (21.8)
		UMC	1,569 (70.5)	148 (6.7)	1.11 (0.57–2.17)	507 (22.8)
Time window 3 (1–9 years)	main surgical procedures	case	116 (69.5)	46 (27.5)		5 (3.0)
		MC	565 (67.7)	245 (29.3)	0.92 (0.62–1.34)	25 (3.0)
		UMC	1,526 (68.6)	645 (29.0)	0.83 (0.58–1.18)	53 (2.4)
	subsidiary procedures	case	116 (69.5)	13 (7.8)		38 (22.8)
		MC	565 (67.7)	70 (8.4)	0.90 (0.48–1.70)	200 (24.0)
		UMC	1,526 (68.6)	177 (8.0)	0.88 (0.48–1.64)	521 (23.4)
All time windows (≥1 year)	main surgical procedures	case	72 (43.1)	94 (56.3)		1 (0.6)
		MC	399 (47.8)	418 (50.1)	1.25 (0.89–1.76)	18 (2.2)
		UMC	1,056 (47.5)	1,127 (50.7)	1.19 (0.86–1.65)	41 (1.8)
	subsidiary procedures	case	72 (43.1)	23 (13.8)		72 (43.1)
		MC	399 (47.8)	118 (14.1)	1.09 (0.64–1.84)	318 (38.1)
		UMC	1,056 (47.5)	316 (14.2)	1.03 (0.62–1.70)	852 (38.3)

Figures in parentheses indicate percentages or 95% CIs.

¹ Reference category. No registered surgery.

² Procedures, either main surgical or subsidiary, other than surgery under study.

³ OR = 2.09, 95% CI = 1.17–3.73 for 1 discharge and OR = 3.37, 95% CI = 1.52–7.45 for 2 or more discharges. Linear increase per discharge: OR = 1.57, 95% CI = 1.13–2.18.

⁴ OR = 2.01, 95% CI = 1.23–3.31 for 1 discharge and OR = 2.90, 95% CI = 1.40–7.76 for 2 or more discharges. Linear increase per discharge: OR = 1.50, 95% CI = 1.18–1.91.

ical onset by 1 or more years (OR = 2.61, 95% CI = 1.08–6.31), and at a 1- to 9-year time lag (OR = 2.61, 95% CI = 1.07–6.24). Five of the 7 cases exposed to heart surgery were definite sCJD patients and 5 of the 7 procedures were coronary anastomosis or bypass.

Finally, complementary analyses using alternative time windows (1–4, 5–14 and ≥15 years predating onset/ID-2; table 5) confirmed most prior significant findings. In these analyses, however, the excess risk of gynecologic and cardiac surgery seen in table 4, and – when controlling for the effect of main SPs – that of subsidiary procedures became statistically nonsignificant.

When major surgery, other than cardiac, was analyzed, there was an increase in risk with time lag after operation compared to both MCs and UMCs (namely OR = 1.06, 95% CI = 1.02–1.09, and OR = 1.05, 95% CI = 1.02–1.08 per latency year, respectively).

We examined spatial patterns for major surgery which took place ≥20 years before onset and for which statistically significant excess risk was observed. Each of the 28 patients concerned had been discharged after such surgery from different hospitals, except for 2 who were admitted to the same clinic within 13 months and developed sCJD 23 and 21 years later, respectively.

Table 3. Complementary analyses: associations for a specific country of residence, study period, sex, age at onset or ID-2, and for *definite* sCJD cases only

Alternative design (time window ≥20 years)	Surgery under study	Subject	Unexposed ¹ , n	Surgery under study		Other surgery ² , n
				n	OR	
Residence at death/ID-1 in Sweden	main surgical procedures	case	90 (83.3)	18 (16.7)		0 (0.0)
		MC	494 (91.5)	45 (8.3)	2.65 (1.31–5.38)	1 (0.2)
		UMC	1,207 (90.1)	131 (9.8)	1.97 (1.13–3.43)	2 (0.1)
Residence at death/ID-1 in Denmark	main surgical procedures	case	44 (74.6)	14 (23.7)		1 (1.7)
		MC	251 (85.1)	44 (14.9)	2.34 (1.11–4.92)	0 (0.0)
		UMC	778 (88.0)	99 (11.2)	2.72 (1.39–5.31)	7 (0.8)
Study period 1987–1998	main surgical procedures	case	158 (94.6)	9 (5.4)		0 (0.0)
		MC	816 (97.7)	18 (2.2)	3.35 (1.31–8.54)	1 (0.1)
		UMC	2,153 (96.8)	67 (3.0)	1.74 (0.84–3.58)	4 (0.2)
Study period 1999–2003	main surgical procedures	case	143 (85.6)	23 (13.8)		1 (0.6)
		MC	764 (91.5)	71 (8.5)	2.25 (1.22–4.15)	0 (0.0)
		UMC	2,056 (92.4)	163 (7.3)	2.27 (1.40–3.67)	5 (0.2)
Men	main surgical procedures	case	67 (85.9)	11 (14.1)		0 (0.0)
		MC	367 (94.1)	23 (5.9)	2.81 (1.21–6.51)	0 (0.0)
		UMC	999 (92.8)	71 (6.6)	2.34 (1.17–4.69)	6 (0.6)
Women	main surgical procedures	case	67 (75.3)	21 (23.6)		1 (1.1)
		MC	378 (84.9)	66 (14.8)	2.22 (1.18–4.18)	1 (0.2)
		UMC	986 (85.9)	159 (13.9)	2.22 (1.30–3.79)	3 (0.3)
Age <68 at onset or ID-2	main surgical procedures	case ³	62 (76.5)	18 (22.2)		1 (1.2)
		MC	362 (89.4)	43 (10.6)	3.36 (1.78–6.33)	0 (0.0)
		UMC	1,362 (89.0)	165 (10.8)	2.71 (1.55–4.75)	4 (0.3)
Age ≥68 at onset or ID-2	main surgical procedures	case ⁴	72 (83.7)	14 (16.3)		0 (0.0)
		MC	383 (89.1)	46 (10.7)	1.85 (0.81–4.21)	1 (0.2)
		UMC	623 (89.9)	65 (9.4)	1.85 (0.98–3.52)	5 (0.7)
Definite sCJD cases	main surgical procedures	case	88 (77.9)	24 (21.2)	2.46 (1.37–4.41)	1 (0.9)
		MC	498 (88.1)	66 (11.7)	2.56 (1.58–4.14)	1 (0.2)
		UMC	1,985 (89.3)	230 (10.3)		9 (0.4)

Figures in parentheses indicate percentages or 95% CIs.

¹ Reference category. No registered surgery.

² Procedures, either main surgical or subsidiary, other than surgery under study.

³ Age at first surgical discharge: mean 34.0 years, SD 7.2 years.

⁴ Age at first surgical discharge: mean 51.5 years, SD 4.2 years.

Discussion

Overall, the present study indicates that a considerable proportion of sCJD may constitute a health care-related disorder, accidentally transmitted during surgery. While this has been suggested before [7–10], the present study is unique because of the unbiased assessment of exposure histories for decades before disease onset, randomly chosen controls, and strict lag time measurement. The lack

of surgical history data prior to the establishment of the National Hospital Discharge Registries in the early 1970s and low statistical power preclude the assessment of early-in-life surgery or specific infrequent procedures. The main findings were supported by analyses including both MCs and UMCs. The UMCs were not essential for this study, but it was reassuring to learn that a similar study could be undertaken in another setting where it was impossible to sample MCs as a reference group.

Table 4. Number of cases and controls, and associations for surgery by body system group at discharge, 20 or more years before onset or ID-2, and statistically significant findings for other windows

Time window	Body system group	Subject	Unexposed ¹ , n	Body system group under study		Other surgery ² , n
				n	OR	
Time window 1 (≥20 years)	endocrine system	case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	0 (0.0)	–	90 (10.8)
		UMC	1,985 (89.3)	6 (0.3)	3.06 (0.40–23.6)	233 (10.5)
	ear, nose and larynx	case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	4 (0.5)	1.92 (0.29–12.8)	86 (10.3)
		UMC	1,985 (89.3)	12 (0.5)	1.23 (0.14–11.0)	227 (10.2)
	teeth, jaws, mouth and pharynx	case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	2 (0.2)	3.59 (0.39–32.8)	88 (10.5)
		UMC	1,985 (89.3)	6 (0.3)	3.40 (0.34–33.6)	233 (10.5)
	chest wall, pleura, lung and other thoracic surgery	case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	0 (0.0)	–	90 (10.8)
		UMC	1,985 (89.3)	1 (0.0)	29.3 (1.83–470)	238 (10.7)
	digestive system and spleen	case	134 (80.2)	10 (6.0)		23 (13.8)
		MC	745 (89.2)	25 (3.0)	2.59 (1.16–5.78)	65 (7.8)
		UMC	1,985 (89.3)	56 (2.5)	2.72 (1.33–5.57)	183 (8.2)
	urinary system, male genital organs and other surgery	case	134 (80.2)	2 (1.2)		31 (18.6)
		MC	745 (89.2)	5 (0.6)	2.49 (0.48–13.0)	85 (10.2)
		UMC	1,985 (89.3)	15 (0.5)	1.71 (0.35–8.38)	224 (10.1)
	female genital organs ³	case	67 (75.3)	11 (12.4)		11 (12.4)
		MC	378 (84.9)	41 (9.2)	1.89 (0.88–4.08)	26 (5.8)
		UMC	986 (85.9)	74 (6.4)	2.17 (1.06–4.45)	88 (7.7)
	obstetric procedures	case	134 (80.2)	2 (1.2)		31 (18.6)
		MC	745 (89.2)	7 (0.8)	2.99 (0.50–17.9)	83 (9.9)
		UMC	1,985 (89.3)	45 (2.0)	1.19 (0.28–5.08)	194 (8.7)
	musculoskeletal system	case	134 (80.2)	5 (3.0)		28 (16.8)
		MC	745 (89.2)	12 (1.4)	2.49 (0.81–7.67)	78 (9.3)
		UMC	1,985 (89.3)	40 (1.8)	2.12 (0.78–5.75)	199 (8.9)
	peripheral vessels and lymphatic system	case	134 (80.2)	3 (1.8)		30 (18.0)
		MC	745 (89.2)	4 (0.5)	4.54 (1.01–20.3)	86 (10.3)
		UMC	1,985 (89.3)	9 (0.4)	4.99 (1.37–18.2)	230 (10.3)
	skin	case	134 (80.2)	3 (1.8)		30 (18.0)
		MC	745 (89.2)	6 (0.7)	3.02 (0.66–13.9)	84 (10.1)
		UMC	1,985 (89.3)	16 (0.7)	3.83 (0.97–15.0)	223 (10.0)
Time window 3 (1–9 years)	heart and major thoracic vessels	case	116 (69.5)	7 (4.2)		44 (26.3)
		MC	565 (67.7)	17 (2.0)	2.03 (0.85–4.89)	253 (30.3)
		UMC	1,526 (68.6)	25 (1.1)	2.58 (1.07–6.24)	673 (30.3)
All time windows ≥1 year	heart and major thoracic vessels	case	72 (43.1)	7 (4.2)		88 (52.7)
		MC	399 (47.8)	20 (2.4)	2.00 (0.83–4.81)	416 (49.8)
		UMC	1,056 (47.5)	28 (1.3)	2.61 (1.08–6.32)	1,140 (51.3)

Figures in parentheses indicate percentages or 95% CIs.

¹ Reference category.

² Other main surgical or subsidiary procedures, other than body system group under study.

³ Analysis restricted to women.

Table 5. Complementary analyses

Alternative design	Surgery under study	Subject	Unexposed ¹ , n	Surgery under study		Other surgery ² , n
				n	OR	
Time window 1 (≥15 years)						
Separate models ³	main surgical procedures	case	114 (68.3)	52 (31.1)		1 (0.6)
		MC	642 (76.9)	188 (22.5)	1.68 (1.11–2.54)	5 (0.6)
		UMC	1,702 (76.5)	508 (22.8)	1.66 (1.17–2.36)	14 (0.6)
	subsidiary procedures	case	114 (68.3)	12 (7.2)		41 (24.6)
		MC	642 (76.9)	35 (4.2)	2.14 (1.08–4.22)	158 (18.9)
		UMC	1,702 (76.5)	95 (4.3)	2.13 (1.09–4.17)	427 (19.2)
	chest wall, pleura, lung and other thoracic surgery	case	114 (68.3)	3 (1.8)		50 (29.9)
		MC	642 (76.9)	1 (0.1)	16.6 (1.6–172.6)	192 (23.0)
		UMC	1,702 (76.5)	4 (0.2)	12.2 (2.52–58.6)	518 (23.3)
	digestive system and spleen	case	114 (68.3)	16 (9.6)		37 (22.2)
		MC	642 (76.9)	55 (6.6)	1.78 (0.92–3.44)	138 (16.5)
		UMC	1,702 (76.5)	120 (5.4)	2.20 (1.26–3.84)	402 (18.1)
	musculoskeletal system	case	114 (68.3)	12 (7.2)		41 (24.6)
		MC	642 (76.9)	30 (3.6)	2.33 (1.17–4.66)	163 (19.5)
		UMC	1,702 (76.5)	103 (4.6)	1.75 (0.92–3.33)	419 (18.8)
	peripheral vessels and lymphatic system	case	114 (68.3)	7 (4.2)		46 (27.5)
		MC	642 (76.9)	14 (1.7)	3.10 (1.23–7.84)	179 (21.4)
		UMC	1,702 (76.5)	35 (1.6)	2.82 (1.23–6.43)	487 (21.9)
	female genital organs	case	53 (59.6)	18 (20.2)		18 (20.2)
		MC	308 (69.2)	75 (16.9)	1.51 (0.74–3.07)	62 (13.9)
		UMC	800 (69.7)	176 (15.3)	1.66 (0.93–2.95)	172 (15.0)
Same model ⁴	main surgical procedures	case	115 (68.9)	52 (31.1)		
		MC	647 (77.5)	188 (22.5)	1.59 (1.03–2.46)	
		UMC	1,716 (77.2)	508 (22.8)	1.56 (1.07–2.27)	
	subsidiary procedures	case	155 (92.8)	12 (7.2)		
		MC	800 (95.8)	35 (4.2)	1.44 (0.73–2.84)	
		UMC	2,129 (95.7)	95 (4.3)	1.43 (0.71–2.89)	
Time window 3 (1–4 years)						
	heart and major ³ thoracic vessels	case	136 (81.4)	5 (3.0)		26 (15.6)
MC		692 (82.9)	10 (1.2)	2.50 (0.85–7.34)	133 (15.9)	
UMC		1,831 (82.3)	17 (0.8)	2.81 (0.97–8.11)	376 (16.9)	

Figures in parentheses indicate percentages or 95% CIs.

¹ Reference category. No registered surgery. In the model with 2 exposure variables, the unexposed groups differ and may include individuals who underwent another type of surgery.

² Procedures, either main surgical or subsidiary, other than surgery under study.

³ Separate regression models with only 1, 3-nominal-level, independent variable for surgical exposure.

⁴ One regression model, with 2, 2-level variables, independent variables for surgical exposures.

The validity of our results could be affected by selection bias if CJD detection rates were higher among surgical patients subjected to medical follow-up due to their underlying disease or to detect possible complications of

surgery. Since most associations were only seen for long latency periods (i.e., 20 years or more prior to onset of CJD), such a mechanism appears highly unlikely. One exception, however, might be the case of coronary sur-

gery, but would only be plausible, if there was considerable CJD underascertainment in persons where coronary surgery was indicated.

Another potential source of selection bias could be changes in diagnostic accuracy which inevitably occur over such a long study period, notably increased awareness of CJD after the report of vCJD in 1996 and availability of the test for protein 14-3-3 in cerebrospinal fluid since 1998. However, at least in Sweden, sCJD incidence for 1970–1998 [25] was similar to that reported during active surveillance thereafter. Consequently, our low study accrual rate for the period 1987–1996 might best be attributed to difficulties in finding hospital records of these old cases, and would thus be unrelated to underascertainment or surgical history.

Differential misclassification of iatrogenic cases as sCJD cases might have occurred due to overlooked use of dura mater grafts in surgery. In Sweden, inspection of medical records revealed the presence of 1 case of iatrogenic CJD who died in 2002 and was removed from the study. While dura mater grafts may, in theory, have been used in gynecologic surgery for urinary incontinence and in other surgery, the lack of reported iatrogenic CJD in Sweden [25], and the shorter incubation periods described for iatrogenic CJD [26] suggest that overlooked use of heterologous dura mater grafts does not explain the excess risk of sCJD for individuals exposed to specific groups of SP in our study.

Surveillance bias, i.e., overascertainment of sCJD among the 54 probable sCJD cases without postmortem confirmation, cannot be ruled out. However, it seems unlikely that such misclassification would be associated with surgical history ≥ 20 years ago, and will therefore be nondifferential.

The geographically based referral system for surgery in both countries, with free and equal access to health care, registration of SPs prior to sCJD diagnosis, and similar expected-versus-registered times of residence should have minimized differential misclassification of exposure. Nondifferential misclassification of exposure to surgery, potentially resulting from our window design [27], errors in person numbers, or coding of SPs should be low. Moreover, since their additional effect is dilution, i.e., OR towards unity [28], true associations should be higher than those observed. Owing to our study design, recall bias can be ruled out.

Potential confounders are overlooked causes of CJD associated with surgery, not implicated in the same causal chain. Intra- or postoperative blood or blood component transfusion and skin incision are potential con-

founders which we did not control for. Neither surgery undergone in the 1970s nor body system groups with highest observed excess risk appear to be especially correlated with considerable loss of blood, blood transfusion or size of surgical incision. Potential confounding by variation in surgical practices or indications was controlled for by the study design with year-to-year entry of cases and controls into the study.

The fact that the highest ORs were observed for the earliest time window (≥ 20 years before CJD onset) fits well with epidemiological theory [24, 27] and with the long latency required for the process of neuroinvasion following surgical transmission [29], thus making a causal association plausible. Since cognitive impairment and brain emboli following coronary artery bypass grafting have been reported [30] and 2 cases exposed to coronary surgery were probable sCJD, bias due to misdiagnosis or indication of surgical treatment cannot be ruled out for heart and major vessel surgery.

Conflicting reports from previously published case-control studies regarding the association between surgery and sCJD may partially be explained by variations in the type of control subjects used and in exposure assessment [31]. Even though we did not find a significant association between surgery performed at any time pre-dating >1 year before onset, our results are consistent with positive results for lifetime surgical history found in recent, large studies using community controls [7, 9, 10]. Like us, one study reports dose-response effects [7]. Hence, in accordance with these studies and other reports suggesting that some types of surgery, e.g. cataract surgery [32, 33], might be performed as a consequence of early sCJD manifestations, it appears that surgery may constitute: (1) a risk factor of sCJD with a considerable time lag, and (2) a risk indicator with yet unknown causal links for specific types of (recent) surgery, possibly including coronary surgery.

What then are the potential implications for public health? Based on period-specific ORs of 1.44 (10–19 years) and 2.44 (≥ 20 years), and 22 and 19% exposed, un-repeated cases for each window, we estimate the population-attributable proportion to be 18%. This figure may constitute a considerable underestimation of the effect of lifetime surgical history on sCJD incidence, because in our study the ascertainment of exposure to surgery before the middle of the 1970s was compromised by the incompleteness of hospital discharge registries. In the UK, a positive lifetime surgical history was recorded from 1980 onwards in 58 and 59% of vCJD cases and controls, with median ages of 26 and 33 years [34]. Since the major-

ity of surgical interventions at such ages was not captured in our study, and our results suggest that the lower the age at surgery, the higher the risk, the figure of 35% proposed by Ward et al. [9] for the population-attributable risk of sCJD due to lifetime surgery in the UK would appear to be a conservative estimate for Denmark and Sweden.

While negative results have been reported for clustered surgical chains [35], studies supporting the hypothesis of a frequent surgical transmission of sCJD might be a French cluster of multioperated cases [36]; the high sCJD incidence in regions with a high incidence of genetic transmissible spongiform encephalopathy, potentially acting as a focus for point source epidemics, such as in the Spanish Basque Country [37] (<http://www.isciii.es/htdocs/pdf/DatosRegistroCreutzfeldtJacob.ppt>), and occasional increases in CJD incidence in countries where iatrogenic transmission has been mentioned as a possible cause [38].

To conclude, we provide evidence to indicate that surgery, acting with long incubation periods, has constituted a risk factor for sCJD in Sweden and Denmark. The associations may have implications for precautionary measures and surveillance.

Acknowledgments

The EUROSURGYCJD group members are grateful to: Prof. Maurizio Pocchiari, Italy, for contributing to this proposal with regard to the biologic plausibility of surgical transmission of prion disorders; Margareta Löfdahl (Swedish CJD Surveillance Unit), Curt-Lennar Spetz, Leif Forsberg (Socialstyrelsen) and Lars Caderius (Population Statistics), Sweden, for their help with data collection; to Fuencisla Avellanal and Javier Almazán for support with the Spanish TSE registry data, and to Else Smith (SSI, Denmark) for support to initiate the Concerted Action. Michael Benedict reviewed the English version. Funding was obtained from the EU Research Commission, Concerted Action QLRG3-CT-2002-81223, NEUROPRION and the Spanish RECSP C03-09, CIEN C03-06 and CIBERNED networks, and from the Karolinska and Carlos III National Health Institutes. Ethical evaluation was cleared by the KI Forskningsetikkommittee Syd (Dnr 452/02) on December 2, 2002. Preliminary results were presented at the EUROCJD/NEUROCJD Public Health EU meeting in Paris on December 5, 2006. J.P.-C. had full access to all study data, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- 1 Prusiner SB: The prion diseases. *Brain Pathol* 1998;8:499–513.
- 2 Weissmann C, Enari M, Kohn PC, Rossi D, Flechsig E: Transmission of prions. *Proc Natl Acad Sci USA* 2002;99(suppl 4):16378–16383.
- 3 Kondo K, Kuroiwa Y: A case-control study of Creutzfeldt-Jakob disease: association with physical injuries. *Ann Neurol* 1982;11:377–381.
- 4 Davanipour Z, Alter M, Sobel E, Asher DM, Gajdusek DC: Creutzfeldt-Jakob disease: possible medical risk factors. *Neurology* 1985;35:1483–1486.
- 5 Harries-Jones R, Knight RSG, Will RG, Cousens SN, Smith PG, Matthews WB: Creutzfeldt-Jakob disease in England and Wales, 1980–1984: a case-control study of potential risk factors. *J Neurol Neurosurg Psychiatry* 1988;51:1113–1119.
- 6 van Duijn CM, Delasnerie-Lauprêtre N, Masullo C, Zerr I, de Silva R, Wientjens DPWM, Brandel JP, Weber T, Bonavita V, Zeidler M, Alperovitch A, Poser S, Granieri E, Hofman A, Will RG: Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993–95. *Lancet* 1998;351:1081–1085.
- 7 Collins S, Law MG, Fletcher A, Boyd A, Kaldor J, Masters CL: Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:69.
- 8 Zerr I, Brandel J-P, Masullo C, Wientjens DPWM, de Silva R, Zeidler M, Granieri E, Sampaolo S, van Duijn CM, Delasnerie-Lauprêtre N, Will RG, Poser S: European surveillance on Creutzfeldt-Jakob disease: a case-control study for medical risk factors. *J Clin Epidemiol* 2000;53:747–754.
- 9 Ward HJT, Everington D, Croes EA, Alperovitch A, Delasnerie-Lauprêtre N, Zerr I, Poser S, van Duijn CM: Sporadic Creutzfeldt-Jakob disease and surgery: a case-control study using community controls. *Neurology* 2002;59:543–548.
- 10 Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Gillies M, Murray K, Knight RS, Smith PG, Will RG: Risk factors for sporadic Creutzfeldt-Jakob disease. *Ann Neurol* 2008;63:347–354.
- 11 Wientjens DPWM, Davanipour Z, Hofman A, Kondo K, Matthews WB, Will RG, van Duijn CM: Risk factors for Creutzfeldt-Jakob disease: a reanalysis of case-control studies. *Neurology* 1996;46:1287–1291.
- 12 Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, Will RG: Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004;363:417–421.
- 13 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW: Preclinical vCJD after blood transfusion in a codon 129 heterozygous patient. *Lancet* 2004;364:527–529.
- 14 Collinge J: Molecular neurology of prion disease. *J Neurol Neurosurg Psychiatry* 2005;76:906–919.
- 15 Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J: Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006;368:2061–2067.
- 16 Olsen SB, Sheikh A, Peck D, Darzi A: Variant Creutzfeldt-Jakob disease, a cause for concern – Review of the evidence for risk of transmission through abdominal lymphoreticular tissue surgery. *Surg Endosc* 2005;19:747–750.
- 17 Ingrosso L, Pisani F, Pocchiari M: Transmission of the 263K scrapie strain by the dental route. *J Gen Virol* 1999;80:3043–3047.

- 18 Rábano A, de Pedro-Cuesta J, Mølbak K, Siden Å, Calero M, Laursen H: Tissue classification for the epidemiologic assessment of surgical transmission of sporadic Creutzfeldt-Jakob disease. A proposal on hypothetical risk levels. *BMC Public Health* 2005;5:9.
- 19 Gravenor MB, Stallard N, Curnow R, McLean AR: Repeated challenge with prion disease: the risk of infection and impact on incubation period. *Proc Natl Acad Sci USA* 2003; 100:10960–10965.
- 20 Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, Bernheimer H, Cardone F, Delasnerie-Lauprêtre N, Cuadrado Corrales N, Ladogana A, Bodemer M, Fletcher A, Awan T, Ruiz Bremón A, Budka H, Laplanche JL, Will RG, Poser S: Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000;55:811–815.
- 21 Klassifikation av operationer, 6:e upplagan. Socialstyrelsen. Stockholm, Norstedts, 1993.
- 22 Operations og Behandlings-Klassifikation, 3 udgave. Sundhedsstyrelsen. Copenhagen, Munksgaard, 1988.
- 23 Nordic Medico-Statistical Committee: NO-MESCO Classification of Surgical Procedures. Copenhagen, NOTEX, 2003.
- 24 Greenland S: Applications of stratified analysis methods; in Rothman KJ, Greenland S (eds): *Modern Epidemiology*, ed 2. Philadelphia, Lippincott & Raven, 1998, pp 281–300.
- 25 Lundberg PO: Creutzfeldt-Jakob disease in Sweden. *J Neurol Neurosurg Psychiatry* 1998;65:836–841.
- 26 Brown P, Preece MA, Brandel J-P, Sato T, McShane L, Zerr I, Fletcher A, Will RG, Pocchiari M, Cashman NR, Huillard d'Aignaux J, Cervenáková L, Fradkin J, Schonberger LB, Collins SJ: Iatrogenic Creutzfeldt-Jakob disease at the millenium. *Neurology* 2000; 55:1075–1081.
- 27 Salvan A, Stayner L, Steenland K, Smith R: Selecting an exposure lag period. *Epidemiology* 1995;6:387–390.
- 28 Norell SE: Obtaining information on exposures; in Norell SE (eds): *Workbook of Epidemiology*. Oxford, Oxford University Press, 1995, pp 75–98.
- 29 Aguzzi A, Heikenwalder M, Miele G: Progress and problems in the biology, diagnostics, and therapeutics of prion diseases. *J Clin Invest* 2004;114:153–160.
- 30 Stroobant N, Van Nooten G, Van Belleghem Y, Vingerhoets G: Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. *Chest* 2005;127:1967–1976.
- 31 Barash JA, Johnson BT, Gregorio I: Is surgery a risk factor for Creutzfeldt-Jakob disease? Outcome variation by control choice and exposure assessments. *Infect Control Hosp Epidemiol* 2008;29:212–218.
- 32 S-Juan P, Ward HJ, De Silva R, Knight R, Will RG: Ophthalmic surgery and Creutzfeldt-Jakob disease. *Br J Ophthalmol* 2004;88:446–449.
- 33 Hamaguchi T, Noguchi-Shinohara M, Nakamura Y, Sato T, Kitamoto T, Mizusawa H, Yamada M: Ophthalmic surgery in prion diseases. *Emerg Infect Dis* 2007;13:162–164.
- 34 Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Leitch M, Cooper S, Heath C, Knight RS, Smith PG, Will RG: Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Ann Neurol* 2006;59:111–120.
- 35 Linsell L, Cousens SN, Smith PG, Knight RS, Zeidler M, Stewart G, de Silva R, Esmonde TF, Ward HJ, Will RG: A case-control study of sporadic Creutzfeldt-Jakob disease in the United Kingdom. Analysis of clustering. *Neurology* 2004;63:2077–2083.
- 36 D'Aignaux JH, Cousens SN, Delasnerie-Lauprêtre N, Brandel JP, Salomon D, Laplanche JL, Hauw JJ, Alperovitch A: Analysis of the geographical distribution of sporadic Creutzfeldt-Jakob disease in France between 1992 and 1998. *Int J Epidemiol* 2002;31:490–495.
- 37 Zarranz JJ, Digon A, Atarés B, Rodríguez-Martínez AB, Arce A, Carrera N, Fernández-Manchola I, Fernández-Martínez M, Fernández-Maiztegui C, Forcadás I, Galdos L, Gómez-Esteban JC, Ibáñez A, Lezcano E, López de Munain A, Martí-Massó JF, Mendibe MM, Urtasun M, Uterga JM, Saracibar N, Velasco F, de Pancorbo MM: Phenotypic variability in familial prion diseases due to the D178N mutation. *J Neurol Neurosurg Psychiatry* 2005;76:1491–1496.
- 38 Glatzel M, Rogivue C, Ghani AC, Streffer JR, Amsler L, Aguzzi A: Incidence of Creutzfeldt-Jakob disease in Switzerland. *Lancet* 2002; 360:139–141.