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Does Improvement in Case Ascertainment Explain the Increase in Sporadic Creutzfeldt-Jakob Disease Since 1970 in the United Kingdom?

Carine H. Cohen

The aim of this study was to quantify the improvements in case ascertainment which are considered to explain the rise in the incidence of sporadic Creutzfeldt-Jakob disease. The numbers of cases, falling into five 10-year age groups starting at the age of 30 and three calendar periods of report since 1970, were analyzed by Poisson regression, assuming a constant age distribution. The age-period and age-cohort models were applied and discussed. The age-period model showed that underreporting in 1970–1979 was greater among patients aged 70 years or older. The age-cohort model indicated that a cohort factor increased over the first half of the 20th century (e.g., the incidence in the generation born in 1940 was almost twice that in the generation born in 1920); this increase was probably an artifact due to the past underascertainment pattern. However, from a statistical viewpoint, both models lead to a good fit; the cohort factor may appear to be as relevant as the period factor in describing the trends in incidence. Thus, one can imagine an unlikely worst case scenario, assuming that an unknown cohort factor is involved. In that case, the age-cohort model gives more optimistic predictions than Neilson's model (*BMJ* 1996;312:1038–9). These results are consistent with both interpretations: The rise in incidence is governed by improvements in case ascertainment, and is greater among old people (the most accepted interpretation); this rise may depend on a cohort factor as well, which may correspond to the zoonotic hypothesis (a totally hypothetical interpretation). Interpreting the increase of sporadic Creutzfeldt-Jakob disease over generations in terms of exposure to putative environmental factors is still a matter of debate; ongoing epidemiologic surveys may provide more information. Presently, this increase can be explained as an artifact due to the past underreporting pattern, with 79% (95% confidence interval: 56, 90) of the cases among persons aged ≥70 years being missed in 1970–1979. *Am J Epidemiol* 2000;152:474–9.

Creutzfeldt-Jakob syndrome; incidence; mortality; time factors

The dramatic increase in sporadic Creutzfeldt-Jakob disease in the United Kingdom (0.53 cases per million person-years in 1970–1979, 0.80 in 1980–1989, and 1.18 in 1990–1997) has been attributed to a diagnostic trend resulting from improvements in case ascertainment, especially among older patients (1). However, so far the etiology of sporadic Creutzfeldt-Jakob disease remains unknown, and there is concern about the possibility that some unrecognized factors may enhance the risk of developing Creutzfeldt-Jakob disease (1–4). Indeed, the new variant of Creutzfeldt-Jakob disease resulted from exposure to the infectious agent of bovine spongiform encephalopathy (BSE) (5, 6), and the unknown origin of BSE might be the infectious agent of scrapie in sheep (7, 8). In the United Kingdom, a greater than expected incidence of sporadic Creutzfeldt-Jakob disease has been found among dairy farm workers and their spouses and among people at increased risk of contact with BSE-infected cattle (1). An increased risk has also been found in Europe in relation to consumption of raw meat and brain (2). Because many factors were studied, these associations were generally considered artifacts. Moreover, the power of any study is limited by recall bias and small numbers of cases: The smallest detectable relative risk was 4.2 for exposures of 1 percent in van Duijn et al.'s survey (2). Presently, several epidemiologic inquiries are ongoing in the European Union to assess putative risk factors for Creutzfeldt-Jakob disease, including medical history, occupation, and diet (http://www.cordis.lu). These studies are investigating the plausible impact of past exposure to prions, particularly scrapie, on the risk of developing sporadic Creutzfeldt-Jakob disease. They are seeking to establish whether the rise in incidence may reflect a trend in past levels of exposure to some unknown environmental factor(s).

Our purpose in this analysis was not to decide whether such a link exists. Rather, it was to quantify the consequences of each plausible interpretation for the rise in sporadic Creutzfeldt-Jakob disease incidence. In descriptive epidemiology, age-period-cohort models are a useful tool whereby temporal variations in disease incidence can be presented and interpreted (9, 10). These models aim to relate incidence rates to the effects of the individuals' age, the period of

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Abbreviation: BSE, bovine spongiform encephalopathy.

From the Institute for Animal Neurology, Berne University, and the Monitoring Group, Federal Veterinary Office, Bern, Switzerland.

Correspondence to Dr. Carine H. Cohen, BVET-Monitoring, P.O. Box CH-3003, Bern, Switzerland (e-mail: carine.cohen@bvet.admin.ch).

observation of those rates, and the generation to which the subjects belong. The period factor accounts for reporting trends, and the cohort factor accounts for influences that affect incidence rates in a specified birth cohort equally throughout life. We applied an age-period model and an age-cohort model to the sporadic Creutzfeldt-Jakob disease data for the United Kingdom from 1970–1997, and we estimated the period factor due to improvements in case ascertainment, which is presently considered the explanation for the rise in sporadic Creutzfeldt-Jakob disease incidence.

MATERIALS AND METHODS

In 1999, the seventh annual report on Creutzfeldt-Jakob disease surveillance in the United Kingdom was posted on the World Wide Web (http://www.cjd.ed.ac.uk) by the National Creutzfeldt-Jakob Disease Surveillance Unit. From this report, we derived the number of deaths due to sporadic Creutzfeldt-Jakob disease in England and Wales for the period 1970–1984 and in the entire United Kingdom for the period 1985–1997. These numbers were documented by age group and by period of observation from January 1, 1970, through December 31, 1997, in agreement with published data (1). Most of the cases identified (80 percent) were neuropathologically confirmed, and the remainder were clinically probable. Analyses were conducted on 716 cases falling into five 10-year age groups starting at the age of 30 (one patient aged 14 years was not included) and three calendar periods. The oldest age group consisted of patients aged 70 years or more (19 cases in 1970–1979 and 110 cases in 1990–1997).

The numbers of person-years of surveillance, corresponding to the numbers of cases reported, were used to calculate incidence rates. The population under surveillance was estimated by linear interpolation from census data for 1971, 1981, 1991, and 1996 provided by the UK Office for National Statistics (see table 1).

Age-period-cohort models assume that the factors' effects on the risk of developing sporadic Creutzfeldt-Jakob disease can be separated. The period factor represents a change affecting equally and simultaneously the individuals of any age, typically a modification in reporting rates. The cohort factor accounts for influences affecting incidence rates in a specified birth cohort equally throughout life. Cohort effects do not arise only from etiologic environmental exposures, nor do period effects necessarily reflect ascertainment; they could arise from an exposure that had a fixed time span. However, transmissible spongiform encephalopathies are characterized by a long and highly variable incubation time. Therefore, a cohort factor will be described better by an age-cohort model than by an age-period model (11). Additionally, the age factor is the physiopathologic effect of age on incidence, stripped of the influences of periods and cohorts. Assuming that no change occurred in the ages of the cases across periods or cohorts, the age factor can be estimated either by an age-period model or by an age-cohort model, which predicts constant ratios of age-specific rates between the different periods or cohorts, respectively. A parameterization is chosen so that the parameters look like age-specific rates for the age factor and have direct interpretations in terms of relative risks for the period or cohort factor, taking one period or one cohort as the reference group (9, 10).

The observed numbers of sporadic Creutzfeldt-Jakob disease cases were assumed to follow a Poisson distribution, and the log-transformed age-specific incidence rates were assumed to be a linear function of age group, calendar period, or cohort effects. Thereby, the cases' distribution was analyzed by Poisson regression, fitting two models: the age-period model, $R_{ij} = e^{K} \times e^{A_i} \times e^{P_j}$, and the age-cohort model, $R_{ij} = e^{K} \times e^{A_i} \times e^{C_k}$, where R_{ij} denotes the expected incidence rate in age group i and calendar period j, K is a constant, A_i is the effect of age group i ($i = 1, 2, 3, 4, 5$), P_j is the effect of period j ($j = 1, 2, 3$), and C_k is the effect of birth cohort k ($k = 5 - i + j$, $k = 1, 2, 3, 4, 5, 6, 7$). To take into account the different sizes of the population at different ages i and in different periods j, we computed incidence rates as the ratio of the number of cases to the corresponding number of person-years of observation, which was set as a constant (called an "offset"). The binomial distribution (large population, low incidence) was approximated by the Poisson distribution. The model's parameters were estimated by the maximum likelihood method, using GLIM software (Numerical Algorithms Group, Oxford, United Kingdom). As a measure of the goodness of fit, GLIM gives the deviance, which for the Poisson distribution is the value of the likelihood ratio test statistic for the model fitted compared with the saturated model with a parameter for every observation unit (12). The models were compared according to the Akaike Information Criterion, which takes account of the fact that the age-cohort model has more parameters than the age-period model.

TABLE 1. Age distribution of the resident population in England and Wales (censuses of 1971, 1981, and 1991) and in the United Kingdom (censuses of 1981, 1991, and 1996)*

Age group (years)	Population in England and Wales (millions)			Population in United Kingdom (millions)		
	1971	1981	1991	1981	1991	1996
30–39	5,657	6,900	7,120	7,771	8,067	9,132
40–49	6,070	5,534	6,820	6,274	7,668	7,933
50–59	5,873	5,710	5,285	6,450	5,987	6,452
60–69	5,241	5,097	5,029	5,736	5,676	5,418
≥70	4,095	5,058	5,651	5,671	6,311	6,605
Total	26,936	28,299	29,905	31,903	33,709	35,540

* Data were obtained from the UK Office for National Statistics.

RESULTS

Tables 1 and 2 give data on the population under surveillance and numbers of cases of sporadic Creutzfeldt-Jakob disease. Figure 1 displays the observed incidence per 50 million person-years, by age group and period (left side of the figure) and by age group and cohort (right side of the figure). Cohorts C1 and C7 corresponded to one observation unit each and are not represented. There is an increasing trend, both by period and by cohort, over cohorts C2 to C6. The models assumed that the curves plotted in the lower half of the figure were parallels.

A preliminary analysis did not take into account a lower reporting rate for patients aged ≥70 years in 1970–1979 (1, 13, 14) and led to a significant lack of fit for the age-period model (8 df; deviance = 25.0, $p < 0.01$). To illustrate the fact that past underascertainment was more important among old people (13), we examined an age-period model in which the number of patients aged ≥70 years in 1970–1979 was estimated by one more parameter, which allowed the reporting rate in 1970–1979 to be lower for this age group. This model's fit was good (7 df; deviance = 13.05, not significant (see table 3)), which confirmed that case ascertainment (the period factor) was lower in 1970–1979 among people aged ≥70 years.

Table 3 shows that the age-period model, specifying similar reporting rates within the different age groups, except in 1970–1979 for cases aged ≥70 years, led to a good fit (7 df; deviance = 13.05, not significant; Akaike Information Criterion = 29.05); and the age-cohort model's fit was also satisfactory (4 df; deviance = 1.93, not significant; Akaike Information Criterion = 23.93). Table 3 also gives the factors' estimates, in terms of relative incidence rate (age effect) or relative risk (period and cohort effects), taking as the reference group the fourth age group (60–69 years), the third period (1990–1997), and the third cohort (1920), respectively. These levels were used as a reference category, since they corresponded to the highest number of cases observed for each factor. For example, the age-period model predicted approximately 50 percent fewer cases (0.45) in the age group 50–59 years than in the age group 60–69 years.

According to the age-period model, by reference to the period 1990–1997, the estimated reporting rate for 1980–1989 was 0.66 (95 percent confidence interval: 0.56, 0.77); for 1970–1979, it was 0.50 (95 percent confidence interval: 0.41, 0.62) among cases younger than age 70 and 0.21 (95 percent confidence interval: 0.10, 0.44) among cases aged ≥70 years. According to the age-cohort model, there was an increasing trend over the cohorts C2 (1910) to C6 (1950), whose risks relative to cohort C3 (1920) were 0.60 and 3.27, respectively. However, this trend disappeared when the data were first corrected for the reporting rates estimated by the age-period model (by estimating the "true" number of cases and then fitting the age-cohort model to these estimated numbers (results not shown)). It clearly indicated that this trend could be interpreted as an artifact due to the past reporting pattern. However, under the worst case scenario, in which such a hypothetical trend continued over the generations born in the second half of the 20th century, the age-cohort model's projections led to an increase of less than 100 additional cases by 2020 (results not shown).

Table 4 gives predictions of the age-period and age-cohort models, together with the numbers of cases observed, by age group and by period. The confidence intervals illustrate that both models can fit. In this context, it would be hazardous to draw conclusions on the basis of a statistical criterion only (14).

DISCUSSION

Our main goal in this analysis was to quantify the improvement in case ascertainment which is thought to account for the rise in the numbers of sporadic Creutzfeldt-Jakob disease cases in the United Kingdom. In fact, national surveillance for Creutzfeldt-Jakob disease was initiated in May 1990 in response to the recommendation of a working party on BSE (the Southwood committee). Between 1970 and 1979 and between 1985 and March 1990, surveillance was retrospective, largely relying on death certificates for case identification. Between 1980 and 1984 and since 1990, surveillance has been prospective: The majority of suspected cases have been seen by members of the National Creutzfeldt-Jakob Disease

TABLE 2. Person-years of surveillance for Creutzfeldt-Jakob disease (estimated by linear interpolation between censuses) and numbers of sporadic cases in England and Wales in 1970–1984 and in the entire United Kingdom in 1985–1997, by age group and by period, 1970–1997*

Age group (years)	Person-years of surveillance (millions)			Cases of sporadic Creutzfeldt-Jakob disease in England and Wales in 1970–1984 and in the entire United Kingdom in 1985–1997		
	1970–1979	1980–1989	1990–1997	1970–1979	1980–1989	1990–1997
30–39	60,921	74,252	68,979	5	7	1
40–49	58,822	64,045	62,318	6	8	17
50–59	58,160	59,173	49,896	44	52	64
60–69	51,905	53,957	44,331	71	112	133
≥70	44,322	55,827	51,658	19	67	110
Total	274,130	307,254	277,183	145	247	326

* Data were obtained from the National Creutzfeldt-Jakob Disease Surveillance Unit.

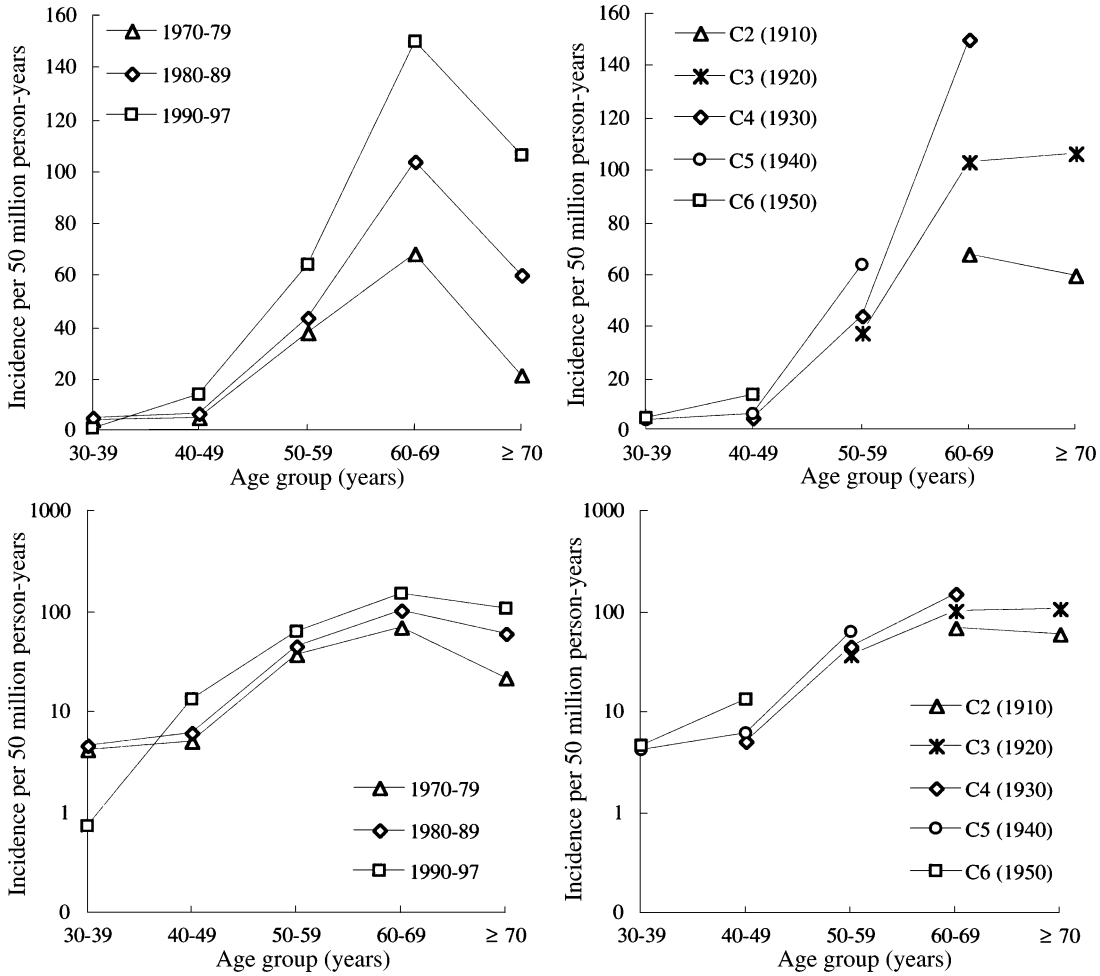

FIGURE 1. Incidence of sporadic Creutzfeldt-Jakob disease per 50 million person-years during the periods 1970–1979, 1980–1989, and 1990–1997 (left side) and in birth cohorts C2 (1910) to C6 (1950) (right side). The upper portion of the figure shows data on the arithmetic scale; the lower portion shows data on the logarithmic scale. Cohorts C1 (1900) and C7 (1960) are not represented because they corresponded to one observation unit each.

Surveillance Unit, which continues to obtain death certificates. In this paper, the post-1990 numbers were not considered to be biased by underreporting, and an age-period model was used to illustrate the assumption of a period effect due to underascertainment before 1990. This model has estimated low reporting rates (e.g., 0.66 in 1980–1989). Low reporting rates were also found for BSE in the 1980s (11). This may be a common feature of rare or new diseases, such as Creutzfeldt-Jakob disease and BSE, respectively.

However, an increase in autopsies since 1979 was not found likely to explain the increase in deaths certified as being due to Creutzfeldt-Jakob disease (15). According to the zoonotic hypothesis (16, 17), which is not supported by any epidemiologic data so far, there may be other unknown factors governing the rise in incidence. An age-cohort model based on this assumption has led to a good fit. The incidence trend was explained equally well by a time factor—such as better ascertainment after a given time—or as a consequence of variation between cohorts. The main point is that a linear trend in the period terms can mimic a cohort factor in an age-cohort model (18). From a statistical viewpoint, it is impossible to designate unambiguously a linear trend in rates as either a period trend or a cohort trend. This technical difficulty makes hazardous any interpretation of the data which does not rely primarily on epidemiologic grounds. Hence, the demonstration of an etiologic cohort factor cannot be based on this sort of statistical analysis alone, which is equally consistent with an interpretation of a time factor of improvement in ascertainment (1) and with a hypothesis relating the rise in incidence to some environmental factor with different exposure levels among the different cohorts. Nevertheless, in the event that such an unrecognized etiologic factor is involved, our models indicated that this factor would cause an increase of less than 100 cases by 2020 (results not shown). This result is more optimistic than Neilson's predictions (19): Assuming an increased exposure to an environmental risk factor, he stated that an "epidemic" may result in a maximum of 4,000 cases over the next 20

TABLE 3. Goodness of fit achieved by fitting an age-period model* and an age-cohort model† to the incidence of Creutzfeldt-Jakob disease in the United Kingdom, assessed by the deviance and the Akaike Information Criterion (AIC), and estimated factors' effects, 1970–1997

Model	Age group (years)	Age effect (e^{A_i}/e^{A_4})	95% CI‡	Period	Reporting effect (e^{P_j}/e^{P_3})	95% CI
Age-period model (8 parameters, 7 df)						
Deviance = 13.05	30–39	0.029	0.017, 0.051	1970–1979	(cases aged ≥70 years)	
(not significant)	40–49	0.078	0.054, 0.112		0.214	0.103, 0.442
AIC = 29.05	50–59	0.454	0.376, 0.549	1970–1979	(cases aged <70 years)	
	60–69	1.000§			0.496	0.410, 0.615
	≥70	0.669	0.553, 0.810	1980–1989	0.655	0.555, 0.773
				1990–1997	1.000§	
				Cohort	Cohort effect (e^{C_k}/e^{C_3})	95% CI
Age-cohort model (11 parameters, 4 df)						
Deviance = 1.93	30–39	0.015	0.007, 0.033	C1 (1900)	0.206	0.128, 0.334
(not significant)	40–49	0.035	0.021, 0.060	C2 (1910)	0.601	0.488, 0.741
AIC = 23.93	50–59	0.319	0.254, 0.402	C3 (1920)	1.000§	
	60–69	1.000§		C4 (1930)	1.336	1.090, 1.639
	≥70	0.949	0.776, 1.161	C5 (1940)	1.838	1.327, 2.547
				C6 (1950)	3.271	1.687, 6.340
				C7 (1960)	0.429	0.052, 3.504

* The age-period model relied on the two extreme assumptions (see "Discussion"); 1) there was no cohort factor (no etiologic environmental factor of exposure involved in the incidence trend) and 2) past underreporting in a given period was of equal importance within the different age groups, except in 1970–1979 among people aged ≥70 years (it was assumed to be different).

† The age-cohort model relied on the two extreme assumptions (see "Discussion"): 1) there was no period factor (no past reporting bias involved in the incidence trend) and 2) past variations in exposure to an unknown etiologic factor were involved in the incidence trend.

‡ CI, confidence interval. The 95% confidence intervals were estimated by considering the risk relative to the fourth age group (60–69 years), the third period (1990–1997), and the third cohort (1920), respectively. These levels corresponded to the highest number of cases and were used as a referent group.

§ Referent group.

years. So far, the key hypothesis of a cohort factor does not rely on any field data, and it might be challenged by current studies. Only in that case, according to the precautionary principle, would the age-cohort model represent an appropriate model. This work illustrates how interpreting sporadic Creutzfeldt-Jakob disease data depends crucially on

TABLE 4. Numbers of cases of sporadic Creutzfeldt-Jakob disease predicted by the age-period model and the age-cohort model, United Kingdom, 1970–1997

Age group (years)	1970–1979			1980–1989			1990–1997		
	Prediction	95% CI*	Obs*	Prediction	95% CI	Obs	Prediction	95% CI	Obs
Age-period model									
30–39	3	1, 7	5	4	2, 10	7	6	3, 12	1
40–49	7	3, 14	6	10	5, 19	8	14	9, 24	17
50–59	39	23, 68	44	53	32, 87	52	68	49, 94	64
60–69	77	54, 110	71	106	78, 144	112	133	115, 153	133
≥70	19	7, 55	19	73	45, 120	67	103	74, 144	110
Age-cohort model									
30–39	4	1, 13	5	8	2, 39	7	1	0, 20	1
40–49	6	3, 15	6	9	3, 25	8	16	4, 60	17
50–59	41	28, 60	44	55	31, 100	52	64	32, 131	64
60–69	68	48, 98	71	118	102, 138	112	130	91, 186	133
≥70	19	8, 44	19	70	40, 123	67	108	75, 153	110

* CI, confidence interval; Obs, observed number of cases.

hypotheses which are still being debated among experts, and encourages us to look further for possible causes of sporadic Creutzfeldt-Jakob disease.

The results of our analyses correspond to the conclusions of field epidemiologic surveys such as those of Wientjens (20) and Will et al. (21):

> Exposure to cows and sheep was associated with a borderline significant increased risk of Creutzfeldt-Jakob disease (OR 1.7, 95% CI 0.9 to 3.1 and OR 1.6, 95% CI 0.9 to 2.9, respectively). Also, there was a nonsignificant increased risk of Creutzfeldt-Jakob disease for subjects living in a rural area at diagnosis (OR 1.4, 95% CI 0.8 to 2.4)… Our data cannot exclude an environmental source of infection that might have occurred early in childhood. The ongoing systematic surveillance of Creutzfeldt-Jakob disease in several European countries might provide evidence for such exposure as residential histories throughout life are studied. These extensive studies with similar design will be highly comparable and therefore will be able to resolve the problem of selection bias and of the limited statistical power of our analysis (20, p. 1290).

> The sharp decrease in mortality at older ages has been described in other studies and is unexplained. Poor case ascertainment in the elderly is a possible explanation, though the clinical features of the disease are striking. An alternative explanation is that Creutzfeldt-Jakob disease has a limited incubation period, albeit measured in decades, and that exposure to the agent early in life results in a maximal age at which the disease is likely to become manifest. There are few precedents for such a mechanism, however, as, in general, if incubation periods are long they are also highly variable (21, p. 753).

Further analyses should be carried out with new European data—especially since the fourth annual report of the National Creutzfeldt-Jakob Disease Surveillance Unit showed that a rise in incidence has also been observed in other countries (France, the United States, etc.) but an excess of female cases has been observed only in the United Kingdom (17).

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