Ocular Tonometry and Sporadic Creutzfeldt-Jakob Disease (sCJD): A Confirmatory Case-Control Study

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30

Abstract

32

Aims: To evaluate the hypothesis that sporadic Creutzfeldt-Jakob disease (sCJD) may be transmitted through ocular tonometry.

Background: The infectious agent of sCJD may be present in the cornea prior to clinical symptoms. Cornea infectiousness has been documented by cornea transplants in guinea pigs and humans. sCJD is resistant to complete inactivity by conventional sterilization techniques. Thus contact tonometry equipment is not disinfected sufficiently to kill sCJD. We previously hypothesized that contact tonometry is a sCJD risk factor.

Study Design: Case-control study.

Place and Duration of Study: Department of Neurology, School of Medicine, Loma Linda University, Loma Linda, CA, USA; 4 years.

Methodology: An 11-state case-control study of pathologically confirmed sCJD cases, individually matched controls, and a sample of control surrogates was conducted. Ocular tonometry histories were obtained from case-surrogates, controls, and a sample of control-surrogates.

Results: The odds ratio (OR) for ever vs never having had a tonometry test was statistically
significant for matched and unmatched analyses for 15 through 3 years prior to disease onset, using both control self-responses and control surrogates: ORs were ∞ and 19.4 with 1-sided p-values < 0.0001 and 0.003 and ORs = ∞ and 11.1, with 1-sided p-values < 0.003 and 0.02, respectively. ORs increased as the number of tonometry tests increased during this age period: trend test, 2-sided p-value < 0.0001. For ≥5 vs <5 tonometry tests, the OR was 5.8 (unmatched) and 3.7 (matched), 2-sided p-value < 0.00005. There was no indication of increased tonometry testing among cases within 2 years of disease onset.
Conclusions: The a priori hypothesis was supported. Contact tonometry, preferred by 55 ophthalmologists, may be capable of transmitting sCJD. Consideration should be given to using 56 disposable instrument covers after each use. The use the disposable covers or non-contact 57 tonometry preferable in the absence of effective disinfectant process at this time.

Key Words:
Sporadic Creutzfeldt-Jakob disease (sCJD); prion diseases, infectious diseases, intraocular 61 pressure (IOP) test; risk factors; iatrogenic transmission; eyes; ophthalmology; case-control 62 study; neuroepidemiology
1. INTRODUCTION

In 1984, the New England Journal of Medicine published a letter presenting the glaucoma testing results of a study of sporadic Creutzfeldt-Jakob disease (sCJD) and various exposures [1]. This study found that glaucoma testing may be a risk factor for sCJD. Prior to 1984 Duffy et al. reported the occurrence of sCJD in an individual who had received a corneal transplant from a subject with definite sCJD [2]. In 1977, Manuelidis et al. reported the transmission of sCJD from the cornea of infected guinea-pigs to healthy guinea-pigs via the anterior chamber of the eye [3]. Subsequently, there have been a few more reports of cornea transplant patients developing sCJD when the donor had either definite, probable or possible sCJD [4,5]. Glaucoma tests are usually performed using intraocular pressure (IOP) Goldmann tonometry, during which the equipment actually touches the cornea. Furthermore, the equipment cannot be disinfected after each use to completely “kill” the sCJD infectious agent (prion, PrP\textsuperscript{Sc}) [6,7]. This is due to resistance of the agent to complete inactivation by conventional sterilization techniques. Thus, we hypothesized that intraocular pressure tests, intraocular tonometry would be a risk factor for sCJD. In our initial study, we did find that a history of glaucoma testing was significantly associated with sCJD [8].

2. MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) of the Loma Linda University School of Medicine. The study participant subjects have signed the IRB approved informed consent form.

2.1 Study Subjects

The present report is based on an 11-state case-control study of neuropathologically confirmed sCJD. The 11 states in the study were chosen because of their size; combined, they contain about 40% of the US population. The process of identifying subjects with a neuropathological
confirmation of CJD has been detailed elsewhere [9]. Neuropathologically confirmed CJD cases were identified through systematic inquiries of hospitals and neuropathologists, and through the use of death certificates. All cases had been diagnosed between 1979 and 1990. The study neuropathologist (BL) reviewed the neuropathology reports and/or slides and tissue blocks for 189 of these cases. One hundred sixty-two (162) were confirmed to have had definite CJD. Thirty-two families declined to participate and another 10 families could not be located. Thus, families for 120 cases participated and provided surrogate information. The 10 familial CJD cases, defined as a case who had a blood relative with at least suspected CJD, were excluded from this analysis because familial CJD is overwhelmingly of genetic, not environmental, origin. If such cases had been included in the analyses, the odds ratio (OR) estimators would have therefore been somewhat biased towards one. Thus, only sporadic CJD cases were used in the analyses.

Controls were obtained by random-digit-dialing. Matching criteria were date of birth (10 years earlier than to 2 years after the case’s birth), gender, ethnicity (black, white, Hispanic, Asian), and residential area 6 months prior to the month of diagnosis. The study protocol called for up to 2 controls per case. One control was found for 56 cases and 2 controls for 29 cases. There were no controls for 25 (23%) cases because of study funding limitations associated with the time needed to recruit matched controls by random digit dialing.

### 2.2 Data Collection Interviews

Due to the nature of the disease (i.e., progressive dementia and death usually within one year), the most knowledgeable surrogate was interviewed for each case. Controls were directly interviewed. However, for a subsample of controls, a knowledgeable surrogate was also interviewed. All interviews were conducted by telephone, which provided an efficient and feasible data collection method for a study which covered a large geographical area. Interviewees were
sent materials describing the categories of information of interest so that they could prepare for the interview. The interviewers were blinded as to the study hypotheses, disease of interest, and case-control status. They knew only that the study was health-related and that sometimes the interview concerned the person being interviewed and sometimes it concerned another person. The questionnaire was quite detailed and covered many areas, including diet, medical problems, occupation, contact with animals, travel, glaucoma testing. Interviewees were unaware of the study hypotheses. Controls and control-surrogates were unaware of the disease being studied.

2.3 Ocular Tonometry Exposures

The questionnaire was similar to the one used in our original sCJD study [10]. It was, however, more focused. Exposure data were obtained for three periods for cases: birth through 14 years of age; age 15 through 3 years prior to symptom onset; within 2 years prior to symptom onset. For the individually matched controls, corresponding periods were used. For each period, interviewees were asked about the occurrence of one or more glaucoma tests and the number of ocular tonometry. Information concerning having contact and non-contact ocular tonometry was requested. However, over 50% of the respondents (case-surrogates, controls, and control-surrogates) could not distinguish between contact and non-contact ocular tonometry.

2.4 Statistical Analyses

Because this is a confirmatory study, we have chosen to use one-sided statistical tests (p-values) for the odds ratio estimates. The p-value for a 2-sided test is simply twice the p-value for the corresponding 1-sided test. Exact conditional logistic regression was used for estimating the P-values and 95% (2-sided) confidence intervals for the standard odds ratio estimates for the ever versus never (dichotomous) comparisons [11]. Odds ratio estimation for the exposure index based on the number of times a subject had had a glaucoma test was performed using
conditional logistic regression with 2-sided P-values [12]. Thus, the case-control matching was retained in all these analyses. We also performed unmatched (unconditional) logistic regression analyses for comparison purposes and for a 1-degree of freedom trend test [12].

As mentioned above, respondents generally were uncertain as to the type of tonometry equipment (pressure vs puff) used. We therefore have conducted all analyses without attempting to differentiate between the two types of equipment.

3. RESULTS

3.1 Study Subjects Forty-eight (56%) of the cases with a control were men. There was very little difference in the mean or median ages at onset between men and women (63.0 vs 62.1; 62.1 vs 63.2). The standard deviations were the same: 8.4 years. The cases without a matched control were, on average, 4 years older at onset and had a smaller onset age standard deviation than the cases with at least one control. The cases without a matched control also had a slightly shorter mean duration of disease with a smaller standard deviation: mean durations of 7.3 vs 8.7 months; standard deviations of 5.6 vs 11.5 months. The differences in the standard deviations were due to a few cases, among those with controls, who had a long duration of illness.

3.2 Ocular Tonometry Test Histories Information about ever having had an intraocular pressure (IOP) test, ocular tonometry between birth and age 14 was missing for 41% of the cases and 47% of the controls using surrogate data, but only for 3.5% of the controls using self-reported data (Table 1). For the age period 15 through 3 years prior to disease onset, missing information was minimal (8%, 12%, and 3%). For the period within 2 years prior to onset, the missing information percentages were 9%, 1%, and 12%). The rates of ever having had a
glaucoma test during the initial period (birth through age 14) were quite low, but were substantial
during the other two periods (Table 1). Information on the number of glaucoma tests within a
specific period was missing somewhat more often for cases than for control self-responses. For
control-surrogate data, the rates of missing information about the number of glaucoma tests was
over 50%. The absolute and relative frequencies of the categorized data are provided in Table
1. The rates of missing data are essentially identical for cases with and cases without controls
(data not shown).

3.3 Dichotomous (Ever vs Never) Exposure Odds Ratios  Table 2 provides the odds ratio
estimates for glaucoma tests using the dichotomy ever vs never by age-period. The data for the
period birth to age 14 were too sparse for the use of matched analyses or control surrogate data.
The analyses using control self-responses clearly indicate a significantly increased risk of CJD
among those who have ever had a glaucoma test from age 15 through 3 years prior to disease
onset. The data for the age period 15 through 3 years prior to disease onset have no discordant
pairs or triples with the case non-exposed. There were 10 discordant pairs and 6 discordant
triples (one control exposed and one not exposed) with the case exposed. This leads to an OR
estimate of $\infty$, $P < 0.0001$. The analysis using the control surrogate data are based on only 32
cases and 34 controls. The results are in agreement with the self-reported control data, but the
estimates are unstable because of the relatively small sample size.

For the period within 2 years of onset, there is no indication of an increased risk associated with
having had a glaucoma test in that period. For this period, the OR estimates are 1.0 or lower, and
are not statistically significant. The relative frequencies of ever having had a glaucoma test during
the middle period and last period were about equal among cases, but the proportion of controls
ever having had a test increased from 84% to 96%, perhaps because decreases in vision often come with older age.

3.4 Odds Ratios Based on Number of Glaucoma Tests

Table 3 presents the results of an analysis using specific categories of the number of glaucoma tests in the middle and last periods. The cut-points are different within each period because of the number of subjects with multiple tests, in part certainly due to the greater duration of the middle period (age 15 through 3 year prior to onset) compared to the last period (within 2 years of onset). For the middle period there is a significantly increased risk associated with each of the categories 1-4, 5-10 and > 10. There is also a clear trend in the increase of the odds ratio estimate with increased number of glaucoma tests (P < 0.0001).

Finally, Table 4 presents the results for the period age 15 through 3 years prior to onset for the number of glaucoma tests with a single cut-point between 4 and 5 tests. Both the matched and unmatched analyses (≥5 vs < 5 tests) are provided using control self-responses. The odds ratio estimates are 5.8 and 3.7 and are highly statistically significant.

4. Discussion

4.1 A Priori Nature of the Study Hypothesis

The hypothesis that ocular pressure tonometry is associated with the occurrence of CJD was an a priori hypothesis based on our previous case-control study of sCJD and on ours and others hypothesis on the transmission of sCJD as described in the Introduction. Cornea is one of the eye structures which may contain PrPSc prior to the clinical onset of disease. There have been demonstrated cases of recipients receiving infected cornea transplants and within a few years developing sCJD [2-5].
Lim et al. [6] have demonstrated that a person who has a contact glaucoma test (the procedure usually preferred by ophthalmologists and optometrists) will shed some cells onto the equipment. The equipment is not disinfected sufficiently between uses to “kill” the CJD infectious agent [6,7]. The infectious agent is resistant to complete inactivation by conventional sterilization techniques. Head et al. [13] have investigated the distribution of prions in the eyes of one patient with sCJD and two patients with vCJD. sCJD and vCJD were confirmed pathologically. PrPSc was not detected in the cornea of the examined eyes. The authors state, however, that because (1) transmission through corneal transplants has been documented and (2) the lack of sufficient sensitivity of the assay they used to detect PrPSc, the lack of detection “cannot be taken as evidence for the absence of infectivity” of the cornea.

4.2 Study Findings In this confirmatory case-control study of sCJD, we have found that ocular tonometry, particularly between age 15 through 3 years prior to disease onset, may be a risk factor for sCJD. We have also shown a dose-response effect in that the larger the number of glaucoma tests the higher the relative risk of disease. Unfortunately, the respondents most often could not differentiate between the puff (non-contact) and the contact tonometry when queried about the history of each type of test. Thus, we simply analyzed tonometry tests without differentiating between types of equipment used. Further studies in countries with health care systems which have national computerized records of glaucoma tests and for which the types of equipment can be determined would be fruitful.

The estimated ORs for the period within 2 years of disease onset were 1.0 or below. Thus, errors in estimating the age or time of onset of disease are unlikely to have resulted in an upward bias in
the results for the period age 15 through 3 years prior to disease onset.

4.3 Multiple Comparison There is no multiple comparison problem complicating the interpretation of our results. The *a priori* hypothesis was based on the results of a previous study combined with knowledge of the infectious nature of the cornea from a donor with sCJD. Furthermore the study protocol stated that this particular hypothesis would be tested.

4.4 Control Surrogates Analyses using control-surrogates generally support the results of the analyses using the control self-responses (Table 2), even though the control-surrogate sample size is small.

4.5 European Study Design and Finding Zerr et al. [14], as part of the European CJD surveillance project, analyzed “ophthalmological tests” and reported no increased risk of CJD associated with ever having had an ophthalmological test. Zerr et al. did not differentiate between types of ophthalmological tests, nor did they list the tests included in the analyses. No information concerning ocular tonometry *per se* was provided. We note that 72% of their 405 controls had a neurologic disease and 25% were hospital controls with non-neurological diseases. There were only 8 population controls. The percentages of both cases and controls in the Zerr et al. study who had ever had an ophthalmological test were 50% and 55%, respectively. This is significantly lower than in our study, where percentages for the age period 15 through 3 years prior to onset were 99% and 84%. Perhaps ocular tonometry was not considered an ophthalmologic test. In addition, ophthalmologic problems are not uncommon among patients with stroke and other neurologic diseases [15-21]. It would therefore appear that controls with neurologic disease are inappropriate for investigating a possible risk of sCJD associated with tonometry or
ophthalmologic tests in general.

5. CONCLUSION

The study was designed and conducted to minimize problems often associated with case-control studies, particularly when the cases are mentally incapacitated or deceased. The findings indicate that ocular tonometry may be an important iatrogenic method of transmission of the infectious agent for sCJD.

We note that disposable protective covers and disposable tonometer tips, which essentially eliminate any risk associated with contact tonometry, are available but are not yet commonly used [22-24]. The British Royal College of Ophthalmologists in a document dated May 2004 recommended that contact tonometry equipment be wiped and disinfected after each use. They further recommended that disposal heads or shields or Tonopens be used, but only when a subject either has or may have or be possibly genetically susceptible to CJD [25]. This recommendation may not be sufficiently strict.

List of Abbreviations

Authors’ contributions

ZD conceived the study. ZD was the PI and study epidemiologist and oversaw the conduct of the study, including the data collection and analyses. ES was the study statistician. ZD and ES designed the study. CS coordinated the study and data collection. AZ did the statistical programming for the data analyses. TB was the study neurologist and BL was the study neuropathologist. Together they determined the final diagnoses. KD was the study
geriatrician-internist and together with TB and BL provided diagnostic and medical expertise for the study.

**Ethical Approval and Consent**

This study was approved by the Institutional Review Board (IRB) of the Loma Linda University School of Medicine. The study participant subjects have signed the IRB approved informed consent form.
REFERENCES


11. EPILOG, Epicenter Software, P.O. Box 90073, Pasadena, CA 91109.


22. Ocu-Film, Tono-Pen Tip Covers, BIO-RAD, Ophthalmic Division, Santa Ana, CA, 92705, USA.


TABLE 1

DISTRIBUTION OF TONOMETRY TEST DATA BY PERIOD: NUMBER AND PERCENT

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PERIOD</th>
<th>CATEGORY</th>
<th>CASES</th>
<th>SELF-REPORT N=110</th>
<th>SURROGATE N=34*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=110</td>
<td>N=114</td>
<td>N=34*</td>
</tr>
<tr>
<td>Ever</td>
<td>Birth-No</td>
<td></td>
<td>59 (91%)</td>
<td>108 (98%)</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>vs</td>
<td>Age 14-Yes</td>
<td></td>
<td>6 (9%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Never</td>
<td>Missing</td>
<td></td>
<td>45 (41%)**</td>
<td>4 (4%)**</td>
<td>16 (47%)**</td>
</tr>
<tr>
<td></td>
<td>Age 15-No</td>
<td></td>
<td>1 (1%)</td>
<td>18 (16%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td></td>
<td>3 Years-Yes</td>
<td></td>
<td>100 (99%)</td>
<td>93 (84%)</td>
<td>27 (90%)</td>
</tr>
<tr>
<td></td>
<td>Prior to Onset</td>
<td>Missing</td>
<td>9 (8)**</td>
<td>3 (3)**</td>
<td>4 (12%)**</td>
</tr>
<tr>
<td></td>
<td>Within 2-0 No</td>
<td></td>
<td>5 (5%)</td>
<td>5 (4%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>3 Years-1-4 Yes</td>
<td></td>
<td>17 (19%)</td>
<td>31 (30%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Prior to Onset</td>
<td>&gt; 10</td>
<td>36 (39%)</td>
<td>22 (21%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td></td>
<td>18 (16%)**</td>
<td>10 (9%)**</td>
<td>19 (56%)**</td>
</tr>
<tr>
<td></td>
<td>Within 2-0 No</td>
<td></td>
<td>5 (5%)</td>
<td>5 (5%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td></td>
<td>3 Years-1 Yes</td>
<td></td>
<td>20 (20%)</td>
<td>14 (14%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td></td>
<td>Prior to Onset</td>
<td>&gt; 2</td>
<td>57 (57%)</td>
<td>19 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td></td>
<td>10 (9%)**</td>
<td>11 (10%)**</td>
<td>18 (53%)**</td>
</tr>
</tbody>
</table>

* Two cases had two controls each with a surrogate control.
However, for neither case did both surrogate controls supply tonometry data.

** Percent is based on the total number of subjects: 110 cases; 114 controls; 34 control surrogates.
### TABLE 2
ODDS RATIO ESTIMATES FOR TONOMETRY TESTS USING THE DICHOTOMY EVER VS NEVER BY PERIOD

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>ESTIMATION PROCEDURE</th>
<th>ODDS RATIO</th>
<th>95% CONFIDENCE INTERVAL (2-sided)</th>
<th>P-VALUE (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth - Unm</td>
<td>Control Self-Response</td>
<td>5.5</td>
<td>1.1 - 28.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Age 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 15 -</td>
<td>Matched: Control Self-Response</td>
<td>∞</td>
<td>3.1 - ∞</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 Years</td>
<td>Matched: Control Surrogates*</td>
<td>∞</td>
<td>0.7 - ∞</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior to Onset</td>
<td>Unmatched: Control Self-Response</td>
<td>19.4</td>
<td>2.5 - 147.9</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>Unmatched: Control Surrogates*</td>
<td>11.1</td>
<td>1.1 - 111.1</td>
<td>&lt; 0.02</td>
<td></td>
</tr>
<tr>
<td>Within 2 Years</td>
<td>Matched: Control Self-Response</td>
<td>1.0</td>
<td>0.2 - 5.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Prior to Onset</td>
<td>Unmatched: Control Self-Response</td>
<td>0.9</td>
<td>0.2 - 3.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Onset Unmatched: Control Surrogates*</td>
<td>0.7</td>
<td>0.07 - 5.8</td>
<td>0.80</td>
<td></td>
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</tbody>
</table>

* Uses only the 32 cases for whom one matched control has surrogate data. No case had 2 matched controls each with surrogate data.
<table>
<thead>
<tr>
<th>PERIOD</th>
<th>ESTIMATION PROCEDURE/ CATEGORIES</th>
<th>ODDS RATIO ESTIMATE</th>
<th>95% CONFIDENCE INTERVAL (1-sided)</th>
<th>P-VALUE (2-sided)</th>
<th>P-VALUE (1-sided)</th>
<th>Trend</th>
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</thead>
<tbody>
<tr>
<td>Age 15 - Unmatched: Control</td>
<td>3 Years Self-Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior to Onset</td>
<td>Never</td>
<td>1.0</td>
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<td></td>
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<tr>
<td>1- 4</td>
<td>9.9</td>
<td>1.2 - 80.5</td>
<td>&lt; 0.04</td>
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<tr>
<td>5-10</td>
<td>20.7</td>
<td>2.6 - 163.8</td>
<td>0.004</td>
<td>&lt; 0.0001</td>
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<td></td>
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<tr>
<td>&gt; 10</td>
<td>29.5</td>
<td>3.7 - 236.3</td>
<td>&lt; 0.002</td>
<td></td>
<td></td>
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<tr>
<td>Within Unmatched: Control</td>
<td>2 Years Self-Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to Onset</td>
<td>Never</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>0.3 - 5.9</td>
<td>0.62</td>
<td></td>
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<tr>
<td>2</td>
<td>3.0</td>
<td>0.8 - 11.5</td>
<td>0.11</td>
<td></td>
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<td>NS*</td>
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<td>&gt; 2</td>
<td>0.2</td>
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<td>&lt; 0.02</td>
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* NS = Not Significant
<table>
<thead>
<tr>
<th>CASES</th>
<th>CONTROLS</th>
<th>NUMBER OF CONTROLS PER CASE</th>
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<td></td>
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<td>1</td>
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<tr>
<td>EXPOSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>YES</td>
<td>74</td>
<td>55</td>
</tr>
<tr>
<td>MISSING</td>
<td>18</td>
<td>10</td>
</tr>
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<table>
<thead>
<tr>
<th>TYPE OF ANALYSIS</th>
<th>ODDS RATIO</th>
<th>95% CONFIDENCE INTERVAL (1-sided)</th>
<th>P-VALUE (2-sided)</th>
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</thead>
<tbody>
<tr>
<td>MATCHED: SELF-RESPONSE</td>
<td>5.8</td>
<td>2.2 - 19.1</td>
<td>&lt; 0.00005</td>
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<tr>
<td>UNMATCHED: SELF-RESPONSE</td>
<td>3.7</td>
<td>1.9 - 7.0</td>
<td>&lt; 0.00005</td>
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</table>