Reliability of Data From Next-of-Kin: Results From a Case-Control Study of Occupational and Lifestyle Risk Factors for Cancer

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Background Use of surrogate responders often needs to be considered in case-control studies with a high case fatality.

Methods Agreement between 98 colon cancer patients and their closest relative was expressed as a percentage of the exact agreement and by Kappa coefficients and intra-class correlation coefficients.

Results The percentage of “don’t know” answers was higher for surrogates than for index cases and the highest percentage was seen for questions on early events like childhood diseases. Agreement was best for responses to dichotomous questions on smoking and for prevalent or chronic diseases like diabetes or psoriasis, and lower (54–64%) when a quantitative response of, e.g., smoking was requested. The next-of-kin reported fewer job periods than the study person, 4.5 and 2.8, respectively, and there was a higher agreement for the latest job held than for the longest held job. We found an overall agreement between 91% and 100% for responses to ever having worked in a specific type of industry or occupation.

Conclusions Use of next-of-kin data will often be a better alternative than excluding severely ill or deceased cases, if the exposure under study correlates with disease progression. Am. J. Ind. Med. 44:298–303, 2003. © 2003 Wiley-Liss, Inc.

KEY WORDS: surrogate cases; next-of-kin; methodology; epidemiologic research design; case-control studies; occupation; cancer research; exposure information

INTRODUCTION

Studies of diseases with a high case fatality or severe dementia often end with poor response rates because the patients die before data can be collected or they may be too ill to be interviewed. The investigator is then faced with two not very attractive alternatives; either to accept low response rates and the associated risk of selection bias, or to get information from next-of-kin and accept a higher risk of misclassification for some data. It is important when designing a study to understand the magnitude of these problems. We provide an analysis of the risk of misclassification.

Hansen [1996] and Lerchen and Samet [1986] found a considerable degree of under-reporting among surrogates, primarily for exposures with a moderate to low prevalence. Poulter et al. [1996], Brown et al. [1991], and Wang et al.
rare cancers [Kaerlev et al., 2000, 2002; Morales Suárez-Varela et al., 2001]. In this larger study, population controls as well as hospital controls with a diagnosis of colon cancer were used and dead index subjects were replaced by next-of-kin for both cases and controls.

MATERIALS AND METHODS

To evaluate the accuracy of the data obtained from next-of-kin, we selected a random sample of 98 subjects among the 254 colon cancer controls who had agreed to participate in the rare cancer study in Denmark during 1995–1996; they ranged in age from 35 to 69 years. We selected the closest relative in the order: spouse, children, siblings, parents, and other relatives or friends identified by a letter to the index subject’s home. For the present study we selected only colon cancer controls that were alive and able to participate in an interview and for whom a next-of-kin was present. An additional 10 pairs of colon cancer controls and surrogates were interviewed but excluded from the study since proper interview conditions with independently reported information from the study subject and the surrogate could not be obtained. After interviewing the closest relatives (88 spouses or partners, seven daughters, one sister, two parents), who had been asked not to discuss the questions with the study subject (the true respondent), the study subject underwent an interview based on the same questionnaire. The interview of colon cancer controls and their next-of-kin were performed by telephone within one week of each other. The mean length of the interviews was 53 min for index subjects and 43 min for next-of-kin.

The questionnaire addressed occupational exposure, medical history, and lifestyle factors and was not presented to the responders before the interview took place. The subjects were asked whether they had ever been engaged in any of 27 specific occupational activities which had a carcinogenic potential due to possible chemical, physical, or biological exposures. Furthermore, a complete list of all employment periods of at least 6 months duration since leaving elementary school was collected. All major job changes within a company were included as separate jobs, i.e., when the products, activities, tasks, materials, or chemicals in which the interviewee was involved, or job title had changed significantly. For each job, the starting and ending year were reported, together with working hours per week, materials handled, chemical exposure, and occupations held by nearby workers.

Exposure Assessment

Responses to questions on lifestyle factors and previous diseases were dichotomized into ever having had this exposure or not. Occupational information about products and production processes was used to code the industry and occupation for each job. All periods were coded according to the National Industrial Classification of All Economic Activities (NACE) classification of industry (four digits) [EUROSTAT, 1993] and the International Standard Classification of Occupations (ISCO) classification of occupation (five digits) [International Labour Organisation, 1968]. One main code and up to two sub-codes for industry and occupation were recorded for each employment period. For the present analysis, the NACE codes and the ISCO codes were evaluated at a two and three digit level. Subjects were classified according to whether they had worked in the specified industries or occupations lately, and according to the longest held employment period.

Strategy of Analysis

The validity of surrogate information was estimated by several indicators: percent exact agreement, Kappa coefficient, sensitivity, specificity, and the percent of missing answers to each question [Fleiss, 1981]. The value of Kappa statistics varies numerically between 0 and 100 and the higher the value the better the agreement, but it is known to be strongly dependent upon the prevalence of a factor under study [Thompson and Walter, 1988]. The intraclass correlation coefficient was calculated for continuous variables [Armstrong et al., 1992]. Sensitivity and specificity was measured using data from the true responders as the standard.

Furthermore, we calculated a bias factor as the ratio between exposed and non-exposed surrogates compared to exposed and non-exposed study subjects, which varies from zero to infinite with “1” as the reference (equal reporting between the two groups) [Hansen, 1996].

The study was carried out in accordance with the requirements of the national and regional ethics committees in Denmark.

RESULTS

Among the 98 colon cancer patients (the study subjects: 63 men and 35 women) with a mean age of 58 years and their corresponding surrogates, we found more than 80% agreements on lifestyle habits such as smoking and regular alcohol use (Table I). Agreement was better for dichotomous
Responses are sorted by the percentage of missing answers among surrogates.

*Education definition: left school at 15 year, no further education vs. further education.

Responses than quantitative estimates (e.g., smoking and drinking quantity in Table II). None of the colon cancer patients and only a few surrogates were unable to answer these questions. Diseases such as diabetes, hepatitis or jaundice, thyroid disease, and psoriasis were reported with Kappa values above 90%. Agreement was not as good for diseases such as mumps, fractures of bone, serious head injury, asthma, eczema, urticaria, and gallstone. Questions on information in the past were reported with a higher percentage of missing answers, especially for surrogates (e.g., mumps: colon cancer patients 7.1%, surrogates 61.2% (Table I), and body mass index (BMI) age 35 years (Table II)). Information about educational level was obtained with a good agreement between the two groups.

### TABLE I. Measures of Agreement Between 98 Colon Cancer Patients and Their Next-of-Kin for Selected Questions on Lifestyle and Medical Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Missing information (%)</th>
<th>Colon cancer patient</th>
<th>Surrogate</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Overall agreement (%)</th>
<th>Kappa</th>
<th>Bias factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle habits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking ever</td>
<td>0</td>
<td>0</td>
<td>95.7</td>
<td>96.6</td>
<td>0.96</td>
<td>0.90</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Regular wine drinking</td>
<td>0</td>
<td>1.0</td>
<td>95.5</td>
<td>80.0</td>
<td>0.94</td>
<td>0.69</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Regular beer drinking</td>
<td>0</td>
<td>2.0</td>
<td>94.0</td>
<td>80.0</td>
<td>0.92</td>
<td>0.70</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td><strong>Ever have had this disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>0</td>
<td>3.0</td>
<td>71.4</td>
<td>100</td>
<td>0.98</td>
<td>0.82</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.0</td>
<td>4.1</td>
<td>100</td>
<td>100</td>
<td>1.00</td>
<td>0.73</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>0</td>
<td>4.1</td>
<td>100</td>
<td>98.9</td>
<td>0.99</td>
<td>0.93</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>Fractures of bones or of the skull</td>
<td>2.0</td>
<td>5.1</td>
<td>66.7</td>
<td>92.9</td>
<td>0.87</td>
<td>0.62</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Admitted to hospital for serious head injury</td>
<td>0</td>
<td>6.1</td>
<td>66.7</td>
<td>98.7</td>
<td>0.93</td>
<td>0.73</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Dermatitis eczema or allergic skin reactions</td>
<td>0</td>
<td>7.1</td>
<td>55.6</td>
<td>94.5</td>
<td>0.87</td>
<td>0.55</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Gallstone</td>
<td>0</td>
<td>8.2</td>
<td>60.0</td>
<td>97.6</td>
<td>0.96</td>
<td>0.58</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>8.2</td>
<td>37.5</td>
<td>98.8</td>
<td>0.93</td>
<td>0.47</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Hepatitis or jaundice</td>
<td>2.0</td>
<td>11.2</td>
<td>77.8</td>
<td>100</td>
<td>0.98</td>
<td>0.86</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Urticaria or nettle rash</td>
<td>2.0</td>
<td>13.3</td>
<td>50.0</td>
<td>97.3</td>
<td>0.92</td>
<td>0.54</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>7.1</td>
<td>61.2</td>
<td>86.2</td>
<td>85.7</td>
<td>0.86</td>
<td>0.62</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status, married</td>
<td>0</td>
<td>1.0</td>
<td>98.9</td>
<td>66.7</td>
<td>0.97</td>
<td>0.71</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>Education, low*</td>
<td>1.0</td>
<td>2.0</td>
<td>97.1</td>
<td>88.5</td>
<td>0.95</td>
<td>0.87</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

*Education definition: left school at 15 year, no further education vs. further education.

### TABLE II. Measures of Agreement Between 98 Colon Cancer Patients and Their Next-of-Kin for Selected Questions on Lifestyle Exposures and Body Mass Index (BMI) as Continuous Variables; Denmark

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Missing information (%)</th>
<th>Colon cancer patient</th>
<th>Surrogate</th>
<th>Intra-class correlation coefficient</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle habits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine drinking quantity</td>
<td>0</td>
<td>1.0</td>
<td>0.43</td>
<td></td>
<td>0.26—0.58</td>
</tr>
<tr>
<td>Beer drinking quantity</td>
<td>0</td>
<td>2.0</td>
<td>0.69</td>
<td></td>
<td>0.58—0.78</td>
</tr>
<tr>
<td>Smoking quantity, pack-years*</td>
<td>1.0</td>
<td>8.2</td>
<td>0.75</td>
<td></td>
<td>0.65—0.83</td>
</tr>
<tr>
<td>Constitution: BMI back in time*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI the last 1—5 years</td>
<td>1.0</td>
<td>12.0</td>
<td>0.94</td>
<td></td>
<td>0.91—0.96</td>
</tr>
<tr>
<td>BMI age 35 years</td>
<td>9.0</td>
<td>37.0</td>
<td>0.78</td>
<td></td>
<td>0.66—0.86</td>
</tr>
</tbody>
</table>

*Pack-years = (number of years as a smoker x number of cigarettes per day)/20.

*BMI = weight in kg at this time/(height in meter)^2, [kg/(m x m)].
We found an overall agreement of 91–100% for responses to selected questions regarding job title, and 94–100% for responses to selected occupational exposures, as shown in Table III. However, only acceptable Kappa values were found for farming, welding, painting, and for work in high temperature, mainly due to a low sensitivity of the surrogate reporting.

Specific exposure information based on dichotomous questions was recorded for use of pesticides, handling of hormones, or specific oils, and for work almost every day in high temperatures or in intense light. The Kappa values were above 50% for these exposures but the percentage of “don’t know” answers was rather high among surrogates (5–17%) compared to colon cancer patients (0–7%).

The agreement between colon cancer patients and their surrogates on lifetime job history is presented in Table IV.

The two groups of respondents reported the latest industry worked in and the latest job held by the study subject with a 76.5 and 74.5% agreement, respectively, based on a two digit code. This agreement declined slightly at a three digit level. The same pattern, but with lower values, was seen for the industry in which the study subject had worked for the longest time and the job held by the subject for the longest time.

The number of reported job periods, counted as the number of times the subject had changed employment, job title, or work task was lower among surrogates than study persons, 4.5 and 2.8%, respectively, which corresponds to more detailed job information obtained from the study person ($\chi^2 = 32.5; P < 0.001$).

The calculated bias factor provided evidence for a certain degree of under-reporting of most exposures except for wine drinking, certain diseases such as psoriasis, and use of pesticides.

**DISCUSSION**

Although data from the next-of-kin was more sparse than data obtained from the index case, the surrogates provided quite accurate information at a general level. A low sensitivity for certain exposures shows, however, that the next-of-kin often are unaware of specific work tasks carried out by the study person. The next-of-kin provided reliable information on longest held job and on common lifestyle factors. Analyses based upon ever held jobs or analyses that must be adjusted for co-morbidity may be biased in both directions if the study uses an unbalanced set of surrogates among cases and controls. The next-of-kin will, however,
produce a bias factor of less than one if lack of recall is the most important factor, which was the case for most of the exposures studied here. In this case, use of surrogates will result in attenuated effect measures. Still, it should be considered to have a balanced set of surrogates for cases and controls even when the selected persons may be available for interview.

Use of surrogates is especially important if exposures are related to prognosis in order to reduce selection bias. The bias factor illustrates how much exposure odds ratios (OR) are influenced by recall error of the next-of-kin or cases. The impact this has on the effect measures is a function of how large a proportion of the cases or the controls is replaced by the next-of-kin.

This study does not provide all the information needed for making a decision on when to accept non-responders or when to replace the non-responders with surrogates. Still, we believe that in many cases these findings support the use of surrogates rather than the exclusion of deceased persons from a study. The study shows that this decision is, of course, context-specific just as the decision of whom to use as surrogate.

In a previous study of small bowel adenocarcinoma (70 cases of which 13 were surrogates; 2,070 population controls of which 24 were surrogates), an OR of 3.5 (1.5–8.0) and 0.8 (0.3–2.1) was found for high intake of beer and wine, respectively [Kaerlev et al., 2000]. When correcting these ORs for the bias introduced by the surrogates (by removing the surrogates from the analyses), the ORs were 3.3 (1.3–8.4) and 0.8 (0.3–2.4), respectively.

Recall bias following the use of next-of-kin is especially a problem for effect measures based upon an “ever held” occupation, since next-of-kin cannot provide a full occupational history [Drews and Greenland, 1990]. Adjusting the analyses by the number of jobs held will, however, to some extent reduce this bias.

Our study compared information obtained while both the study subjects and their surrogates were alive. The interview with the study subject and the surrogate were performed separately, and the subjects were told not to speak about the interview with their relatives. Even so, it is possible that the study person and the surrogate exchanged some information, and thus made their interviews “too” similar. The interviewers were asked to evaluate the conditions for interview and only interviews with satisfactory conditions were included in the database. Ninety-eight pairs of interviews fulfilled the criteria while 10 pairs did not and were excluded from the study. We do not believe that the index subject’s type of cancer has played a major role for the reporting from the next-of-kin in this study since colon cancer is not commonly known to be associated with certain occupational or medical factors.

In conclusion, the bias introduced by using next-of-kin is expected to be low in most situations and will most often cause a bias towards no effect. The size of the bias introduced will depend on the question to be addressed. The answers from the surrogates included a higher percentage of missing answers, and the degree of discrepancies was higher when a quantitative response was requested and for questions regarding information back in time. The use of information from the next-of-kin should be considered in situations where the exposures might play a role not only in causation but also for the prognosis of the disease. We believe this type of quality control is a necessary element in any large-scale case-control study.

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REFERENCES


