LETTERS TO THE EDITOR

RE: “VALIDATED QUESTIONNAIRE FOR THE IDENTIFICATION OF PREVIOUS PERSONAL OR FAMILIAL VENOUS THROMBOEMBOLISM”

We read with interest the article by Frezzato et al. (1) on questionnaire validation among persons who had had venous thromboembolism in the past and among a group of normal controls. Administration of the questionnaire was predicated on the belief that recognition of previous episodes of venous thromboembolism is central to the diagnosis of familial thrombophilia, a condition characterized by the presence of several affected family members (2). The correct identification of affected family members is of critical importance in family studies; however, it is often impossible to directly assess family members’ status because in many cases they are dead or unavailable. The questionnaire referred to above for the identification of a personal history of thromboembolism was validated in terms of accuracy (1); previously, no other studies had been available on the validation of a questionnaire on the history of familial thromboembolism.

We assessed the validity of a questionnaire on family history of thrombosis as reported by the proband, while one mother reported a history of thrombosis. We selected 97 probands, for whom at least one family member was seen at the clinic. The agreement between the proband’s answer and the relative’s answer was calculated using the kappa statistic (3): (observed agreement - chance-expected agreement) / (1 - chance-expected agreement).

A total of 468 relatives were examined. Table 1 shows the percentage of agreement between the proband’s answer about family history of thrombosis and the answer of his or her relatives. The agreement is 99.6 percent; only one relative (cousin) did not confirm the history of thrombosis reported by the proband, while one mother reported a history of thrombosis that was not known to the proband.

We then restricted the analysis to the families in which all those declared affected by the proband were evaluated at the ambulatory (n = 48), and all the relatives declared affected by the proband were evaluated at the ambulatory, except for those who had died (n = 11). We calculated the percentage of agreement between the number of family members declared affected by the proband and the number of family members found affected at the visit to the clinic. The agreement was 97 percent (table 2). Agreement between the proband’s answer and the relative’s answer was independent of the number of family members affected, family members seen, and degree of relationship.

Our study shows that a questionnaire administered to patients with thrombosis is able to correctly evaluate the history of thrombosis of their relatives.

This study has some limitations in that the probands are a selected sample, since they come from a thrombosis center specialized in the diagnosis of inherited abnormalities pre-

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**TABLE 1.** Agreement between proband answer on family history of thrombosis and relative answer, Milan, Italy, 1991-1995

<table>
<thead>
<tr>
<th>Relative answer</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>397</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>69</td>
</tr>
</tbody>
</table>

* Kappa, 0.98; sensitivity, 69/70 = 98.6%; specificity, 397/398 = 99.7%.

**TABLE 2.** Agreement between number of identified relatives by the proband and number found affected by direct interview (number of families = 59), Milan, Italy, 1991-1995

<table>
<thead>
<tr>
<th>No. of family members declared affected by the proband</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>No. of family members found</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Kappa, 0.91.
disposing to thrombosis. Therefore, they are younger than the general population of thrombosis patients. Furthermore, we could not verify the history of thrombosis in those family members who had died, although those subjects were not included in the analysis, to avoid any bias in the results. However, many second and third degree relatives came to the clinic (34.7 percent of the healthy relatives, 24.3 percent of the affected relatives), and the agreement between their reported history of thrombosis and the proband’s answer was near perfect, with disagreement on one subject only.

The results of our study are very important, considering that, in 31 percent of the families selected for the study, none of the relatives declared affected by the proband came to the clinic, mostly (60 percent) because all the affected relatives were dead. Our study shows that it is possible to use the information recorded from the proband to define familial thrombophilia.

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REFERENCES

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THE AUTHORS REPLY

We appreciate the interest shown by Taioli et al. (1) in our article (2) on the validation of a questionnaire for family history of thrombosis. Their data provide support to the idea that a careful family history, using a standardized questionnaires, may be reliable for the diagnosis of familial thrombophilia. However, one should be cautious in applying their conclusions. Taioli et al. show that a questionnaire has a high sensitivity (98.6 percent) and specificity (99.7 percent). These numbers were, however, estimated from families already selected for thromboembolic disease, and it is reasonable to assume that these families have been already “sensitized” to the presence of previous thrombotic events within the family. Likely, these figures may thus overestimate the true sensitivity and specificity.

In this regard, in our previous study we found that eight of 12 first-degree relatives correctly recalled an episode of venous thromboembolism in their relative (2). This corresponds to a sensitivity of 66 percent (95 percent confidence interval 35–90 percent) in our population of thrombotic patients never before evaluated at our institution. Moreover, in a recent evaluation of thrombophilic families of the VITA Project (3), 15 of 65 subjects described episodes of superficial thrombophlebitis in relatives as deep vein thrombosis. Sixteen additional subjects correctly described episodes of deep vein thrombosis but did not remember the presence of specific risk factors (e.g., surgery) in their affected relatives. Thus, in an unselected population, also the specificity of family history may be substantially lower (77 percent; 95 percent confidence interval 65–87 percent) and unreliable concerning risk factors. For this reason, in the VITA Project, all suspected episodes of thrombosis in relatives are further investigated using our proposed standardized approach for personal thrombosis (3).

Notwithstanding these limitations, family history remains the cornerstone for the diagnosis of thrombophilia. It should always be collected from the proband by an experienced clinician first, but it should subsequently be validated with a personal interview of relatives using a standardized approach.

REFERENCES

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RE: “ASSESSMENT OF SURVEILLANCE FOR MENINGOCOCCAL DISEASE IN NEW YORK STATE, 1991”

Meningococcal disease is a serious condition the prognosis of which has not changed since the introduction of antibiotic treatment. Surveillance for meningococcal disease is therefore important since a decrease in morbidity and mortality must be achieved by early antibiotic treatment, by preventing spread of the disease, and by prophylaxis of secondary cases. Ackman et al. (1) in an interesting paper have assessed the notifiable disease surveillance system and
the hospital discharge data set for meningococcal disease in New York State in 1991. They concluded that the notifiable disease surveillance system is relatively complete; however, frequent errors made the hospital discharge data set unsuitable for communicable disease surveillance. Concurrently and in a similar design we assessed the data quality in two parallel population-based registries over a 14-year period in the County of Northern Jutland in Denmark (approximately 485,000 inhabitants) (2). The two systems are the Danish System of Notifiable and Communicable Diseases and the Hospital Discharge Registry for in-patients. All records of patients in the two registries were reviewed with respect to the criteria for the diagnosis of meningococcal disease. In addition, records from the regional clinical microbiology department where all microbiologic examinations were carried out were reviewed. The degree of completeness was 90 percent for the Hospital Discharge Registry and 92 percent for the System of Notifiable and Communicable Diseases.

In the Hospital Discharge Registry, 296 cases were registered, but only 254 cases (86 percent) fulfilled the criteria for meningococcal disease. In the System of Notifiable and Communicable Diseases, 273 cases were registered, but only 261 cases (96 percent) fulfilled the criteria for meningococcal disease. A capture-recapture analysis showed that 1–2 cases escaped registration. The Danish study showed that the System of Notifiable and Communicable Diseases was not totally complete but that the notification rate was on the same level as that in the American study, both considerably higher than in, for instance, Britain and Belgium (3–6). In contrast to the American study, we found an acceptable data quality for hospital discharge data. The prevention and control of serious infectious diseases depend on the setting up of surveillance mechanisms and registries nationally and internationally. In general, public health surveillance systems are validated only to a small extent. A number of decisions with important consequences concerning clinical and public health issues rest on information collected through such information systems. The existing studies (1–6) underline that there should be greater efforts to ensure the quality of such systems.

REFERENCES


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THE AUTHORS REPLY

In their analysis of the Danish Hospital Discharge Registry cases of meningococcal disease, Sørensen et al. (1) found a relatively high degree of accuracy of discharge codes (86 percent), as compared with that of the New York State database discussed in our paper (2). There may be many reasons for this, including differences in rules for coding discharge diagnoses, the accuracy of physician discharge summaries, and the quality and training of nosologists in medical record departments. Because hospital discharge data are collected for reimbursement and hospital planning purposes, there is no direct assessment of the accuracy of the principal or secondary diagnoses. One factor that we were unable to assess was the effect that diagnosis-related group-based reimbursement may have had on the likelihood of adding multiple secondary diagnoses to the medical record.

We agree that surveillance systems often go unvalidated and that there should be greater efforts to ensure the quality of their data. However, even with improved accuracy, the timeliness of hospital discharge data is insufficient for the needs of communicable disease surveillance. While administrative data and billing data sets may be useful for comparison, they should not substitute for independently collected case reports, even if validation is sometimes lacking.

REFERENCES


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RE: "OCCUPATIONAL RISK FACTORS FOR GASTRIC CANCER: AN OVERVIEW"

In a recent review of occupational risk factors for gastric cancer, Cocco et al. (1) discussed the evidence for an association between exposure to nitrosamines and an increased risk of gastric cancer among workers employed in the rubber industry. Cocco et al., referenced most of the studies in the rubber industry evaluated by the International Agency for Research on Cancer in 1982 (2-6) and three studies published after this evaluation: two Italian studies (7, 8) and the latest update of the cohort of the British Rubber Manufacturers Association (9). On the basis of this referenced literature, Cocco et al. state, "With the exception of one study (170) ([8]), an increased mortality from gastric cancer has been consistently found in cohort studies of rubber workers." (1, p. 225). However, Cocco et al. did not report two cohort studies published before (10, 11) and seven cohort studies (12-18) as well as three subcohort analyses (19-21) published after the International Agency for Research on Cancer evaluation in 1982. Considering all cohort studies published since 1982, seven cohorts and three subcohorts observed no increased risk while only three cohort studies (7, 9, 15) reported an excess occurrence of stomach cancer among their entire cohorts (range of standardized mortality ratios, 110-142).

Cocco et al. reviewed also the risk of stomach cancer by work areas and noted an excess in compounding, mixing, and milling that was the only presumed job category listed by the International Agency for Research on Cancer in association with stomach cancer (22). Cocco et al. also described excess risks in other work areas, such as rubber processing (5, 23), tire building (3), and general rubber goods production (8). It is important to note, however, that "rubber processing" refers largely to the same work areas as compounding, mixing, and milling. Sometimes it may be distinguished into front processing (compounding, mixing, milling) and back processing (extrusion and calendering) (24). Cocco et al. referenced an excess of deaths from stomach cancer among tire builders to a study that observed a small deficit of deaths from stomach cancer among "component builders" in the tire sector (standardized mortality ratio = 84) (3). Finally, a high risk in the general rubber goods sector was referenced to an Italian cohort among workers in the tire sector (8), which actually observed a deficit of deaths from stomach cancer (standardized mortality ratio = 0.78, 95 percent confidence interval 0.54-1.08).

Of all the cohort studies that were published since 1982 and that investigated risks by work area, three studies observed excess deaths in the compounding, mixing, and milling department (range of standardized mortality ratios, 134-160) (9, 13, 17), including two studies which observed less than expected stomach cancer deaths for their entire cohorts (13, 17). Analyses by work area of our historical cohort study among male German rubber workers (25) also corroborate this finding. In other departments, however, such as curing, reclaim, tubes, and industrial products, or after exposure to solvents, no elevated risks were determined (17, 19-21, 26). A nested case-control study investigated risk factors for stomach cancer in the US rubber industry (27). Significantly increased risks and trends by duration of employment and years since hire were observed among workers exposed to detrackifiers in one company. It was suggested that asbestos contamination of talc might be the underlying cause. An increased risk of stomach cancer was also determined among workers exposed to carbon black. Results for nitrosamines and polycyclic aromatic hydrocarbons were not conclusive (27).

Thus, elevated mortality from stomach cancer is still observed in studies published after 1982, but, contrary to the conclusions of Cocco et al., the risk seems to be largely confined to mixing, milling, and compounding. On the basis of this evidence, asbestos, talc, and carbon black should be considered for further exposure-specific analyses of stomach cancer risks in the rubber industry. Nitrosamines also warrant further investigation. However, exposure to volatile nitrosamines in the rubber industry was much higher in work areas, where the risk of stomach cancer was not consistently found to be elevated (28). Therefore, nitrosamines are unlikely to be a major risk factor for stomach cancer in this industry.

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TWO AUTHORS REPLY

We thank Straif et al. for their comments (1) on our review of occupational risk factors for gastric cancer (2). In our review, we dedicated two paragraphs to the rubber industry under the subheading “Nitrosamines,” based on published reports indicating nitrosamine exposure as a major problem in this industry (3–6). As a detailed analysis of the epidemiologic literature on the rubber industry was beyond the scope of our paper, we considered mainly IARC monograph 28 (7), and we cited a few cohort studies. We mentioned work areas where the stomach cancer excess was reportedly highest, but we didn’t make any analysis or conclusion about which exposures or processes may be responsible for the increased stomach cancer risk among rubber workers. Instead, table 4 in our review indicates occupational exposure to nitrosamines as a possible stomach cancer risk factor. However, we acknowledge that our wording may not have made that clear for the readers.

We are also grateful to Straif and colleagues for having noticed that reference 170 (8) in our paper (2) was miscited with regard to an excess stomach cancer risk in general rubber goods production. The same reference was cited correctly as number 176 (9).

In their letter, Straif et al. refer to 13 papers that we did not cite in our review. Two of them, published before the 1982 IARC monograph on the rubber industry, were actually considered in the IARC monograph itself. One is a study of a Swiss rubber goods factory that showed a 75 percent increase in stomach cancer mortality (10), and the other is a mortality and incidence study of male production workers of a tire manufacturing plant in southwestern Connecticut (11), which did not find an excess. Stomach cancer was not investigated in more detail in both studies, which report results only for the total cohort. Straif et al. also cite 11 papers published since 1982. Three of these were subcohort analyses (12–14), updating and confirming results of a more comprehensive study we cited, which showed that among white employees the observed overall excess in stomach cancer deaths was concentrated in rubber-processing work areas (15). The other studies were a Polish study (16), of which we had only an English abstract not mentioning stomach cancer; a small American study (17), which observed only one stomach cancer death against 0.98 expected in the total cohort; three studies, including the recent study coauthored by Straif and colleagues (18–20), which did not explore stomach cancer risk by work area; and three studies (21–23), which reported an excess stomach cancer risk in production areas overall, in weighing and mixing areas, or in latency/duration subgroups.

We agree with Straif et al. that the published literature, including the studies since the 1982 IARC review, seems to suggest an increase in stomach cancer risk concentrated early in the rubber production process, including compounding, weighing, mixing, and milling. We confirm their and our statement that nitrosamine exposure warrants further investigation, which should include industrial hygiene and biologic monitoring of nitrosamine exposure. Straif et al. express the opinion that asbestos, talc, and carbon black may be more likely candidates. Our review of the literature for exposure to asbestos, talc, and carbon black in other industries was not conclusive in suggesting a role in increasing gastric cancer risk. However, we agree that these exposures should be considered for further exposure-specific analyses of stomach cancer risk in the rubber industry.

In concluding our review of occupational risk factors for stomach cancer, we raised the hypothesis that inorganic dusts, including asbestos, silica, and other mineral and metal dusts, may play a role in gastric carcinogenesis, by causing superficial gastritis and/or delivering carcinogens to the gastric mucosa. Results from the rubber industry suggesting that the excess stomach cancer risk is concentrated in work areas with the heaviest dust exposure seem to support this hypothesis. However, we wouldn’t exclude a causative role also for workplace exposure to nitrosamines by inhalation and contact. We are conducting new analyses based on large data sets with the aid of job-exposure matrices. Hopefully, this study and other future studies will be able to discriminate among the effects of numerous potential workplace risk factors for gastric cancer.

REFERENCES

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