Reviewer's report

Title: Risk factors for operated carpal tunnel syndrome: A multicenter population-based case-control study

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Major compulsory revisions:

This study focuses on identifying risk factors for carpal tunnel syndrome (CTS) based on analyses of surgically treated patients from 13 regions in central and northern Italy. The sampling frame comprised all residents in these regions in the year 2001 who had been admitted to hospital with CTS as the principal diagnosis (ICD-9 code 354.0) and who had undergone surgical treatment for CTS (DRG code 06). Each center identified 20 cases and 40 controls to be included in the study. The goal was to perform a population-based case-control study of surgically treated CTS to identify both occupational and non-occupational risk factors for CTS. This is a very important issue since, as noted by the authors, almost all studies of CTS have focused on either occupational or non-occupational factors, or have not been designed in a manner that allows extrapolation of results to the general population.

Question: What about patients with CTS who do not undergo surgical treatment? What fraction of patients diagnosed with CTS in Italy do not have surgery? In the United States a rather large fraction of patients diagnosed with CTS do not undergo surgical release. How might such patients differ from those who have surgery? This is a particularly important question in the current study, which, like many previous studies, found that blue collar workers were at higher risk compared to white collar workers. If white collar workers are not ‘occupationally disadvantaged’ by CTS to the same extent as blue collar workers, then a study based only on surgically treated cases would be biased.

Question: Twenty cases and 40 controls were selected from the records at each center. Presumably the selection process involved some sort of random selection...
so as to maximize the likelihood that the selected cases and controls would be representative of the underlying population of eligible cases and controls at each center. Exactly how were cases and controls selected in order to ensure randomness?

Question: It is asserted that this study is “population based”, and this is, in fact, one of the potential strengths of the study. The number of cases and controls selected from each of the 13 centers was the same, but we don’t know the underlying number of eligible cases and controls for each center. The assumption appears to be that the latter numbers are roughly the same, in which case the implicit weights assigned to cases and controls from different centers is roughly equal and so no formal adjustments or ‘weights’ are needed in analyses to make the results representative of the underlying populations. However, if the number of eligible cases and controls differed substantially by center, then the true relative weights of the selected cases and controls would be unequal between centers, and this should have been adjusted for in models. This becomes particularly important in making calculations of population attributable risk (PAR). Furthermore, if the population rates of surgical CTS differed much by center, this may suggest a number of important issues, including: 1) the underlying risk factors for surgical CTS may have varied across centers; or 2) the diagnostic and/or treatment criteria for CTS may have varied across centers. The authors appear to confirm that the first item may hold true (see Discussion: “many industrial job titles were poorly represented due to regional employment characteristics”). This study appears to not have been set up as a prospective trial with uniform diagnostic and treatment criteria for all participating centers and so the latter issue is of particular concern and needs to be addressed.

It is stated that at the time of the study almost all CTS release surgeries were performed “on hospital premises after diagnostic confirmation by nerve conduction studies”.

Question: In Italy are all patients who have surgery for CTS “admitted” to a hospital? In the US almost no one is ‘admitted’ to hospital (i.e., spend at least one night in the hospital) for CTS release surgery – this is considered an ‘outpatient’ procedure – even though many CTS surgeries are performed on hospital premises. Many surgeries are also performed in non-hospital settings, such as doctors’ offices or outpatient surgical centers. Does this apply in Italy? This question may revolve on the meaning of the words ‘admitted to a hospital’, and requires clarification. Also, use of nerve conduction tests to confirm the diagnosis of CTS is a strength of the study. However, as mentioned above, there is no mention of uniform diagnostic criteria, particularly electrodiagnostic criteria, that may have been applied in all 13 centers.

Selection of controls was based on random sampling from the national health service registries covering each of the thirteen administrative centers included in the study. Control subjects who had received surgical treatment for CTS were excluded.

Question: What about controls who may have been diagnosed with CTS but did
not have surgical treatment for CTS? Could such potential controls be identified from the administrative data (or the questionnaire), and, if so, were they excluded?

In the Results section, under ‘Response’, it is stated that for only one case was the questionnaire filled in by the next of kin.

Question: For how many controls was the questionnaire filled in by the next of kin? Responses from next of kin probably should be excluded from analyses for both cases and controls.

In Table 1, which includes non-retired men and women combined, the cases = 191, and the controls = 286. The numbers shown in Table 2 appear to match these overall numbers for non-retired men and women, and also show the genders separately: female cases = 163, female controls = 238; male cases = 28, male controls = 48. In Supplemental Table C, which reports results for non-retired women, the number of cases = 169 (last 10 years), and cases = 184 (lifetime), and the controls = 249 and 285, respectively.

Question: The number of female cases and controls presented in Tables 1, 2, & C appear to differ, and it is difficult to reconcile the differences. How come the number of non-retired female cases is listed as 163 in Table 2, but 169 and 184 in Supplemental Table C? Similarly, the number of non-retired female controls also varies: Table 2 = 238; Supplemental Table C = 249 (last 10 years) and 285 (lifetime)?

Minor Essential Revision:

In the Methods section, under Statistical Analysis, a number of factors are listed as categorical variables including “familiarity”.

Question: Does “familiarity” refer to ‘family history of CTS’? It might be better to use the latter terminology.

In the Discussion it is mentioned that “Another possible association which needs to be tested in larger studies regards surgical treatment for CTS in siblings. This putative risk factor could be attributed to genetic and/or familial environmental factors.” Presumably, the authors are referring to the high odds ratio for CTS in a sibling as a risk factor for CTS in the study population (unadjusted OR = 8.1, adjusted OR = 5.7; see Table 1). This is an important finding, and possibly should be stated more explicitly.

Question: The twin study by Hakim et al. (2002) is cited in the Background. Hakim et al. found that inherited factors explained almost 50% of the variance in a classical twin study analysis. The finding in the current study that CTS in a sibling was an important risk factor is therefore notable. The study by Hakim et al should also be cited and mentioned here in the Discussion in conjunction with discussion of the sibling results.
Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.