Author's response to reviews

Title: Leukaemia Incidence among Workers in the Shoe and Boot Manufacturing Industry: A Case-Control Study

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Author's response to reviews: see over
Point by point response to comments

Leukemia Incidence among Workers in the Shoe and Boot Manufacturing Industry: A Case-Control Study

Steven P. Forand

Reviewer #1,

1) The author should add a section indicating the power of the study giving the limited number of cases.

Reply:
The following paragraph discussing study power was added to the discussion section.

The power to detect a true increase in risk was limited by the population size of the study. Because this study was a follow-up to a previous study, the population was limited by the constraints of the previous study. Leukemia is a fairly rare disease and the population of white males over 65 in the study area was only approximately 3,500. For the current study the power to detect an increased risk of 50% (similar to the observed risk for leukemia) with a 95% confidence interval was only 20%. In order to achieve a power of 80% the study population would have had to have been approximately eight times as large. This could have been achieved by either increasing the study area to include neighboring cities or by increasing the period under observation. However, as mentioned previously we were limited by the parameters of the previous study.

2) A further section is warranted that deals in a systematic way with the potential forms of bias in this specific situation.

   √ The best way to do so is a table describing the potential form of bias and indicating the direction in this specific situation.

Reply:
The following paragraph discussing the overall effects of bias present in the study was added to the discussion section. A table summarizing the forms of bias was also added.

Most types of bias identified in this study would tend to lead to an underestimation of the true risk (i.e. bias the results toward the null). A summary of the types of biases identified and their effects is given in Table 4. Because most would lead to an underestimation of risk it is likely that the true association between working for Endicott Johnson and the risk of leukaemia is somewhat higher than indicated. However to fully evaluate these biases a more thorough study design is needed.

3) One kind of bias that is until now not mentioned in the paper results from the fact that only dead individuals are eligible as controls. Since working in the shoe and boot
manufacturing industry is not only associated to leukaemias but also to other kinds of cancer, e.g. lung cancer, may artificially increase the prevalence among controls biasing the odds ratio towards the null.

Reply:
The following paragraph was added to the discussion.

In addition, only dead individuals were eligible as controls in the study. Since working in the shoe and boot manufacturing industry is associated with other kinds of types of cancer, such as lung and bladder cancer, in addition to leukemia, this may have artificially increased the prevalence among controls. This would also bias the odds ratio towards the null.

4) In the paper the author restricts this argumentation too narrowly to the role of benzene. Besides benzene, there may be a lot of other exposures bearing a potential carcinogenic risk. Given the complex nature of exposure in the shoe and boot manufacturing industry varying over time the focus on benzene may be rather misleading. Accordingly, it is recommended not to draw any conclusions from speculations of exposure to benzene.

Reply:
Some of the discussion of benzene has been removed from the introduction to downplay its role as one of possible etiologic agents responsible for the increase in leukemia and I added a sentence which mentions some of the other carcinogenic chemicals that have been used in the industry over the years. However I still feel that benzene is worthy of mention because occupational studies of shoe workers have indicated that excess leukaemia is limited to workers in areas where exposure to benzene occurred and because benzene is a known leukaemogen. Much of the discussion specific to benzene exposure has also been removed from the discussion section especially where conclusions were inferred.
Reviewer 2:

1. Although all men with a leukaemia diagnosed in 1981-1990 could be identified, only those who have been deceased as of 1997 were included in the analysis. Controls were chosen among other deceased persons in the town of Union. This design is unusual and may have lead to selection bias if mortality among controls was related to previous employment at Endicott Johnson. This problem is potentially important and may have biased the odds ratio in either direction.

Reply:
Because determination of occupation was made from the death certificate it was necessary that all cases be deceased at the start of the study. It is true that the cases and controls could have been previously employed at Endicott Johnson and not have it mentioned on the death certificate. However the death certificate asks for “usual” occupation, thus if one were to work for EJ for the majority of his life it should be reflected on the death certificate. Further this should help by limiting those considered exposed to men who had worked for the company for a number of years and eliminate those who had only worked there for a short period of time. In addition any bias that may have resulted from this type of misclassification would likely have biased the results toward the null. (Also see replies to comments #2 and #3 from Reviewer 1)

2. Method of exposure assessment is another major weakness of the study. Employment at Endicott Johnson as reported on the death certificate is not a valid indicator of exposure to benzene. An analysis by duration of employment in the company should be a minimum requirement to study a possible link between employment in the company and leukaemia risk. However, the data collected did not permit such an analysis to be done.

Reply:
Company records were not available to assess length of employment (see reply below). However, as indicated above, the occupation on the death certificate is supposed to be the “usual” occupation of the decedent, thus it would not be expected to reflect individuals who only worked for the company for a short time. There is also a lengthy discussion on the use of occupation from death certificates in the discussion.

3. It is not clear why an effort was not made to improve study design and exposure assessment. For example, did the author attempt to use company records, or to make interview with next of kin of deceased persons?

Reply:
The company has not allowed previous researches access to company records for previous studies including a proportionate mortality study conducted by NCI in 1987 (citation 18). In addition, because of a fairly generous benefits package, labour unions
were never able to organize most of the workers under investigation thus union records could not be used as a source of information. The following sentences were added to the methods section under “Assessment of Occupation/Exposure”

The company has not allowed previous researches access to company records for occupational health studies [18]. In addition, because of a fairly generous benefits package, labour unions were never able to organize most of the workers under investigation thus union records could not be used as a source of information. [20].

Other comments

4. Crude odds ratios not adjusted on age are unnecessary

Reply:
Took crude ORs out of both tables and results section

5. It may be interesting to look at the causes of death listed on the death certificate, to evaluate the possibility of a selection bias among controls. For example did the causes of death differ between men employed and those not employed at Endicott-Johnson?

Reply:
I looked at the causes of death between men employed at Endicott-Johnson and those not employed by the company and found the proportion who died of other cancers and heart disease was similar to the overall proportion of those employed by the company while the proportion who died of lung disease and cerebrovascular disease was lower among Endicott Johnson workers than expected. The numbers of men who died of other causes were too small to realistically compare. I did not include this in the discussion however as I felt that is did not relate to the study objective.