Author's response to reviews

Title: Cancer diagnosed by emergency admission in England: an observational study using the General Practice Research Database

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Version: 3 Date: 21 May 2013

Author's response to reviews: see over
20th May 2013

Dr Christopher Morrey
Executive Editor
BMC Health Services Research
BioMed Central
236 Gray's Inn Road
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Dear Dr Christopher Morrey,

RE: Cancer diagnosed by emergency admission in England: an observational study using the General Practice Research Database (MS:1514945811931627).

As indicated in the cover letter to the editors, our point by point response to the reviewers’ comments is provided at the end of this document.

Sincerely,
Carmen Tsang

On behalf of co-authors Dr Alex Bottle, Professor Azeem Majeed and Dr Paul Aylin.
Author's response to reviewers' comments

Reviewer 1 - Dr Ileana Baldi
Reviewer 2 – Dr David Goldsbury
Reviewer 3 – Dr Alex Dregan

Associate Editor's comments:
The paper is an interesting piece of research. However, reviewers have raised many questions that should be replied before taking any further decision on the manuscript. It would be of particular relevance replying carefully to those methodological and statistical issues posed on by Dr Baldi and Dr Goldsbury. Being BMC Health Service Research an international journal, readers not familiar with GPRD would benefit of some further description of this dataset.

Table 1 Point by point response to reviewers’ comments

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| R1.1 | 1. Even though GPRD is a well-established source for epidemiological research, I think that some additional information, especially on Read codes and matching to ICDs, should be given for readers who are not familiar with this UK specific data source. Please extend the description in “Cases of first-ever diagnosis” subsection by including a table with selected Read codes and matched ICDs. | • We have changed the subheading in Methods from “Data source” to “General Practice Research Database” to emphasise the subject of that section.  
• Additional information has been added about Read codes and ICD-10 mapping to Methods – Integrated dataset section. Reference to cross mapping using the NHS terminology browser has been moved from Methods - Cases of first-ever diagnosed cancer section to Methods – Integrated dataset section.  
• Two tables with cross-mapped diagnosis codes have been added as additional files and referenced in the Methods – Cases of first-ever diagnosed cancer section.  
• Please also see R2.18.                         |
| R1.2 | 2. Please build a distribution of %emergency diagnosis by cancer type and/or clearly explain which criticality prevented it. | • We have added a table with the frequency of cancer diagnoses where diagnosis was by emergency admission only (new Table 1).  |
• We have not presented a distribution of cancer types by diagnosis route (i.e. percentage diagnosed by emergency admission out of all diagnoses) because of the incompatible coding between primary care and secondary care (Read codes vs ICD-10 codes). Please also see our responses to R1.1 and R1.3.
• As we have already detailed in the paper our reasons for not providing a breakdown of cancer types by route of diagnosis, we have not expanded on our original text which included:
  o Methods – Cases of first-ever diagnosed cancer section, we explained the limitations due to non-matching Read and ICD-10 codes which prevented the pooling of results.
  o We reiterated this limitation in the Results - Patient characteristics and Discussion - Strengths and limitations sections.

R1.3 3. As to model fitting, the sentence on page 15 line 15 [We performed...diagnoses] is unclear since either an analysis stratified or adjusted by cancer type, carried out at individual-level, is feasible even in presence of multiple events (i.e. dual cancers). This aspect must be dealt with.

• We thank Dr Baldi for this comment. While we would have liked to carry out analysis (stratified/adjusted) by cancer type, we could not do so easily because the denominator population comprised records from primary care and secondary care – thus two separate coding systems were involved. While Read codes from primary care can be mapped to ICD-10 codes from secondary care, cancer diagnosis codes could not be directly mapped.
• Our original paper highlighted the coding limitation in the Results - Patient characteristics section.
• We have extended our reasoning for patient-level analyses (rather than by cancer type) in the Discussion – Strengths and limitations section.

R1.4 Furthermore, when pooling all cancer diagnoses, the need to perform a selection of 8 covariates out of 12 does not seem justified. The trade-off between degrees of freedom and sample size appears satisfactory even including all predictors.

• While we considered a final model with full retention of all predictor variables, we were concerned about collinearity (e.g. age, time at practice and follow up time; as well as prior consultations and referrals). Therefore we decided to use stepwise selection to reduce multicollinearity, with recognition of the weaknesses of this semi-automated selection method (e.g. sensitivity to variable ordering and combinations).
• To determine the suitability of this selection method, we compared the model using stepwise selection with models built using forward, backward and an interactive-forward approach (with forced entry of variables known to be associated with cancer diagnosis, e.g. age and ethnicity). The models’ performances were compared (by QIC score). The QIC (Quasi-Likelihood...
under the Independence model Criterion) is similar to the Akaike and Bayesian Information Criteria (AIC and BIC, respectively) and applicable for the GEE regression method.

- Reassuringly, the models produced by all selection methods and the full model were not dissimilar in fit nor in the variables retained. The model using an interactive-forward approach had the best goodness-of-fit (QIC score 6193) followed by stepwise and backward selection (both with QIC scores of 6215). These models performed better than the full model (QIC score 6309) and the model using forward selection (QIC score 6387).

- Compared with the interactive-forward model which contained 5 variables, the stepwise model contained the same 5 variables plus the Charlson index score. As comorbidity is an important factor in cancer diagnosis and treatment, the stepwise model that included this variable was considered the final adjusted model.

Please re-analyze data in the light of the previous considerations and convey results in a single table. In any case, I would recommend a model building approach based on a sensitive choice of predictors taking into account collinearity issues, number of missing, etc... rather than using an automatic procedure. For example the inclusion of ethnicity, with 50% of missing in all routes, is likely to increase residual confounding rather than improve adjustment.

We thank the reviewer for her suggestions and have carried out re-analysis, with results presented in a single table as suggested by Dr Baldi and Dr Goldsbury.

- Please see our response to comment R1.4 about model building. We appreciate that inclusion of variables with missing data may affect the validity of results. However, we believe it was important to include variables that are known to be key predictors of cancer diagnosis and patient outcomes. Omission of these variables (e.g. ethnicity) would greatly limit the relevance of our findings to researchers, clinicians and policy makers.

We have added a sentence to Discussion – Strengths and limitations section to address the issue of missing data on our findings.

4. In the last section the authors draw attention to the importance of retrieving information on cancer staging and treatment to better understand why some groups are at higher-risk for delayed diagnosis. This is absolutely true but first, they should assess if some cancers are at higher-risk for delayed diagnosis and if these trends varied over time.

We agree with the reviewer that it is necessary to understand the risk of delayed diagnosis by individual cancer types and ascertain temporal trends. We were limited by the nature of our dataset in this study (incompatible Read codes and ICD-10 codes) as commented in R1.2-R1.4, which is why we suggest that additional data from the cancer registry and other sources would improve case ascertainment.

1. Is there a look-back or black-out period used to help prevent the inclusion of cancers that have already been diagnosed? If not, this

This study used lifetime diagnosis to exclude prior cancer diagnoses, thus the look-back period was from first GP consultation record to first record of
could contribute to the higher incidence in the early years of the study and explain part of the reduction over the study period. As a sensitivity analysis, the authors could compare the reported rates in say 2004-2008 (all have at least 5 prior years without a cancer diagnosis) with the rates that would have been calculated if only the data for 2004-2008 were available.

| R2.2 | 2. The authors need to explain the modelling results more clearly and use more stable reference categories. For example, the abstract states that patients aged 85+ years have RR of 9.21. No reference category for the comparison is given (people aged 0-14 years) and the actual reference category used has a relatively small sample size. The latter also applies to the reference category for ethnicity. Reference categories would be better with more events/people to give more precise RR estimates. |
| R2.3 | 3. Figure 1 shows the overall incidence rate is lower than both the male and female rates in 2002-2004. Is this possible? Was some form of standardisation used that hasn’t been described? |
| R2.4 | 4. The results list ethnicity and continuity of care as significant predictors for diagnosis by emergency admission but with “no difference between patient groups”. This is not true, as the group of people with unknown values for both variables have lower rates and more generally there needs to be a difference in order to be significantly associated. |
| R2.5 | 5. From the discussion: “Although the adjusted results are inconsistent, crude analyses showed national variation in diagnoses by emergency admission, supporting previous results [11].” The term cancer diagnosis. As a (possibly excessively) stringent look-back period was applied, the decreasing incidence over time is unlikely to be due to the length of look-back time. |

- We thank the reviewer for his suggestion and have revised the reference categories used in the crude and adjusted models for three variables – age group, ethnicity and follow up time.
- Our explanation of the modelling results has been improved, including reference to the comparison category wherever appropriate in the abstract and main text.
- Thank you for highlighting our error in Figure 1. We have re-created Figure 1 with the correct overall incidence rate displayed.
- Thank you for drawing our attention to our poor wording. Our intended meaning was that ethnicity and continuity of care remained statistically significant predictors in the adjusted model. However, where ethnicity status was known, there was no statistically significant difference in risk of diagnosis by emergency admission between patients by ethnicity. The same finding was applicable to continuity of care. As the reviewer noted, the risk of diagnosis by emergency admission by ethnicity was lower in patients with unknown ethnicity status. By continuity of care, the risk was lower for patients with an invalid continuity of care classification.
- Please note that because we have used a different reference group for ethnicity in the re-analysis, the results have changed. We have amended the Results - Adjusted risk factors for diagnosis by emergency admission section to reflect the new results and also the above point for continuity of care.
- Thank you, we have amended the Discussion to better explain the lack of regional variation found in the Summary of findings and Comparison with other studies sections.
“inconsistent” seems inappropriate here and might underplay the importance of the results. If the previous study reported crude national variation then the lack of variation after adjusting for other factors means that emergency diagnosis rates don’t vary by region.

| R2.6 | 1. Table 2 is essentially a repeat of Table 1 with two extra columns and a couple of variables removed. These could be combined into one table, with blank values in the “Adjusted” fields where the variables were not included in the final model. | • Table 1 and 2 have been combined. |
| R2.7 | 2. In the table(s), do not list the p values for every intra-variable comparison, just give the overall p value for each variable. | • To assist readers in intra-variable comparisons, individual p-values have been retained for variables that remained statistically significant (at 95% level) in adjusted analyses. While this means that the table is “busy”, we feel that these data are important to the overall interpretation of the results. |
| R2.8 | 3. Leave the results for referrals before diagnosis out of the table(s) and just describe it as being <5 cases in the text. The “<5” in the table does not mask the actual numbers as they can be figured out via the column totals. | • Thank you for the suggestion. We have removed the breakdown of referral results from the table and added a description of <5 patients having a recorded referral in to 30 days before diagnosis in Results – Service use. |
| R2.9 | 4. Explain why skin cancer cases were excluded. Also, why were they then listed in the results as being among the most frequently recorded? | • Thank you for this comment. We only excluded certain skin cancers (non-melanomas) but we were unclear about our distinction between melanomas and “other skin” cancers (ICD-10 C43 and C44 codes, respectively). The sentence in Methods - Cases of first-ever diagnosed cancer has been amended. • Non-melanoma skin cancers were excluded in line with published data including from the National Cancer Intelligence Network (NCIN). This is due to differences in diagnosis and treatment between the types of skin cancers, with non-melanomas typically treated in outpatients or primary care. |
| R2.10 | 5. The service use results list the mean and SD for number of consultations, but are these the means among people who had at least one consultation? If 0.46% of people have a consultation then a mean of 1.2 per person seems unlikely. | • Mean and SD values for consultations in 30 days before diagnosis for emergency and non-emergency routes have been corrected in the Results - Service use section. The results now show mean and SD values for consultations by diagnosis route (all patients diagnosed by emergency admission vs all patients diagnosed by non-emergency routes). |
| R2.11 | 6. The service use results say that among emergency diagnoses 3.3% had a prior admission and gives n=817, but this is 100% of those who had an emergency diagnosis. The same applies to the non- | • The numbers of patients who had prior admissions in emergency and non-emergency groups have been amended to now include numerator as well as denominator values (i.e. n=x/y). |
| R2.12 | 7. Is the number of prior emergency admissions treated as a continuous variable in modelling? If so, the RR should be listed as 0.31 per emergency admission prior to the first diagnosis. | • The prior emergency admissions variable was treated as continuous. The Abstract – Results and Results – Service use sections have been amended to include “per prior emergency admission” in the description of the relative risk result. |
| R2.13 | 8. The results list the cancer types diagnosed by emergency admission as being most commonly breast, colorectal or “Other”, but these three groups do not comprise 100% and the “Other” group is not defined anywhere. | • We had omitted to describe our use of the National Cancer Intelligence Network’s 22 cancer types to group cancers diagnosed by emergency admission. We have now added descriptions and reference to this categorisation in the Methods - Cases of first-ever diagnosed cancer and Results - Patient characteristics sections. The sentence referred to by the reviewer has been amended. |
| R2.14 | 9. The third paragraph of the discussion says there were crude differences by the number of consultations, and also differences based on having a consultation. Is this repetition or is there a difference that needs to be clarified? | • Thank you for pointing out the confusing section. We have amended the paragraph in the Discussion - Comparison with other studies section. |
| R2.15 | 10. Is there a gold standard for identifying cancer diagnoses? Is it the cancer registry? How do the sources of cancer diagnoses used in this study compare? | • We have expanded the Discussion - Comparison with other studies section to discuss data sources and comparability between GPRD, HES and cancer registry data. We have also included an additional reference to support our discussion (Palser et al, 2013). |
| R2.16 | 11. Give some indication of the representativeness of this sample compared to all cancer cases in the region over a similar period. | • It is difficult to compare the study sample to other studies/published data by all cancer cases because of incompatible units of measurement. Like most data on disease incidence, our results were presented by conventional “person-years”. However, we reported only those events that were diagnosed by emergency admission rather than all diagnoses. We also provided aggregated results for all cancers, while studies within similar time periods have tended to focus on single or small groups of common cancers. • However, Dregan et al (2012) evaluated the validity of cancer diagnoses in the GPRD compared with cancer registry data as the gold standard. Looking at 4 common cancer types over 7 calendar years (2001-2007), they found a relatively similar proportion of cancer diagnoses to us in their combined GPRD and cancer registry sample (including non-linked records) - 6.22% |