PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Social and geographical factors affecting access to treatment of colorectal cancer: a cancer registry study.
AUTHORS	SM Crawford, V Sauerzapf, R Haynes, D Forman and AP Jones

VERSION 1 - REVIEW

REVIEWER	Ula Nur Lecturer in Cancer Survival Cancer Survival Group Department of Non-Communicable Disease Epidemiology London School of Hygiene and Tropical Medicine
REVIEW RETURNED	24/10/2011

THE STUDY	1. The analysis was based on colon and rectum cancer data for patients diagnosed during the period1994-2002. One would expect information of stage to be more complete and reliable for more recent data. The authors should justify the use of such old data. 2. The last paragraph of Patients and Methods (page 8), states that logistic regression models were fitted to determine how the covariates of hospital travel time and deprivation quartile were associated with the odds of receiving treatment. It is however well known that logistic regression models estimate odds ratios.
RESULTS & CONCLUSIONS	3. The first paragraph of the results section does not clarify how the cells of tables 1 and 2 were estimated. For example the cell of deprivation quartile 2 and travel quartile 3 in table 1 is 1.235 is the odds of what? And how was that adjusted for age and sex. If a logistic regression model was fitted I would expect odds ratios, which can never be presented in the form of a cross tabulation between deprivation quartile and travel quartile. 4. Titles of table 1 & 2 are not clear. One would expect (adjusted for age and sex) and (*P<0.05, **P<0.01, 95% confidence interval) to be presented as a footnote and may be in the methods section. Double parenthesis in the last part!! 5. According to the first paragraph of results table 1 and table 2 present odds of being diagnosed at stage 4 compared to stages 1-3 in colon and rectum cancers. However Table 1 present deprivation quartile by travel quartile, while table 2 present deprivation quartile by hospital quartile. 6. The same concerns detailed above in point 4, apply to the odds of treatment presented in tables 3 and 4
GENERAL COMMENTS	The manuscript explores the effect of socio-economic f and accessibility to hospitals, on the survival of colon and rectum cancer for patients registered at the Northern & Yorkshire Cancer Registry and Information Service. I however have

	some concerns on how the analyses were carried out and presentation of results. 1. The analysis was based on colon and rectum cancer data for patients diagnosed during the period1994-2002. One would expect information of stage to be more complete and reliable for more recent data. The authors should justify the use of such old data. 2. The last paragraph of Patients and Methods (page 8), states that logistic regression models were fitted to determine how the covariates of hospital travel time and deprivation quartile were associated with the odds of receiving treatment. It is however well known that logistic regression models estimate odds ratios. 3. The first paragraph of the results section does not clarify how the cells of tables 1 and 2 were estimated. For example the cell of deprivation quartile 2 and travel quartile 3 in table 1 is 1.235 is the odds of what? And how was that adjusted for age and sex. If a logistic regression model was fitted I would expect odds ratios, which can never be presented in the form of a cross tabulation between deprivation quartile and travel quartile. 4. Titles of table 1 & 2 are not clear. One would expect (adjusted for age and sex) and (*P<0.05, **P<0.01, 95% confidence interval) to be presented as a footnote and may be in the methods section. Double parenthesis in the last part!! 5. According to the first paragraph of results table 1 and table 2 present odds of being diagnosed at stage 4 compared to stages 1-3 in colon and rectum cancers. However Table 1 present deprivation quartile by travel quartile, while table 2 present deprivation quartile by hospital quartile. 6. The same concerns detailed above in point 4, apply to the odds of treatment presented in tables 3 and 4

REVIEWER	Paolo Bruzzi MD MPH PhD Head, Unit of Clinical Epidemiology Director, Department of Epidemiology and Prevention National Cancer Research Institute Genova - Italy
REVIEW RETURNED	02/11/2011

RESULTS & CONCLUSIONS	This paper presents new analyses of the colorectal cancer part of the data reported in a previous paper from the same group (Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer. Jones AP, et al, Eur J Cancer. 2008 May;44(7):992-9) with a more specific focus, beside that on distance from hospital which was already discussed in the original paper, on the role of deprivation as assessed by the place of residence. An original analysis is included on the association between these two variables and stage at presentation. The issue is an important one, even though studies on quality of care based on current data are proving of questionable reliability. The methodology is that of the original study, the study population is the same (39000 colorectal cancer patients diagnosed during the period 1994-2002 in Northern England), and also the data analyzed are the same. Even though the indications provided by this paper are somewhat clearer than those given by the previous one, mostly because of the focus on a single disease, it provides little original evidence of real interest, and has several weaknesses: a) The presentation of the results is poor: no crude numbers, simple stratified analyses, wrong tests of significance (p-values for single

	odds ratios instead of tests for trend). No attempt was made to formally assess the interactions (i.e. synergisms) between the two variables, even though this was declared as the primary aim of the study (last sentence of the introduction section). b) At first glance, some the results are very difficult to believe (e.g. the odds of receiving any treatment for colon or rectal cancer are almost halved). This, obviously, derives from the use of the odds ratio as a summary indicator of association. However, as previously stated, without the Odds ratios without the support of the crude figures cannot be meaningfully interpreted : c) The discussion is long (4 pages), and unfocused, with conjectures and unwarranted statements. d) The limitations of this study are not discussed at all, nor are the differences between this study and the previous one. The results and the observed associations are taken for granted, without even mentioning some of the possible fallacies and biases that may affect studies of this kind, where both the exposures (deprivation and accessibility to hospital) and the outcome (quality of care) are indirectly estimated from proxy variables. Furthermore, these studies may suffer from biases related to the increased diagnostic pressure in more affluent socio-economic subgroups, leading to an increase in the absolute number of early disease without a corresponding decrease in the absolute numbers of late disease, which however appears to be reduced in absolute terms.
REPORTING & ETHICS	As stated in the previous section, this paper analyses the same data presented in a previous paper

VERSION 1 – AUTHOR RESPONSE

Reviewer: Ula Nur
Lecturer in Cancer Survival
Cancer Survival Group
Department of Non-Communicable Disease Epidemiology London School of Hygiene and Tropical Medicine

The manuscript explores the effect of socio-economic f and accessibility to hospitals, on the survival of colon and rectum cancer for patients registered at the Northern & Yorkshire Cancer Registry and Information Service. I however have some concerns on how the analyses were carried out and presentation of results.

1. The analysis was based on colon and rectum cancer data for patients diagnosed during the period 1994-2002. One would expect information of stage to be more complete and reliable for more recent data. The authors should justify the use of such old data.

RESPONSE: The data set we used was, as stated in the paper, used for a previous analysis. Since the issues we discuss regarding the pathway from primary care to diagnosis have not been addressed by any changes in practice since these patients were diagnosed, the observations are unlikely to be affected. Because the comparisons we make are all from groups within this data set, any deficiencies in the quality of recording of stage will apply to all groups of patients, that is all cells in the tables and not affect the analysis. Using an older data set means that future studies can test our analyses from patients diagnosed subsequently and if they are confirmed move on to measure the effect of policy changes.
In our dataset staging was available for 64.5% of records. In 2009, this figure stood at 65.1% so there was no significant improvement in staging over this time. Furthermore, registry clerks' access to notes is not affected by any of the things we have studied, so we believe any biases associated with

incomplete staging would be random. We have added discussion of these issues to paragraph 8 of the Discussion section.

2. The last paragraph of Patients and Methods (page 8), states that logistic regression models were fitted to determine how the covariates of hospital travel time and deprivation quartile were associated with the odds of receiving treatment. It is however well known that logistic regression models estimate odds ratios.

RESPONSE: We apologise for the omission of 'ratios' here and the confusion it may have caused – we have now corrected the manuscript accordingly.

3. The first paragraph of the results section does not clarify how the cells of tables 1 and 2 were estimated. For example the cell of deprivation quartile 2 and travel quartile 3 in table 1 is 1.235 is the odds of what? And how was that adjusted for age and sex. If a logistic regression model was fitted I would expect odds ratios, which can never be presented in the form of a cross tabulation between deprivation quartile and travel quartile.

RESPONSE: We have reworded the article to state "For all models the reference group was those patients that fell into the closest quartile for access and the least deprived quartile for residence, and the odds ratios in each cell represent the outcome for each deprivation/travel time quartile relative to that." and we hope this is now clear. By definition the cell that represents this group has a value of 1 and the other cells are odds ratios relative to this, with the stated adjustment by logistic regression, "for Stage 4" compared with "Stage 1-3". We estimated the model by fitting cross-term dummies for each deprivation/travel time quartile. To clarify for the reviewer, we present the raw model for Table 2 below:

Variables in the Equation (We have uploaded the MS Word version of these comments so this table is easier to follow)

	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a diag_age	-.010	.002	28.408	1	.000	.990
gender	.142	.042	11.578	1	.001	1.153
col_dep1_trav2	-.064	.152	.176	1	.675	.938
col_dep1_trav3	-.007	.143	.002	1	.962	.993
col_dep1_trav4	-.031	.131	.057	1	.811	.969
col_dep2_trav1	.145	.145	1.004	1	.316	1.156
col_dep2_trav2	.142	.140	1.025	1	.311	1.152
col_dep2_trav3	.133	.140	.904	1	.342	1.142
col_dep2_trav4	.200	.138	2.086	1	.149	1.221
col_dep3_trav1	.288	.138	4.388	1	.036	1.334
col_dep3_trav2	.052	.140	.137	1	.712	1.053
col_dep3_trav3	.278	.137	4.131	1	.042	1.320
col_dep3_trav4	.207	.144	2.055	1	.152	1.230
col_dep4_trav1	.146	.133	1.208	1	.272	1.157
col_dep4_trav2	.124	.137	.830	1	.362	1.133
col_dep4_trav3	.328	.142	5.364	1	.021	1.388
col_dep4_trav4	.229	.167	1.883	1	.170	1.257
Constant	-.361	.175	4.245	1	.039	.697

4. Titles of table 1 & 2 are not clear. One would expect (adjusted for age and sex) and (*P<0.05, **P<0.01, 95% confidence interval) to be presented as a footnote and may be in the methods section. Double parenthesis in the last part!!

RESPONSE: Double parenthesis is a typographical error which has been corrected, and we have reworded the table titles accordingly. We hope they are now clear.

5. According to the first paragraph of results table 1 and table 2 present odds of being diagnosed at stage 4 compared to stages 1-3 in colon and rectum cancers. However Table 1 present deprivation quartile by travel quartile, while table 2 present deprivation quartile by hospital quartile.

RESPONSE: This inconsistency is corrected

6. The same concerns detailed above in point 4, apply to the odds of treatment presented in tables 3 and 4
RESPONSE: This has been corrected.

Reviewer: Paolo Bruzzi MD MPH PhD
Head, Unit of Clinical Epidemiology
Director, Department of Epidemiology and Prevention National Cancer Research Institute Genova - Italy

This paper presents new analyses of the colorectal cancer part of the data reported in a previous paper from the same group (Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer.
Jones AP, et al, Eur J Cancer. 2008 May;44(7):992-9) with a more specific focus, beside that on distance from hospital which was already discussed in the original paper, on the role of deprivation as assessed by the place of residence. An original analysis is included on the association between these two variables and stage at presentation. The issue is an important one, even though studies on quality of care based on current data are proving of questionable reliability.
The methodology is that of the original study, the study population is the same (39000 colorectal cancer patients diagnosed during the period 1994-2002 in Northern England), and also the data analyzed are the same.
Even though the indications provided by this paper are somewhat clearer than those given by the previous one, mostly because of the focus on a single disease, it provides little original evidence of real interest, and has several weaknesses:

a) The presentation of the results is poor: no crude numbers, simple stratified analyses, wrong tests of significance (p-values for single odds ratios instead of tests for trend). No attempt was made to formally assess the interactions (i.e. synergisms) between the two variables, even though this was declared as the primary aim of the study (last sentence of the introduction section).

RESPONSE: We have added some descriptives providing crude numbers and sample sizes at the start of the results section. Rather than add sample sizes of each cell of every table, which we feel would considerably complicate them, we have added ‘n’ values at various points in the results. We are unsure why the reviewer is not happy with our stratification. We do not agree that the test for significance is incorrect – as we state in the paper the aim is to make comparisons with the most benefitted group (shortest travel time and lowest deprivation) rather than identify trends down the

individual columns. Therefore the use of p-values for single odds ratios is appropriate. We feel the format of presenting data cell by cell in comparison with a group which has the least socioeconomic and geographic disadvantage enables the pattern of diagnostic (including diagnosis at late stage) and therapeutic disadvantage to be seen most clearly. We also do not agree that we have failed to address the synergy between deprivation and travel time as our models consist of the cross terms between the two measures, not their independent effects. We hope that our response to the third comment of the first reviewer will clarify this.

b) At first glance, some the results are very difficult to believe (e.g. the odds of receiving any treatment for colon or rectal cancer are almost halved). This, obviously, derives from the use of the odds ratio as a summary indicator of association. However, as previously stated, without the Odds ratios without the support of the crude figures cannot be meaningfully interpreted :

RESPONSE: We feel the odds ratios are consistent with expectations from clinical practice. We hope that that addition of key sample sizes in the text will aid interpretation.

c) The discussion is long (4 pages), and unfocused, with conjectures and unwarranted statements.

RESPONSE: We believe that the interpretations of the findings we have presented can be tested in confirmatory studies within similar health services to the UK NHS. If confirmed, they offer opportunities for interventions to give poorer UK residents to have access to care for colorectal cancer which matches that elsewhere in Western Europe. We have made some modifications to the discussion and hope the reviewer now feels it is more coherent.

d) The limitations of this study are not discussed at all, nor are the differences between this study and the previous one. The results and the observed associations are taken for granted, without even mentioning some of the possible fallacies and biases that may affect studies of this kind, where both the exposures (deprivation and accessibility to hospital) and the outcome (quality of care) are indirectly estimated from proxy variables. Furthermore, these studies may suffer from biases related to the increased diagnostic pressure in more affluent socio-economic subgroups, leading to an increase in the absolute number of early disease without a corresponding decrease in the absolute numbers of late disease, which however appears to be reduced in absolute terms.

RESPONSE: We agree the study limitations were not well covered in the previous draft of the manuscript. We have added a section covering them in the discussion section of the manuscript. We do not agree that increased diagnostic pressure generates a bias. Diagnosis at an early stage ought to be regarded as the norm which members of more affluent socioeconomic groups are more likely to attain. Perhaps the reviewer is making comparisons with prostate cancer and to some extent breast cancer where there is evidence that some cancers can be detected that are no threat to the patients' future wellbeing. There is no known equivalent in colorectal cancer.

VERSION 2 – REVIEW

REVIEWER	Paolo Bruzzi MD MPH PhD Head, Unit of Clinical Epidemiology Director, Department of Epidemiology and Prevention National Cancer Research Institute Genova - Italy
REVIEW RETURNED	20/12/2011

THE STUDY	The revised version of this paper has addressed several of my

	previous concerns. However, it still contains mistakes that call for an adequate statistical support. This is clear from the answers of the Authors to my previous comments. I apologise for lack of clarity and I have tried to explain some concepts more clearly. AUTHORS: "We do not agree that the test for significance is incorrect – as we state in the paper the aim is to make comparisons with the most benefitted group (shortest travel time and lowest deprivation) rather than identify trends down the individual column." My Comment: Any time an outcome variable (in this instance, stage) is contrasted with another variable (e.g. distance from hospital) the test for significance is a test of the independence between the two variables, that is a test of the hypothesis that the probability of a given value of variable A is not affected by the value of the variable B. When the two variables are categorical, testing for significance each odds ratio within each stratum of the covariate is equivalent to test for independence between the two variables several times, each time removing the other strata. In some instances, this might apparently make sense: for instance, if one is assessing the toxicity of several drugs, he is interested in knowing if drug A, or drug B, or drug C is associated with increased toxicity as compared to a placebo. Even in these instances, however, stratum-specific tests are not correct, for several reasons: 1) They fail to take into account the overall variability in the sample. As a consequence, a) multiple significance testing leads to an increased risk of false positive results; b) these multiple tests are not independent, because they use the same reference group, and no simple correction for multiplicity is possible. The approach adopted by the Authors is equivalent to replace an analysis of variance with a series of t tests: 2) Stratifications leads to decreased power When the covariate (or explanatory variable) is not a categorical multinomial variable without a natural order, but it is an ordered variable or, worse, a continuous variable transformed into a categorical, ordered variable by using cut-off points (as in this instance), stratum-specific tests of significance not only are incorrect: they make little sense, because they depend on the cut-offs chosen and may lead to absurd conclusions: for example, a significant difference may appear in one stratum because of its large size and not appear in another, smaller one, where the odds ratio is larger. Or you can observe a clear trend of increasing odds with increasing value of the explanatory variable, and yet, no significant association is found within each stratum. "AUTHORS: We also do not agree that we have failed to address the synergy between deprivation and travel time as our models consist of the cross terms between the two measures, not their independent effects. We hope that our response to the third comment of the first reviewer will clarify this." My comment: The Authors apparently ignore the statistical meaning of the terms ‘synergy’, or ‘interaction’. In statistics, two factors are considered synergistic (i.e. to interact) if the effect of each of them changes depending on the value of the other one. For instance, the effect of alcohol consumption and smoking on the risk of head & neck cancers is synergistic, since little or no effect of alcohol is seen in non-smokers while a remarkable effect is seen in smokers. Similarly, Estrogen receptor status and Tamoxifen interact in

	determining the prognosis of breast cancer patients, because the effect of Tamoxifen is limited to patients with estrogen receptor positive cancers. Synergism is assessed by the so called 'test for interaction, which is a test of the null hypothesis that the effect of one factor is homogeneous across the strata of the second one. I do not see any test for interaction in their analyses. Instead, I see extensive use of cross classifications that do not assess the presence of interaction, and fail to provide a clear indication of the meaning of the data. Statistical models were invented to overcome the difficulties arising when several factors have to be taken into account. My suggestion is that the logistic model already used in this study to adjust for age and sex, is fully exploited to allow a straightforward interpretation of the results.

VERSION 2 – AUTHOR RESPONSE

The statistical analyses in this paper have been comprehensively revised in hte light of Dr Bruzzi's comments and with the advice of a specialist statistician, Professor Shepstone, as acknowledged. as a consequence our assessment of the importance of distance from home ot hospital has been tempered.