

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study
AUTHORS	Allemani, Claudia; Rachet, Bernard; Weir, Hannah; Richardson, Lisa; LEPAGE, Côme; FAIVRE, J J; Gatta, Gemma; Capocaccia, Riccardo; Sant, Milena; Baili, Paolo; Lombardo, Claudio; Aareleid, Tiiu; Ardanaz, Eva; Bielska-Lasota, Magdalena; Bolick, Susan; Cress, Rosemary; Elferink, Marloes; Fulton, John; Galceran, Juame; Gózdź, Stanisław; Hakulinen, Timo; Primic-Žakelj, Maja; Rachtan, Jadwiga; Safaei Diba, Chakameh; Sánchez, María-José; Schymura, Maria; Shen, Tiefu; Tagliabue, Giovanna; Tumino, Rosario; Vercelli, Marina; Wolf, Holly; Wu, Xiao-Cheng; Coleman, Michel

VERSION 1 - REVIEW

REVIEWER	Nereo Segnan MD MSc Epi Head, Department of Cancer Screening and Unit of Cancer Epidemiology Centre for Epidemiology and Prevention in Oncology, CPO Piedmont Hospital "City of Health and Science", Turin, Italy No conflict of interest
REVIEW RETURNED	29-Apr-2013

THE STUDY	<p>1.The participating Cancer Registries in EU and US cover only a non probabilistic sampling fraction of the population in the two continents. It is unclear whether the study took into account the different size and the different age and sex distributions of the population in the sample, compared with the age and sex distributions in Europe and in US population. If not, the results would be applicable only to those areas where the participating Registries are positioned. In tables 1,2, 3 it seems that no adjusted estimates by size, age, gender have been performed (no mention about in the legenda of the tables) Also the results survival analysis, which is statistically appropriate, could be biased if not weighted by population sizes.</p> <p>2.The 5 years survival follow up ended , at latest, in 2003. The cases were diagnosed between 1996 and 1998. The study reflects the clinical practice for treatment (and staging) of 15 -17 years ago. The authors should acknowledge this limitation, saying that the current situation could be different.</p> <p>3.Around 40% of US citizens ever had FOBT or sigmoidoscopy in US in 1997 as reported by a survey. Any effect on survival? (http://www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm)</p>
RESULTS & CONCLUSIONS	I would prefer to not respond to the first 2 previous questions,

	waiting further answers from the authors about the representiveness of the sample of colon cancer cases.
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REVIEWER	<p>María-Dolores Chirlaque. MD, Pblc Hlth specialist, MHSc. My institution is:</p> <p>1) Murcia Cancer Registry, Murcia Regional Health Authority, Spain 2) CIBER Epidemiología y Salud Pública (CIBERESP), Spain</p> <p>I declare No conflict of interest.</p>
REVIEW RETURNED	07-May-2013

REPORTING & ETHICS	The authors should indicate whether conflict of interest exists. Also they should add some information about the ethical aspects of the study and the confidentiality of the information.
GENERAL COMMENTS	<p>You have prepared an good paper on colorectal cancer survival. The complexity of variables influencing the outcome on colon and rectum cancer prognosis is a challenge for clinical and epidemiological research, and novel results are always welcome. Besides, the study has been well designed and analysed, involving a large amount of work and data.</p> <p>A limitation in high resolution studies on cancer prognosis is the difficult integration between clinical results and populations results. It is appreciated the effort realized in the present work just to integrate this two worlds.</p> <p>The main concern is about the clarification and description in methods sections of the main quality indicator of care use in the present study related to colon and rectum cancer process. The definition of standard care use in the present analysis to evaluate the adherence to guidelines is scarce and only in the last paragraph of the method is mentioned. The percentage of completeness of standard care indicators is an important issue to interpreter differences in prognosis. Besides, standard care indicator will need a reference.</p> <p>Abstract</p> <p>The objective of the study is not specified in the abstract. The background only mentions colorectal cancer survival but also adherence to standard care in patients suffering from colorectal cancer have also been evaluated.</p> <p>It is not clear whether the 12523 adults diagnosed with colorectal cancer during 1996-98 correspond to all incident cases or are a selection of cases. The authors should add that the cases included represent a sample.</p> <p>The survival estimates it supposed be at 5 years of first diagnosis (incidence date) and it should be detailed in M&M.</p> <p>In the conclusion you said 'Elderly patients received surgery.... less often than younger patients...' and in results no data about surgery and age have been showed.</p> <p>Introduction / Material and methods / Discussion</p> <p>Second paragraph of the introduction: 'in one of 31 countries', do you want to say: in each one of the 31 participating countries or countries included in the study?</p> <p>In methods, more information is required to understand the number of cases included and the method use to calculate the sample.</p> <p>The population based sample of patient diagnoses in Finland was representative of Finland, but, what happen with the other countries without national coverage? You should specify the percentage of cover population in countries without national coverage (in methods) and comment (in discussion) possible differences within the</p>

countries in adherence to standard care.

Following the international rules for multiple primary cancers (ICD-O 3rd Edition), colon and rectum site (C18 and C19-C20 respectively) are considered two different primary tumours. Thus, in the present study, what is the meaning that only primary malignant colorectal were included? If a patient had a colon cancer and afterwards a rectum cancer, the last one was excluded? Moreover, only if the first primary tumour corresponds to colon or rectum has been included in the present analysis? Otherwise, colon and rectum tumour diagnosed after other tumour site (breast, prostate, etc.) are excluded? This point should clarify in methods and take into account in the results and the discussion.

A suggestion is that briefly explain the meaning of net cancer-specific survival like cancer survival in the absence of other causes of death (the confounding effects of death from other causes are removed), if so.

Resected patient for whom no pathology report was available were classified as stage unknown. Is this the same percentage that cases no verified microscopically? If not, you should include this information in results.

A sub-analysis could be done with the age group of the screening programs of colorectal cancer that mainly are focused in the 50-69 year age group. For instance, 15-49, 50-69 and 70+. This could be an exploratory or additional analysis. It will be useful to interpreter differences in results attributable to irregular development of screening programs across countries or continents, or to the varying nature (population or opportunistic) of the program.

An important factor to take into account is the interpretations of results on prognosis of colon and rectal cancer in a wider context is the increasing presence of adenomatous polyp, villous adenoma or tubulovillous adenoma and their respective adenocarcinomas in situ suppose a better survival. All these cases are not included in the study and their prognosis is excellent. The higher premalignant lesions remove the better prognosis of colon and rectal cancer. Some comment could be addressed in the discussion about the effect of early diagnosis at population level in the general prognosis of colorectal cancer. This aspect can not be measure in the present study but should be commented.

The draft should describe the correspondence between Dukes A, B, C D, the TNM and local, locally advanced, node-positive and metastatic disease in methods.

On page 9, paragraph between lines 9-11, information on surgical procedures is not mentioned after in all the analysis, neither results nor discussion. That, is this a relevant information to include if no results are given?

If the incidence date is the date to calculate the days/month/ or years of follow-up and the definition of incidence date is different in the Europe and the USA, should be specify in methods and commented in the discussion. This comment is relevant perhaps only in the interpretation of death within 30 days.

A suggestion is to comment the incidence rate in US and in Europe, by sex and how it could this influence in survival.

References

In the reference 8 the authors are repeated.

Figures and tables

Table 1, column of colon: add a little explanation, like versus rectum.

Table 2: the fourth last column add to Staged: known staged. The same in Table 2-web appendix, in the column of Staged.

In one table (for example table 1) the authors could add the countries included in Northern, Western, Southern and Eastern

	<p>European regions.</p> <p>In the Figure 5-web appendix change the scale of the graph Dukes A to 500 (number of excess death by 1000) just to compare with Dukes B and C.</p> <p>In table 3 the authors show the percentage of adjuvant chemotherapy and radiotherapy by Dukes stage, but how much is the optimal range of the percentage? This information is only mentioned in the discussion and this point is related to the description in method of quality indicator of care.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: Nereo Segnan MD MSc Epi
 Head, Department of Cancer Screening and Unit of Cancer Epidemiology
 Centre for Epidemiology and Prevention in Oncology, CPO Piedmont
 Hospital "City of Health and Science", Turin, Italy
 V.San Francesco da Paola 31

No conflict of interest

R1_C1. The participating Cancer Registries in EU and US cover only a non probabilistic sampling fraction of the population in the two continents. It is unclear whether the study took into account the different size and the different age and sex distributions of the population in the sample, compared with the age and sex distributions in Europe and in US population. If not, the results would be applicable only to those areas where the participating Registries are positioned.

In tables 1,2, 3 it seems that no adjusted estimates by size, age, gender have been performed (no mention about in the legenda of the tables)

Also the results survival analysis, which is statistically appropriate, could be biased if not weighted by population sizes.

R1_A1. We completely understand the importance of the sampling of patients for studies of this kind. Doug Altman's text "Practical statistics for medical research" (Chapman and Hall, 1992, p6) notes: "In theory we can obtain a truly representative sample only by choosing patients at random but even then the sample would be specific to a time period and geographical area. In practice, samples are nearly always chosen systematically and the subjects' characteristics are described so that their representativeness can be judged." We need to emphasise that we took truly random samples of patients from each cancer registry.

The remainder of this comment appears to arise from a misunderstanding of the design of high-resolution studies. Participating cancer registries are population-based, in that they register all persons diagnosed with a relevant malignancy in the defined territory that they cover. The patients included in high-resolution studies are large, randomly selected subsets of all persons diagnosed with a given cancer (here, colorectal), in a given calendar period (1996-98), in that territory. These samples are not intended to be "representative" of all cancer patients, either in Europe or the US. But they are representative of all colorectal cancer patients diagnosed during 1996-98 in the territory of each registry. And that is precisely the point. We are not attempting to establish international or inter-continental league tables of cancer survival. We are attempting to obtain robust and genuinely representative estimates of the differences in survival between populations (whether those populations are regional or national) and of the impact on those population-based differences in cancer survival of covariables such as stage at diagnosis. For a more extended discussion of this point, see Coleman MP et al. EURO CARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003; 14 (Suppl 5); 128-149.

We only report the actual estimates of survival to confirm that those international differences reported in previous studies are reflected in our data. There is thus no reason to weight the survival estimates by the age and sex distributions of persons in Europe and the US (and if any such weighting were required, it would be by the age-sex distribution of cancer patients, and not of the general population:

the same point applies to age standardisation of cancer survival estimates).

When only a single participating cancer registry is available for a wider region, such as Finland in the Nordic area of Europe, we need to be careful not to overemphasise the survival estimates for that region, but this point was clearly mentioned in the “strength and limitations” section of the bullet points we were asked to prepare to summarise the study. To make clear which geographical areas we are actually comparing, we have added a footnote to all tables and graphs.

Table 1, 2 and 3 are simple descriptive distributions of the numbers of cases in various categories: such tables are not usually adjusted, and it is not clear what standard weights would be appropriate!

R1_C2. The 5 years survival follow up ended, at latest, in 2003. The cases were diagnosed between 1996 and 1998. The study reflects the clinical practice for treatment (and staging) of 15 -17 years ago. The authors should acknowledge this limitation, saying that the current situation could be different.

R1_A2. We agree. We included exactly this point under the heading “strengths and limitations” among the same bullet points:

- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.

R1_C3. Around 40% of US citizens ever had FOBT or sigmoidoscopy in US in 1997 as reported by a survey. Any effect on survival?
(<http://www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm>)

R1_A3. Thank you for this point and for the helpful reference.

European guidelines on population-based screening for colorectal malignancy were published in 2003, and none of the countries involved in this study had introduced it before 2006.

We agree that opportunistic testing with faecal occult blood or sigmoidoscopy was more common in the US than in Europe in the late 1990s. We do not have information on whether or not the patients in this study had undergone FOBT or endoscopic examination at any time before their diagnosis, because these facts are not routinely recorded at cancer registration, and we cannot rely on partial information that may be available in the clinical record. Given that a higher proportion of patients in the US than in Europe had undergone a diagnostic procedure that could have resulted in removal of a premalignant polyp or an in situ neoplasm, it is worth considering the impact of this potential bias on the difference in survival between the US and Europe. It would be expected to reduce incidence, shift the spectrum of malignancy to the right, and reduce survival. In fact, incidence in the US is higher, the stage distribution less advanced, and survival higher than in Europe. In short, to the extent that the bias suggested by the referee exists, it would be expected to have reduced the difference in survival between the US and Europe.

We have added a comment to this effect to the discussion.

R1_C4. I would prefer to not respond to the first 2 previous questions (Do the results answer the research question? Are they credible?), waiting further answers from the authors about the representiveness of the sample of colon cancer cases.

R1_A4. We have addressed this point higher up (R1_A1).

Reviewer: María-Dolores Chirlaque. MD, Pblc Hlth specialist, MHSc. My institution is:

- 1) Murcia Cancer Registry, Murcia Regional Health Authority, Spain
- 2) CIBER Epidemiología y Salud Pública (CIBERESP), Spain

I declare No conflict of interest.

The authors should indicate whether conflict of interest exists.

Also they should add some information about the ethical aspects of the study and the confidentiality of the information.

As requested by BMJ Open, we reported this information in the website ad hoc space during the submission. In the light of this comment, we have now added this information to the article.

Dear colleagues

You have prepared an good paper on colorectal cancer survival. The complexity of variables influencing the outcome on colon and rectum cancer prognosis is a challenge for clinical and epidemiological research, and novel results are always welcome. Besides, the study has been well designed and analysed, involving a large amount of work and data.

A limitation in high resolution studies on cancer prognosis is the difficult integration between clinical results and populations results. It is appreciated the effort realized in the present work just to integrate this two worlds.

The main concern is about the clarification and description in methods sections of the main quality indicator of care use in the present study related to colon and rectum cancer process. The definition of standard care use in the present analysis to evaluate the adherence to guidelines is scarce and only in the last paragraph of the method is mentioned. The percentage of completeness of standard care indicators is an important issue to interpreter differences in prognosis. Besides, standard care indicator will need a reference.

We appreciate these constructive comments.

We have added references to the indicator of standard care.

Abstract

R2_C1 The objective of the study is not specified in the abstract.

The background only mentions colorectal cancer survival but also adherence to standard care in patients suffering from colorectal cancer have also been evaluated.

It is not clear whether the 12523 adults diagnosed with colorectal cancer during 1996-98 correspond to all incident cases or are a selection of cases. The authors should add that the cases included represent a sample.

R2_A1: Thank you for your thorough reading of the abstract, which is unfortunately very tightly constrained on word length. We have not explicitly stated the objective, as requested, but we feel the objective is nevertheless clear from the second paragraph of materials and methods in the abstract. Evaluation of adherence to standard care is also covered in this paragraph.

R2_C2: The survival estimates it supposed be at 5 years of first diagnosis (incidence date) and it should be detailed in M&M.

R2_A2: We assume this comment also refers to the abstract. The same constraints on length applied. In the Material and Method paragraph we wrote: "Net survival and excess risk of death were estimated with flexible parametric models", but in the Results section we wrote: "Age-standardised five-year net survival was..."; we therefore believe it is clear that we estimated 5-year net survival. It is also explicit in the Statistical analysis section of the body of the article: "Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models."

R2_C3: In the conclusion you said 'Elderly patients received surgery.... less often than younger patients...' and in results no data about surgery and age have been showed.

R2_A3: We are puzzled by this point. We have written: "Patients aged less than 75 years were only half as likely to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site." (Table 4)

Introduction / Material and methods / Discussion

R2_C4: Second paragraph of the introduction: 'in one of 31 countries', do you want to say: in each one of the 31 participating countries or countries included in the study?

R2_A4: Thank you for the clarification: "... in 31 countries"!

R2_C5: In methods, more information is required to understand the number of cases included and the method use to calculate the sample.

R2_A5: This point is reported in the Material and Methods section: "Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US)."

We asked the registries for a random (and thus representative) sample of about 500 cases as reported below, but we did not instruct the registries to use a specific method to obtain their random samples. A few registries simply sent all colorectal cancer patients registered in 1, 2 or 3 years during the period 1996-98.

R2_C6: The population based sample of patient diagnoses in Finland was representative of Finland, but, what happen with the other countries without national coverage? You should specify the percentage of cover population in countries without national coverage (in methods) and comment (in discussion) possible differences within the countries in adherence to standard care.

R2_A6: It is important not to see the description and comparisons of patterns of care within and between countries (or regions of countries) as an international league table. The percentage of the (national) population covered by a given cancer registry does not influence adherence to standard care in that region. If a registry is population-based, its data provide, by definition, a picture of the effectiveness of the health system in the territory covered by the registry, regardless of its size. The design of studies such as this is intended to provide robustly comparable estimates of the relative importance of covariables in explaining the survival differences that are observed in each region or country. If the health system is not working properly in a given area, this should be considered a problem for the whole country.

R2_C7: Following the international rules for multiple primary cancers (ICD-O 3rd Edition), colon and rectum site (C18 and C19-C20 respectively) are considered two different primary tumours. Thus, in the present study, what is the meaning that only primary malignant colorectal were included? If a patient had a colon cancer and afterwards a rectum cancer, the last one was excluded? Moreover, only if the first primary tumour corresponds to colon or rectum has been included in the present analysis? Otherwise, colon and rectum tumour diagnosed after other tumour site (breast, prostate, etc.) are excluded? This point should clarify in methods and take into account in the results and the discussion.

R2_A7: We included cases with a cancer of colon or rectum (ICD-9 153-154; herein: colorectum) diagnosed during 1996-98. Only invasive malignant (behaviour code 3) and in situ (2) tumours were collected. Uncertain and borderline (1) tumours were excluded. Both histologically verified and not verified cases were included.

A colorectal tumour diagnosed after another primary cancer was included only if the first tumour occurred in a different organ. Second colorectal cancers therefore were not notified as independent cases.

Persons with two or more synchronous colorectal cancers were included and treated as a single case; both (all) localisations were recorded, as well as the most advanced stage.

R2_C8: A suggestion is that briefly explain the meaning of net cancer-specific survival like cancer survival in the absence of other causes of death (the confounding effects of death from other causes are removed), if so.

R2_A8: We explained the meaning of net survival with phrasing similar to that suggested by the reviewer in the Statistical analysis paragraph (page 9): "Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of

death; it may be interpreted as cancer survival after controlling for competing causes of death.”

R2_C9: Resected patient for whom no pathology report was available were classified as stage unknown. Is this the same percentage that cases no verified microscopically? If not, you should include this information in results.

R2_A9: Thank you for pointing out this weakness in the drafting. For the purposes of describing a broad category of patients whose disease was advanced at diagnosis, we combined patients whose pathology reports identified metastatic disease with patients who were not resected and for whom no pathology was available. The second of these two groups is widely accepted as likely to have had advanced disease, the absence of invasive diagnostic procedures being most probably attributable to a decision not to attempt surgery of curative intent (e.g. a bypass procedure in the biliary or digestive tract, or insertion of a stoma), because of the extent of disease, usually peritoneal carcinomatosis. This is the category described as “advanced stage” in table 2, with the definition in footnote 1.

This broad category was not used in stage-specific survival analyses, however. For those analyses, we use the classical Dukes’ stage, where available.

We have made this more clear in the text.

R2_C10: A sub-analysis could be done with the age group of the screening programs of colorectal cancer that mainly are focused in the 50-69 year age group. For instance, 15-49, 50-69 and 70+. This could be an exploratory or additional analysis. It will be useful to interpreter differences in results attributable to irregular development of screening programs across countries or continents, or to the varying nature (population or opportunistic) of the program.

R2_A10: We adopted these age groups to be the same as those in previous studies of the patterns of care for colorectal malignancy (Gatta et al. *Acta Oncol.* 2010; 49: 776-783). The Council of the European Union indicated the utility of population-based screening for colorectal cancer in 2003, but the European guidelines were not written until a couple of years later. Population-based screening was only introduced in 2006, and is still not very widespread. We did not have information on whether the patients in this study had undergone faecal occult blood testing or endoscopy prior to diagnosis.

R2_C11: An important factor to take into account is the interpretations of results on prognosis of colon and rectal cancer in a wider context is the increasing presence of adenomatous polyp, villous adenoma or tubulovillous adenoma and their respective adenocarcinomas in situ suppose a better survival. All these cases are not included in the study and their prognosis is excellent. The higher premalignant lesions remove the better prognosis of colon and rectal cancer. Some comment could be addressed in the discussion about the effect of early diagnosis at population level in the general prognosis of colorectal cancer. This aspect can not be measure in the present study but should be commented.

R2_A11: We agree that exclusion from the analyses of tumours with better prognosis will lead to higher estimates of survival. (Referee 1 comment 3 addresses a similar point). In turn, the frequency with which premalignant polyps, adenomas and in situ malignancies are removed (reducing the recorded incidence of invasive disease and shifting the biological spectrum of malignancy to the right), can influence population-based survival estimates. Again, although it is a fairly safe assumption that this frequency is higher in the US than in the range of European countries included in the study, we had no specific information on whether the patients in this study had undergone endoscopic removal of any premalignant lesions. In situ tumours were not included in the analyses because data for these tumours were only supplied by US registries (396, 3.1%).

We have added a suitable comment to the discussion.

R2_C12: The draft should describe the correspondence between Dukes A, B, C D, the TNM and local, locally advanced, node-positive and metastatic disease in methods.

R2_A12: We have tried to keep this complex paper as simple as possible! Dukes’ stage can be constructed from complete TNM data, but we have used Dukes’ stage in the analyses for the reasons mentioned in the text, and have preferred to add a note to all tables including information about stage.

R2_C13: On page 9, paragraph between lines 9-11, information on surgical procedures is not mentioned after in all the analysis, neither results nor discussion. That, is this a relevant information to include if no results are given?

R2_A13: We agree, and we removed this sentence. Much more detailed information was collected about surgical procedures, and this was initially used to categorise the site and extent of surgery, but in the end, this was not used to analyse outcomes because it was insufficiently complete.

R2_C14: If the incidence date is the date to calculate the days/month/ or years of follow-up and the definition of incidence date is different in the Europe and the USA, should be specify in methods and commented in the discussion. This comment is relevant perhaps only in the interpretation of death within 30 days.

R2_A14: There are international rules to define the date of incidence. These rules are followed by all registries contributing data to international studies such as Cancer Incidence in Five Continents. If a registry considered a given date as the date of incidence we had no reason to assume it was not coded according to the international rules. More importantly, differences in 30 day post-operative mortality were small, and we did not see fit to comment on them in the discussion.

R2_C15: A suggestion is to comment the incidence rate in US and in Europe, by sex and how it could this influence in survival.

R2_A15: We appreciate that incidence, survival and mortality are closely related, but our main concern was to explore the predictors of differences in survival, rather than to describe the overall patterns of survival, and in particular their trends over time; if we had been carrying out such an exercise, comparisons of incidence would certainly have been helpful. We have preferred not to accept this suggestion, partly also for reasons of space.

References

R2_C16: In the reference 8 the authors are repeated.

R2_A16: Thank you. We have corrected the reference.

Figures and tables

R2_C17: Table 1, column of colon: add a little explanation, like versus rectum.

R2_A17: In table 1 colon indicates the No. and % of patients with colon cancer out of all the colorectal cancer patients.

R2_C18: Table 2: the fourth last column add to Staged: known staged. The same in Table 2-web appendix, in the column of Staged.

R2_A18: We prefer to leave this one! "Staged" does make clear that stage was known.

R2_C19: In one table (for example table 1) the authors could add the countries included in Northern, Western, Southern and Eastern European regions.

R2_A19: Thank you. We have added a footnote to all tables and graphs.

R2_C20: In the Figure 5-web appendix change the scale of the graph Dukes A to 500 (number of excess death by 1000) just to compare with Dukes B and C.

R2_A20: We agree in principle that it is preferable to use the same scale for the y-axis when there are several similar graphics, in order to facilitate visual comparison. However, adopting this suggestion would completely suppress the visual difference in the excess hazard by region for Dukes' A malignancy. We did try it!

R2_C21: In table 3 the authors show the percentage of adjuvant chemotherapy and radiotherapy by

Dukes stage, but how much is the optimal range of the percentage? This information is only mentioned in the discussion and this point is related to the description in method of quality indicator of care.

R2_A21: No optimal percentage had been proposed in the late 1990s. During the early and mid-2000s, chemotherapy was considered to be indicated for all patients with a Dukes C' tumour, but some co-morbidities or other contraindication to chemotherapeutic agents also applied. In practice about 90% of patients under 75 are treated with chemotherapy in France and about 60% in older patients. (Bouvier et al. Dig Liver Dis 2013; Quipourt et al. J Am Geriatr Soc 2011; Phelip et al. Gastroenterol Clin Biol 2010)

VERSION 2 – REVIEW

REVIEWER	<p>Nereo Segnan MD MSc Epi</p> <p>Head, Department of Cancer Screening and Unit of Cancer Epidemiology Centre for Epidemiology and Prevention in Oncology, CPO Piedmont Hospital "City of Health and Science", Turin, Italy IARC Senior Visiting Scientist</p>
REVIEW RETURNED	12-Jun-2013

THE STUDY	<p>The title of the study "Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study", the results section of the abstract , the article focus and the key messages are suggesting that the authors attempt to compare the survival in US and Europe . Only 7 of US cancer registries are included , and in Europe countries like Germany or UK are excluded. The title, abstract and "focus" should be modified according to. Perhaps the presentation of the limits of the study and of its generalisability was not complete in the manuscript.I would suggest to report in the text the following sentence in order to avoid in the reader any risk of over-interpretation or misunderstanding of high resolution studies. The sentence is part of the authors reply R1_A1 to the the R1_C1 comment:" Participating cancer registries are population-based, in that they register all persons diagnosed with a relevant malignancy in the defined territory that they cover. The patients included in high-resolution studies are large, randomly selected subsets of all persons diagnosed with a given cancer (here, colorectal), in a given calendar period (1996-98), in that territory. These samples are not intended to be "representative" of all cancer patients, either in Europe or the US. But they are representative of all colorectal cancer patients diagnosed during 1996-98 in the territory of each registry. And that is precisely the point. We are not attempting to establish international or inter-continental league tables of cancer survival.</p> <p>In the same reply R1_A1 the corresponding author wrote: "Table 1, 2 and 3 are simple descriptive distributions of the numbers of cases in various categories: such tables are not usually adjusted, and it is not clear what standard weights would be appropriate!" A rectangular sample by age and gender (or stratified proportions by age and gender) would permit to compare the distributions across the registries of cancer site, stage, chemotherapy</p>
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	The tables 1-3 which document the sampling results , show for instance a proportion of colorectal cancer in males in European registries between 45% and 60%e and of colon cancer between 49% and 68%. The proportions by gender or site of colorectal cancer of course reflect the age distribution of patients. Perhaps an effort to prevent any not appropriate interpretation by the not thoughtful reader could be considered by presenting the data as suggested.
RESULTS & CONCLUSIONS	The answers to unanswered questions in the "Results and conclusion" section depends on presenting the results according to their content.

VERSION 2 – AUTHOR RESPONSE

Claudia Allemani

R1_C1: The title of the study "Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study", the results section of the abstract, the article focus and the key messages are suggesting that the authors attempt to compare the survival in US and Europe . Only 7 of US cancer registries are included, and in Europe countries like Germany or UK are excluded. The title, abstract and “focus” should be modified according to.

R1_A1: We understand the concern of the referee, which relate to the title, the abstract (results), the article focus and the key messages.

We would argue that the title is precisely accurate. We are indeed comparing survival in the US and Europe – but the comparison is clearly not between the whole of the US and the whole of Europe. We do not accept that this could possibly be considered misleading. No study has ever included data from all of the US cancer registries. Many of those registries only started operation in the late 1990s. Despite that, the data from the SEER programme are widely reported as if they were, in fact, the only US data (SEER covered 10% of the US population up to 1992 and from 14% up to the current 26% only much more recently), and as if they were indeed representative of the US, which they are not.[1,2] Nor has any study ever included data from all European countries, quite a few of which either have no cancer registry or a registry which only began operation within the last 10 years.

The abstract for this paper emphasises that “21 population-based registries in 7 US states and 9 European countries” participated in the study.

The key messages state that “Stage at diagnosis varied more widely between [participating] European countries than between [participating] US states”: we have modified this to meet the referee’s concern by the inclusion of the word “participating”.

1. Merrill RM, Dearden KA. How representative are the surveillance, epidemiology, and end results (SEER) Program cancer data of the United States? *Cancer Causes Control* 2004; 15: 1027-34
2. Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, Azevedo e Silva G, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL, CONCORD Working Group. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; 9: 730-56

R1_C2: Perhaps the presentation of the limits of the study and of its generalisability was not complete in the manuscript. I would suggest to report in the text the following sentence in order to avoid in the reader any risk of over-interpretation or misunderstanding of high resolution studies. The sentence is part of the authors reply R1_A1 to the the R1_C1 comment:” Participating cancer registries are population-based, in that they register all persons diagnosed with a relevant malignancy in the defined territory that they cover. The patients included in high-resolution studies are large, randomly selected subsets of all persons diagnosed with a given cancer (here, colorectal), in a given calendar period (1996-98), in that territory. These samples are not intended to be “representative” of all cancer patients, either in Europe or the US. But they are representative of all colorectal cancer patients diagnosed during 1996-98 in the territory of each registry. And that is precisely the point. We are not attempting to establish international or inter-continental league tables of cancer survival.

R1_A2: Thank you. We have added this material to the discussion.

R1_C3: In the same reply R1_A1 the corresponding author wrote: "Table 1, 2 and 3 are simple descriptive distributions of the numbers of cases in various categories: such tables are not usually adjusted, and it is not clear what standard weights would be appropriate!"
A rectangular sample by age and gender (or stratified proportions by age and gender) would permit to compare the distributions across the registries of cancer site, stage, chemotherapy The tables 1-3 which document the sampling results , show for instance a proportion of colorectal cancer in males in European registries between 45% and 60%e and of colon cancer between 49% and 68%. The proportions by gender or site of colorectal cancer of course reflect the age distribution of patients. Perhaps an effort to prevent any not appropriate interpretation by the not thoughtful reader could be considered by presenting the data as suggested.

R1_A3: The referee is correct that age-incidence differs between males and females, primarily for rectal rather than colon cancer. This information is readily available from standard publications, and it does not seem appropriate to reproduce these distributions here, when the purpose is to examine broad international differences in treatment among large random samples of the cancer patient population, taking due account of age and sex.

To break down Tables 1-3 by sex and by three or four categories of age would make these already substantial tables 6 to 8 times larger than they currently are, and we do not believe this is likely to be publishable, or greatly to enhance the interpretability of the information by readers – especially if the expansion of the tables also included data for individual registries rather than broad geographic regions. It is surely more important that the key analyses are adjusted for age and sex where necessary. The models of treatment by sub-site and stage (Table 4) all include age: the age-specific differences in treatment, particularly in the elderly, are fully discussed in the article. We would also point out that the odds of resection for curative intent (Table 4) are adjusted for sub-site, but there is no evidence that sex is a confounder. The model for radiotherapy in Dukes' stage A-C rectal cancer includes sex: there is no evidence of a difference between the sexes in the odds of receiving radiotherapy (95% CI 0.77-1.10); it seems unlikely that a thoughtful reader would misinterpret these data.