

Elsevier Editorial System(tm) for The Lancet
Manuscript Draft

Manuscript Number:

Title: Authors' response♣

Article Type: Invited Correspondence

Keywords: survival, cancer, breast, colorectal, lung, ovary

Corresponding Author: Prof. Michel P Coleman, BA BM BCh MSc FFPH

Corresponding Author's Institution: London School of Hygiene & Tropical Medicine

First Author: Michel P Coleman, BA BM BCh MSc FFPH

Order of Authors: Michel P Coleman, BA BM BCh MSc FFPH; Manuela Quaresma, MSc; Bernard Rachet, MD PhD

Manuscript Region of Origin: UNITED KINGDOM

Sir,

We are grateful for the opportunity to respond to these comments. Prof Lachmann found our paper "... impenetrable (as such meta-analyses often are...)". Our study is not a meta-analysis in which patient records from various studies with a more or less similar design are analysed jointly to obtain a single pooled estimate of a treatment effect with greater precision than individual randomised trials can offer. It is a single study with a detailed protocol agreed in advance by 12 population-based cancer registries, from which anonymised individual cancer patient records were submitted for virtually all cancer patients diagnosed in their jurisdiction (country or region). We applied standardised quality control procedures to these data sets, then estimated relative survival for each cancer in each jurisdiction. For countries with more than one participating registry we also provided a pooled estimate, but we did not provide an overall estimate of survival for all 6 countries combined. On the contrary, our purpose was to evaluate international differences and trends in cancer survival, in order to compare the overall effectiveness of the various healthcare systems. Such differences cannot be examined in randomised trials, only with observational data.

We agree with Prof Lachmann that early diagnosis and treatment improve the outcome for many cancers. Our findings suggest that the international differences in survival arise soon after diagnosis. Earlier studies based on large random samples of clinical records suggest that in Europe, later stage at diagnosis and differences in treatment could account for much of those differences¹⁻⁴. We are now evaluating the impact of stage and treatment on the survival trends and differentials that we reported. For lung cancer (ICD-10 C34), we will also examine small-cell and other lung cancers separately. Mesothelioma (ICD-10 C45) was not included in the study.

The size of a population does not determine the cancer survival estimate, but the variance of the estimate depends on the number of cases and the lethality of the tumour. We did not estimate survival in samples of patients, but for all cancer patients diagnosed and registered in each population. All the registries met the quality criteria for inclusion in *Cancer incidence in five continents*, published by the International Agency for Research on Cancer⁵. Analysis of variance is not used in population studies of cancer survival. We analysed relative survival with maximum likelihood methods for individual data: these are appropriate regression models for the excess hazard of death, which underpins relative survival^{6,7}, and they are analogous to the Cox proportional hazards model for death rates. We reported 95% confidence intervals for all the survival estimates by age, sex, cancer, jurisdiction and calendar period (webappendix). However, we were not testing a hypothesis that survival is higher or lower in a given country, but reporting the patterns and trends of population-based cancer survival, just as is routinely done for incidence and mortality, without significance tests^{5,8}.

The "proportion of cancer registration to the population" presented in the graphic by Dr Jinichi Mori and colleagues seems to be the total number of cases included in the survival analyses for a given country over the 13 years 1995-2007 divided by the national population. If so, this quantity takes no account of differences in population coverage of the data analysed from each country (43-100%), or differences in cancer incidence by age and sex, or demographic trends. We do not see how the correlation between this quantity and relative

survival can be safely interpreted. Regional variation in survival in Australia and Canada is small, and within the limits of random variation⁹.

We share the concern of Prof Pritchard and Dr Hickish that politicians may make selective use of evidence. We analysed no data on health service structure, and the survival estimates we report provide no evidence for or against any particular style of health service organisation. Survival in Denmark is broadly similar to that in the UK, but the Danish health service is more akin to that of the other Nordic countries, which have higher survival, than it is to the UK health system. Conversely, the UK and Canadian health systems are similar, but survival is higher in Canada.

We are not convinced by Prof Pritchard and Dr Hickish's argument that extrapolated values of health expenditure as a proportion of gross domestic product (GDPHE) and changes in the UK ranking among 10 major developed countries for all-cancer mortality rates can lead to the conclusion that "the NHS, in terms of economic input compared with cancer mortality rates output, has achieved more [cancer control than those countries] with proportionately less." Cancer mortality trends cannot be expected to respond quickly or exclusively to trends in health expenditure, partly because of the time-lags cited above, and partly because important long-term preventive measures are not included in health expenditure. Our article documents cancer survival trends, which show progress in the UK (and other countries), particularly for breast cancer. We made no statement about whether or how the UK health service should be reformed or re-organised.

We see no evidence to agree with Prof Pritchard and Dr Hickish (or with other authors^{10,11}) that cancer mortality rates are "a better measure for determining the effectiveness of services ... and international comparisons". Mortality trends are invaluable, and we reported them, but it is not possible to draw conclusions about the effectiveness of health services from trends in mortality alone, because mortality rates obviously depend on both incidence and survival. Incidence rates and survival estimates refer to the year when the patients were diagnosed; mortality rates refer to the year when the persons died¹². More than 40% of women who die of breast cancer in any given year will have been diagnosed at least 5 years previously. Mortality trends thus provide a time-lagged and blurred picture of changes in the effectiveness of health services. Where survival has been very low for decades, e.g. for lung cancer, mortality trends are largely parallel with incidence trends, as our report showed: the substantial fall in lung cancer mortality in men is attributable more to the long-term decline in tobacco use than to increasingly effective treatment. Further, mortality rates are subject to error in certification of the cause of death: quality control of the cause of death is far more limited than that for the anatomy, pathology and behaviour of the cancer in population-based incidence data, especially at older ages^{13,14}. That is why cancer mortality trends are often presented with an upper age limit^{10,15}, such as 74 years. An increasing proportion of cancer patients are diagnosed at 65 years and over, however, and evidence on outcomes for elderly cancer patients is also required. Relative survival provides this evidence. It is not affected by errors in the cause of death¹⁶, and we were able to present survival estimates for elderly patients (webappendix).

We and others have argued for joint interpretation of trends in incidence, survival and mortality to assess progress in cancer control^{17,18}.

1. Sant M, EUROCARE Working Group. Differences in stage and therapy for breast cancer across Europe. *Int J Cancer* 2001; **93**: 894-901
2. Sant M, Allemani C, Capocaccia R *et al.* Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer* 2003; **106**: 416-22
3. Allemani C, Storm H, Voogd AC *et al.* Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. *Eur J Cancer* 2010; **46**: 1528-36
4. Gatta G, Zigon G, Aareleid T *et al.* Patterns of care for European colorectal cancer patients diagnosed in 1996-98: a EUROCARE high-resolution study. *Acta Oncol* 2010: 1-8, last accessed 5 October 2010
5. Curado MP, Edwards BK, Shin HR *et al.*, eds. *Cancer incidence in five continents. Vol. IX. IARC Scientific Publications No. 160*. Lyon: IARC; 2007
6. Estève J, Benhamou E, Croasdale M *et al.* Relative survival and the estimation of net survival: elements for further discussion. *Stat Med* 1990; **9**: 529-38
7. Remontet L, Bossard N, Belot A *et al.* An overall strategy based on regression models to estimate relative survival and models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Stat Med* 2007; **26**: 2214-28
8. World Health Organisation. WHO Statistical Information System (WHOSIS), WHO Mortality Database. <http://www.who.int/healthinfo/morttables/en/index.html> 14 Apr 2008, last accessed 16 February 2011. <http://www.who.int/healthinfo/morttables/en/index.html>
9. Coleman MP, Quaresma M, Berrino F *et al.* Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; **9**: 730-56
10. Beral V, Peto R. UK cancer survival statistics are misleading and make survival look worse than it is. *Br Med J* 2010; **341**: c4112
11. Autier P, Boniol M. Caution needed for country-specific cancer survival. *Lancet* 2011; **377**: 99-101
12. Coleman MP, Babb P, Stockton DL *et al.* Trends in breast cancer incidence, survival and mortality [Erratum in *Lancet* 2000;356:774]. *Lancet* 2000; **356**: 590-1
13. Mathers CD, Fat DM, Inoue M *et al.* Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; **83**: 171-7
14. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer* 2009; **45**: 747-55
15. Coleman MP, Estève J, Damiecki P *et al.* *Trends in cancer incidence and mortality (IARC Scientific Publications No. 121)*. Lyon: International Agency for Research on Cancer, 1993, pp1-806.
16. Coleman MP, Babb P, Damiecki P *et al.* *Cancer survival trends in England and Wales 1971-1995: deprivation and NHS Region. (Studies on Medical and Population Subjects No. 61)*. London: The Stationery Office, 1999, pp1-695.
17. Extramural Committee to Assess Measures of Progress Against Cancer. Measurement of progress against cancer. *J Natl Cancer Inst* 1990; **82**: 825-35
18. Karim Kos HE, de Vries E, Soerjomataram I *et al.* Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008; **44**: 1345-89