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Feature Articles

Cancer Mapping: Why Not Use Absolute Scales?

Nikolaus Becker

Cancer atlases frequently use relative scales which rank regional mortality rates relative to the countrywide mean (if relative risks are used) or median (if percentile colour schemes are used). This method has various disadvantages which limit comparability and interpretation. An alternative is absolute scaling which is well-known from geographic atlases: the natural rank order of altitudes is mapped into a colour scheme which is preserved over all maps of an atlas. Applied to cancer atlases this means that the different magnitudes of mortality for different cancer sites and sexes is preserved and leads to the use of different ranges of a relatively wide common colour scheme. This technique is applied to the data of the German Cancer Atlas published in 1984. Its properties are outlined and it is shown that it overcomes many of the unfavourable characteristics of the convenient procedures.
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INTRODUCTION

IN THE past decade, numerous cancer atlases have been published (for an overview see Smans *et al.* [1]) and a considerable proportion of these have come from European countries [2–19]. Contributions such as the one by Kemp *et al.* [16] have become a kind of standard for subsequent atlases. Pukkala *et al.* [6] have introduced an important new mapping technique. Nevertheless, comparative papers have pointed out that the basic methods of presentation remain remarkably different and seriously complicate the use of those atlases [20, 21]. It can be concluded that one of the major problems of cancer mapping is the application of relative scaling. It is applied in an apparent way if 'indirect' age-standardisation is used and relative risks are plotted, and in a less obvious way even if data are 'directly' age-standardised, but plotted in a percentile presentation. The latter case can be seen, e.g. in the German or the Polish cancer atlas [9, 14]; the colour scheme refers to a medium level (yellow) which includes the median, and marks the percentiles above in reddish colours (orange and red) and those below in greenish colours (light green and dark green). Thus, the perception of these maps, which are actually based on absolute rates, is also predominantly relative, because they depend upon the countrywide overall median of rates per cancer map. Thus, they are similar to maps based on relative risks which depend on the countrywide mean of rates per cancer map.

Both types of presentation create a series of problems regarding comparability and interpretation:

(1) Comparisons across national boundaries are impossible, because the medians or means of rates are mostly different for different countries. This is a very unfavourable effect, especially in Europe, where many countries are located close together and such examinations are informative.

(2) The convenient solution for this problem is the generation of supranational atlases, e.g. the Cancer Mortality Atlas of the European Economic Community [1] or the Cancer Mortality Atlas of Central Europe (to be published in 1994). The latter includes data from the former socialist countries which are accessible now, but have, partially questionable reliability. Those data also influence overall medians or means and may, thus, distort the total patterns of mortality presented by the cancer map. This means that even supranational atlases cannot overcome the above problem.

Table 1. Colour levels, covered range of mortality and red/green/blue code (RGB code) for computing colours using SAS procedure MAP version 6.07

Colour level	Range of mortality rates	RGB code
1	0.0	FFFFFF
2	>0.0– 0.5	FFFFE5
3	>0.5– 1.5	FFFFCC
4	>1.5– 3.0	FFFF99
5	>3.0– 5.0	FFFF66
6	>5.0– 7.5	FFF266
7	>7.5–10.5	FFE566
8	>10.5–14.0	FFD34C
9	>14.0–18.0	FFB233
10	>18.0–22.5	FFA019
11	>22.5–27.5	FF8C00
12	>27.5–33.0	FF6600
13	>33.0–39.0	FF3300
14	>39.0–45.5	FF0C00
15	>45.5–52.5	FF0000
16	>52.5–60.0	D80019
17	>60.0–68.0	A50033
18	>68.0–76.5	7F004C
19	>76.5–85.5	590066
20	>85.5–95.0	330066

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(3) Emphasis is put on geographical variation, and magnitude of mortality appears unimportant in comparison. This arises from the fact that all cancer sites and both sexes are mapped on to the same colour scheme. The fact that in the percentile presentation red colours in brain tumours or leukaemia denote much lower rates than green colours in lung cancer among males perishes in a firework of colour. This addresses the question of the main public health message to be transported by a cancer atlas.

(4) Red colours, e.g. in a lung cancer map, suggest the need of public health activities; green colours do not, or suggest even satisfactory conditions. This is clearly an incorrect public health message, especially in the lung cancer example.

Cancer atlases cannot be designed purely for experts who are well acquainted with their use. Due to a remarkable increase in public awareness of environmental and health problems, they have attracted public attention and offer the chance to emphasise relevant public health messages. However, it is essential that misleading perceptions be avoided. Politicians and persons responsible for research policy are not independent of public opinion. Thus, public discussion on cancer atlases may have consequences on decisions made about future foci of environment and health research.

If it is true that relative scaling is one reason for difficulties in comparability and interpretation of cancer maps, efforts should be undertaken to find alternatives. In the present paper, the use

Table 2. Colour levels used by the different cancer sites, number of different colour levels and standardised mortality rates for the total FRG

Cancer site	Sex	Colour level																			Mean ASR†	Number of colours*
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19		
Oesophagus	M	*		*	*	*	*	*													3.8	6
Oesophagus	F	*	*	*	*																0.7	4
Stomach	M									*	*	*	*	*	*	*					23.3	7
Stomach	F						*	*	*	*	*	*									12.0	6
Colon	M							*	*	*	*										13.6	4
Colon	F						*	*	*	*											11.9	4
Rectum	M					*	*	*	*	*	*										9.3	6
Rectum	F				*	*	*	*													5.6	4
Liver	M		*	*	*	*	*														2.4	5
Liver	F	*	*	*	*	*															1.3	5
Gallbladder	M	*	*	*	*	*	*	*													2.7	7
Gallbladder	F			*	*	*	*														4.9	5
Pancreas	M					*	*	*	*	*											7.5	5
Pancreas	F				*	*	*	*													4.7	4
Larynx	M	*	*	*	*	*	*														2.5	6
Larynx	F	*	*	*																	0.2	3
Lung	M											*	*	*	*	*	*	*	*	*	50.2	9
Lung	F			*	*	*	*	*													5.5	5
Bone	M	*	*	*	*	*															1.1	5
Bone	F	*	*	*	*																0.6	4
Melanoma	M	*	*	*	*	*	*	*													1.6	7
Melanoma	F	*	*	*	*	*															1.1	5
Breast	F								*	*	*	*	*								20.8	5
Cervix uteri	F			*	*	*	*	*													4.7	5
Corpus uteri	F			*	*	*	*														3.5	4
Ovary	F					*	*	*	*	*											8.1	5
Prostate	M						*	*	*	*	*	*									15.6	6
Testis	M	*	*	*	*	*															0.9	5
Urinary bladder	M			*	*	*	*	*	*												7.2	6
Urinary bladder	F	*	*	*	*	*															1.7	5
Kidney	M				*	*	*	*													5.4	4
Kidney	F		*	*	*	*	*														2.5	5
Brain	M	*	*	*	*	*															1.7	5
Brain	F	*	*	*	*	*	*														1.1	6
Thyroid	M	*	*	*	*	*															0.6	5
Thyroid	F	*	*	*	*	*															0.9	5
Hodgkin's disease	M	*	*	*	*	*															1.5	5
Hodgkin's disease	F	*	*	*	*																0.9	4
Lymphoma	M	*	*	*	*	*	*														2.2	6
Lymphoma	F	*	*	*	*	*															1.3	5
Leukaemias	M				*	*	*	*	*												6.4	5
Leukaemias	F			*	*	*	*	*													4.3	5

* Denotes each colour level which occurs in any of the 328 regions of the Federal Republic of Germany. † Mean ASR represents the national, overall level for each cancer site.

of absolute scaling is proposed, and it is outlined that some of the problems addressed above might be overcome by it. Absolute scaling is a well-known method of presentation in geographical atlases: the colour scale has the same meaning all over the atlas. Green coloured landscapes, e.g. in Poland indicate the same altitude as green coloured areas in the U.S.A., and red colours occur mainly among the highest mountains of Himalaya or the Rocky Mountains and never in the Netherlands. In contrast, convenient cancer atlas design would colour the highest elevation of the Netherlands (322 m) red, like Mount Everest. Technically, absolute scaling requires a direct transformation of mortality rates into a reasonable number of colours which governs all maps for all sites and both sexes.

In the following, the procedure is outlined and analysed. Readers are invited to send comments and suggestions to the author in order to promote the decision as to whether it is useful to proceed in this way and to elaborate on this method for future cancer atlases on the national level as well as on the supranational level.

MATERIAL AND METHODS

Data material

The investigation is carried out on the basis of the mortality data of the official mortality statistics of the Federal Republic of Germany (FRG) for the years 1976–1980. These are the same data as used in the German Cancer Atlas [9]. As in the cancer atlas, 24 cancer sites are included. Thus, the present results are comparable to the results already published in the atlas.

Methods

As in the cancer atlas, for each cancer site the regional mortality rates in the 328 counties are calculated as age-standardised rates (ASR) with the world population as standard. In contrast to the published atlas, the mapping from these rates to a colour scheme has been carried out by a mathematical function namely

$$c = I(2 \times \sqrt{\text{ASR}}),$$

where I denotes the next integer to the result of twice the root and c denotes the colour level. Thus, all cancer mortality rates of the 24 cancer sites are mapped to a scale from 1 to 19 (see Table 1). To each integer value, a colour is assigned. The colour scale starts at white (1) and shifts from yellow (2–6) and orange (7–12) to reddish (13–18) and blackish-red (19–20) colours. The colour change from one level to the next has been determined in such a way that also the darkness increases continuously. Thus, the maps can also be printed in black and white. This is the reason why the scale starts at white and not at any colour, e.g. green, as traditionally done, because any colour would increase darkness again in the direction towards lower rates. The colours are defined by red/green/blue codes (RGB codes) which are included in Table 1.

Notice that the relative length l of each interval of mortality rates, taken as a fraction of the respective midpoint m, can easily be obtained by

$$l = \frac{2}{c-1} \times m .$$

For example, the third interval (0.5–1.5) has the length $2/(3\text{–}1) \times 1.0 = 1.0$, or, taken as a percentage, 100% of the midpoint, whereas the 11th interval (22.5–27.5) has the length $2/(11\text{–}1) \times 25.0 = 5.0$, or 20% of the midpoint. Thus, variations of rates must be relatively large for low rates to cross boundaries to neighbouring colour levels than for higher rates. From a practical point of view, this is a desirable property of the transformation function: our experience from the German Cancer Atlas has been that considerably high relative variations of low rates depend frequently upon plus or minus one cancer case per region. Thus, they are less reliable than higher rates in the same region which are based on a larger number of observed cases. From a theoretical point of view, this behaviour of the transformation function just reflects the property of the standard error of the ASR which is also a square root transformation of the involved rate [22].

The calculation of the maps has been carried out using the SAS procedure GMAP [23] version 6.07 which provides postscript files with colour information. The files have been stored in the public domain of a computer of the German Cancer Research Center and can be received from there by data networks according to details given in the Appendix. Thus, the reader can print out the maps if he has the appropriate devices at hand.

RESULTS

Firstly, we have examined the number of colours being used in each cancer map, and which colour levels are involved (Table 2). The table demonstrates that only lung cancer among males covers the highest levels, and only a few further sites (stomach, breast and prostate) use the medium levels. The majority of maps are located at the lower levels. This corresponds well to the rank order of the overall rates of the different sites which can be seen, e.g. at a bar chart in the German atlas [9], p. 21.

For clarity, Figure 1 gives a graphical presentation of the number of cancer maps in dependence upon the number of involved colours. It shows that nearly half of the maps (20) use five colour levels. For one map (larynx among females) only three colours occur (laryngeal cancer among women is very rare in Germany [9]). Nine colour levels are involved in one map, namely lung cancer among males.

Five colours per map were also applied in the published German Cancer Atlas on the basis of a partition into quintiles (20% of all regions per colour level). In the Polish atlas [14] five colour levels were also applied, however, according to the partition scheme 10%, 20%, 40%, 20%, 10%. For the present colour scheme, Figure 2 presents a series of histograms showing

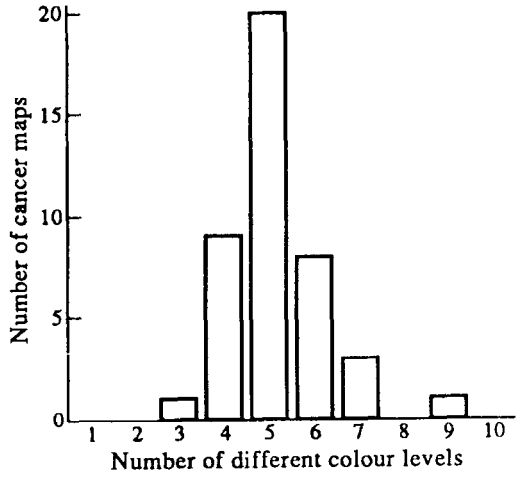

Figure 1. Number of different cancer maps by number of colour levels used within each map.

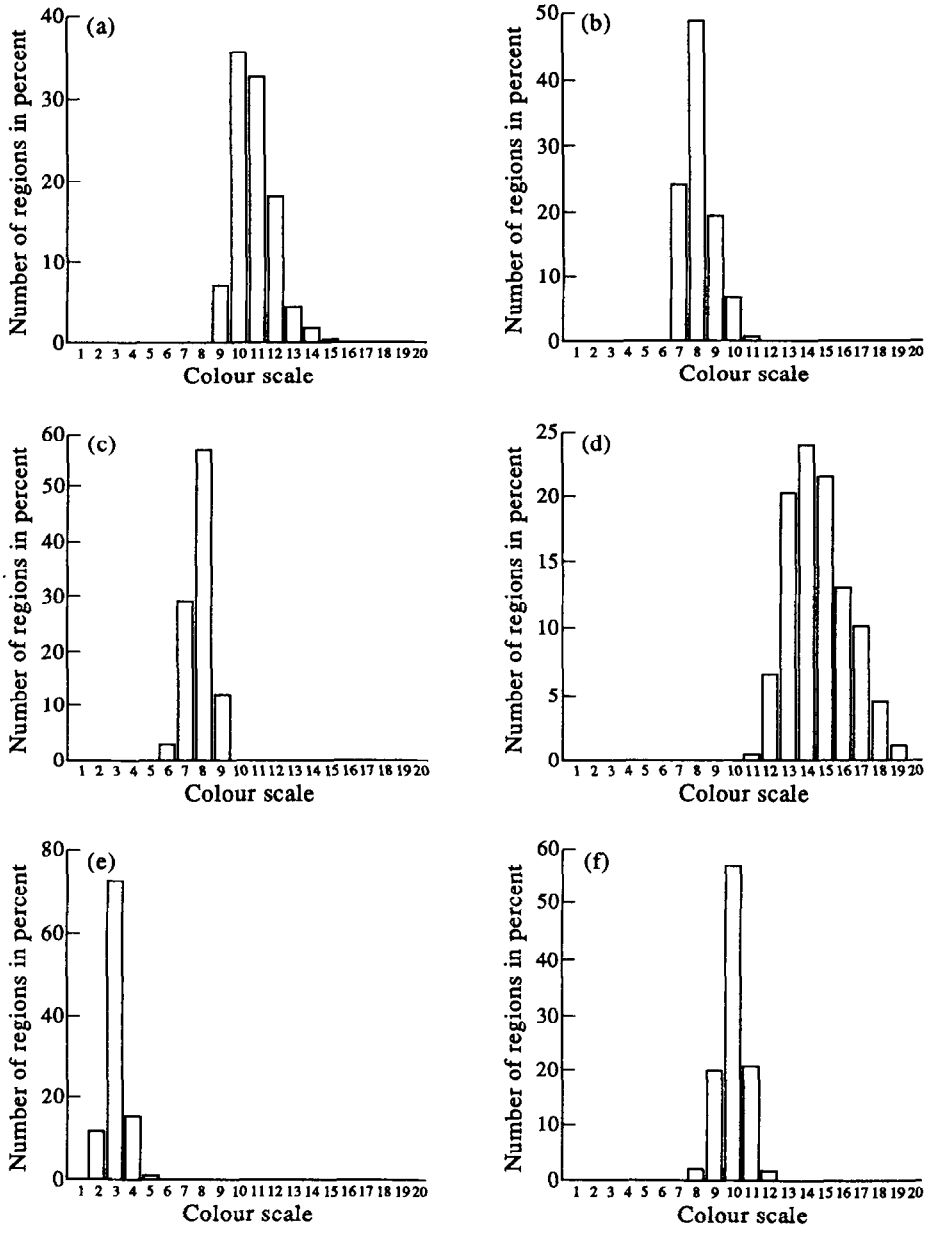

Figure 2. Frequency of colour levels within a map for different cancer sites: (a) stomach (males); (b) stomach (females); (c) colon (females); (d) lung (males); (e) melanoma (females); (f) breast (females).

the distribution of regions to the different colour levels in percent. It indicates that the maps are much more centralised around the mean than by the conventional methods. For most of the maps, more than 50% of the regions fall into the medium colour level. The extreme is melanoma among women with more than 70% in the medium level (Figure 2e). The most partitioned site is lung cancer among males with nine colour levels and the maximal filling of the medium levels is below 25% (Figure 2d).

On the other hand, the figures show that partitioning based on the present mathematical transformation is able to reflect to some extent differences in variability of rates between different cancer sites in contrast to the conventional methods of presentation. For example, the rates of stomach cancer among males (Figure 2a) are clearly distributed over a wider range than they are among females (Figure 2b). The mortality rate for colon cancer among females in the total FRG is approximately the same as for stomach cancer among females (see Table 2); the comparison between Figure 2b and Figure 2c, however, demonstrates that variability of rates between the regions is lower in colon cancer than in stomach cancer. Analogously, the map for melanoma among women (Figure 2e) indicates a low regional variation.

Figure 3(a–d) shows the colour maps for stomach and lung cancer for both sexes. The figure confirms that the present method puts primary emphasis on the overall level of rates and secondary emphasis on regional differences. By far the highest rates occur for lung cancer among men. Thus, the overall impression of this map (Figure 3c) is essentially red. Blackish red indicates especially high rates in the western Rhineland, while light red in the south of the FRG reflects somewhat lower rates of lung cancer. The black and white print of the same map (Figure 4c) reproduces the essential information of the coloured map relatively closely. The dark grey tones correspond to the overall red of the coloured map. The blackish grey indicates the

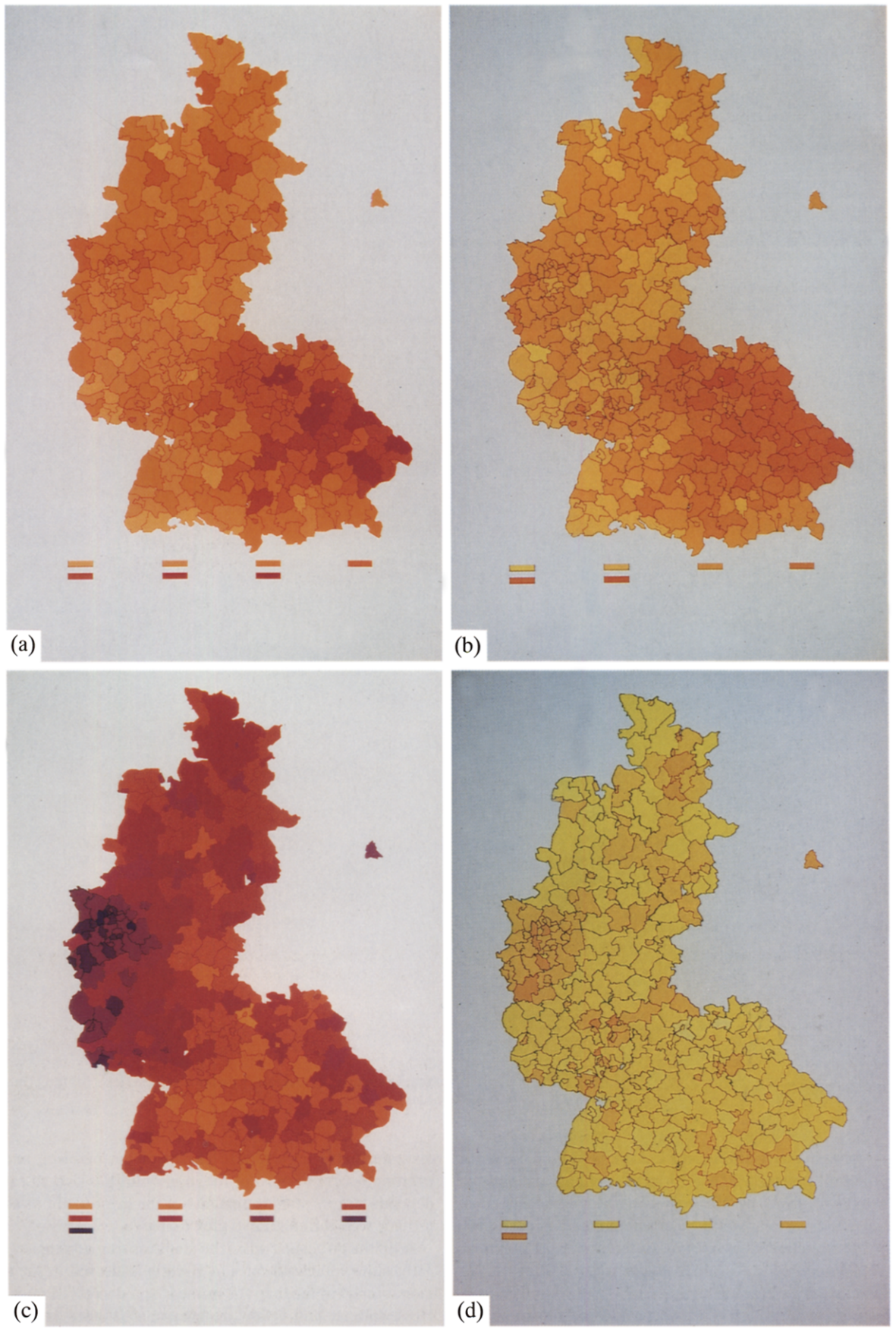

Figure 3. Colour maps for different cancer sites: (a) stomach (males); (b) stomach (females); (c) lung (males); (d) lung (females).

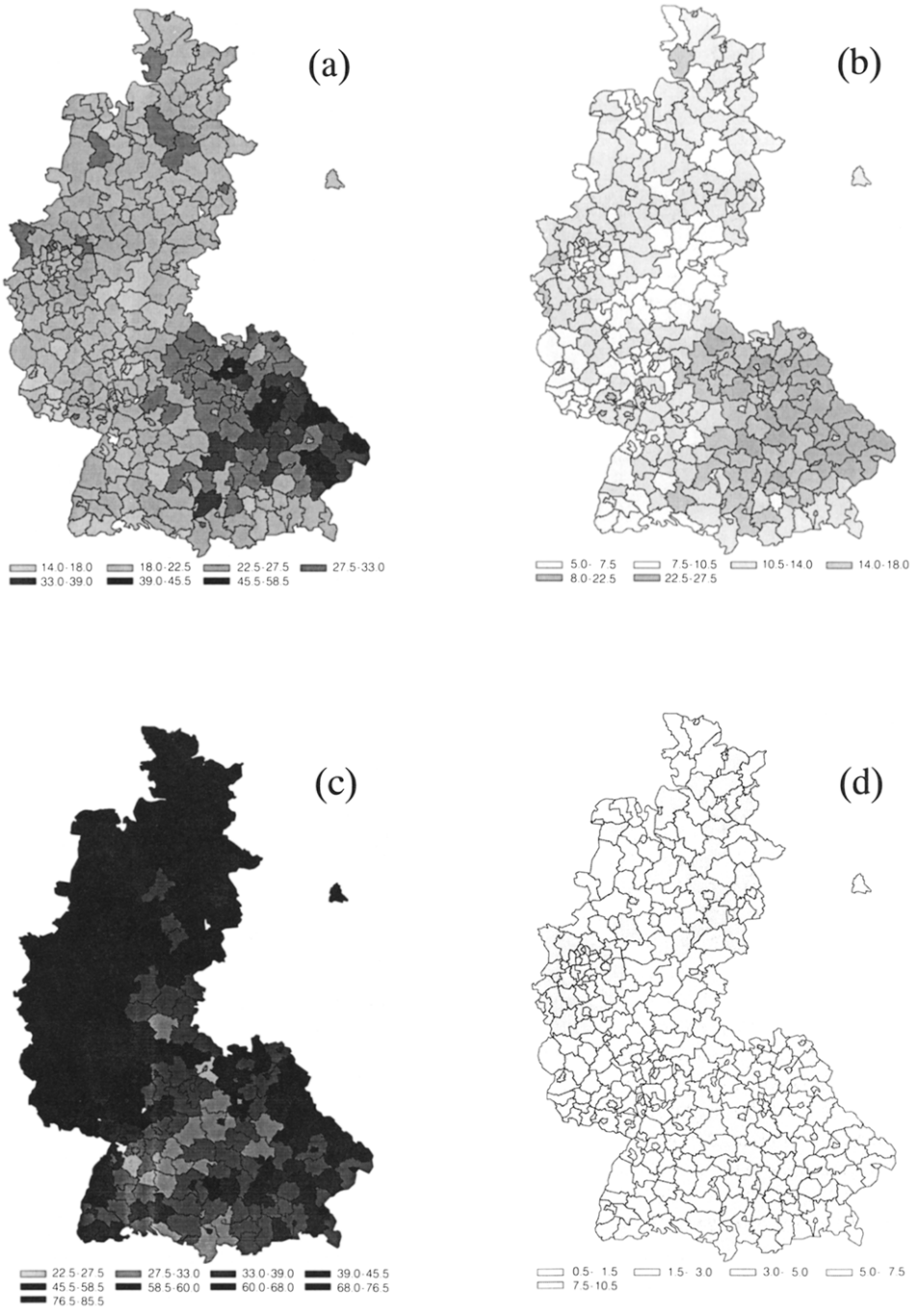

Figure 4. Black and white representation of maps for different cancer sites: (a) stomach (males); (b) stomach (females); (c) lung (males); (d) lung (females).

high rates in the western Rhineland and the light grey the lower rates in the south of the FRG. Both presentations fit closely to the information given by the maps in the published atlas. Comparison with the map of lung cancer among females (Figure 3d) demonstrates clearly the relevant difference in information: the overall yellow indicates much lower rates of lung cancer among women. The second message of the coloured map is similar to men, higher rates in the western Rhineland and lower rates in the south. This information has been blurred by the black and white print (Figure 4d) which does not yield any clear information within the map. The reason is that the printer translates the involved colours only in two or three hardly distinguishable grey tones. This problem of black and white printing occurs in most of the maps with low overall rates, but depends largely upon the quality of the printer and its ability to provide well-differentiated grey tones.

As in the published atlas, the maps for stomach cancer (Figure 3a,b) show increased rates in Bavaria (light red in the map for men, orange in the map for women) and decreased rates, e.g. in Hesse (orange and yellow, respectively). Figure 4a and b show that for these maps efficient black and white prints can be reproduced.

The overall colour levels of all four maps fit well into the rank order of the mortality rates: stomach cancer has lower rates for

both sexes (with men higher than women) than lung cancer in men and higher rates than lung cancer in women. The order of grey tones in Figure 4 reproduces this accurately.

A general result is that reading of the main messages of the maps, including the geographical variation within the individual maps, is facilitated by the fact that colours within each map are much closer together by this kind of presentation than within the red/green scheme of the previously published atlas. One reason for this effect is that the red/green scheme does not follow the logical rank order of darkness: green for low rates has a comparable darkness to red for high rates, while yellow for medium rates has a much lower darkness and thus disturbs the desirable order.

DISCUSSION

Use of absolute scaling appears beneficial for various reasons: (1) if there is agreement between different countries on a common colour scale, cancer maps are directly comparable across boundaries. (2) Unreliable data in some regions do not influence the total texture of maps; if deviations from reasonable expected values occur for some regions, it is only a matter of commentary. (3) Magnitude of mortality appears at equal priority as geographical variation: for example, lung cancer among males stands out, and within the map some regions with especially high rates stand out. The relatively low levels of lung cancer among females avoid predominant focus of perception on geographical variation. Differences in levels of mortality between cancer sites are clearly visible and may help to introduce this aspect of cancer landscape into public discussion. (4) The colour scheme does not suggest contrasting in 'good' (green) and 'bad' (red), which is a rather misleading message in most cases from a public health point of view. (5) In the usual presentation, small differences in rates between regions could cause ranking in different percentiles, the relevance of which has frequently been overestimated, especially in public discussion. In the 19-colour scheme, this effect may also occur, but its interpretation is mitigated: small differences of rates result in small differences of colours. (6) The facilities of colours are fully exhausted; the three or five levels of the traditional maps can actually also be printed in black and white instead of expensive coloured books (see e.g. the supplementary maps in the Polish atlas [14]). (7) The root transformation attaches less importance to the relatively large variations of low rates by plus or minus one cancer case than to those of higher rates on the basis of numerous cases. (8) Geographical variations are only emphasised if they exist; the usual cancer maps emphasise them by the method of presentation even if they do not exist.

The following disadvantages have to be taken into consideration: (1) neighbouring colours might be hard to distinguish, especially if regions to be identified are small. (2) Geographical variations might be inadequately disclosed due to the fact that frequently 50% and more of the regions fall into the same medium colour level (Figure 2). (3) The procedure might accentuate accidental outliers which are covered in a percentile presentation.

As previously emphasised, this paper intends to bring forward this alternative to classical cancer mapping techniques for discussion. Clearly, this method does not yet have its final shape and various trials with different datasets are required to examine its usefulness. Combinations of methods are conceivable, e.g. additional presentations by classical methods in black and white. Completely left out of the present discussion are valuable advances with a smoothing procedure [8] which appears not to be in conflict with the present proposal though it is so far based on a relative scale. Because it is, however, independent of the chosen scaling mechanism it might also be able to be combined with the present mechanism.

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APPENDIX

The data resulting from the MAP procedure of SAS version 6.07 are postscript files and can be printed by a postscript film plotter, e.g. AGFA matrixpcr. Alternatively, prints are possible with each postscript printer which then transforms the colours to different grey levels.

The files are stored in the public domain of a computer of the German Cancer Research Center (dkfz). They can be received over a network and the file transfer program (ftp). The internet address is ftp.dkfz-heidelberg.de, the user-identification is anonymous, the password is arbitrary and the name of the directory is pub/atlas.

The names of the maps are constructed according to the following rule: it begins with an m, continues with the three-digit ICD-code and ends with an m for male or f for female. The filetype is generally posts (for postscript). Examples: m162m.posts is the postscript file of the lung cancer (ICD 162) map for males, m174f.posts is the file of the breast cancer (ICD 174) map for females.

The maps are only test versions. They do not include a complete legend. Rate levels and ranges of colours can be found in Tables 1 and 2 of this paper. There are four small regions with a 'blackout', where the maps remain uncoloured in all maps. This origins from a technical error in the boundary data and has not been corrected because this map of the old FRG will not be used in future atlas projects which will cover the unified Germany.

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Pharmacokinetics and Cancer Chemotherapy

P. Workman and M.A. Graham

As in all areas of medicine and, indeed, arguably more so than in most other therapeutic disciplines, pharmacokinetic studies are essential to the efficient, safe, state-of-the-art development of new anticancer drugs. Moreover, our emerging understanding of the relationships between pharmacokinetics (the quantitative study of the concentration–time profile of the drug in the body, incorporating absorption, distribution, metabolism and excretion) and pharmacodynamics (the quantitative study of the effects of the drug on the body, including both efficacy and toxicity) is encouraging a more systematic and rigorous analysis of the potential role of pharmacology in the day-to-day management of individual cancer patients. The latest issue of *Cancer Surveys* [1] provides an up-to-date, critical analysis of current developments in the pharmacokinetics of cancer drugs. The contents of the monograph cover three broad subject areas: (1) novel concepts in pharmacokinetics and metabolism in relation to drug development and therapy, including locoregional delivery, (2) pharmacokinetics of a range of drug classes and (3) selected techniques for analytical detection.

Surprisingly, it is 10 years since this specific topic was reviewed in equivalent detail in a dedicated monograph format [2]. During this time, the whole face of anticancer drug discovery and development has changed. Not only are we now dealing with highly innovative and distinct classes of molecules in terms of both mechanism of action and chemical structure—for example, recombinant therapeutic antibodies, cytokines, antisense oligonucleotides, therapeutic genes and signal transduction inhibitors—but we are also deploying an impressive array of new techniques and ideas.

Since the effects of a therapeutic entity in the body are generally a function of its concentration at the molecular site of action (usually a receptor), it now appears obvious to us that a description of the spatio-temporal behaviour of the drug will be helpful, if not essential, in understanding and predicting normal tissue toxicity and tumour response. Given the multiple factors which can cause drug concentrations to vary, even after a fixed dose, it is clearly much more meaningful to talk about drug exposures (usually expressed as the area under the drug concentration against time curve, or as time above a minimum effective level) rather than absolute dose. Ideally, this would be at the molecular locus of action or at least at the tissue level but, most commonly, drug concentrations must be measured in the plasma as a more readily accessible surrogate.

It seems extraordinary in the 1990s that many of our commonly used cancer drugs were introduced with little or no pharmacokinetic experimentation in the modern sense of the term. The crucial importance of pharmacokinetics in the evaluation and use of new therapeutic entities has now become widely accepted by the academic community, pharmaceutical companies and the regulatory authorities alike. The extent to which this thinking has advanced is illustrated by the timely and influential recommendations on opportunities for integration of pharmacokinetics and toxicokinetics in rational drug development, published recently by Peck and colleagues [3]. A central feature of these proposals is the advocacy of concentration–response models in place of the more common dose–response models. Although the extent to which these concepts should be embodied in mandatory requirements for drug registration, as opposed to undergoing detailed evaluation as investigational research tools, remains controversial in some quarters, the scientific good sense of these developing ideas and the growing

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