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Original Paper

Problems Related to the Coding of Multiple Primary Cancers

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There is growing interest in multiple primary cancers (MPs), but the lack of a universally agreed definition can both modify the results for one series and hamper comparisons among cancer registries. The aim of this study was to compare agreement on the coding of MPs between two cancer registries, the Danish Cancer Registry and the Tuscany Tumour Registry, that adhere to different rules for accepting MPs, and to study whether coding according to common international rules (IACR) would increase the comparability. Data on 200 patients recorded as having more than one cancer were extracted at random from the two registers. The agreement on MP status between coders, one from each registry, using local rules and definitions on MP, was good (kappa value, 0.70). Exclusion of 11 expected discordant cases increased the agreement (kappa = 0.86). The agreement reached with the use of the IACR rules was very high (kappa = 0.80). We conclude that registries should present data according to international rules, in particular for the study of MPs. Registries should at least clearly indicate deviations from the agreed international standards, in order to facilitate comparisons on incidences. **Copyright © 1996 Elsevier Science Ltd**

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INTRODUCTION

THE OCCURRENCE of multiple independent cancers (multiple primaries, MPs) in the same patient has been reported since the end of the last century. The combination of improved prognoses for several cancers and systematic cancer registration means that large cohorts of cancer patients can be observed for life and their risk of developing new malignancies can be estimated. Increased risks for developing a second primary cancer may be due to a number of factors, such as the first and second primary being associated with the same exposure, increased host susceptibility (e.g. immunodeficiency), increased medical surveillance, or a consequence of antineoplastic therapy. The identification of high-risk groups of cancer patients may change the treatment of primary cancers and result in intensified follow-up of patients at high risk of developing a new neoplasm. The main population-based studies on the incidence of MPs have been carried out by the cancer registries of Connecticut, U.S.A. and Denmark [1]. These have been followed and confirmed by other population-based cancer registries [2, 3].

MPs account for a relatively small proportion (5%) of the total cancer incidence. Interestingly, although differences in coding practices of, for example, multifocal cancers [4] may explain part of the observed differences [2, 5–7], the overall findings and patterns of risk are fairly similar, as exemplified by the occurrence of multiple breast cancers [8–14]. However, the comparability of data on MPs in different areas is made difficult by the lack of universal agreement on the definition of 'independent cancers' in the same patient. The most widely used definition of MPs is that proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) [15]; however, the definition has been modified over time [16], and revised rules were recently published [17, 18], as summarised in Table 1. The Danish Cancer Registry (DCR) and the Tuscany Tumour Registry (RTT) currently define MPs according to different rules, although both originate from the IACR recommendations.

The aim of this study of a series of MPs was to quantify the effects on incidence rates when coders follow their own registry rules for defining MPs and when they use the same rules. The sources of disagreement and the importance of the differences are discussed.

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Table 1. *IACR rules for defining multiple primary cancers (modified from IARC,* 1994)

1.	NO TIME FACTOR	
2.	PRIMARY, ORIGINATES IN SITE	
3.	ONE TUMOUR PER ORGAN (ICD-O SITE, 3 DIGIT) OR ORGAN PAIR *EXCEPT IF*:	
	3.1: SYSTEMIC/MULTICENTRIC (LYMPHOMAS, LEUKAEMIAS, KAPOSI'S)	
	3.2: DIFFERENT MORPHOLOGY—as indicated below (from Berg, 1994 modified)	
Group	Name	ICD-0 Codes
1	Epidermoid carcinomas	805–813
2	Adenocarcinomas	814, 816, 818–822, 825–850, 852–855, 857, 894
3	Other specific carcinomas	803–804, 815, 817, 823, 824, 851, 856, 858–867
4	Unspecified carcinomas	801–802
5	Sarcomas and other STT	868–871, 880–892, 899, 904, 912–913, 915–934, 937, 954–958
6	Other specified	872–879, 893, 895–898, 900–903, 905–911, 935–936, 938–953, 972–974 (976 for ICD-O-2 only)
7	Lymphomas	959–971 (975 for ICD-O-2 only)
8	Leukaemias	980–994
9	Kaposis's sarcoma	914
10	Unspecified	800 (999 for ICD-O-2 only)

STT, soft tissue tumours.

MATERIALS AND METHODS

The DCR is one of the oldest population-based cancer registries in the world, having been active since 1942. For this study, only cases who had a first primary cancer after 1978, when ICD-O coding was introduced, were included. The operation of the registry has been fully described elsewhere [19]. The RTT, one of the nine Italian population-based cancer registries, has been active since 1985 in the Province of Florence, central Italy. The ICD-O is used for coding. The Registry has been described elsewhere [20].

Rules for coding multiple primary cancers

The DCR defines and records MPs as tumours arising in the same patient in different organs, identified through the three-digit site code of the ICD-O-1 [21]. Cancers in paired organs, e.g. breasts, are counted only once, unless their morphology indicates otherwise. Since 1978, tumours that differ in morphology, even if they arise in the same organ, are considered to be MPs. Subsites of the colon and of the urinary system are also considered as different organs.

The RTT also defines MPs as tumours arising in the same subject in different organs according to the three-digit code for site of the ICD-O-1. The two breasts are considered different organs. In addition, separate tumours with different morphology (at least in the third digit of ICD-O morphological code) arising in the same organ are classified as MPs.

Although both the DCR and the RTT register carcinomas *in situ* of different organs and severe dysplasias of the cervix, these are not included in the incidence figures and were therefore not considered in the present study.

Methods

The level of agreement between the two registries was estimated on the coding of 200 patients 'presumably' affected by MPs, 100 of which were from the DCR and 100 from the RTT. The 200 patients were randomly extracted from among those recorded with more than one tumour, irrespective of whether it had been accepted as true MP or not. Only invasive malignant tumours counted in the incidence figures were considered. *In situ* tumours, tumours of doubtful behaviour and benign tumours of the central nervous system, although registered, were excluded from the study.

The original documents were reviewed, and all the relevant information was summarised in English. In particular, the month and year of diagnosis, the site, the morphology, the behaviour and the most valid basis for the diagnosis were reported for each tumour. The tumours were coded independently by one coder from each registry. For each patient, the number of independent cancers was attributed by the coder twice: once following the local registry rules and once according to the IACR rules as interpreted by the coder. For each cancer, the site (four digits), the morphology and the behaviour were coded according to the ICD-O-1. The agreement between the two coders was computed as the Cohen Kappa statistic, a measure of the probability of agreement, apart from random associations, for coding both according to the original registry rules and by the IACR rules [22]. A kappa value of 1 represents complete agreement, whereas 0 represents an agreement due completely to chance. The following system of grouping was used for summarising the results: kappa = <0.20, poor agreement; kappa = 0.21–0.40, slight agreement; kappa = 0.41–0.60, moderate agreement; kappa = 0.61–0.80, good agreement; and kappa = 0.81–1, very good agreement. The measure of agreement when the rules of each registry were used indicates the effect of different classifications, although discrepancies between coders may also affect the results. When the IACR rules were used, only the effect of differences between coders was measured.

RESULTS

The DCR coder coded 184 patients out of 200 as having more than one independent tumour, while 180 MPs were identified by the RTT coder, when each used the local rules (Table 2). The overall kappa value for the 200 patients was 0.70 (0.80 for patients with no tumour, 0.62 for patients with one tumour, 0.74 for those with two tumours, 0.77 for those with three tumours and 0.39 for those with four tumours).

Part of the disagreement on the number of MPs was to be expected *a priori*, on the basis of different rules of the two registries. For 8 patients, the DCR coded more tumours than the RTT because the DCR considers cancers at subsites of the colon and urinary system to be independent; similarly the RTT coded cancers of two breasts as independent tumours, whereas the DCR did not.

Table 2. Numbers of primary cancers for each patient out of a series of 200 cases as codified by DCR and RTT coders according to the original rules of the two registries. The kappa values are given in parentheses for each class of number of cancers per patient

RTT* No. of cancers/patient	DCR† No. of cancers/patient					
	0	1	2	3	4	Total
0	2 (0.8)	–	–	–	–	2
1	–	10 (0.6)	8	–	–	18
2	1	3	158 (0.7)	3	–	165
3	–	–	–	11 (0.8)	1	12
4	–	–	–	2	1 (0.4)	3
	3	13	166	16	2	200
	Overall kappa = 0.70					

*Tuscany Tumour Registry coder. †Danish Cancer Registry coder.

When these 11 expected discordant cases were excluded, the kappa for the remaining patients was 0.86. The residual difference is due to disagreement on 7 cases.

Three tumours with no histological confirmation were not accepted as MPs by the DCR coder. In two of these cases the RTT coder stated the need for further information. One neurofibromatosis of connective tissue was counted only by the DCR coder. One case of a squamous-cell carcinoma of the epiglottis and a squamous-cell carcinoma of the mesopharynx were counted as two MPs (sites 161.1 and 146.9) by the DCR coder and as only one cancer (146.9) by the RTT coder. A clinically malignant tumour of the lung following a lymphoepithelioma of the submaxillary glands was considered to be a metastasis by the RTT and was not counted. An adenocarcinoma of the sigmoid colon, followed after 11 years, by a diagnosis of a metastasis of an adenocarcinoma from an unknown site to the lung was counted as only one cancer at the RTT.

Overall, the DCR coder coded 402 cancers and the RTT coder 396 in the 200 patients. A comparison of the site coding by the two coders showed no differences in site definition (three digits), but there were 17 discordant codings for subsite (fourth digit), 11 of which were systematic.

Leukaemias (4 patients) are coded at the RTT as 1690, independently of the availability of histological confirmation, while at the DCR the code 1691 is used systematically. In 7 cases, the differences were due to use of the code 8 by the RTT, indicating that more than one subsite of the same site is involved, instead of the code for each subsite used by the DCR, where these are counted as independent events. There were nine discrepancies in the morphology code, of which four were due to different coding rules.

(i) malignant lymphoma (lymph node) = code 9590 (RTT) and code 9591 (DCR);
(ii) two papillary carcinomas (urinary bladder) = code 8130 (RTT) and code 8050 (DCR);
(iii) bilateral breast cancer (ductal and ductal tubular variety) = one code, 8500/3 (DCR), and two codes, 8211/3 and 8500/3 (RTT).

The other differences were probably due to misinterpretation of the available information by one of the two coders. No quality control procedures were used for these series, although they are routinely performed in the registries; some of the observed errors would probably have been detected in the running systems.

There were also some differences in the behaviour codes, mostly due to the use of the behaviour code 9 at the DCR when the coder is not sure whether a tumour is a primary or not. In such cases, more information is requested from the reporting bodies.

The results of the analysis for agreement between coders when using local rules is shown separately in Table 3 for the 100 patients selected at the DCR and the 100 selected at the RTT. In this analysis, the overall agreement was 0.72 for the Danish and 0.56 for the Italian subjects.

MPs are rare, and most cancer registries cannot individually

Table 3. Numbers of primary cancers for each patient out of a series of 200 cases as codified by DCR and RTT coders according to the original rules of the two registries for the Danish (a) and Italian (b) patients. The kappa values are given in parentheses for each class of number of cancers per patient

a. Danish patients

RTT* No. of cancers/patient	DCR† No. of cancers/patient					
	0	1	2	3	4	Total
0	2 (0.8)	–	–	–	–	2
1	–	10 (0.6)	7	–	–	17
2	1	2	66 (0.7)	1	–	70
3	–	–	–	8 (0.8)	–	8
4	–	–	–	2	1 (0.4)	3
	3	12	73	11	1	100
	Overall kappa = 0.72					

b. Italian patients

RTT* No. of cancers/patient	DCR† No. of cancers/patient					
	0	1	2	3	4	Total
0	–	–	–	–	–	0
1	–	– (0.0)	1	–	–	1
2	–	1	92 (0.6)	2	–	95
3	–	–	–	3 (0.7)	1	4
4	–	–	–	–	– (0.4)	0
	0	1	93	5	1	100
	Overall kappa = 0.56					

*Tuscany Tumour Registry coder. †Danish Cancer Registry coder.

provide reliable results for MPs. An analysis was therefore carried out to evaluate the possibility of combining a series of MPs from different cancer registries, coded by the same rules, with the aim of improving the power of such studies. This is possible only if good intercoder agreement is achieved. The entire case series was thus coded by the two coders according to the last version of the IACR rules. The agreement was evaluated by analysing the reproducibility of the number of cancers assigned to each patient according to this classification. The agreement reached was good, with a kappa value of 0.80 (0.0 for patients with no tumour, 0.76 for patients with one tumour, 0.83 for those with two tumours, 0.95 for those with three tumours and 1 for those with four tumours) (Table 4).

DISCUSSION

In the sixth volume of *Cancer Incidence in Five Continents* [23], which gives incidence data from 136 cancer registries, only 41.9% of the contributors stated that they adhered strictly to the IACR rules on MPs, while 31.6% used rules that differ to some extent from those of the IACR, and 19.9% used other definitions (for 6.6% of the registries, no information was available).

The IACR rules have a topographical basis, and different organs are defined with different three-digit codes. Organs are not distinguished on the basis of the existence of anatomical walls or of histological differences. Therefore, organs with the same tissue may have difference codes, e.g. colon (153) and rectum (154); in contrast, the same three-digit code may be used for different organs, e.g. anus and rectum (154). According to the same rules, two cancers within the same organ are classified as separate when they are different in morphology, grouped as defined by Berg [18] (Table 1). The IACR scheme does not satisfy the needs of all cancer registries [24], and other classifications, based on histomorphological or pathological rules, are sometimes adopted [25]. Such diversity between registries will strongly affect the comparability of data in international comparisons if not accounted for and may hamper the development of multicentre studies on MPs.

When the case series were coded according to the rules of each registry, 182 patients out of 200 were classified in the same way with respect to MPs status. This result confirms that use of different definitions can significantly modify the number of cancers attributed to each patient (9.0% of difference in attributions). However, the overall agreement between the two coders was quite good (kappa = 0.70). Some of the disagreement may be related to a possible 'coder effect', but most of the disagreement was strictly dependent on systematic differences (e.g. subsites of the colon and of the urinary system were considered independent by the DCR coder, and the two female breasts were considered independent organs by the RTT coder). After allowance for the expected differences, the agreement increased to 0.86.

When the subjects registered by the RTT and DCR were analysed separately, a low kappa value was found for the Italian patients (kappa = 0.56), but the agreement (not chance-adjusted) was very high (95%). This may represent one of the 'paradoxes' that are well documented in relation to kappa interpretation [26, 27] and are related to a decrease in the kappa value when the agreement expected by chance is, as in this case, particularly high (89%) [28], because of the small dispersion of the cases in different classes.

We also evaluated the comparability of the specific codes for each patient, as each coder coded the site, the subsite, the morphology and the behaviour of a mean of 399 cancers. All of the differences with regard to site were restricted to the fourth digit (subsite) and, again, were often systematic.

Most of the morphological disagreements were of minor importance, and none were likely to influence significantly a comparative study of incidence. The coders had only summarised information and could not review the original documents or obtain additional information. They may also have had different degrees of confidence in their own and the other's data. Although the general quality parameters were better for the Danish cases than for the Italian ones (e.g. percentage of histological verification: 96.5% in the Danish series, 90% in the Italian one), both coders identified the need for further information on the series from the other registry (22% of the Italian series for the DCR coder and 15% of the Danish series for the RTT coder).

When the IACR definition was used by both coders, good agreement was registered. This result is encouraging from the point of view of conducting collaborative studies among different registries on MPs and of comparing results for different areas. The number of discordant cases might be reduced even further with use of the international classification, since some of the differences were also due to unfamiliarity with this classification.

The case series studied could be used as a standard for extending the comparison to different classifications and coders in other registries interested in research into MPs. Cancer registries should be urged to publish data on MPs coded in accordance with the proposed IACR rules, either alone or as a supplement to local rules, with the objective of comparison and joint analysis. As a minimum, cancer registries should publicise their rules and their definitions of MPs and any deviations from the agreed, recommended IACR rules.

Table 4. Numbers of primary cancers for each patient out of a series of 200 cases as codified by DCR and RTT coders according to the IARC rules. The kappa values are given in parentheses for each class of number of cancers per patient

RTT* No. of cancers/patient	DCR† No. of cancers/patient					
	0	1	2	3	4	Total
0	– (0.0)	–	–	–	–	0
1	2	18 (0.8)	–	–	–	20
2	1	8	160 (0.8)	–	–	169
3	–	–	1	9 (0.9)	–	10
4	–	–	–	–	1 (1)	1
	3	26	161	9	1	200
	Overall kappa = 0.80					

*Tuscany Tumour Registry coder. †Danish Cancer Registry coder.

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