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Original Paper

Multiple Primary Cancers and Estimation of the Incidence Rates and Trends

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The use of different registration rules from one registry to another, both generally and also for paired organs, leads to variations in the proportion of multiple primary cancers: in men, from 0.4 to 4.9% for the colon, 0.1 to 2.7% for the lung, and 4.1 to 8.6% for the mouth and pharynx. Subjective factors, often impossible to verify, contribute to these variations. The impact on the estimation of incidence rates and trends is not negligible for cancers of the mouth and the pharynx and for all the cancers taken together. The trend towards an increase of cancers of the mouth and pharynx in the Bas-Rhin disappeared when the incidence was expressed taking only the first cancer (*incidence by individual*) into consideration, and the differences in incidence between the Calvados and the Bas-Rhin registries for the same site also disappeared. In the absence of harmonisation of the rules and methods followed for registration, *incidence by individual* is the only approach which makes it possible to compare incidence rates and trends between registries. Copyright © 1996 Elsevier Science Ltd

Key words: incidence rates, trends, multiple primary cancers, registration, coding rules, harmonisation, comparisons between registries

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INTRODUCTION

INTEREST in multiple primary cancers is nothing new. In 1889 Billroth, quoted by Boice and associates [1], reported for the first time the existence of two successive malignant tumours in the same individual. Observations of this type were at the time considered isolated and exceptional cases. However, as a result of longevity and of a parallel increase in survival after specific treatment for a cancerous disease, the number of multiple primary cancers has continued to grow.

Many authors and in particular the cancer registries, when

faced with the problems of recording multiple primary cancers, have established rules to define the circumstances in which an individual is considered to be suffering from one or more tumours, but these rules differ from registry to registry. Thus, it can be readily understood that if these data are used as they stand for calculating the incidence of cancers, the estimations will not be comparable among the different registries. Similarly, chronological trends are influenced by the rules used.

We have undertaken this study in order to assess the importance of registering multiple primary cancers and their impact on the estimation of the incidence and chronological trends of cancers.

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Many studies on the chronological trends of cancers indicate a significant increase of cancers over the years. This increase is quite considerable for breast cancer, cancers of the upper aerodigestive tract, of the mouth and pharynx, of the skin, colon and rectum [2]. Since, according to convention, the cancer registries record the primary cancers and not the individuals suffering from them, one might wonder what the relative importance of multiple primary cancers in the calculation of the traditional rates of incidence (*incidence by case*) might be. In 1932, Warren and Gates [3] put forward a first definition of multiple primary cancers. In brief, they defined multiple primary cancers when, in an individual who has presented a cancer, one or more malignant lesions appear which are neither extensions, recurrences nor metastases of the first cancer. In the practice of the cancer registries, the definition of multiple primary cancer depends *inter alia* on the ICD-O (International Classification of Diseases for Oncology) site [4], on the time lag between two tumours and on the histological type. There are several recommendations for recording multiple primary cancers to which the registries can refer: the rules of the ICD-O [4], the IARC (International Agency for Research on Cancer) [5] system, the recommendations of the SEER programme (Surveillance, Epidemiology and End Results) [6], or even the new IARC/IACR (International Association of Cancer Registries) recommendations [7]. These rules differ considerably. They could explain in a fairly significant manner the difference in incidence between certain registries and the developmental trends for certain cancerous sites. The ICD-O defines the first three digits as representing the site and the fourth digit as representing the subsite. This means that an individual with several cancers of the colon is registered once according to the IARC system, which only records one single case per site as defined by the first three digits of the ICD-O. However, the SEER system records as many as eight different anatomical subsites, since this latter system records one case for each of the eight subsites established by the ICD-O. The same applies for skin cancer. In the IARC system, wherever the site, for the same histological type, at most a melanoma and a spinocellular epithelioma would be registered, whereas the SEER system records as many times as there are lesions on the different topographical subsites.

In the cases of paired organs such as breasts or lungs, certain registries record only one case and others two when both organs are affected. Some do not take into consideration synchronous but only asynchronous cancers. Furthermore, the definition of synchronous depends on the time which has elapsed between the two cancers; this time lag may be 2, 3, 6 months or 2 years, depending on the definitions used by the registries.

When one tries to assess the importance of the problem arising from the registration of the multiple primary cancers, using only the rules followed by each registry, one never achieves entirely satisfactory results. What happens is that, in addition to the very disparate rules applied in the registries, subjective factors linked to the interpretation of data, experience and practice, also come into play. In 1979, a study [8] showed that, among the registries of Romance language speaking countries, the percentage of multiple primary cancers varied between 0.4 and 4.4%.

MATERIALS AND METHODS

Various registries of France and Switzerland with at least 10 years experience participated in this study. Apart from the

registry of the Bas-Rhin, we were able to analyse the data of the registries of Basel, Calvados, Côte d'Or, Doubs, Geneva, Isère, and the canton of Vaud. The registry of Côte d'Or only concerns digestive tumours. For cancer sites with a good prognosis, the early years will tend to include second cancers not counted as multiple because they occurred in people who had their first cancers diagnosed before the registry began to operate. The numbers and the characteristics of each registry appear in Table 1.

To obtain a thorough knowledge of the scale of the phenomenon, we studied multiple primary cancers for all the cancerous sites taken together. Skin cancers other than melanoma were excluded (ICD-O = 173). Furthermore, we selected certain sites for which the comparative number of the multiple primary cancers seemed *a priori* high. For men, we selected first the sites of mouth, pharynx, larynx, oesophagus and the lung taken together, and then studied the sites of mouth and pharynx alone, and the lung alone, and finally the colon and rectum. For women, we restricted ourselves to breast cancers and the colorectal cancers. The lung and breast sites concern paired organs where the registration rules were not clear. The respiratory-digestive cancers were of the squamous type, with similar aetiopathogeny, and it was probably for these that the risks of coding errors were the highest. For each site or group of sites studied, we only considered the multiple primary cancers of the same site or group. We did not analyse secondary lesions of the other sites. The definition we decided upon of a multiple primary cancer was simple: a cancer registered for an individual who had previously presented a cancer at the same site and which had already been registered.

To make the incidences comparable and so avoid a bias, we applied, to all the registries, the same method of estimation of the populations. For France, we used exhaustive data from the censuses of 1975, 1982 and 1990, provided by the Institut National de la Statistique et des Études Économiques, and for Switzerland those of 1970, 1980 and 1990 from the Office Fédéral de la Statistique, Section de la Structure et des Ménages.

On the basis of the censuses, we used the "diagonal" methods of calculation which means following the generations over the years. This method of linear interpolation presupposed that the annual variation within each cohort remained constant between two censuses.

The age of a subject suffering from a cancer was that calculated at the moment of diagnosis whereas the age calculated in the population at large was that given on the first of January of that year. If we presume that the moments of diagnosis of cancers are uniformly spread throughout the year, we can then consider that, on average, the diagnosis is made halfway through the year. To have a more precise estimation of the population at risk, the numbers should be recalculated on 30 June of the year.

If a subject was likely to produce several primary cancers, he remained a subject at risk and was counted as part of the population at risk. When the incidence was calculated *by individual*, a subject suffering from cancer was no longer part of the population at risk for that site and therefore was not considered in the calculation of the person-years. In practice, an individual who had already had a cancer was either a prevalent case or deceased. If deceased, he had already been withdrawn from the population at risk; if prevalent for the given site, he was subtracted from it. We used the survival rates available in the Bas-Rhin and calculated for each site

Table 1. Distribution of subjects by registry and by site

	Basel canton	Bas-Rhin departement	Doubs departement	Calvados departement	Côte d'Or* departement	Isère departement	Genève canton	Vaud canton
<i>a. Characteristics of the registries</i>								
Population (in 1987)								
Men	205646	457587	239005	295716	238047	488679	173661	261251
Women	217786	480673	243260	315417	249849	501203	189722	283490
Beginning of study period	81	75	78	78	76	79	70	79
End of study period	91	87	90	87	90	89	91	88
<i>b. Number of multiple primary cancers throughout the whole period studied, by registry and by site</i>								
<i>Men</i>								
All cancers	753	1697	589	525		1071	1194	747
Mouth and pharynx	16	271	111	63		81	79	62
Lung	38	113	1	11		23	60	32
UADT and lung	94	888	316	282		344	326	259
Colon and rectum	73	66	6	20	52	38	41	33
<i>Women</i>								
All cancers	537	842	166	262		811	897	535
Breast	147	172	10	68		72	202	104
Colon and rectum	42	27	8	21	20	12	31	23
<i>c. Number of cancers throughout the whole period studied, by registry and by site</i>								
<i>Men</i>								
All cancers	10003	23594	10463	9313		16131	15686	11258
Mouth and pharynx	394	3165	1293	1544		1661	1071	726
Lung	1998	4246	1839	1568		3068	3165	2301
UADT and lung	2719	9372	4021	4405		6019	5062	3655
Colon and rectum	1494	3110	1392	957	1872	2200	1907	1411
<i>Women</i>								
All cancers	9622	18244	7494	6795		13543	15391	10198
Breast	2982	5136	2362	2299		4818	4850	3095
Colon and rectum	1323	2569	1209	888	1576	1899	2013	1440

*Only concerns digestive cancers.

UADT, upper aerodigestive tract.

the prevalent cases of cancers. On the basis of the survival calculated in the Bas-Rhin, we estimated the population at risk for the other registries when calculating the *incidence by individual*.

We counted the number of multiple primary cancers for each registry and calculated, in addition to the *incidences by case*, the *incidences by individual* obtained by considering the first cancer of the site or groups of sites as described above. We compared the incidences and the chronological trends resulting from these two approaches.

The incidences were standardised for the European population. The proportion of multiple primary cancers for a given year represents the percentage of multiple primary cancers amongst the cases of cancers registered in the course of the same year for the same site. The mean proportion represents the proportion of second tumours out of the total number of tumours counted in the course of this period. The relative difference is defined as the relative decrease of the *incidence by individual* as compared with the *incidence by case*. This difference may be negative. The calculation of *incidence by individual* was done by subtracting from the denominator all the prevalent cases. So, the number of person-years used for the calculation of the incidence by individual was lower or equal to the number of person-years used for the calculation of the *incidence by case*. For instance, if, for a given year, the proportion of multiple primary cancers was equal to zero, then the *inci-*

dence by individual becomes greater than the *incidence by case*. The relative difference is in such a case negative.

RESULTS

All cancers

The proportion of multiple primary cancers in men was approximately identical in the registries of Geneva, the Bas-Rhin, Basel, Vaud and the Isère (6.6–7.6%; Table 2). The registries of the Doubs and the Calvados had lower but similar values (5.6%). After 10 years of registration the proportions fluctuated between 6.1 and 10.5% and seemed to stabilise in time around these percentages (Table 3). The estimation of the incidence calculated *by individual* was smaller than the incidence presented *by case* but this moderate change did not eliminate the difference in incidence which exists between the registries. (Table 4).

Whereas for the men's cancers, we found a certain homogeneity, the proportion of multiple primary cancers in women was very different from one registry to the next. This proportion varied between 2.2% in the Doubs to 6% in the Isère, while the three Swiss registries had similar figures (Table 2). For the women, after 10 years of registration, we still found the same variation (Table 2). The *incidence by individual* was decreased compared with the *incidence by case*, except for the Doubs where it remained almost unchanged (Table 4), but this decrease was slight (3–4.7%).

Table 2. Proportion* of multiple primary cancers by site and by registry

	Basel	Bas-Rhin	Doubs	Calvados	Côte d'or	Isère	Geneva	Vaud
Men								
All cancers	7.0	7.2	5.6	5.6		6.6	7.6	6.6
	<i>9.0</i>	<i>10.3</i>	<i>7.5</i>	<i>7.9</i>		<i>8.9</i>	<i>9.1</i>	<i>8.1</i>
Mouth and pharynx	4.1	8.6	8.6	4.1		4.9	7.4	8.5
	<i>7.2</i>	<i>14.8</i>	<i>9.3</i>	<i>6.0</i>		<i>6.2</i>	<i>9.4</i>	<i>10.7</i>
Lung	1.9	2.7	0.1	0.7		0.7	1.9	1.4
	<i>2.2</i>	<i>4.6</i>	<i>0.0</i>	<i>0.9</i>		<i>0.3</i>	<i>2.1</i>	<i>1.7</i>
UADT and lung	3.5	9.5	7.9	6.4		5.7	5.8	7.1
	<i>4.7</i>	<i>15.3</i>	<i>9.5</i>	<i>9.1</i>		<i>6.2</i>	<i>8.0</i>	<i>9.1</i>
Colon and rectum	4.9	2.1	0.4	2.1	2.8	1.7	2.1	2.3
	<i>3.0</i>	<i>4.4</i>	<i>0.7</i>	<i>3.3</i>	<i>3.1</i>	<i>2.4</i>	<i>2.6</i>	<i>3.1</i>
Women								
All cancers	5.6	4.6	2.2	3.9		6.0	5.8	5.2
	<i>8.3</i>	<i>6.4</i>	<i>3.2</i>	<i>4.7</i>		<i>8.4</i>	<i>7.1</i>	<i>6.7</i>
Breast	4.9	3.3	0.4	3.0		1.5	4.2	3.4
	<i>6.9</i>	<i>4.3</i>	<i>0.7</i>	<i>3.4</i>		<i>1.7</i>	<i>4.8</i>	<i>4.5</i>
Colon and rectum	3.1	1.1	0.7	2.4	1.3	0.6	1.5	1.6
	<i>3.1</i>	<i>1.9</i>	<i>1.1</i>	<i>1.0</i>	<i>0.3</i>	<i>0.8</i>	<i>1.9</i>	<i>1.3</i>

*Percentage of multiple primary cancers among the cancers for the same site.

For each site: the first line represents the average proportion over the whole period of registration; the second line (in italics) represents the proportion after 10 years of registration. UADT, upper aerodigestive tract.

Table 3. Proportion of multiple primary cancers and relative difference of the estimations of incidence depending on the time lag after the beginning of registration for all the sites* in men

Time after the beginning of registration§	1	3	5	10
Basel	3.1	5.7	6.5	10.2
	<i>3.2</i>	<i>3.9</i>	<i>4.7</i>	<i>7.2</i>
Bas-Rhin	1.2	4.3	6.4	10.5
	<i>0.8</i>	<i>2.5</i>	<i>4.1</i>	<i>7.6</i>
Doubs	2.1	4.3	4.6	7.4
	<i>1.6</i>	<i>2.6</i>	<i>2.3</i>	<i>4.4</i>
Calvados	2.6	5.0	5.6	8.5
	<i>2.3</i>	<i>3.4</i>	<i>3.6</i>	<i>4.4</i>
Isère	4.7	5.4	6.9	8.1
	<i>4.4</i>	<i>4.1</i>	<i>4.8</i>	<i>5.3</i>
Geneva	1.9	3.8	4.6	6.1
	<i>1.5</i>	<i>2.3</i>	<i>2.2</i>	<i>2.9</i>
Vaud	3.3	6.5	5.5	9.3
	<i>2.9</i>	<i>4.9</i>	<i>3.2</i>	<i>6.3</i>

For each site: the first line represents the proportion of multiple primary cancers†; the second line (in italics) represents the relative difference‡.

*Skin cancers other than melanoma are excluded (ICD-O = 173).

†Proportion of multiple primary cancers in a given year. ‡Relative difference = (incidence by case - incidence by individual) × 100/incidence by case. §In years.

Cancers of the mouth and pharynx

We observed the highest percentage of multiple primary cancers in the mouth and pharynx. Two groups of registries emerged from the average proportion of multiple primary cancers (Table 2). Basel, the Calvados and the Isère had a similar average whereas the four other registries had an average which was twice as high. After 10 years of registration, the percentages of multiple primary cancers were very heterogeneous among the registries (Table 2).

The incidences by case were very different from one registry to the next (Table 4). There was no progression of incidence over time for the Basel registry. As is shown by Figure 1, for this registry there is no difference between the incidence by case and the incidence by individual. For the Vaud registry, there was a slight upward trend, the two curves progressing in parallel and the difference between them negligible. For the Bas-Rhin registry, the two incidence curves separated over time, to such an extent that the increase of the incidence by case was not apparent when the incidence was presented by individual.

Lung cancers

The proportion of multiple primary lung cancers was generally low (Table 2). These percentages were variable both from one registry to the next and also within registries. Whereas the Bas-Rhin had the highest percentage (5.8% in 1987), the Doubs registry counted only one single case of multiple primary cancer in 10 years of existence. The registries of Geneva and of Vaud showed values which varied greatly over the years. Yet the averages of the three Swiss registries were similar. The proportion of multiple primary cancers had little influence on the incidence rate except in the Bas-Rhin in 1987 (Table 4).

Cancers of the upper respiratory-digestive tracts and of the lung

Amalgamating several sites, the proportion of multiple primary cancers became much more stable. In all the registries, a regular increase over the years was seen. However, the percentages remained very stable among the registries whether taken as a whole or after 10 years of registration (Table 2). The Bas-Rhin registry has a rate three times as high as the Basel registry. As for the cancers of the mouth and of the pharynx, the incidence calculated by individual no longer showed an increase in the Bas-Rhin. For the Doubs, the Calvados, the Isère, Geneva and Vaud, the values of the relative differences were comparable to the values of the

Table 4. Standardised incidences* (1985–1987)

	Basle	Bas-Rhin	Doubs	Calvados	Côte d'or	Isère	Geneva	Vaud
Men								
All cancers	483.3	545.5	422.3	425.7		376.7	498.4	412.5
	<i>456.2</i>	<i>508.8</i>	<i>406.0</i>	<i>406.0</i>		<i>358.9</i>	<i>469.6</i>	<i>393.0</i>
	5.6	6.7	3.9	4.6		4.7	5.8	4.7
Mouth and pharynx	15.3	78.3	51.1	68.6		39.4	35.2	29.2
	<i>14.8</i>	<i>65.5</i>	<i>47.8</i>	<i>64.4</i>		<i>37.0</i>	<i>32.2</i>	<i>26.0</i>
	3.3	16.3	6.5	6.1		6.1	8.5	11.0
Lung	88.1	98.0	77.3	69.0		72.5	92.4	83.8
	<i>86.4</i>	<i>94.0</i>	<i>77.5</i>	<i>68.5</i>		<i>72.0</i>	<i>90.8</i>	<i>83.1</i>
	1.9	4.1	-0.3	0.7		0.7	1.7	0.8
UADT and lung	117.5	218.8	165.6	190.0		142.5	152.2	134.1
	<i>113.1</i>	<i>185.4</i>	<i>152.6</i>	<i>175.6</i>		<i>134.0</i>	<i>142.1</i>	<i>123.4</i>
	3.7	15.3	7.9	7.6		6.0	6.6	8.0
Colon and rectum	66.2	70.9	55.7	46.8	61.3	55.2	64.0	47.5
	<i>62.8</i>	<i>68.1</i>	<i>55.9</i>	<i>45.8</i>	<i>60.0</i>	<i>54.3</i>	<i>62.3</i>	<i>46.4</i>
	5.1	3.9	-0.4	2.1	2.1	1.6	2.7	2.3
Women								
All cancers	311.8	311.6	236.5	233.4		244.5	331.0	290.0
	<i>302.3</i>	<i>301.0</i>	<i>237.3</i>	<i>227.5</i>		<i>236.6</i>	<i>318.2</i>	<i>279.1</i>
	3.0	3.4	-0.3	2.5		3.2	3.9	3.8
Breast	100.6	96.6	83.1	83.4		98.8	100.7	100.7
	<i>95.9</i>	<i>93.0</i>	<i>83.5</i>	<i>80.7</i>		<i>98.3</i>	<i>97.6</i>	<i>96.1</i>
	4.7	3.7	-0.5	3.2		0.5	3.1	4.6
Colon and rectum	38.4	41.8	38.0	27.5	30.9	29.6	39.1	36.2
	<i>37.4</i>	<i>41.0</i>	<i>37.6</i>	<i>26.9</i>	<i>30.8</i>	<i>29.4</i>	<i>38.8</i>	<i>35.6</i>
	2.4	1.8	1.0	2.2	0.3	0.6	0.8	1.7

For each site: the first line represents the *incidence by case*, the second line (in italics) represents the *incidence by individual*, the third line (bold) represents the relative difference. Relative difference = $(\text{incidence by case} - \text{incidence by individual}) \times 100 / \text{incidence by case}$.

*To the European population.

UADT, upper aerodigestive tract.

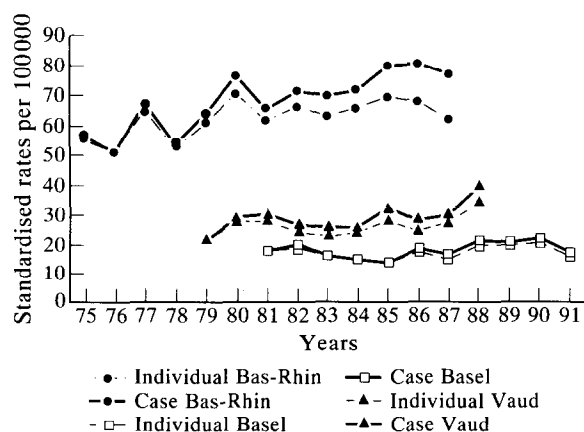


Figure 1. Incidences of cancers of the mouth and pharynx.

percentages of the multiple primary cancers, and were between 6 and 8%, but these multiple primary cancers did not change the trends.

Cancers of the colon and rectum

For the multiple primary cancers in men, four registries had identical average percentages (Table 2): the Bas-Rhin, the Calvados, Geneva and Vaud. The Basel registry had the highest average. The Doubs registry had zero values or values close to 0%. The incidences of colorectal cancers were hardly

decreased when the calculations were carried out *by individual* except for the Basel registry.

For women, the proportion of multiple primary cancers was significantly lower than for men. The Basel registry once again had the highest values. There was great variability within registries. Zero annual values were not rare for all registries, except for Basel. The influence upon the calculation of the incidence rates and on trends was negligible.

Breast cancers

The average proportion for multiple primary breast cancers was disparate for certain registries. The same applied after 10 years of registration (Table 2). The values were increasing in all registries with no stabilisation. The proportion of multiple primary cancers was increased for the registries of Basel and the Bas-Rhin. The Isère and the Doubs had very low if not zero figures which fluctuated. Basel had the highest percentage, followed by Vaud and the Bas-Rhin, which had values comparable over the period of the registries. The variability of the Geneva registry was great with values of 9% in 1981 and 3% in 1991.

DISCUSSION

Most of the cancer registries whose data appear in this paper state that they use the IARC rules for coding the multiple primary cancers. Could it be that differing application of these rules, particularly when the cancers have the same morphological type, as well as the explanations offered by the

IARC, might explain the differences in the proportions of multiple primary cancers in all the registries?

Even if it appears as though the registries applied the same rules, the analysis of the answers to a questionnaire addressed to each registry shows that while some of them use the first three digits for the registration of the cancers, others use the four digits of the ICD-O. By the same token, the coding of the multiple primary cancers affecting paired organs was not identical for all registries: some only register one cancer, others two for all paired organs or only for certain sites such as lungs or breasts. Our study shows too that the registration of multiple primary cancers of the mouth and pharynx raises certain problems: the ICD-O allocates nine sites to this tiny region of the organism which makes the coding difficult and complex. In addition, the subjectivity of the clinician and of the person carrying out the survey gives rise to yet another source of heterogeneity.

The registration of several cancers of the colon is a good illustration of the impact of the use of the third or fourth digit of the ICD-O on the frequency of the multiple primary cancers. Some registries record 1 case, no matter how many cancers of the colon there may be, and others 2 or 3 at most. The SEER programme [6] considers an anatomical region by subsite to be defined by the fourth ICD-O digit, whereas the rules of the IARC restrict registration to the first three digits of the ICD-O [5,7,10–12].

In our study, the proportion of colorectal multiple primary cancers in males was 10 times as high in the Basel registry as in that of the Doubs region. These values can be perfectly well explained by the rules applied: the Basel registry can record a multiple primary cancer for each of the colorectal sub-sites because it uses the four digits of the ICD-O, whereas the Doubs registry only records one case whatever the morphology or site (Table 5). The Côte d'Or registry records the multiple primary cancers of all the subsites, but uses the first case for the calculation of the incidence. When the registration of the multiple primary cancers only concerns the first case, the average proportions for men and women are, respectively, 2.8 and 1.3%. The data from this registry also make it possible to estimate the proportion of multiple primary cancers if it registered cancer by subsites: in this case, the proportion of men and women is, respectively, 5.9 and 3.9%. This example shows the disparity of results when the rules used are not the same. In the Connecticut registry, with which we compared our results, the proportion of multiple primary cancers is only

2.4%, whereas given the utilisation of the rules of the SEER programme, one might expect higher values. This may partly be explained by the time period covered by this work, for the SEER programme dates back to 1973. Thus, between 1935 and 1972, the rules probably did not take into consideration the eight sub-sites of the SEER programme [13]. In Denmark, the other registry with which we compared our results, the proportion is 0.7%, close to that calculated for the Doubs which had the lowest results in our study. It should be noted that the Danish registry only counts one cancer per site defined by the third digit [14].

IARC provides no precise rules for registering multiple primary cancers occurring in paired organs, but a group of proposals was provided after a consultation organised by the IARC in 1981. Our questionnaire sent to the registries participating in the study showed that each registry has established its own rules. This is explained by the fact that the registries do not find it satisfactory to deliberately exclude the existence of several primary cancers. In the SEER programme two cases are registered except for ovarian cancers.

There appear to be several methods of registering multiple primary cancers occurring in paired organs. When the two organs are affected, some registries record one case whatever the morphological type, others two cases, and some only register two cases if the morphology is different. Some, for example, agree to record two breast cancers but not two lung cancers.

Can the variations of the rules used explain the different percentages of multiple primary cancers for breast cancer? The proportions of the multiple primary breast cancers, after 10 years of registration, were 0.7% for Doubs, 4.3% for Bas-Rhin, and 6.9% for Basel. The Doubs registers one case whereas the Basel and the Bas-Rhin register two cases when both breasts are affected (Table 2). After 10 years of registration, the registries of Bas-Rhin, Calvados, Geneva and Vaud had identical proportions (Table 2), probably due to their application of the same rules.

The same difficulties apply to multiple primary lung cancers. The percentages observed after 10 years of registration were 0% for the Doubs, 2.2% for Basel and 4.6% for the Bas-Rhin (Table 2). These three registries apply the same rules as those they use for breast. This makes it possible to understand the results of the Doubs but not those of the Bas-Rhin registry, for which one might have expected lower percentages than those of Basel (Table 2). The registries of Denmark and Connecticut have very similar percentages of multiple primary lung cancers, similar to those found in the registries of Doubs, Isère and Calvados (Tables 2 and 6).

The ICD-O allocates nine distinct sites (ICD-O = 140–148) to the bucco-pharyngeal area, although this is a limited anatomical region for which the cancers which appear have the same aetiological factors. This probably explains the large proportion of multiple primary cancers, as seen in the majority of registries. In fact, for these sites, it is often difficult, particularly in the absence of surgery, to distinguish between an extension and a second cancer. This is the site where the proportion of primary multiple cancers is by the far the greatest. In our study we noted significant differences between the registries, despite very clear coding rules, which are identical in all the coding systems. After 10 years of registration, the proportion of multiple primary cancers varies from 6.0% for the Calvados to 14.8% for the Bas-Rhin. This example is striking since in these two regions, the incidence and the risk

Table 5. Rules used by the registries and methods for registering the breast lung and colon when the morphological types are same

	Rules	Breasts	Lungs	Colon	Time (months)*
Basel	ICD-O	2	>2	>3	2
Bas-Rhin	IARC	2	2	3	—
Doubs	IARC	1	1	1	6
Calvados	IARC	2	2	1	2
Côte d'or	—	—	—	1	6
Isère	IARC	2	1	1	—
Geneva	IARC	2	2	>3	—
Vaud	IARC	2	2	2	—

*For which two primary multiple cancers are considered as synchronous.

Table 6. Characteristics of the registries of Connecticut (1935–1982) and Denmark (1943–1980) [13]

	Number of cancers*		Number of multiple primary cancers†		Proportion of multiple primary cancers‡	
	Connecticut	Denmark	Connecticut	Denmark	Connecticut	Denmark
Men						
All cancers	120253	171749	7507	6370	6.2	3.7
Mouth and pharynx	8298	8802	205	34	2.5	0.4
Lung	18764	25338	84	13	0.4	0.1
UADT and lung	33150	40262	920	527	2.8	1.3
Colon and rectum	20881	28535	502	188	2.4	0.7
Women						
All cancers	133283	208192	9220	8714	6.9	4.2
Breast	41109	54964	1927	—	4.7	—
Colon and rectum	21383	27552	451	169	2.1	0.6

*Numbers of cases of cancers diagnosed from 1935 to 1982 for Connecticut and from 1943 to 1980 for Denmark. †Numbers of multiple primary cancers diagnosed after the first cancer. ‡In per cent. §Skin cancers other than melanoma are excluded (ICD-O = 173).

Table 7. Proportion of multiple primary cancers by age group (1985–1987) among all cancers

	Basel		Bas-Rhin		Calvados		Doubs		Isère		Geneva		Vaud	
Age	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65
All cancers (women)	4.1	6.9	5.7	7.7	4.4	6.2	1.9	3.4	5.7	6.1	5.9	8.8	7.8	10.0
All cancers (men)	4.1	9.5	10.5	9.9	8.1	6.7	7.3	6.2	6.2	8.5	7.3	11.7	9.8	11.5
Mouth and pharynx (men)	3.1	3.1	18.1	11.6	7.5	2.9	9.2	1.1	7.2	5.0	11.3	3.4	17.5	14.5
Breast (women)	4.7	4.4	4.9	4.7	4.5	2.9	0.3	0.4	1.2	1.5	3.3	5.9	6.0	7.2

factors were the same and only a different interpretation by both clinicians and registry registrars can explain these differences.

Varying interpretation of the rules is another factor which complicates the problem. Data from the anatomopathological examinations do not always make it possible to distinguish between a multiple primary cancer, a metastasis and a recurrence and it is possible for the second site to be classified as a multiple primary cancer, a recurrence or a metastasis. This problem will certainly be the most difficult to verify. Storm and associates [14] have pointed out the role of autopsies whose practice differs between registries (Tables 7 and 8). Nevertheless this factor cannot explain solely the observed differences.

The analysis of our results showed that the proportion of multiple primary cancers was generally higher amongst men than amongst women. This fact is due to a different distribution of cancers among women and men. No satisfactory explanation has been found for the wider variations observed

between the registries for the women. It is also highly interesting to note that, for majority of the registries of our study, with the exception of the registries of the Doubs and Basel, the proportions of colorectal multiple primary cancers in women were lower than in men, although the incidence of these cancers is identical in men and women. This phenomenon does not appear in the registries of Connecticut and Denmark where these percentages are similar for both.

The variations observed in the registration of the multiple primary cancers obviously have an effect on the estimation of the incidence rates and the chronological trends. Our results show that this effect is not negligible. We can consider, in those registries which date at least 10 years, that 10% of the registration of male cancers concern individuals who are already known. This phenomenon may be more or less significant according to the site; thus, for the cancers of the mouth and pharynx, the difference of incidence observed between the registries of the Calvados and the Bas-Rhin can be explained entirely by the registration of multiple primary

Table 8. Proportion of multiple primary cancers by age group found by necropsy

	Basel		Bas-Rhin		Calvados		Doubs		Isère		Geneva		Vaud	
Age	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65	<65	>65
All cancers (women)	1.9	13.3	1.5	2.8	0.0	0.2	0.1	0.0	0.0	0.0	—	—	0.5	2.1
All cancers (men)	4.0	18.1	4.1	4.7	0.1	0.1	0.3	0.2	0.0	0.0	—	—	1.5	4.2
Mouth and pharynx (men)	1.5	3.1	2.9	0.7	0.0	0.0	0.0	0.0	0.0	0.0	—	—	0.6	0.0
Breast (women)	0.9	3.8	0.6	0.5	0.0	0.0	0.2	0.0	0.0	0.0	—	—	1.3	4.3

cancers (Table 4). When the incidence was calculated *by case*, it was respectively 78.3 and 68.6 for 100000. When this incidence was calculated *by individual*, the differences between these two registries disappeared (65.5 for the Bas-Rhin and 64.4 for the Calvados). The upward trend for these cancers, which appears in the Bas-Rhin, disappeared when the incidence was expressed *by individual* (Figure 1). The impact on other sites is relatively low. If a registry does not modify its methods of coding, then as of the 10th year, the impact on the incidence of breast cancer will be almost stabilised.

There are many problems raised by this study. The disparities which exist between certain registries are notable, both with regard to the results and to the rules used. The impact of these multiple primary cancers on incidence rates and trends is not negligible, as our study showed, for the cancers of the mouth and the pharynx and for cancers taken as a whole. A study of the risks of a second cancer carried out by Storm [15] has already noted an impact of this kind on the risks calculated in Denmark and in Connecticut. A more rigorous harmonisation of the rules of registration would certainly make it possible to reduce the variations in the registration. Training the registrars and checking the data collection would lessen the degree of subjectivity which occurs in the registration of multiple primary cancers. Given the lack of harmonisation of the rules and methods of registration, the *incidence by individual* is the only way to make comparisons between the registries since the multiple primary cancers are then automatically treated in the same way.

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