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European Journal of Cancer 39 (2003) 1603–1609

European Journal of Cancer

www.ejconline.com

Comparison of stomach cancer incidence and survival in four continents

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Received 23 August 2002; received in revised form 18 December 2002; accepted 22 December 2002

Abstract

The aim of this study was to compare stomach cancer incidence and survival rates between four very distinct areas: Campinas (Brasil), Latin America, Iowa (USA), Northern America, Varese (Italy), Europe and Osaka (Japan) in Asia, and determine which of the differences are due to variations in the case mix and which are due to the care received. A proportional hazards regression method was applied to the relative survival rates to obtain geographical differences that were adjusted for age, gender, period of diagnosis, sub-site and stage. Age, gender, period and stage explained most of the variability between the areas (50–100% excess risk of death with respect to Osaka) in the survival rates for stomach cancer patients. In Iowa and Varese, information on the sub-site fully explained the remaining variability. The large survival differences between the four areas were almost totally due to the different case mixes of the stomach cancer patients. The importance of stage indicates that diagnostic delay may be a major clinical factor affecting survival.

Keywords: Stomach cancer; Incidence; Survival; Confounding factors

1. Introduction

Stomach cancer is the second most common cancer worldwide [1]. The incidence of stomach cancer has been decreasing in most industrialised countries over the past two decades. In spite of this favourable trend, a large geographical variability in both incidence and mortality rates still persists. There is a substantial variation in patients' survival among European countries, with 5-year relative survival rates varying from 10 to 20% [2,3]. Within, country variability in survival has been documented in Italy [4] and the United Kingdom (UK) [5]. Survival rates from stomach cancer in the United States are worse than those reported in Italy and other European countries. This, in contrast with the very high survival levels generally reported for other cancer sites in the USA [6].

The incidence of stomach cancer is thought to be strongly influenced by both exogenous and unknown endogenous factors. Areas with high levels of stomach cancer are likely to be mostly influenced by exogenous factors, such as nutrition, food conservation and additives, *Helicobacter pylori* infection and a low socio-economic status [7]. Conversely, areas with low levels of stomach cancer are likely to be less influenced by exogenous factors, but rather by known and unknown endogenous genetic or biological factors, such as a family history of gastric cancer, blood type A and a family history of non-polyposis colon cancer syndrome [7]. Changes in exogenous factors are expected to be the most important determinants of the worldwide declining trend in stomach cancer incidence [8]. Exogenous and endogenous factors are also expected to determine different types of stomach cancers, e.g. cancers with a different histological type (intestinal versus diffuse type lesions) and/or specific sub-sites of the stomach (distal gastric versus gastro-oesophageal and proximal gastric carcinomas) [9]. Proximal stomach

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doi:10.1016/S0959-8049(03)00360-5

cancers are mostly related to endogenous stable factors, while distal cancers are prone to varying exogenous factors. The prognosis of stomach cancer patients can differ according to both the sub-site and histology. Population-based survival estimates are expected to be influenced by the different incidence of certain histological types and sub-sites, which act as confounding factors.

The objective here is to compare stomach cancer incidence and survival rates between four very distinct areas in four continents: Campinas (Brasil) in Latin America, Iowa (USA) in Northern America, Varese (Italy) in Europe and Osaka (Japan) in Asia. Combining the data from these four registries, we aimed to study the differences in patients' survival in light of a different mixing of incident cases with respect to age, stage, histological type and sub-site. The net differences in patients' survival from stomach cancer that might exist after adjusting for stage, sub-site, histological type and other common confounding factors are expected to reflect possible differences in the management of cancer patients and in the performance of the healthcare systems worldwide.

2. Patients and methods

2.1. Data

Population-based cancer registry data from four areas in four continents were chosen in order to maximise the variability in both incidence and patients' survival: Campinas, Brazil (Latin America), Iowa state, US (North America), Varese province, Italy (Europe) and Osaka, Japan (Asia). Data for the Iowa state are available from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use CD-ROM (1973–1997) [10], data for Varese (1978–1992) are available from the EUROCARE-2 Study [2], while data from Osaka (1978–1989) and Campinas (1991–1994) were kindly provided from the specific registries. Population and mortality rates (life tables) for the general population of the four areas were available from the same data sources.

The SEER programme uses an active search for vital status. For the Iowa data, less than 0.1% were lost to follow-up on 31 December 1992. The follow-up of cases in the Campinas registry is routinely done in a passive way, i.e. by cross-checking the incident cases with deaths recorded in the mortality data-bank; 14% of the cases were lost to follow-up on 12 December 1994. The Varese cancer registry uses an active search for vital status with a very low proportion (0.7%) of patients lost to follow-up. The Osaka cancer registry also performs active follow-up (proportion of those lost to follow-up is equal to 0.9%).

The data contained information on age at diagnosis, microscopic confirmation, topographic International Classification of Diseases (ICD)-9 code, morphology ICD-O five-digit code, stage, survival, time of censoring or time to death and status of life. *In situ* tumours, the cases recorded from death certificates only (DCO) and those discovered at autopsy were excluded from the analysis. The period of diagnosis was restricted to 1978–1992 for comparison purposes. Overall, a total of 38 019 cases were analysed.

2.2. Methods

Relative survival was used to eliminate the effect of mortality by other causes, which differ from country to country, and to estimate stomach cancer survival where the risk of death due to stomach cancer alone is considered. Relative survival was defined as the ratio between the observed survival probability of patients, calculated using incidence and follow-up data from the cancer registries, and the expected survival rates (life tables) of the general population. The incidence data and the expected survival rates for all of the registries were prepared and formatted by means of the SEER* Prep system (http://seer.cancer.gov/ScientificSystems/SEERPrep/) to be used with SEER*Stat system of the SEER Program Public-Use CD-ROM. The relative survival rates were then calculated using the SEER*Stat system. A proportional hazards regression method [11] was then applied to relative survival rates to obtain geographical differences adjusted for all of the considered factors. The PHREG and GENMOD procedures from the SAS package [12] were used to calculate the risk ratios (RR) for the proportional hazard regression analysis on the relative survival rates.

2.3. Variables

Data were grouped to fit the needs of the proportional hazards method used. Age was categorised into four groups: 0–59, 60–69, 70–79 and over 80 years of age. Period was categorized as 1978–1985 and 1986–1992. Stage for the Iowa data was grouped according to the SEER historical stage into four categories: localised, regional, distant and unstaged. The stage variable reported in the EUROCARE study was re-coded in order to be as close as possible to the SEER historical staging. Tumours confined to the site of origin (equivalent to T0-3 N0M0) were re-coded as localised. Tumours which spread to immediately adjacent tissues and/or regional lymph-nodes (equivalent to T4, any T N1-3M0) were re-coded as regional. Tumours spread to distant organs (equivalent to any T, any N M1) were re-coded as distant. Finally, the aggregation of tumours not confined to the site of origin, but not specified as regional (equivalent to TXNXMX) or distant or no

distant metastasis, but not specified if localised or regional were re-coded as unstaged or no information on stage. Sub-site was classified according to the ICD-9 as cardia (151.0), pylorus (151.1), pyloric antrum (151.2), fundus of stomach (151.3), body of stomach (151.4), lesser curvature (151.5), greater curvature, unspecified (151.6), other specified sites (OSS) of the stomach (151.8) and stomach, unspecified (NOS) (151.9). We considered only the first 7 years of follow-up for all of the registries. Since the registries had different lengths of follow-up, a covariate considering year of follow-up was also included in the model.

Histology was classified according to a prognostic meaning, basically separating diffuse carcinomas from intestinal adenocarcinomas. Therefore, we identified a large group of 'differentiated adenocarcinomas' which included all the differentiated intestinal type adenocarcinomas, the tubular, mucinous, papillary carcinomas, plus all of the adenocarcinomas without any specific description (ICD-O 8140, 8144, 8050, 8200, 8210, 8211, 82600–8481, 8560, 8570). In a second large category, we included all the 'non-differentiated adenocarcinomas', which mostly included the diffuse, signet-ring cell, scirrous and medullary carcinomas (ICD-O 8020, 8021, 8231, 8032, 8141–8143, 8145, 8230, 8245, 8490, 8510, 8550). A third category of 'non adenocarcinoma' mainly included the squamous metaplasia, adenosquamous and epidermoid carcinomas, carcinoids and sarcomas (ICD-O 8041, 8070–8072, 8076, 8240, 8241, 8246, 8720, 8800, 8801, 8810, 8830, 8890, 8891, 8896, 8980, 9130, 9140, 9150, 9540, 9560). We further identified a group of 'not specified neoplasms' including all of the malignant lesions for which it was impossible, for several reasons, to have a definitive histological descriptions, as well as those that were not microscopically verified (ICD-O 8000, 8001, 8010, 8012, 9990).

Unless otherwise specified, age group 70–79 years, men, Osaka, regional stage, differentiated adenocarcinoma, ICD-9 code 151.9 and period 1978–1985, and the first year of follow-up were the reference categories for the regression analysis.

3. Results

A description of the data in terms of the prognostic factors considered is given in Table 1. Osaka was the registry with the largest proportion of younger patients, having almost 70% of patients aged under 70 years, while Iowa has the smallest proportion, 41% being aged uner 70 years. Campinas and Osaka had the largest proportion of ICD-9 151.9 (NOS), 77 and 65%, respectively, making the sub-site distribution in these registries less informative. Iowa had the largest proportion of cancers of the cardia and also cancers staged as distant. The distribution by histological type was quite similar among the different areas and is not likely to explain the variability in patients' survival.

Table 1
Distribution of stomach cancer cases by age class, subsite histology category and stage for data from the Iowa, Varese, Campinas and Osaka cancer registries

Variable	Iowa *N* (%)	Varese *N*	Campinas *N* (%)	Osaka *N*
Total cases	3451	3513	337	30 718
Gender				
Men	2117 (61)	2064 (59)	209 (62)	19 612 (64)
Age groups (years)				
0–59	572 (17)	812 (23)	96 (28)	13 265 (43)
60–69	855 (25)	904 (26)	99 (29)	8133 (26)
70–79	1046 (30)	1217 (35)	95 (28)	7146 (23)
80+	978 (28)	580 (17)	47 (14)	2174 (7)
Subsite				
Cardia (151.0)	973 (28)	243 (7)	8 (2)	1736 (6)
Pylorus (151.1)	102 (3)	43 (1)	9 (3)	513 (2)
Antrum (151.2)	519 (15)	1058 (30)	43 (13)	3554 (12)
Fundus (151.3)	168 (5)	102 (3)	2 (1)	14 (<1)
Body (151.4)	171 (5)	363 (10)	16 (5)	4375 (14)
Lesser curvature (151.5)	333 (10)	419 (12	0 (0)	87 (<1)
Greater curvature (151.6)	186 (5)	79 (2)	0 (0)	37 (<1)
OSS (151.8)	345 (10)	385 (11)	0 (0)	438 (1)
NOS (151.9)	654 (19)	821 (23)	259 (77)	19 964 (65)
Histotype				
Adenoc. diff.	2496 (72)	2428 (69)	235 (70)	21 076 (69)
Adenoc. non-diff	488 (14	954 (27)	56 (17)	3621 (12)
Non-adenoc.	172 (5)	137 (1)	4 (1)	187 (1)
Not specified	295 (9)	94 (3)	42 (12)	5834 (19)
Stage				
Localised	579 (17)	738 (21)	8 (2)	9183 (30)
Regional	1076 (31)	1018 (29)	47 (14)	11 271 (37)
Distant	1287 (37)	822 (23)	54 (16)	5556 (18)
Unstaged	509 (15)	935 (27)	228 (68)	4708 (15)

Adenoc, adenocarcinoma; Diff. differentiated; OSS, other specified sites; NOS, stomach, unspecified.

Table 2
5-year relative survival rates by calendar period, age class, gender, and area

	1978–1985				1986–1992[a]			
	15–59	60–69	70–79	80+	15–59	60–69	70–79	80+
Men								
Iowa	0.14	0.10	0.09	0.10	0.14	0.19	0.16	0.07
Varese	0.33	0.17	0.17	0.11	0.39	0.22	0.18	0.16
Campinas	–	–	–	–	0.33	0.39	0.28	0.11
Osaka	0.19	0.39	0.30	0.12	0.54	0.49	0.37	0.16
Women								
Iowa	0.18	0.22	0.15	0.17	0.31	0.26	0.18	0.18
Varese	0.31	0.34	0.25	0.20	0.33	0.33	0.29	0.21
Campinas	–	–	–	–	0.43	0.42	0.43	0.38
Osaka	0.40	0.37	0.24	0.10	0.51	0.48	0.38	0.18

[a] Period for Campinas is 1991–1994 and for Osaka is 1986–1989.

Table 2 reports 5-year relative survival rates by area, age, gender and period. Iowa has the poorer relative survival and Osaka the better relative survival, with respect to the other areas. However, for elderly patients

Table 3
Summary of the proportional hazard regression (Hakulinen) analysis on relative survival controlling for age, gender, period and stage[a]

	Model	Deviance	D.F.[b]	RR estimates (95% C.I.)		
				Iowa	Varese	Campinas
1	Total	40 674				
2	7 initial years of follow-up	21 660	6			
3	+ Reg	20 727	3	2.03 (1.93, 2.12)	1.52 (1.45, 1.59)	1.67 (1.43, 1.91)
4	+ Reg + age	19 875	3	1.67 (1.59, 1.75)	1.35 (1.28, 1.41)	1.55 (1.33, 1.77)
5	+ Reg + age + per	19 652	1	1.70 (1.62, 1.78)	1.38 (1.31, 1.44)	1.80 (1.54, 2.05)
6	+ Reg + age + per + sex	19 644	1	1.70 (1.61, 1.78)	1.37 (1.31, 1.44)	1.79 (1.53, 2.05)
7	+ Reg + age + per + sex + stage	5924	3	1.21 (1.15, 1.27)	1.14 (1.08, 1.20)	1.19 (1.02, 1.37)
Excluding Campinas						
8	+ Reg + age + per + gender	19 568	–	1.69 (1.61, 1.78)	1.37 (1.31, 1.44)	–
9	+ Reg + age + per + gender + stage	5819	3	1.21 (1.15, 1.27)	1.14 (1.08, 1.20)	–

95% C.I., 95% Confidence Interval; per, period; Reg, registry.
[a] Estimated death risk ratio (RR) for stomach cancer estimates for registries with respect to Osaka.
[b] D.F. is the difference of degrees of freedom between the current model and previous model.

(aged over 80 years) survival differences between the registries were greatly reduced, leading to survival rates that were approximately the same. Age at diagnosis scarcely affected the relative survival in Iowa, while in Osaka survival differed according to the age of the patient, with lower rates being observed in the more elderly patients. Although the differences in relative cancer survival rates among men and women were small, women showed a better survival than men in Iowa and Campinas. Improvements over time survival were observed in all of the registries for which data were available.

Table 3 reports the results of the stepwise procedure used to select the most important factors explaining the differences in relative survival. The relative risk of death from stomach cancer, controlling for general population mortality, for Varese, Iowa and Campinas with respect to Osaka, and the 95% confidence intervals (C.I.) are presented. Histological type was non-significant in the preliminary analyses (i.e. did not differ substantially between the registries), as can be seen from Table 1. Histological type was therefore removed from the final analysis. Stage was the most important factor explaining the variability in survival (even more so than age). When stage was included in the model, most of the survival differences between the four registries disappeared. The risk of death, with respect to Osaka, for persons diagnosed with stomach cancer changed from 1.38 to 1.14 in Varese, 1.70 to 1.21 in Iowa and 1.80 to 1.19 in Campinas. The variability that existed between the Iowa, Varese and Campinas registries almost disappeared in model 7. These registries therefore presented a 14–21% higher risk of stomach cancer death than Osaka. Since Campinas had 68% of cases with an unknown stage, we re-estimated the last two models using data from Iowa, Osaka and Varese alone. The estimated relative risks for Varese and Iowa with respect to Osaka did not change.

We must mention that the second time period, 1986–1992, is not the same for all of the registries. For Campinas, this time period was 1991–1994 and for Osaka it was 1986–1989. Provided that stomach cancer survival in the Osaka registry had in fact improved in 1990–1992 compared with 1986–1989, the estimated RR would be slightly underestimated and the differences with respect to Osaka outlined above would have been slightly larger.

Since the quality of sub-site information cannot be ascertained in the Osaka registry, due to the large number of ICD-9 151.9 cases, and is not reliable for Campinas, we restricted this analysis to data from the Iowa and Varese registries. Table 4 shows the results of the stepwise procedure and the estimates (95% C.I.) of the risk of death for Iowa with respect to Varese for the models considered. Although stage is the variable that contributed the most to reduce survival differences between Iowa and Varese, subsite information further contributed in reducing the variability. The inclusion of sub-site information lowered the risk ratio of Iowa (with respect to Varese) from 1.10 to 1.04 (statistically non-significant), after controlling for age, gender and stage, whereas the period did not significantly affect the ratio. Although not presented in this table, the histological type did not reduce the differences in survival, once stage and sub-site had been considered in the analysis.

In the multivariate analysis, we checked for possible non-proportionality of the hazards. Actually, some interaction terms with the first year of follow-up were significant in models 4–6, but this significance disappeared when stage was included as a prognostic factor (model 7). Stage was therefore responsible for some of the non-proportionality of hazards in the first year of follow-up.

Table 5 shows the large variability in the age-standardised stomach incidence rates by area: Osaka and

Table 4
Summary of the proportional hazard regression (Hakulinen) analysis on stomach cancer relative survival considering only Iowa and Varese[a]

	Model	Deviance	D.F.[b]	RR for Iowa relative to Varese	
				Est.	(95% C.I.)
1	Total	10 052	–	–	–
2	7 initial years of follow-up	6917	6	–	–
3	+ Reg	6835	1	1.34	(1.23, 1.44)
4	+ Reg + age	6753	3	1.29	(1.09, 1.19)
10	+ Reg + age + stage	5175	3	1.10	(1.02, 1.19)
11	+ Reg + age + stage + gender	5166	1	1.10	(1.02, 1.18)
12	+ Reg + age + stage + period	5173	1	1.10	(1.02, 1.18)
13	+ Reg + age + stage + gender + subsite	5049	8	1.04	(0.96, 1.12)

Est., estimated; Reg, registry.
[a] Estimated death risk ratio (RR) for stomach cancer estimates for registries with respect to Varese.
[b] D.F. is the difference of degrees of freedom between the current model and previous model.

Table 5
World age standardised incidence rates[a] of stomach cancer (ICD-9 151) and cardia (ICD-9 151.0), 1988–1992, (0–85+ years) (from Ref. [1])

	Stomach (ICD-9- 151)				Cardia (ICD-9- 151.0)			
	Men		Women		Men		Women	
	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates
Iowa	661	6.57	379	2.2	271	2.88	260	0.77
Varese	786	19.23	636	12.73	84	2.83	26	0.57
Campinas	209	20.33	128	10.18	–	–	–	–
Osaka	17 241	64.99	9509	27.3	642	2.44	260	0.77

[a] Rates per 100 000.

Varese having rates that were 10-fold and more than 3 to 6 times larger than Iowa, respectively. However, when comparing age standardised incidence rates of the cardia alone (ICD-9 151.0), no differences were evident for Iowa, Varese and Osaka.

4. Discussion

This study used data available from registries in four continents to compare survival differences in patients with stomach cancer. The four areas chosen are very distinct, and showed very large differences in the incidence and survival rates, due to different socio-economic conditions, quality of life and dietary habits. Choosing areas that maximise the variability in both the survival estimates and prognostic factors is important in order to improve the efficiency of the statistical analysis and the potential use of the subsequent results.

Available data from the four areas were of variable quality. Information on the sub-site was lacking for Campinas, Brasil, and Osaka, Japan, where 76 and 65% of patients were unclassified, respectively. This is expected to be mainly due to the different attitudes of surgeons in reporting the localisation of the tumour within the stomach, particularly given that more than 77% of stomach cancer cases in Osaka underwent surgical operation. Patients with cardia and proximal stomach cancers undergo surgical resection less frequently than patients with cancers in the other stomach sub-sites, and the information on the proximal localisation of the tumour is commonly used to define the treatment. The high proportion of unclassified sub-sites in some areas is not expected to have a great influence on the reliability of the incidence estimates for cardia cancers. Conversely, the distribution of stomach cancer cases by sub-site is rather biased and therefore we did not use the data from these areas in the analysis. A variable extent of misclassification of stomach and lower oesophageal cancers is a possible explanation for the differences in the frequency of cardia cancers in Table 1 and can thus have an artefactual effect on the survival estimates. Nevertheless, we think misclassification did not play a major role in the striking difference observed between the survival rates of Varese and Iowa (Table 4). Data from Campinas also include 68% of patients who were unstaged and the estimated RR for Campinas in model 7, Table 3, is of limited use. Indeed, in an analysis of model 7 with data from the Campinas tumour registry removed (model 9), the RRs for Varese and Iowa did not change. Data for Iowa and Varese were fairly complete in all of the items studied, and allowed us to derive a detailed regression analysis of stomach cancer relative survival rates for these two areas (Table 4), explaining the differences in terms of age, stage and sub-site distribution. Although registries had different data quality, all of them have well described norms and procedures, guaranteeing adequate quality and making the results comparable.

Other studies have recently compared the prognosis of cancers among different areas, e.g. between Canada and US [13], Europe and US [6] as well as between European countries [2] or between developing countries [14]. The innovation of this study is that we compared stomach cancer survival rates from very different areas and interpreted differences with respect not only to

common factors such as age, period, gender and stage, but also with respect to factors such as sub-site and histological type, in a regression approach.

The results showed that a large part of the differences in stomach cancer relative survival rates remained unexplained in the four areas even after controlling for age, period and gender (Table 3). However, after including stage in the model, the differences in survival were greatly reduced. Stage therefore best explains the differences in stomach cancer survival rates in these four areas. Sub-site information, when available, was able to further reduce and eliminate the difference in the survival rates between Iowa and Varese (Table 4).

Diagnostic procedures may vary in these very different areas, thus making information on stage difficult to compare. The definition of stage can also vary with time as diagnostic facilities improve and this makes international comparisons even more problematic. Stomach cancer screening, widely conducted in Japan, may have caused a lead-time bias in the survival rates. Furthermore, some differences in diagnostic criteria for gastric cancer were reported between Japanese and Western pathologists, in particular for intestinal, early gastric cancers [15]. Notwithstanding, stage classified in broad categories such as localised, regional, distant metastasis and unstaged, proved to explain most of the variability in the stomach cancer survival rates between the study areas. One implication of these results is that, although some misclassification may exist, information on stage was comparable, at least in terms of the prognosis of the stomach cancer patients. The good comparability of the data is also confirmed by the striking similarity in the distribution of histological types between the four registries (see Table 1) Although histological type was not a prognostic factor for stomach cancer survival, its consideration is relevant to ascertain the comparability of the data across the four continents.

Although there was a large variability in stomach cancer incidence among the areas, the incidence of cancers of the cardia was more stable. This supports the idea that the cancer of the cardia is likely to be due to biological or genetic factors which are common all around the world, rather than to exogenous factors. The larger variability in the incidence of distal sub-sites, generally associated with better prognosis, may suggest that exogenous factors, such as additives, salt and/or smoke used for food conservation, play an important role in the incidence of these most common stomach cancers.

Importantly, our results also infer that differences in survival are mainly due to a different mixing of cancers with different prognoses, rather than to a different management of care of the patients. The elective therapy for stomach cancer is surgical resection, that is more effective and less problematic for young people and localised cancers. Surgical skill is not expected to vary worldwide, while stage of the disease is strongly related to the eligibility for treatment, the extent of resection, prognosis and the quality of life of the patients.

Stomach cancer survival was observed to be higher in areas with higher stomach cancer incidence rates. Higher incidence rates are due to distal stomach cancers rather than proximal cancers, the latter being quite constant among populations and over time. The declining incidence of gastric carcinomas has been observed throughout the world, although with different patterns, as generally the decline has been confined to distal subsites and not to cardia cancers [16]. Case mixes are expected to vary accordingly and to be reflected in a potential worsening of survival rates with time. Despite this, all of the registries, with the exception of Campinas (due to a lack of data), showed improvements in survival in the last time period observed. These improvements might be associated with a more common use of endoscopy and recent improvements in surgical treatments. However, after controlling for stage and sub-site, very small survival differences between the areas remained, suggesting that differences in the management of patients had little effect on survival rates.

Acknowledgements

We would like to thank Anna Valéria de Britto and Djalma de Carvalho Moreira Filho for allowing us to use data from the 'Registro de Câncer de Campinas, Universidade Estadual de Campinas—UNICAMP, São Paulo, Brasil'.

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