Trends in gastric and esophageal cancer incidence in northern Portugal (1994-2009) by subsite and histology, and predictions for 2015

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ABSTRACT

Introduction: Gastric cancer (GC) and esophageal cancer (EC) share risk factors, and the incidence trends reflect differences in etiology according to their subtypes. We aimed to describe the incidence trends of GC (by topography) and EC (by histological type) in northern Portugal for 1994-2009 and to estimate the incidence for 2015. We further analyzed exposure to the main risk factors for these cancers in the region over the last decades.

Methods: GC and EC data were obtained from the North Region Cancer Registry of Portugal (RORENO). Joinpoint regression was used to compute annual percent changes (APC) in incidence trends. Poisson regression yielded estimates for 2015. A literature review up to 2014 provided data on exposure to risk factors.

Results: GC rates decreased in 1994-2009 (men, APC = -1.3; women, APC = -1.6); GC, unspecified subtype, had the steepest decline since the early 2000s (men, APC = -4.9; women, APC = -6.3). The incidence for 2015 will increase for EC in men (up to ≈190 cases) and stabilize in women (≈30) and for GC (≈730 men, ≈500 women). Increasing prevalence of tobacco smoking among women and overweight/obesity, fairly stable prevalence of alcohol, fruit and vegetable consumption, and no trend for *Helicobacter pylori* infection were observed.

Conclusions: The declining incidence of GC unspecified subtype indicated an improvement in cancer registration accuracy, but precluded a sound assessment of trends by subtype. Variations in the prevalence of exposure to some risk factors were consistent with observed incidence trends, and future studies should aim to quantify their contribution to the GC and EC burden in the region.

Keywords: Esophageal cancer, Incidence, Stomach cancer, Trends

Introduction

Gastric cancer and esophageal cancer are among the 10 most common cancers worldwide, jointly accounting for 10% of the overall number of incident cases (1). Both are characterized by low survival rates: in Europe, a recent study yielded 5-year relative survival rates of 25% and 12% for gastric and esophageal cancer, respectively (2).

The stomach cancer incidence and mortality have been decreasing for several decades, which is mainly attributable to a decrease in the frequency of *Helicobacter pylori* (*H. pylori*)

infection, smoking, salt intake, and low consumption of fruits and vegetables (3, 4). However, the trends are not homogeneous across gastric cancer subtypes, as the decline has been greater for noncardia gastric tumors, while for cardia tumors, in many settings, the pattern of variation resembles more closely that observed for esophageal cancer (3, 5).

Esophageal cancer is much less frequent than gastric cancer in more developed countries. There is a heterogeneous distribution of its main histological types, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), across countries, reflecting differences in the etiology of these subtypes. Overall, the incidence of esophageal cancer has been increasing in many of the most developed countries, mainly due to upward trends in EAC, possibly on account of higher prevalences of obesity and gastroesophageal reflux (6). The main risk factors for ESCC are smoking and alcohol consumption, and studies have shown their independent and synergistic effects (7). *H. pylori* infection is negatively associated with EAC (8) and decreases in the prevalence of infection are expected to translate into a higher esophageal cancer morbidity (9). Low fruit and vegetable intake increases the risk of both EAC and ESCC, and variations in consumption are also

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expected to influence the trends in esophageal cancer incidence and mortality.

This study aimed to describe subtype-specific incidence trends in stomach (cardia and noncardia) and esophageal cancers (ESCC and EAC) in northern Portugal between 1994 and 2009, and to estimate the number of incident cases and age-standardized rates for 2015. It further analyzed the exposure to the main risk factors for these cancers in the region over the last decades.

Methods

Incidence data on stomach and esophagus cancers for the period 1994–2009 were retrieved from the North Region Cancer Registry of Portugal (RORENO). This is a population-based cancer registry, set up in 1988, which covers approximately 3.2 million people who live in the 5 districts of northern Portugal (Braga, Bragança, Porto, Viana do Castelo and Vila Real). For the same period, population figures based on official censuses were obtained from Statistics Portugal (10).

Sex-specific incidence rates were computed for each 5-year age group and calendar period, and age-standardized rates were calculated by the direct method, using the European standard population (11), for all ages and the age groups <65 and ≥65 years. Poisson regression analyses were performed using the Joinpoint software (12), in order to identify significant changes in incidence trends (allowing for up to 2 joinpoints). For each of the segments obtained in the best model, the estimated annual percent change (APC) and corresponding confidence intervals (CI) were computed by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.

Stomach cancer incidence trends were analyzed overall and by sublocation according to the International Classification of Diseases for Oncology, third edition (ICD-O-3), i.e., cardia (C16.0), noncardia (C16.1–C16.6), and unspecified topography (C16.8–C16.9). Esophageal cancer incidence trends were analyzed overall and by histological type: ESCC (M8050/3–M8084/3), EAC (M8140/3–M8384/3), and other and unspecified esophageal cancers (all other morphology codes).

Population predictions up to 2015 were computed by RORENO, using a scenario of the evolution of the resident population based on a constant fertility rate and on migration rates derived from available population figures from Statistics Portugal up to 2012. Predicted absolute numbers of cases of stomach and esophageal cancer for the year 2015, and the corresponding 95% prediction intervals (13, 14), were computed through linear (for increasing or stabilizing trends) or log-linear (for decreasing trends) Poisson regression analyses, by age group (0–34, 35–44, 45–54, 55–64, 65–74, 75–84 and ≥85 years). The last periods of time obtained in sex- and site-specific joinpoint models were used as the basis for the predictions. Age-standardized incidence rates were computed using the projected absolute number of cases and corresponding population estimates. The year 2015 was chosen as the prediction limit to allow for international comparisons, using data from GLOBOCAN (1).

The variation in the prevalence of exposure to the major determinants of gastric and/or esophageal cancer (tobacco smoking, alcohol drinking, overweight/obesity, *H. pylori* infection,

and low fruit and vegetable consumption) was evaluated by reviewing studies published up to 2014 that provided data from northern Portugal. For tobacco smoking, overweight/obesity and *H. pylori* infection, previously published systematic reviews of Portuguese studies (15–17) were used as the primary source of published reports. For *H. pylori* infection, the systematic review was based on searches in PubMed and the online database of publications in Portuguese medical journals, from inception to July 2014. For smoking and overweight/obesity, PubMed was searched from inception up to 2011. Data obtained in these reviews were complemented by information from national health surveys. For alcohol drinking, and fruit and vegetable consumption, information was collected from national health surveys and from studies using the population-based cohorts EPIPorto (adults), EPITeen (adolescents) and Geração XXI (children) from Porto, the largest city in the region. Overall, sex- and age-group-specific estimates were collected, whenever available. To describe the variation in exposure to the risk factors, only the overall and sex-specific estimates were used. For a graphical display of results, when 2 studies described the prevalence of exposure to the same risk factor in the same period of time, the estimate used was the one with the most similar selection criteria to the remaining studies on that risk factor.

Results

In northern Portugal, the standardized gastric cancer rates decreased significantly from 1994 onwards, both among men (APC = -1.3, 95% CI: -1.6 to -0.9) and women (APC = -1.6, 95% CI: -2.3 to -1.0), while for the incidence of esophageal cancer, no significant variation was observed in the same period (Fig. 1). The age groups <65 and ≥65 years presented similar trends, both for gastric cancer (men: <65 years, APC = -0.6, 95% CI: -1.4 to 0.2, ≥65 years, APC = -0.3, 95% CI: -0.9 to 0.3; women: <65 years, APC = -1.3, 95% CI: -2.1 to -0.5, ≥65 years, APC = -0.2, 95% CI: -1.0 to 0.7) and esophageal cancer (men: <65 years, APC = 2.1, 95% CI: 0.2 to 3.9, ≥65 years, APC = 0.8, 95% CI: -0.8 to 2.4; women: <65 years, APC = -1.5, 95% CI: -3.4 to 0.5, ≥65 years, APC = -1.5, 95% CI: -4.7 to 1.9).

The estimated number of cases in northern Portugal for 2015 was 1,224 (men, 728; women, 496) for gastric cancer and 218 (men, 184; women, 34) for esophageal cancer. In relation to the estimated overall number of incident cancer cases in the region (18), these figures corresponded to 8.0% and 2.1% among men, respectively, and 6.0% and 0.4% among women, respectively (Fig. 1 and Tab. I).

Figure 2 depicts the trends between 1994 and 2009 according to gastric cancer sublocation and esophageal cancer histological type. For gastric cancer, the steepest variation was a decline since the early 2000s in the rates of tumors with unspecified locations within the stomach, both among men (APC = -4.9, 95% CI: -7.6 to -2.0) and women (APC = -6.3, 95% CI: -10.6 to -1.7), along with increasing trends of a similar magnitude in noncardia cancers in the same period (APC = 5.2, 95% CI: 2.1 to 8.3 for men and APC = 5.4, 95% CI: 3.0 to 7.9 for women). The incidence of cardia cancer decreased since 1994, although the variation was statistically significant only among women. In 2003–2007, gastric cancer with unspecified location accounted for more than two-thirds of all

Fig. 1 - Sex-specific trends* in the absolute number of cases and age-standardized (all ages, direct method, European standard population) incidence rates for stomach and esophageal cancer in 1994-2009, and predictions up to 2015.

TABLE I - Absolute number of new cases (n) of gastric and esophageal cancers expected for 2015 and corresponding proportion in relation to the total number of cases in northern Portugal and selected countries (source: GLOBOCAN [1]), by sex

Sex	Country/region	All cancers*	Gastric cancer		Esophageal cancer	
		n	n	% of all cancers	n	% of all cancers
Men	RORENO	9,057 [†]	729	8.0	186	2.1
	Portugal	29,397	1,898	6.5	550	1.9
	Spain	135,954	5,147	3.8	1,865	1.4
	Germany	286,424	10,845	3.8	5,816	2.0
	Italy	200,137	7,915	4.0	1,395	0.7
	Sweden	29,128	524	1.8	356	1.2
	Ukraine	69,649	6,877	9.9	1,647	2.4
	Australia	75,377	1,457	1.9	1,127	1.5
	USA	903,319	14,408	1.6	14,799	1.6
	Japan	441,132	79,350	18.0	17,468	4.0
Women	RORENO	8,243 [†]	497	6.0	32	0.4
	Portugal	21,241	1,223	5.8	77	0.4
	Spain	91,122	3,100	3.4	353	0.4
	Germany	232,229	6,231	2.7	1,485	0.6
	Italy	167,768	5,654	3.4	490	0.3
	Sweden	23,486	327	1.4	126	0.5
	Ukraine	71,980	4,547	6.3	260	0.4
	Australia	56,096	765	1.4	450	0.8
	USA	827,542	8,473	1.0	3,744	0.5
	Japan	308,370	36,217	11.7	3,333	1.1

* Except nonmelanoma skin cancer.

[†] source: Castro et al (18).

APC: annual percent change; 95% CI: 95% confidence interval.

* figures depict 3-year moving averages

Fig. 2 - Sex-specific trends* in the absolute number of cases and age-standardized (all ages, direct method, European standard population) incidence rates for stomach cancer by sub-location and esophageal cancer by histological type, in 1994-2009.

gastric cancer cases registered by RORENO, while the ratio noncardia/cardia was 3.4 in men and 5.4 in women (Tab. II).

For esophageal cancers, no significant variation was observed for any subtype among men, despite an upward trend for ESCC and a decline in EAC and unspecified/other tumors. Among women, there was a significant downward trend in ESCC (APC = -3.1) and nonsignificant increases for EAC and unspecified/other tumors (Fig. 2). In 2003-2007, the overall proportion of esophageal cancers of other/unspecified histological types was less than 10%, and the ratio ESCC/EAC was 6.0 in men and 3.6 in women (Tab. II).

Figure 3 depicts the variation in the prevalence of exposure to tobacco smoking, alcohol drinking, overweight/obesity, *H. pylori* infection, and fruit and vegetable consumption in northern Portugal. Overall, sex- and age-group-specific estimates are presented in Supplementary Table S1 (Exposure to the main determinants of esophageal and gastric cancers in northern Portugal. Available online at www.tumorjournal.com). Among adults, the prevalence of tobacco smoking (19-29) decreased for men, from 35% in 1987 to 25% in 2007, while for women it increased from 4% to 19%. The prevalence of alcohol drinking (22-25, 30-34) slightly increased among adult men, from 81% in 1987 to 86% in 2011, and decreased

among adult women, from 58% to 53%. Among adults, the prevalence of overweight varied from 18% to 40% for men and from 16% to 33% for women; the prevalence of obesity varied from 8% to 15% for men and from 11% to 15% for women. Among children/adolescents aged 6-13 years, overweight increased from 21% to 23% for boys and from 19% to 22% for girls between 2003 and 2008, while obesity increased from 7% to 9% for boys and from 6% to 10% for girls in the same period (23-25, 35-37). For *H. pylori* infection (38-44), 7 studies were conducted in northern Portugal which targeted populations at different age ranges, and no clear trends were observed among adults or children. The consumption of fruit and vegetables (23, 24, 32, 45-48) showed relatively stable trends, with the consumption of fruit being higher than that of vegetables, except among children, reflecting a high consumption of vegetable soup in this age group.

Discussion

In northern Portugal, the incidence of gastric cancer has been declining, but it remains the fourth most frequent cancer, whereas for esophageal cancer there was no statistically significant variation, and it currently accounts for a much

TABLE II - Number of cancer cases (n) diagnosed in 2003-2007 in northern Portugal and selected geographical areas* (source: *Cancer Incidence in Five Continents*, volume X (50)) and corresponding proportion of cancer subtypes (%) by cancer site and by sex

Sex	Country/region	Gastric cancer [†]					Esophageal cancer [†]				
		n	% unspecified	% cardia	% noncardia	Ratio noncardia/cardia	n	% unspecified	% ESCC	% EAC	Ratio ESCC/EAC
Men	RORENO	3,525	68.1	7.3	24.7	3.4	748	7.4	79.4	13.2	6.0
	Spain (13 registries)	5,914	50.3	14.7	35.0	2.4	2,373	11.6	62.2	26.2	2.4
	Germany (9 registries)	13,411	40.4	21.9	37.7	1.7	6,336	16.7	56.1	27.2	2.1
	Italy (33 registries)	16,148	50.6	12.3	37.1	3.0	3,247	18.6	57.1	24.3	2.3
	Ukraine (national)	39,350	38.1	12.4	49.5	4.0	8,078	36.5	52.9	10.6	5.0
	Sweden (national)	2,909	71.8	28.2	0.0	-	1,486	6.5	38.8	54.7	0.7
	Australia (national)	6,165	42.9	34.1	23.1	0.7	4,088	13.0	31.1	55.9	0.6
	USA (42 states)	56,113	36.6	36.0	27.4	0.8	52,617	11.8	26.0	62.2	0.4
	Japan (8 registries)	56,165	39.8	6.5	53.7	8.2	11,756	18.9	78.0	3.2	24.6
Women	RORENO	2,390	67.8	5.0	27.2	5.4	168	13.1	67.9	19.0	3.6
	Spain (13 registries)	3,424	52.5	6.9	40.6	5.9	375	16.5	60.0	23.5	2.6
	Germany (9 registries)	10,202	45.8	10.6	43.5	4.1	1,693	22.5	59.3	18.2	3.3
	Italy (33 registries)	11,623	51.6	5.8	42.5	7.3	1,093	28.6	57.0	14.4	4.0
	Ukraine (national)	26,720	39.2	8.9	51.9	5.8	1,256	51.2	31.6	17.2	1.8
	Sweden (national)	1,839	86.0	14.0	0.0	-	535	7.1	59.3	33.6	1.8
	Australia (national)	3,317	55.1	17.7	27.2	1.5	1,913	17.3	58.3	24.4	2.4
	USA (42 states)	36,044	46.8	16.5	36.7	2.2	15,211	14.3	49.1	36.6	1.3
	Japan (8 registries)	27,069	42.9	4.6	52.5	11.4	2,209	26.3	70.1	3.6	19.6

ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma; RORENO = North Region Cancer Registry of Portugal.

* When data from more than one cancer registry were available in the same country, we added up the number of incident cases from all registries.

[†] Includes ICD-O-3 codes C16.0 as cardia, C16.1-C16.4 as noncardia, and C16.5-C16.9 as unspecified location in the stomach.

[‡] Unspecified tumors include ICD-O-3 morphologies other than ESCC and EAC.

smaller proportion of all cancers registered, especially among women, ranking below 10th (49).

A wide variation between populations was observed, especially among men, regarding the proportion of gastric and esophageal cancers in the total number of expected cancers for 2015 (1, 50). Among the regions/countries considered in our study, male gastric cancer was estimated to account for between 1.6% (in the USA) and 18.0% (in Japan) of all cancers diagnosed in 2015, while male esophageal cancer represented between 0.7% (in Italy) and 4.0% (in Japan) of all cancers. For gastric cancer, the variability in the proportions found followed the patterns observed in cancer incidence, with countries with the highest incidence rates also presenting the highest proportions in relation to all cancers diagnosed; northern Portugal had the third highest values, after Japan and Ukraine, and presented approximately double the expected values for Spain (8.0 vs. 3.8% for men and 6.0 vs. 3.4% for women). Portugal as a whole presented lower values, which was expected since gastric cancer is more frequent in the northern region than in the rest of the country (51).

In relation to the proportion of cases of cardia and noncardia subtypes, the differences observed are in accordance with a recent study showing that countries with high

gastric cancer mortality rates present the lowest proportions of cardia cancers (3). Regarding trends by subtype, the steep decline in the rates of tumors with unspecified location within the stomach is noteworthy. However, since unspecified gastric cancers still comprise the majority of stomach cancer cases in northern Portugal, this precludes a sound interpretation of the trends in the rates of cardia and noncardia cancers; the increasing rates observed for noncardia cancers are unexpected, and most likely explained by a reduction of tumors with unspecified location mostly among the noncardia cancers, which in northern Portugal are much more frequent than those located in the cardia. The decreasing trends in rates of tumors with unspecified location within the stomach reflect improved cancer registration accuracy in RORENO, although there is still room for improvement at this level (52).

For esophageal cancer, the proportion of unspecified tumors was among the lowest compared with other European countries (5) and with the USA, Australia and Japan. The only significant change in trends regarding esophageal cancer subtypes in northern Portugal was observed for ESCC among women, which was found to be declining. This pattern has also been observed in European countries such as France and Poland (5), although it is difficult to interpret in terms of

Fig. 3 - Variation in the exposure to major gastric and/or esophageal cancer determinants in northern Portugal.

changes in exposure to risk factors on account of the much lower rates observed for women in comparison with men. Among men, joinpoint analyses were unable to detect significant changes in trends, although a peak and a minimum were observed for ESCC in 2003 and 2006, respectively. These variations may be due to random fluctuations, but overdispersion in data could also be present. For both sexes, the majority of the esophageal cancers in northern Portugal were ESCC, as observed in most European countries (5).

The prevalence of smoking in northern Portugal increased steadily among women and decreased among men over the last decades, which is in accordance with the prevalence previously observed for Portugal as a whole (15). The patterns of alcohol consumption found in the region seemed different from the ones previously described for the country, for which a long-term and marked decrease in overall alcohol consumption had been portrayed in international evaluations (53). However, these comparisons are not straightforward: in international studies, data are usually related to availability, estimated from production, import, export and sales data in each country (54); in our study, we described the prevalence of alcohol consumption rather than dose, since such data were not available at a regional level. Our results suggest that in northern Portugal alcohol drinking is an important contributor to ESCC risk (the trends in the prevalence of alcohol consumption and ESCC incidence rates are upwards in men and downwards in women); for EAC, tobacco was more important (the trends in the prevalence of tobacco consumption and EAC incidence rates are downwards among men and upwards among women), which was expected given that alcohol intake influences the ESCC risk but has no association with EAC (55, 56). Further studies should be performed in the region to quantify the contribution of each risk factor to the observed cancer trends, also taking into account the lag times between exposure and outcomes.

The increasing prevalence of overweight and obesity previously described for Portugal was also found in the northern region (16), although the interpretation of these figures is limited by the fact that no data could be obtained for the region in the years preceding 1995. Since a lag of 10 years has been described for the association between excess body mass index and EAC (57), this rising prevalence may contribute to an increase in EAC incidence in the next few years, which has not yet been observed in the area.

H. pylori infection is a determinant of both gastric and esophageal cancer. Worldwide, the steady decline in gastric cancer incidence and mortality trends over the last 5 decades has been mainly attributed to an increase in socioeconomic status, namely through a reduction of *H. pylori* infection (3) and better nutrition and food preservation practices (4). However, the prevalence of *H. pylori* infection in northern Portugal was found to be persistently high, with no clear trend detected, showing that there is room for further reduction of the burden of gastric cancer by lowering the prevalence of infection (17).

Regarding nutrition, we were only able to evaluate the consumption of fruit and vegetables and alcohol intake, since information on the consumption of salt and of smoked and pickled foods in the region is scarce, not allowing a trend evaluation.

Although this study is based on data from a relatively small country, Portugal presents the highest gastric cancer mortality rates in Western Europe, along with some of the highest prevalences of *H. pylori* infection in the most recent years; within Portugal, the northern region has the highest gastric cancer incidence and mortality rates. Nevertheless, we have recently described different patterns of variation in gastric cancer mortality (3), showing that Portugal, Japan, Chile and Ukraine, among others, share the same pattern, characterized by some of the highest rates in the world and declines of around 2.5% per year over the last 3 decades. For esophageal cancer, Portugal is also among a group of countries including, for example, Russia, France and Italy, which have ESCC as the predominant histological type and decreasing mortality rates (5). Finally, our extensive review provides easy access to data on the main risk factors for these cancers, which may be useful for understanding the observed trends and for international comparisons with this objective.

In conclusion, the declining incidence of cancers with unspecified subtypes suggests an improvement in cancer registration in northern Portugal, but limits, to a certain extent, the interpretation of trends according to cancer subtypes, mainly regarding gastric tumors. Further studies should be performed in the region to quantify the individual and joint contribution of risk factors to the observed cancer trends, to yield more informed predicted estimates.

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