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# PRE-DIAGNOSIS LIFESTYLE EXPOSURES AND SURVIVAL OF GASTRIC CANCER PATIENTS

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A dissertação de Mestrado teve como base dois artigos. No primeiro colaborei activamente na definição das hipóteses em estudo, na recolha, armazenamento, análise e interpretação dos dados; no segundo artigo, colaborei activamente na definição das hipóteses em estudo, na análise e interpretação dos resultados. Elaborei as versões iniciais de ambos os artigos:

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## 1. Gastric cancer as a public health problem

Cancer is a leading cause of death in the world that has accounted for 7.6 million deaths (around 13% of all deaths) in 2008 [1] and the GLOBOCAN projections suggest that oncological diseases are likely to remain a major cause of mortality over the next couple of decades [2]. This increase will be determined for the most part by growth and aging of populations and will be largest in low- and medium-resource countries [3].

Gastric cancer is the fourth most common malignancy in the world, and it is estimated that approximately one million new cases of gastric cancer have occurred in 2008 [1].

The global burden of the gastric cancer can be measure by the economic value of disability-adjusted life years (DALY) [4]. In the year of 2008, in the world, gastric cancer is the second cancer accounting for the highest number of DALYs [5-6], with the mortality component contributing more for the burden of disease than the disability.

### 1.1. Gastric cancer incidence

Behind lung, breast and colorectal cancer, gastric cancer represents 9.7% of all cancers (excluding skin non-melanoma) in men and 5.8% in women (Table 1) [2]. Additionally, 72.2% of cases occur in developing countries (Table 1) and half the world total occurs in Eastern Asia [1]. Gastric cancer age-standardized incidence rates are about twice as high in men than in women [1, 7].

**Table 1. Gastric cancer incidence for men and women in 2008**

| | **World** | | **Region** | | | |
|---|---|---|---|---|---|---|
| | | | **More developed Countries** | | **Less developed countries** | |
| | ***Men*** | ***Women*** | ***Men*** | ***Women*** | ***Men*** | ***Women*** |
| Number of cases | 640031 | 348571 | 173014 | 101681 | 467017 | 246890 |
| Percentage of all cancers (excluding skin nonmelanoma) | 9.7 | 5.8 | 5.8 | 3.9 | 12.8 | 7.1 |
| Crude incidence rate (/100 000) | 18.8 | 10.4 | 29.0 | 16.1 | 16.6 | 9.1 |
| Age-standardized * incidence rate (/100 000) | 19.8 | 9.1 | 16.7 | 7.3 | 21.1 | 10.0 |

* World standard population

**Source:** GLOBOCAN 2008 [1]

In Europe, 145,889 new cases occurred in 2008, 86,865 in men and 59,024 in women, corresponding to an age-standardized incidence rate (European standard population) of 14.5/100,000 men and 7.0/100,000 women, respectively [1]. The highest age-

standardized incidence rates are observed in countries like Japan (46.8/100,000 men) or Korea (62.2/100,000 men) [1]. In Africa, the age-standardized incidence rates are the lowest (4.7/100,000 men) [1].

Despite these differences between the countries, in the last 50 years there have been widespread reductions in the gastric cancer incidence [8-9], mainly non-cardia gastric cancer [10-11]. Several studies showed an increasing [12-17] or unchanging incidence [18-21] of gastric cardia cancers. Cancers of the antrum and pylorus (non-cardia gastric cancer) tend to be most frequent in high-risk regions such as China, Japan, Eastern Europe and Central/South America [21-23], while gastric cardia cancers are more common where the overall gastric cancer incidence is lower [24].

The classification of the anatomical cardia region has changed over the years and cardia cancer was coded separately from other gastric cancers only after the 8$^{th}$ revision of the International Classification of Diseases (ICD-8) [25]. Difficulties in distinguishing between gastric cardia cancers and cancers of the lower third of the oesophagus are usual in the studies. In a report from the Swedish Cancer Register 15% of cardia cancer cases were classified as non-cardia gastric cancer and the observed increase in the incidence of cardia adenocarcinoma in the Swedish Cancer Register might be explained by disparities in tumour classification over time [25].

The Laurén classification [26] categorizes the gastric tumours in two major types: intestinal or diffuse. Some carcinomas may not fit into one type or another, and thus fall into 'mixed' or 'unclassified' categories [27]. The decline in incidence rates has been more pronounced in the intestinal type [28-29].

The reasons for the generalized decline in gastric cancer rates are complex and not completely know. A more varied and affluent diet and better food conservation, like a decreased reliance on salted and preserved foods; smoking decline in some parts of the developed world [9] and the decline in the frequency of *Helicobacter pylori* infection are potential explanations for the downward trends in gastric cancer incidence [7, 9, 30-32].

### 1.2. Gastric cancer mortality

Worldwide, gastric cancer is the second leading cause of cancer death [33] in both sexes with 737419 deaths in 2008 [1] and a corresponding age-standardized rate (world standard population) of 10.3 deaths/100,000 inhabitants (Table 2). About fifteen percent of the gastric cancer deaths occur in the more developed countries (Table 2).

**Table 2. Gastric cancer mortality for men and women in 2008**

| | Region | | | | | |
|---|---|---|---|---|---|---|
| | **World** | | **More developed countries** | | **Less developed countries** | |
| | ***Men*** | ***Women*** | ***Men*** | ***Women*** | ***Men*** | ***Women*** |
| Number of cases | 463930 | 273489 | 110245 | 70703 | 353685 | 202786 |
| Percentage of all cancers (excluding skin nonmelanoma) | 11 | 8.2 | 7.2 | 5.8 | 13.1 | 9.6 |
| Crude mortality rate (/100,000) | 13.6 | 8.2 | 18.5 | 11.2 | 12.6 | 7.5 |
| Age-standardized * mortality rate (/100,000) | 14.2 | 6.9 | 10.3 | 4.7 | 16.0 | 8.1 |

* World standard population

**Source:** GLOBOCAN 2008 [1]

The highest mortality rate estimates (age-standardized – world standard population) are observed for Eastern Asia, in countries like Mongolia (36.9/100,000 men; 17.6/100,000 women) or China (30.1/100,000 men; 14.6/100,000 women), and the lowest in Northern America (2.8/100,000 men; 1.5/100,000 women), in the United States of America (2.7/100,000 men; 1.4/100,000 women) [1].

The gastric cancer mortality rate has fallen throughout Europe during the past decades [34-35], primarily due to the decrease of gastric cancer incidence rates, mostly as an effect of the extraordinary improvement of living conditions in European societies [36-38]. The reduction of 80,000 cancer deaths that was observed in the European Union from 1988 to 1997 was largely attributed to the decline in gastric cancer rates, as in the same period the number of gastric cancer deaths decreased in 24,000 [39].

In addition to the impact of the mortality rates in the global burden of gastric cancer and taking into account the combination of the highest DALYs with the economic value of DALYs, the contribution of gastric cancer to economic value of DALYs varies from the 2$^{th}$ highest for lower middle income countries to the 4$^{th}$ highest in high income and upper middle income countries. In low income countries, gastric cancer is the 10$^{th}$ [5] (Table 3).

**Table 3. Estimated number of DALYs and the economic value of DALYs in the top five types of cancer country-income group in 2008 (current US $ billion)** [5]

| | Cancer Type | DALY ('000) | Economic value (US $ bl.) |
|---|---|---|---|
| **High-income** | Trachea/bronchus/lung cancers | 3754.7 | 151.8 |
| | Colon/rectum cancer | 2117.9 | 85.0 |
| | Breast cancer | 1828.9 | 73.9 |
| | ***Stomach cancer*** | ***1033.6*** | ***41.8*** |
| | Lymphomas/multiple myeloma | 900.3 | 36.4 |
| **Upper-midlle income** | Trachea/bronchus/lung cancers | 1433.7 | 12.8 |
| | Colon/rectum cancer | 854.8 | 7.6 |
| | Breast cancer | 846.1 | 7.5 |
| | ***Stomach cancer*** | ***806.3*** | ***7.2*** |
| | Leukaemia | 507.2 | 4.5 |
| **Lower-midlle income** | Trachea/bronchus/lung cancers | 5902.0 | 12.6 |
| | ***Stomach cancer*** | ***4792.1*** | ***10.2*** |
| | Liver cancer | 4589.2 | 9.8 |
| | Esophagus cancer | 2961.3 | 6.3 |
| | Breast cancer | 2448.4 | 5.2 |
| **Low-income** | Mouth and oropharynx cancers | 2252.4 | 1.3 |
| | Cervix uteri cancer | 2191.0 | 1.3 |
| | Breast cancer | 1899.3 | 1.1 |
| | Lymphomas/multiple myeloma | 1844.3 | 1.1 |
| | Trachea/bronchus/lung cancers | 1720.7 | 1.0 |

**Source:** Jonh et al [5]

## 1.3. Gastric cancer in Portugal

In Portugal, gastric cancer is the third most common malignant tumour (Table 4) in both sexes with 2889 new cases in 2008, corresponding to age-standardized incidence rates of 19.2/100,000 men and 9.2/100,000 women [1].

In 2001, the incidence rates ranged from 32.1/100,000 in north region, 14.9/100,000 in the center (age-standardized, European reference population) [40]. Considering separately men and women, the incidence rates for men are higher in the north of Portugal (45.0/100,000 men), followed by the south (25.0/100,000 men) and the center region (21.8/100,000 men) (age-standardized, European reference population) [40]. In women the

rates are 22.0/100,000 women in the north region, 11.9/100,000 women in the south and 9.3/100,000 in the center (age-standardized, European reference population) [40].

**Table 4. Proportion of cases of the most frequent cancers in Portugal**

| | **Both sexes** | | **Men** | | **Women** |
|---|---|---|---|---|---|
| | **Incidence** | | **Incidence** | | **Incidence** |
| Colorectum | 16.1% | Prostate | 21.4% | Breast | 27.7% |
| Lung | 7.6% | Colorectum | 16.4% | Colorectum | 15.6% |
| **Stomach** | 6.7% | Lung | 10.9% | **Stomach** | 5.7% |
| Bladder | 4.5% | **Stomach** | 7.4% | Cervix uteri | 4.9% |
| Non-Hodgkin lymphoma | 3.4% | Bladder | 6.2% | Corpus uteri | 4.4% |

**Source:** GLOBOCAN 2008 [1]

According to RORENO (North Region Cancer Registry), in the north of Portugal, between 1997 and 2006 the incidence rate of gastric cancer decline in both sexes and was twice higher in men than in women [41]. In ROR Centro (Center Region Cancer Registry), in the same period, the incidence rate varied between years, but the smallest incidence rate was in 1998 and the highest was 2004 with differences between sexes (women with a lower incidence of gastric cancer) [42-51].

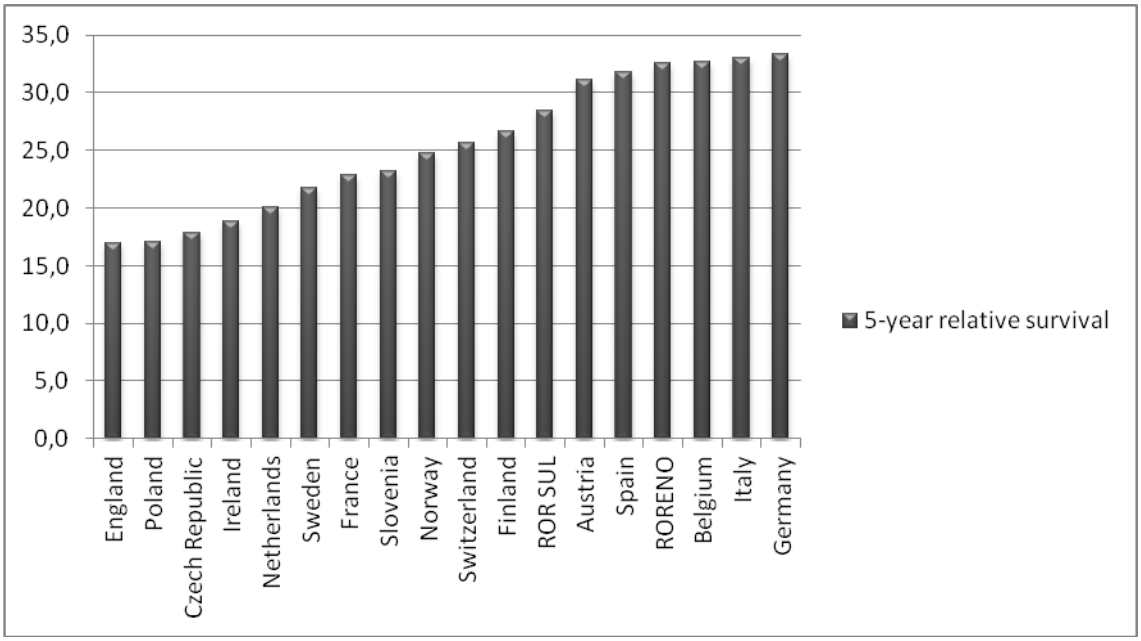
The last date available for the three registries combined in Portugal is from 2005 and the incidence rate for gastric cancer is 27.5/100,000 in men and 13.8/100,000 in women (age-standardized, European reference population) [52].

Population-based survival data in Portugal is available only from RORENO [53] and ROR-Sul (South Region Cancer Registry) [54].

In RORENO [53], the 5-year relative survival for cases diagnosed between 2000-2001 was 32% for men and 37% for women. Regional differences were also observed, with the highest 5-year relative survival in Braga (42%) and the lowest in Viana do Castelo (22%). Considering both sexes, the ages group 55-64, 65-74 and ≥75 years present the lowest survival compare with the younger patients (15-44 years) [53]. In the south [54], the 5-year relative survival for cases diagnosed in the same period was 29% in men and 32% in women, and was higher in the region of Lisboa and Vale do Tejo.

Five-year relative survival for gastric cancer in the region of RORENO, adjusted for age (population – International Cancer Survival Standards) was 32.6%, and 28.4% in ROR-Sul (Figure 1) [53]

**Figure 1. Five-year relative survival of gastric cancer patients diagnosed in 2000/2001 in 16 European countries and two population based cancer registries from Portugal (RORENO and ROR-Sul)**




**Source:** RORENO [53]

In Portugal, gastric cancer was responsible for 2423 deaths in 2008, corresponding to an age-standardized mortality rate of 10.5/100,000 inhabitants [1]. Gastric cancer is the third most common cause of oncological death in both sexes (Table 5). Separately, in men is the four most common cancer with 10.2% cases and in women the third most common with 9.6% (Table 5) and a age-standardized mortality rates in men of 15.0/100,000 and women 6.8/100,000 [1].

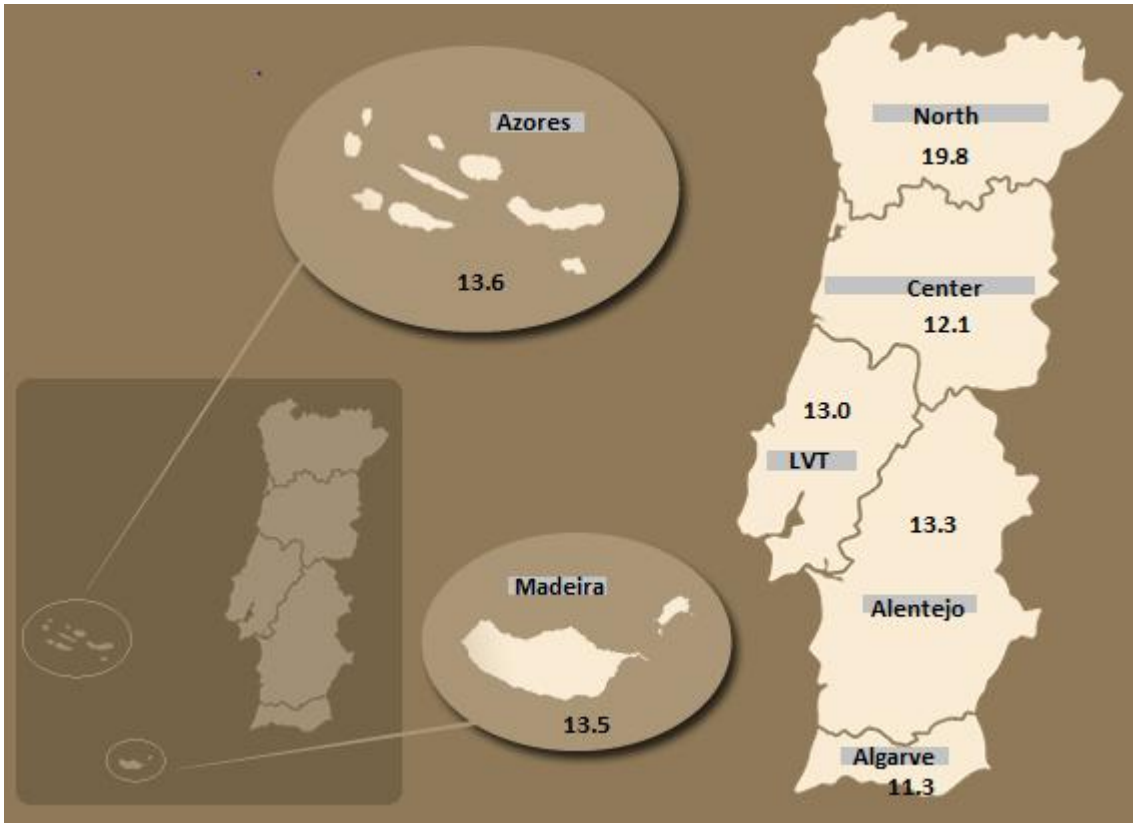
**Table 5. Proportion of oncological deaths due to the most frequent cancers in Portugal**

| | **Both sexes Mortality** | | **Men Mortality** | | **Women Mortality** |
|---|---|---|---|---|---|
| Colorectum | 15.2% | Lung | 18.2% | Colorectum | 16.4% |
| Lung | 13.7% | Colorectum | 14.4% | Breast | 15.9% |
| **Stomach** | **10.0%** | Prostate | 13.8% | **Stomach** | **9.6%** |
| Pancreas | 4.4% | **Stomach** | **10.2%** | Lung | 6.8% |
| Leukaemia | 3.2% | Pancreas | 3.9% | Pancreas | 5.0% |

**Source:** GLOBOCAN 2008 [1]

Gastric cancer mortality in Portugal varies between regions, being higher in the north (19.8/100,000 inhabitants) and lower in the south (11.3/100,000 inhabitants) (Figure 2) [55].

**Figure 2. Age-standardized (European reference population) gastric cancer mortality rates (/100,000), by health region in 2006**




**Source:** Risco de Morrer em Portugal 2006 [55]

Like in other European countries, the mortality rates in Portugal have been declining in the last decades [34].

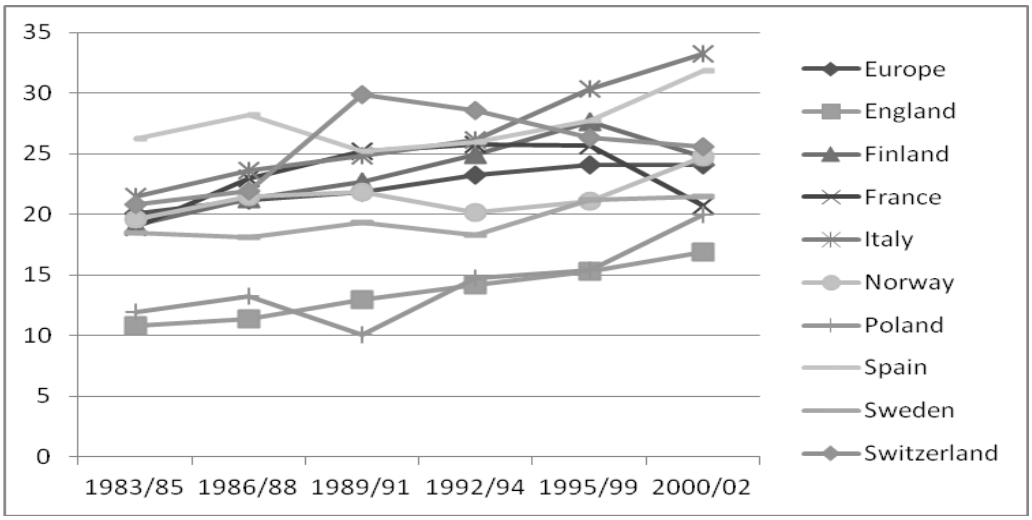
## 2. Survival of gastric cancer patients

Gastric cancer survival tends to be poorer in developing countries, most likely because of a delayed stage at diagnosis and a limited access to timely and standard treatment [7]. With few exceptions, survival tended to be higher amongst female than amongst male gastric cancer patients [56-57].

In Europe, the 5-year mean relative survival increased from 15.0%, between 1978-1980, to 21.0% in 1987-1989 [58]. Between 2000 and 2002 the 5-year mean relative survival estimate was 24.9%, similar to the observed in the USA (25.0%) [59] and furthermore in USA, the survival rates varies by race (between 2001-2007 5-year relative survival was 26.1% for white race and 27.2% for black race) [60].

Figure 3 depicts the variation in 5-year relative survival for gastric cancer in European countries between 1983 to 2002, with an increase being observed in most countries [61].

**Figure 3. Trends in 5-year relative survival for adults (aged 15-99 years) diagnosed with gastric cancer in Europe between 1983 and 2002**




**Standart population:** (1983-1999) – age-distribution of cases of the overall European; (2000/02) – European standard cancer populations.

**Source:** Eurocare database (1983-1999) [62] and Verdechia *et al* (2000/02) [59].

The variation in gastric cancer survival across settings and with time is largely related with the relative weight of cancers with different characteristics regarding subsite, histological type and stage [63]. The countries with higher incidence rates of gastric cancer, in general have better survival rates than countries with lower incidence [63]. This is mainly due to differences in the proportion of cases with better or worse survival. There is an excellent

probability of long-term survival in patients treated in an early stage, while in patients with serosal involvement and lymph node metastasis the prognosis is extremely poor [64-68]. Efforts to increase the proportion of stage I cancers presenting for surgery can be shown to improve prognosis, by diagnosing the cancers when still surgically curable [67].

Regarding the Laurén classification of tumour, the histological type is an important independent determinant of survival, with the risk of dying being higher in the diffuse type cancers than in those of the intestinal type [69-70].

Some authors [71-72] consider that age has prognostic value because young patients with gastric cancer have a poorer prognosis than older patients. Perhaps they present with more advanced disease because the index of suspicion for malignant disease is low and so the symptoms are allowed to progress for a longer period before investigation is considered, or there may be a greater biological activity of the tumour, which is more likely to be of the Laurén diffuse type.

In the USA, between 1995-2000, the 5-year relative survival for distant stage and unstaged category was worse than for the localized and regional stage [6]. In Japan, as a result of population screening and probably a greater knowledge of early symptoms and a low threshold for diagnostic evaluation, 50% of gastric cancers are diagnosed at a localized stage, and the overall 5-year survival has increased from 20% in 1962 to 40% in 1992 [73].

Gastric cardia tumours have a much poorer prognosis compared to those in the pyloric antrum, with lower 5-year survival and higher operative mortality [74].

Gastric cancer survival differences may be explained also by differences in the socioeconomic status of the patients [64, 75-78]. Patients with a higher income occupation and/or a higher educational level showed a better life expectancy. This may be associated with environmental exposures that may influence gastric cancer incidence [8] as well as prognosis [8]. The relation between behaviours before the diagnosis and the survival of gastric cancer patients remains poorly understood, and may contribute to a more comprehensive characterization of the burden associated with these exposures.

It is reasonable to argue that diet could affect the progression of diet-related neoplasms and the probability of disease recurrence but only few studies address this topic. Frequent intake of fruits and vegetables appears to have a protective effect on survival [79-80]. Huang *et al.* refer, in contrast, that other dietary items like salted fished, pickled food or red meat failed to show relationship with survival [79] and Palli *et al.* explain that a diet rich in animal protein may raise disease development in patients who are affected with familial gastric neoplasm [80].

## 3. Objectives

There is a large variation in gastric cancer survival across regions. The geographical and temporal differences in gastric cancer survival may be explained by a heterogeneous distribution of the access to early diagnosis and treatment across populations, as well as differences in the socioeconomic status of the patients. The latter may also be associated with environmental exposures with potential impact both in the risk of gastric cancer and the patients' prognosis.

This dissertation addresses the association between pre-diagnosis lifestyle exposures and the survival of gastric cancer patients. It includes two studies with the following specific objectives:

- To review systematically the published studies assessing the association between pre-diagnosis lifestyle exposures and the survival of gastric cancer patients (Paper I).
- To quantify the association between pre-diagnosis lifestyle exposures and survival of gastric cancer patients in a Portuguese setting (Paper II).

**Pre-diagnosis lifestyle exposures and survival of gastric cancer patients: systematic review and meta-analysis.**

**ABSTRACT**

The relation between lifestyles and gastric cancer has been thoroughly investigated, but few studies addressed the impact of these exposures on prognosis. Therefore, we quantified the association between pre-diagnosis smoking, alcohol intake and other dietary exposures and the survival of gastric cancer patients, through systematic review and meta-analysis. We searched Pubmed® and EMBASE® up to April 2011, and computed summary Hazard ratio (HR) estimates and respective 95% confidence intervals (95%CI) through random-effects meta-analysis (DerSimonian and Laird). Heterogeneity was quantified using the $I^2$ statistic. Seven articles, providing data from 6856 cases evaluated in seven countries (Canada, Japan, Italy, USA, Korea, Iran and Sweden), were eligible for meta-analysis. The summary HR was 1.08 (95%CI: 0.90-1.30) for smoking (current vs. never smokers, 7 studies; $I^2$=56.2%) and 1.13 (95%CI: 1.00-1.28) for alcohol consumption (drinkers vs. non-drinkers, 5 studies; $I^2$=13.2%). Only two studies assessed the effect of other dietary factors. This study summarizes the best evidence available on the relation between pre-diagnosis lifestyles and survival of gastric cancer patients. Alcohol drinkers have lower survival, but results on the effect of smoking lack consistency and there is almost no information on the effects of dietary factors.

**Key Words:** Stomach neoplasms; Survival; Smoking; Alcohol Drinking; Meta-analysis.

## Introduction

Gastric cancer is worldwide the fourth most common malignancy, after lung, breast and colorectal cancers, despite the geographical differences in its frequency [1] and the widespread decline in incidence and mortality over the last decades [2]. The number of new cases and deaths continues to increase worldwide because of population growth and aging in high-risk countries.

In Europe, 5-year relative survival increased from 15.0% between 1978-1980 to 21.0% in 1987-1989 [3]. Among cases diagnosed between 2000 and 2002 the 5-year relative survival estimate was 24.9%, with wide geographical differences (*e.g.*, 16.6% in Scotland and 33.2% in Italy) [4]. Within-country variability in survival has also been observed in several settings (*e.g.*, Italy [5], United Kingdom [6]).

The geographical and temporal differences in gastric cancer survival may be explained by a heterogeneous distribution of the access to early diagnosis, and treatment across populations [7] as well as differences in the socioeconomic status of the patients [8]. The latter may also be associated with environmental exposures with potential impact both in the risk of gastric cancer [9-10] and the patients' prognosis [11].

The understanding of the relation between pre-diagnosis lifestyles and survival may contribute to a more accurate characterization of the burden associated with these exposures. Therefore, we conducted a systematic review and meta-analysis of the published original research.

## Materials and methods

We searched Pubmed® and EMBASE®, from inception to April 2011, with no language restrictions. Reports of cohort studies that evaluated lifestyle determinants of survival in gastric cancer patients were eligible for the systematic review whenever providing quantitative estimates of the association and respective precision estimates. Review articles and conference proceedings were not included in the present review. The search expressions and the systematic review flow-chart are presented in Annex 1.

The electronic database searches, the selection of articles and the extraction of data were conducted independently by two researchers (IF, AB), following a previously defined protocol. Discrepancies were resolved by consensus or involving another researcher (NL).

Hazard ratios (HR), and respective precision estimates, for the association between lifestyle exposures and survival were extracted. When a study provided more than one estimate, we selected the one adjusted for the largest set of variables. When sex or gastric cancer subtype-specific HR estimates were available, the stratum-specific HRs were considered as if were obtained from different studies.

From each study we further extracted data on the following variables: country; year of publication; characteristics of the participants; sample size; study design (methods of data collection, duration of follow-up); control of potential confounding. We contacted the authors by email to obtain information on these issues when not provided or not clearly presented in the original reports; some of the authors provided complementary information that was included in Annex 2.

Random-effects meta-analyses, conducted using the DerSimonian and Laird method, were conducted to obtain summary measures for the association between pre-diagnosis lifestyles (highest vs. lowest exposures) and survival of gastric cancer patients.

Publication bias was examined through visual inspection of the funnel plot. The Begg adjusted rank correlation test and the Egger´s regression asymmetry test were used for further assessment of bias through hypothesis testing.

All analyses were conducted using STATA® version 11.2 (StataCorp, College Station, Texas, USA).

## Results

Seven studies [11-17] were eligible for the systematic review. All of them quantified the relation between smoking and survival of gastric cancer patients and the effects of alcohol consumption were addressed in five reports; dietary exposures were evaluated in two studies (Figure 1).

The studies were published between 1985 and 2008; each of them referred to an investigation conducted in a different country: two in Europe (Italy and Sweden [11, 14]); three in Asia (Japan, Korea and Iran [13, 16-17]); two in North America (Canada and USA [12, 15]).

In most studies the assessment of lifestyle exposures was accomplished by trained interviewers, and referred to the period before diagnosis. In two studies the interview was done with patients or families [15, 17]. Park *et al*. [16] evaluated participants with a self-administrated questionnaire. Sundelof *et al.* [11] estimated the alcohol intake 20 years before the interview. In the report by Bako *et al*. [12] the period of exposure and the method used to obtain behavioural information from cancer patients was not specified.

Only three studies [11, 13-14] provided HR estimates adjusted for the stage of the disease at diagnosis and one [15] provided the crude HR estimates (Annex 2).

The summary HR for the relation between smoking (current *vs.* never smokers) and survival of gastric cancer patients was 1.08 (95%CI: 0.90-1.30), with a high heterogeneity across the HR estimates from each individual report ($I^2$=56.2%). Alcohol consumption was significantly associated with a poorer survival (current *vs.* never drinkers – summary HR=1.13, 95%CI: 1.00-1.28), and results were homogeneous ($I^2$=13.2%) (Figure 1). Only one study presented results for cardia and non-cardia cancers [15], with no differences according to cancer subsite, and Sundelof *et al.* [11] only evaluated cases of cancer of the cardia.

In one of the reports [14] that assessed the effect of dietary exposure on survival, no significant associations were observed for any specific food or food group, except for α-tocopherol (HR=0.75; 95%CI: 0.56-0.99). In the other study [13] the consumption of raw vegetables (HR 0.74; 95%CI: 0.56-0.99), bean curd (HR=0.65; 95%CI: 0.42-0.98) and chicken meat (HR=0.61; 95%CI: 0.39-0.94) were associated with a significantly higher survival.

For alcohol consumption there was no evidence of publication bias by the visual inspection of the funnel plot (Figure 2), in accordance with the results from the Begg adjusted rank correlation test (*P*=0.851) and the Egger´s regression asymmetry test (*P*=0.840). For smoking the funnel plot suggests that small studies with a negative association may be

underrepresented (Begg adjusted rank correlation test, *P*=0.297; Egger´s regression asymmetry test, *P*=0.003).

## Discussion

This systematic review and meta-analysis summarizes the best evidence available on the relation between the lifestyles before diagnosis and survival of gastric cancer patients.

Only 7 eligible studies, published over more that 20 years, were identified despite the comprehensiveness of the search strategy. We searched the two most important electronic databases – Pubmed® and EMBASE® – with no language restrictions, and using highly sensitive and unspecific search expressions, including the main terms referring to smoking, alcohol drinking and other dietary exposures. The "number-needed-to-read" was 277, which confirms the low specificity and high sensitivity of the searches. Furthermore, there was no evidence of publication bias for alcohol drinking, and the conclusions regarding the effects of smoking on gastric cancer survival are not likely to be influenced by a potential bias.

The main findings of the present quantitative synthesis are naturally influenced by intrinsic limitations of the primary sources of information. In addition to the heterogeneous methods used in the different studies, all addressed the effects of pre-diagnosis exposures without taking into account possible behavioural changes occurring after the baseline evaluation. Previous investigations showed lifestyle modifications in cancer patients after diagnosis or treatment [18-19] and healthier lifestyles than the subjects at higher risk of developing a cancer [20-21]. However, despite the potential impact of post-diagnosis lifestyles in the survival of gastric cancer patients, the disease duration is relatively low and we may hypothesise that the cumulative exposures throughout life are more relevant as a potential determinant of survival. The conclusions of our meta-analyses apply only to pre-diagnosis exposures, and further research is needed to address the impact of behavioural changes occurring after cancer diagnosis.

Lifestyle predictors of survival have been studied for other cancers, namely breast [22-23], lung [24-25] and laryngeal carcinoma [26-28]. The results suggest that patients with a higher intake of fruits and vegetables before diagnosis have a better survival, and that smoking and drinking may be detrimental for prognosis, which is compatible with our observations for gastric cancer.

The relatively small number of reports addressing this subject precludes more robust conclusions. However, our study provides a transparent and reproducible assessment of the published evidence on this topic. The potential effects of pre-diagnosis lifestyle exposures in the prognosis of gastric cancer patients seem relatively modest and well designed epidemiologic studies with large samples are needed for a more robust assessment of these determinants of survival.

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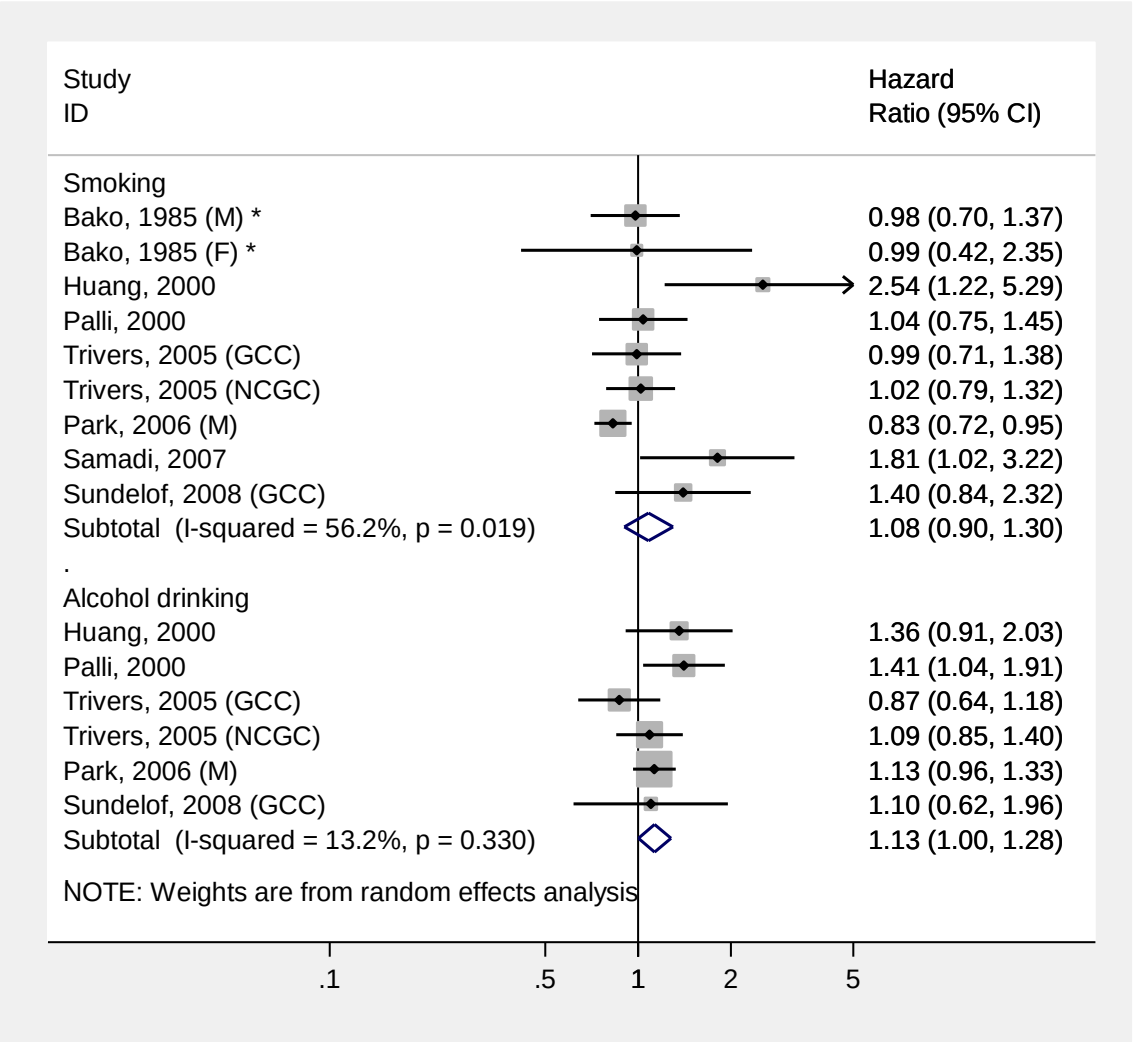
**Conflicts of interest**

There are no conflicts of interest.

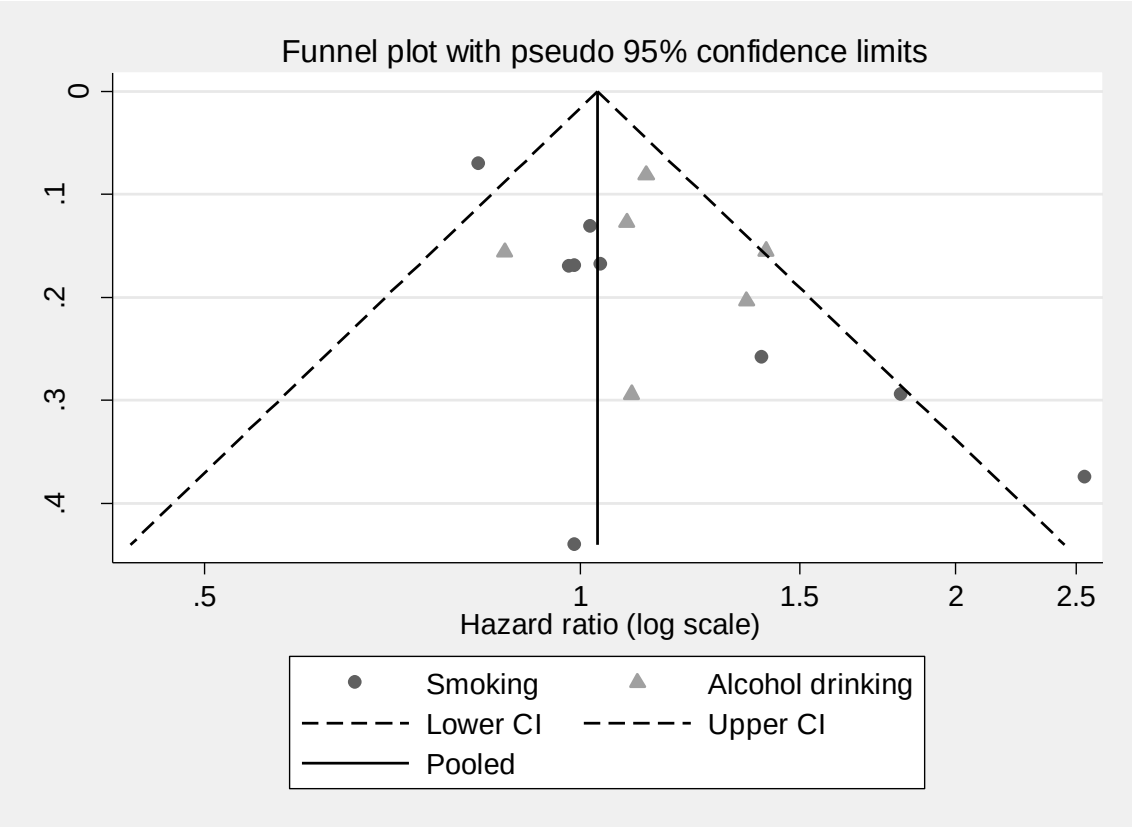
Figure 1. Meta-analyses for the relation between smoking (current *vs.* never smokers) and alcohol drinking (current *vs.* never drinkers) and survival of gastric cancer patients




Abbreviations: M – male; F – Female; GCC – Gastric Cardia Cancer; NCGC – Non-Cardia Gastric Cancer; 95%CI – 95% Confidence Interval.

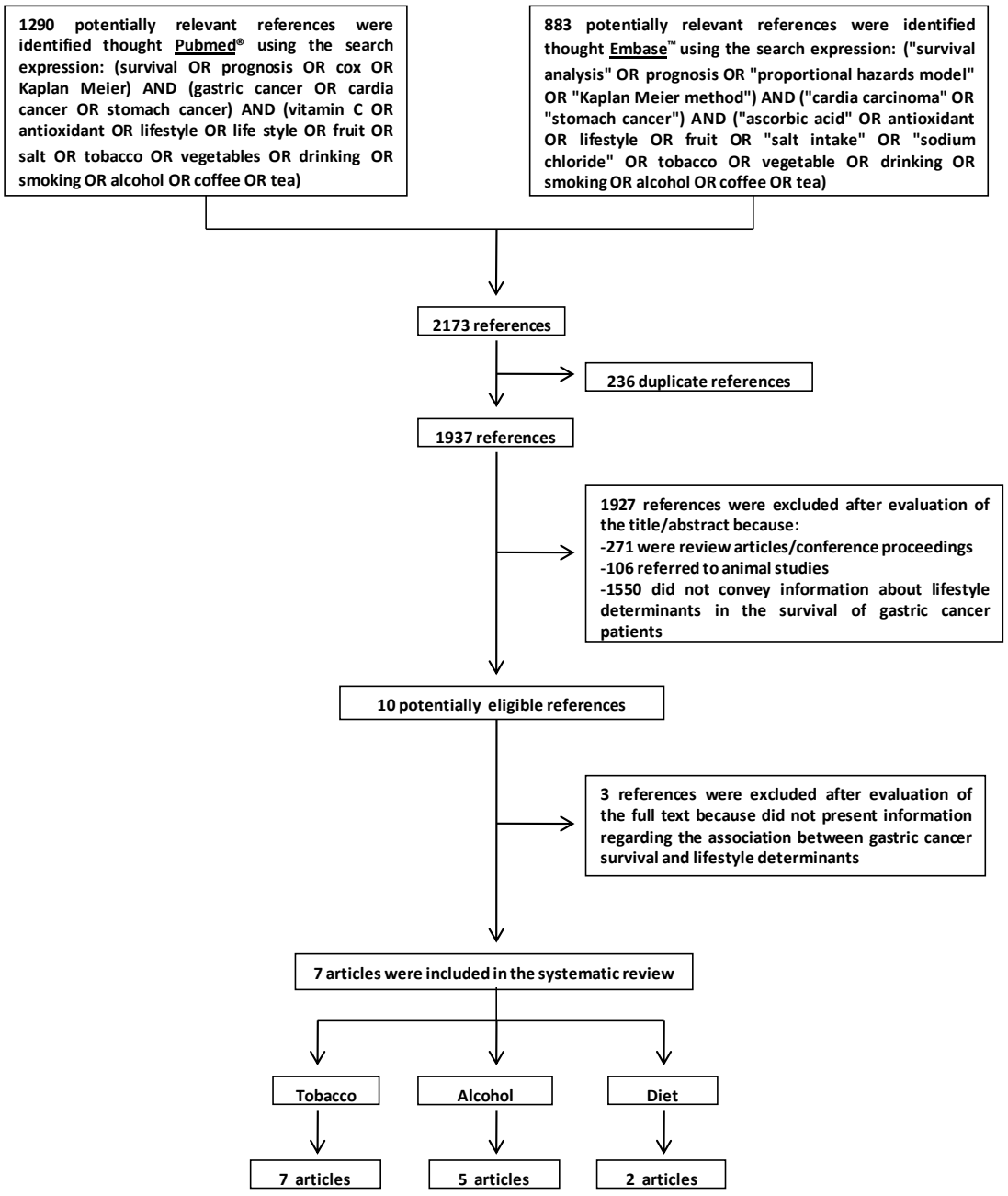
* The Hazard Ratio and respective 95%CI for the highest *vs.* lowest exposures were computed by the authors of the present review using the results for the lowest *vs*. highest exposure levels provided in the original report.

Figure 2. Funnel plot of studies evaluating the association between smoking and alcohol drinking and survival of gastric cancer patients




Abbreviations: CI – Confidence limits

Annex 1. Systematic review flow-chart



Annex 2. Summary of the studies evaluating the pre-diagnosis lifestyle exposures and survival of gastric cancer patients included in the systematic review

| 1st author, yr Country (region) | Participants' characteristics | Participants' evaluation | Follow-up | Lifestyle factors HR (95% CI) | Control of confounding |
|---|---|---|---|---|---|
| **Bako, 1985 USA (Alberta)** | - Gastric cancer (n=467)<br>- Recruitment: 1969-1973<br>- The diagnosis of stomach cancer was confirmed in 97% of cases by pathology and in 3% by radiology or by clinical investigation<br>- Men/women: 332/135<br>- Age range (years): ≤30 to ≥80<br>- Cancer site (cardia/pylorus/other specified parts/unspecified location):<br>men – 16/30/149/137;<br>women – 6/16/48/65<br>- Stage (localized/regionalized/remote metastases/not stated): men – 40/190/105/1;<br>women – 18/70/45/2 | The instruments used for data collection or the timing of the evaluation are not described | -Outcome: "mortality data for this study are based on death determined by the Alberta Cancer Registry and not by vital statistics"<br>- The date of the diagnosis was used as the start of observation<br>- Follow-up: up to December 31, 1981<br>- All subjects had a minimum of 8-years of potential follow-up<br>- Median survival (15 months) for both sexes<br>- At the end of the study period, 33 males and 13 females patients had been withdraw alive from the study or had been lost to follow-up | Smoking (smoker vs. never smoker)<br>men – 0.98 (0.70-1.37) [a]<br>women – 0.99(0.42-2.35) [a] | Not available |
| **Huang, 2000 Japan** | - Gastric cancer (n=877)<br>- Recruitment: 1988-1994<br>- Pathologically confirmed cases of gastric adenocarcinoma that survived through the immediate postoperative period<br>- Men/women: 578/299<br>- Age range (years): 40 to >79<br>- Pathological stage (I/II/III/IV):<br>men – 329/64/69/116;<br>women – 66/32/47/54<br>- Histological type [b] (PA/TA/PDA/SRCC/MA/ST):<br>men – 13/289/184/51/14/25;<br>women – 6/86/133/62/5/7 | - Questionnaire survey started in 1988 covering all first-visit outpatients before their examination and diagnosis in the ACC [c].<br>- Questionnaire topics: personal behaviour, habitual smoking and drinking, and beverage and food intake, as well as reproductive and general health status, before symptoms appeared | - Outcome: gastric cancer as the primary cause of death, determined by the records of the ACC<br>- The date of the diagnosis was used as the start of observation<br>- Follow-up: up to December 31, 1998<br>- At the end of follow-up 636 patients were still alive (72.2% males vs. 73.2% females)<br>- All patients were traced completely | Smoking (current vs. never)<br>2.54 (1.22-5.29)<br>Number of cigarettes (<30 vs. 0/day)<br>1.49 (0.89-2.49)<br><br>Habitual drinking (current vs. never)<br>1.36 (0.91-2.02)<br>Quantity of alcohol [d]<br>≥2.0 vs. 0 go/day<br>1.08 (0.70-1.66)<br><br>Fruit (>3 vs. ≤ 3 times/wk)<br>0.98 (0.73-1.31)<br>Raw vegetables (>3 times/wk vs. ≤ 3 times/wk)<br>0.74 (0.56-0.99) | Age<br>Pathological type<br>Stage of cancer<br>Gender (only fruit/ raw vegetables) |
| **Palli, 2000 Italy (Florence)** | - Gastric cancer (n=382)<br>- Recruitment: 1985-1987<br>- Histologically confirmed cases with staging information available<br>- Men/women: 239/143 | - Questionnaire topics: smoking history, alcohol use and other dietary information (done by trained dietitians focused on the 12-month period 1 year prior to the onset of symptoms or prior to surgery) | - Outcome: mortality data was based on all causes determined by the records of Municipal Population Offices and to the Regional Mortality Registry on December 31, 1997 | Smoking (current vs. never)<br>1.04 (0.75-1.45)<br><br>Alcohol (3rd vs. 1st third)<br>1.41 (1.04-1.91) | Age (continuous)<br>Gender<br>Social status<br>Pathologic stage at diagnosis (T |

| | | | | | |
|---|---|---|---|---|---|
| | - Age range (years): <50 to >64<br>- Laurén classification (intestinal/diffuse/mixed): 234/89/57<br>- Histopathologic grading (G1/G2/G3): 38/80/264<br>- Lymph node involvement (no/yes): 73/309<br>- T classification (T1/T2/T3/T4): 34 /68/130/150 | - Diet was assessed by asking the usual frequency of consumption of 181 food items and beverages | - The information on mortality at 10 years was available for all but three patients (0.8%) – these patients were censored<br>- The date of the interview was used as the start of observation<br>- The 65 patients who were still alive at the end of the study had a mean follow-up of 134 months (range, 120–150 months) | Total calories (3 rd vs. 1st third) 0.91 (0.68-1.20)<br>Vitamin C (3 rd vs. 1st third) 1.02 (0.77-1.36)<br>Retinol (3 rd vs. 1st third) 1.13 (0.86-1.49)<br>Beta carotene (3 rd vs. 1st third) 1.13(0.85-1.49)<br>Vitamin E (3 rd vs. 1st third) 0.75 (0.56-0.99) | and N classification)<br>Lymph node involvement |
| **Trivers, 2005 USA (Washington state/ New Jersey/ Connecticut)** | - Gastric cardia cancer (GCC [e]) (n=261) and non cardia gastric cancer (NCGC [f]) (n=367)<br>- Recruitment: 1993-1995<br>- Men/women: GCC – 223/38; NCGC – 253/114<br>- Age range (years): 31 to 79<br>- Stage (localized/regional/distant/unknown): GCC – 34/120/70/37; NCGC – 70/161/104/32<br>- Tumor grade (WMD/PDU/ND) [g]: GCC – 97/137/27; NCGC – 101/214/52 | - Questionnaire topics: tobacco and alcohol history (done by trained interviewers focused in anytime prior to one year before the interview)<br>- The mean length of time between cancer diagnosis and the interview was 3.7 months when the interview was conducted with the case subjects and 8.5 months when the interview was conducted with a proxy. | - Outcome: mortality data was based on " any cause" determined by the records of the National Death Index, with maximum follow-up of 90 months<br>- The date of the diagnosis was used as the start of observation<br>- Follow-up: up to July, 2000 in Washington state; September, 2000 in New Jersey and October, 2000 in Connecticut<br>- Three patients were excluded from all analyses (2 patients lost to follow-up, 1 patient owing to a discrepancy between the date of diagnosis and death). | Alcohol drinking (ever [h] vs. never) GCC – 0.87 (0.64-1.18) NCGC – 1.09 (0.85-1.40)<br>Cigarette smoking (ever [i] vs. never) GCC – 0.99 (0.71-1.38) NCGC – 1.02 (0.79-1.32) | Only crude HRs were provided |
| **Park,2006 Korea** | - Gastric cancer (n=3979)<br>- Recruitment: 1996-2002<br>- Patients who were diagnosed with multiple primary cancer were excluded (n=418)<br>- Only men<br>- Age range (years): ≥20 | - Information regarding tobacco history, alcohol use and dietary preferences was obtained with a self-administered questionnaire that could be applied before or after the diagnosis | - Outcome: "mortality data by linkage to the National Statistical Office" between 1996 and 2004<br>- The date of the diagnosis was used as the start of observation<br>- Follow-up: up to December, 2004 | Smoking (current vs. never) 0.83 (0.72-0.95)<br>Alcohol consumption ≥124.2 vs. 0 1.13 (0.96-1.32) | Age<br>Alcohol consumption<br>Body mass index<br>Fasting serum glucose level<br>Cholesterol level<br>Physical activity<br>Food preference<br>Blood pressure<br>Heart disease<br>Liver disease<br>Cerebrovascular disease |
| **Samadi, 2007 Iran (Ardabil Province)** | - Gastric cancer (n=279)<br>- Recruitment: 2000-2004<br>- Biopsy-proven patients<br>- Men/women: 217/62<br>- Age range (years): >20 to <90 | - Face to face interview (patients or families) at the time of diagnosis at Aras Clinic | - Outcome: "direct interview with patients or their families" and "evaluation of death certificates" (n=55)<br>- The date of the diagnosis was used as the start of observation<br>-Follow-up was from diagnosis until death | Smoking (yes vs. no) 1.81 (1.02-3.23) | Sex<br>Age<br>Residence<br>Surgery<br>Chemotherapy<br>Radiotherapy |

| | | | | | |
|---|---|---|---|---|---|
| | | | or immigration | | Smoking<br>Differentiation<br>Education |
| **Sundelof, 2008**<br>**Sweden** | - Gastric cardia cancer (n=244)<br>- Recruitment: 1994-1997<br>- Cases born and still living in Sweden<br>- Men/women: 208/36<br>- Age range (years): <80 | - Questionnaire topics: history of tobacco use; alcohol intake 20 years before interview | - Outcome: "through cross-linkage to the nationwide Swedish Death Register"<br>- The date of the diagnosis was used as the start of observation<br>- Follow-up: from the date of diagnosis until the date of death or end of study (December, 31 of 2004), whichever occurred first. | Smoking (current smokers vs. never)<br>1.4 (0.8-2.2)<br><br>Alcohol intake (>70 g/week vs. never)<br>1.1 (0.6-1.9) | Tumour stage<br>Sex<br>Age<br>Education Level<br>Symptomatic reflux<br>Body mass index<br>Smoking<br>Alcohol intake<br>Physical activity<br>Oesophagectomy |

**Abbreviations:**

[a] The Hazard Ratio and respective 95%CI for the highest *vs.* lowest exposures were computed by the authors of the present review using the results for the lowest vs. highest exposure levels provided in the original study; [b] Histological type: PA – Papillary Adenocarcinoma; TA – Tubular adenocarcinoma; PDA – Poorly differentiated adenocarcinoma; SRCC – Signet-ring cell carcinoma; MA – Mucinous adenocarcinoma; ST – Special types; [c] ACC – Aichi Cancer Center; [d] 1 go = 180 ml Japanese wine; [e] GCC – Gastric cardia cancer ; [f] NCGC – Non-cardia gastric cancer; [g] Tumor grade: WMD – Well/moderate differentiated; PDU – Poorly differentiated/undifferentiated; ND – Not determined; [h] at least 1 alcoholic drink (12 oz. beer, 4 oz. glass of wine, 1 drink with hard liquor) per month, for 6 months; [i] at least 1 cigarette(s)/day for 6 months.

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**Pre-diagnosis lifestyle exposures and survival of gastric cancer patients: a cohort study from Portugal**

**Abstract**

Dietary habits and smoking are recognized as important gastric cancer determinants. However, their impact on prognosis remains poorly understood. We aimed to quantify the association between lifestyles and the survival of gastric cancer patients in a large sample of gastric cancer cases with a long follow-up. The study included 568 patients recruited in the two major public hospitals in the north of Portugal (2001-2006). Participants were inquired about pre-diagnosis smoking and dietary habits regarding the year preceding the diagnosis. The latter were recorded using a validated semi-quantitative food frequency questionnaire and data were analysed by food group and dietary pattern. The vital status of all participants, up to 2011 (maximum follow-up: 10 years), was assessed through the North Region Cancer Registry. Survival curves were estimated by the Kaplan-Meier method. Cox proportional hazards regression models were used to estimate age-, sex-, education- and extent of disease-adjusted hazard ratios (HRs) and 95% confidence intervals (95%CI). Only a dietary pattern characterized by high consumptions of most food groups and low vegetable soup intake was significantly associated with a better prognosis among patients with the extent of disease classified as regional spread (HR=0.45; 95%CI, 0.22-0.93). No significant associations were observed for other variables (alcohol, smoking, consumption of fruits and vegetables, red and processed meat or foods with the highest contribution for sodium intake). This study shows that pre-diagnosis lifestyles have a small impact in the survival of gastric cancer patients.

**Key Words:** Stomach neoplasms; Survival; Smoking; Alcohol Drinking; Diet.

## Introduction

Gastric cancer is the fourth most common malignancy in the world [1]. Although its frequency has been declining for decades it remains the second leading cause of cancer mortality [2] and ranks second among the cancers accounting for the highest number of disability-adjusted life years (DALYs) (9.6%) [3-4]. In Europe, the average 5-year relative survival rate of patients diagnosed between 2000 and 2002 was estimated in 24.9%, however varying widely across countries [5].

The prognosis of gastric cancer patients varies with the tumour's characteristics, namely location and histological type, and it is also likely to be related with the socioeconomic status of the patients [6].The latter, in addition to its relation with access to health care and stage at diagnosis [7], may also be associated with environmental exposures with potential impact both in the risk of gastric cancer and in the survival of cancer patients [8-9]. The understanding of the relation between pre-diagnosis lifestyles and survival may contribute to a more accurate characterization of the burden associated with these exposures. However, the effect of behavioural factors, such as alcohol drinking, tobacco smoking and dietary habits, on the survival of gastric cancer patients has seldom been addressed and available evidence showed inconsistent results [10].

Therefore, we aimed to quantify the association between pre-diagnosis lifestyles and the survival of gastric cancer patients, in a large sample followed prospectively for up to 10 years, with special emphasis on the potential modification of the effects according to the time of survival.

## Methods

Setting and selection of participants

As part of a case-control study previously described in detail [11-13] we evaluated incident cases of gastric cancer selected among those admitted to the surgery wards of the two major public hospitals for cancer patients in the north of Portugal (Hospital de S. João and Instituto Português de Oncologia Francisco Gentil, both in Porto), between June 2001 and December 2006.

Eligible patients were incident gastric cancer cases that had not been previously diagnosed with cancer (except skin non-melanoma), nor had been subjected to subtotal gastrectomy for benign conditions; they also had to be able to provide informed consent. To evaluate cognitive function, all individuals older than 64 years took a Mini-Mental State Examination [14] and we restricted the analysis to participants without serious cognitive impairment at baseline (score ≥18 points) [15].

Evaluation of environmental exposures

The participants completed a comprehensive structured questionnaire providing information on demographic, social, behavioural and medical characteristics, applied by trained interviewers during in-hospital stay, shortly after admission, mostly before surgical treatment. Since illness duration is related with changes in food intake, the assessment of the dietary intake referred to the previous year or the year before onset of symptoms, as applicable. We excluded from the analyses the patients declaring to have changed dietary habits more than one year before the interview.

Dietary exposures were quantified using a semi-quantitative food frequency questionnaire (FFQ) comprising 82 food/beverage items or categories, designed according to Willett [16] and adapted by inclusion of a variety of typical Portuguese food items. Foods with a similar nutrient composition were grouped together as a single item. The FFQ was validated with a 7-day food record and, regarding the fatty acid composition, with the composition of subcutaneous adipose tissue [17-18]. For each FFQ item, subjects were asked the average frequency of consumption (nine possible responses ranging from never to six or more times per day), the portion size usually consumed (based on a photograph manual with small, medium, and large portion sizes), and the number of months during which it had been consumed in the previous year. Also, for each item, this information was used to estimate the frequency of consumption of medium servings, corrected for seasonality by multiplying the reported consumption by the ratio between the number of months during which the food item was reported to be consumed and 12 months. For analysis, the

frequency of consumption of each food group was categorized using the tertiles of the overall distribution as cut-offs.

The overall intake of fruits and vegetables, red and processed meat and foods with a high contribution to salt intake was established by adding up the amounts of single items or groups consumed per day, as follows: fruits and vegetables (apple or pear, orange or mandarin, banana, kiwi, strawberry, cherry, peach or plum, melon or watermelon, persimmon, fig or loquat or apricot, grapes, natural fruit juices, lettuce, watercress, tomato, cucumber, green and white cabbages, broccoli, cauliflower or Brussels sprout, spinach or spring greens or turnip greens, spinach, bean pod, carrot, turnip, green beans, green pepper, onion, beans and peas); red and processed meat (beef, pork, liver, tongue, ham, sausage, bacon, hamburger); food items with the highest contribution to sodium intake (namely grains, cereals, rice, pasta, potatoes, bread, meat, meat products, offal, vegetable soup, fish and cheese). The latter were defined according to the results of a previous nutrition survey conducted in same setting [19].

Dietary patterns were defined by principal components and cluster analyses, as previously described in detail [20]. Three dietary patterns were identified (Pattern I – high consumption of fruits and dairy products, and low consumption of alcoholic beverages; Pattern II – low consumption of fruit, salads, vegetables, dairy products, fish and meat; Pattern III – high consumptions of most food groups and low vegetable soup intake). Pattern II was shown previously to be associated with a higher risk of gastric cancer when compared with patterns I or III [20].

Smoking and alcohol consumption status were assessed. Individuals smoking regularly at least one cigarette per day were classified as current smokers and those who stopped smoking at least 6 months before the interview as former smokers [21]. Individuals drinking regularly at least one alcoholic drink per day were classified as current drinkers and those who stopped drinking at least 6 months before the interview as former drinkers.

Clinical characteristics

The anatomic site (cardia/non-cardia/not defined) and histological type of the tumours (intestinal/diffused/mixed) were classified according to the routine procedures of both institutions, based on gastrectomy specimens or endoscopic biopsy material. To guarantee a standard pathologic classification according to the Laurén criteria, a single experienced pathologist reviewed all pathology reports and slides were reassessed whenever necessary. For a more accurate classification of the tumour histological type [22-23] only those cases from whom a surgical specimen was available were considered for the analyses including information on the tumours' histological type (78% of the patients eligible for data analysis).

The information on the extent of disease, according to the European Network of Cancer Registries criteria [24], was obtained from the North Region Cancer Registry (RORENO).

Follow-up

The vital status of the participants was assessed by the RORENO. The event of interest was death by all causes. Patients were followed until the end of July, 2011, or date of death, whichever occurred first. No follow-up information could be obtained for 10 patients. The median duration of follow-up was 6.6 years for patients alive at the end of study and 1.2 years for those reported dead, with a maximum follow-up of 10 years.

Statistical analysis

A total of 568 gastric cancer patients with follow-up information were available for data analysis. We used the Kaplan-Meier survival function to estimate the observed survival at 1, 3 and 5 years of follow-up, and Cox proportional hazard regression analysis to compute adjusted hazard ratios (HR) with the corresponding 95% confidence intervals (95%CI). Differences in survival estimates between groups were tested using the Log-rank test.

All analyses were conducted using STATA®, version 11.2 (StataCorp, College Station, Texas, USA).

Ethics

The study was approved by the ethics committees of the involved hospitals and the participants provided written informed consent.

## Results

Characteristics of the participants

Incident gastric cancer patients were mostly men (62.1%) and nearly one-quarter were aged 50 years or less (median age of 63 years). Approximately three-quarters of the participants had 4 or less schooling years. Most cancers were located in the non-cardia region (78.6%), and 55% of those from whom a surgical specimen was available were of the Laurén's intestinal histological type. No information was available to classify 16.9% of the cases according to the extent of disease, and one-quarter were advanced cancers (Table 1).

At baseline, approximately one-fifth of the patients were smokers and one-quarter ex-smokers, while 72.9% reported being current drinkers. The median daily consumption of fruits and vegetables, red and processed meat and foods accounting for high salt intake was 3.4, 0.7 and 2.0 servings, respectively (Table 2).

Observed survival

Survival decreased significantly with age (*P*=0.001). Patients aged 24-50 years and 51-60 years had a similar survival until the third year of follow-up, diverging only after that (Figure 1). Only 32.0% and 7.0% of the patients with an advanced cancer were alive at one and three years after diagnosis, respectively. The patients with unknown stage had a survival in-between the observed for the regional spread and advanced cancers until the 5 years of follow-up, and thereafter closer to the observed for cases with regional spread (Figure 2).

Women presented a significantly lower survival than men (35.8% vs. 44.2% at 5 years, *P*=0.016). Cardia cancers had worse survival than the non-cardia (29.0 vs. 46.3 at 5 years), as well as those of the Laurén's diffuse type compared with the intestinal (36.2 vs. 56.6 at 5 years) (Table 1).

Regarding the relation with lifestyle characteristics, significant differences were observed only according to the smoking status (*P*=0.039), with never smokers having a poorer survival than current smokers (36.8 vs. 43.7 at 5 years) (Table 2).

There were virtually no changes in the results when excluding the patients who died up to one week after the surgery that could be considered due to postoperative complications (data not shown).

Multivariate analysis

No independent meaningful or statistical significant associations were observed between the pre-diagnosis lifestyles and gastric cancer survival, overall or across strata defined by cancer subsite, histological type or stage, except for a significantly lower hazard

rate among regional spread patients with dietary pattern III (high consumptions of most food groups and low vegetable soup intake), compared with those with pattern I (high consumption of fruits and dairy products, and low consumption of alcoholic beverages) (HR=0.45, 95%CI; 0.22-0.93). A similar relation was observed among those with localised/local spread patients, though not statistically significant.

The strongest associations with an increased hazard rate, though not statistically significant, were observed among the patients with localised/local spread cancer for smoking (current vs. never, HR=2.17, 95%CI, 0.51-9.23) and consumption of higher amounts of fruits and vegetables ($3^{rd}$ third vs. $1^{st}$ third, HR=2.30, 95%CI, 0.78-6.74) and red and processed meat ($3^{rd}$ third vs. $1^{st}$ third, HR=2.03, 95%CI, 0.66-6.24).

## Discussion

The present study shows no significant associations between pre-diagnosis lifestyles and gastric cancer survival, with the exception of a lower hazard rate among patients with less advanced disease reporting a dietary pattern that is also associated with a lower risk of gastric cancer.

This is one of the few investigations [10] on the association between pre-diagnosis behaviours and gastric cancer survival. In addition to providing evidence on a topic that has seldom been addressed before, there are several distinctive methodological characteristics of the present investigation that contribute to the robustness and validity of the findings. It is based in a large case series of patients followed for a long period, which allows a stratified analysis according to the extent of disease, and consequently the estimation of the impact of these exposures specifically for subgroups of patients with short and long survival periods. This strategy of analysis has not been used in the previous studies, although we may hypothesise that lifestyles adopted for several years before diagnosis are unlikely to be responsible for the differences in mortality of gastric cancer patients shortly after the disease is diagnosed. This is supported by our results that showed significant associations only among the patients that survived for longer periods, although it contributes for two limitations of our study. On the one hand, the endpoint was all-cause mortality, because no information on the cause of death was available. Although the former may be a surrogate of gastric cancer mortality due to the low overall survival of gastric cancer patients, this is less likely among the subjects presenting with less advanced disease. Therefore, the factors that we identified as being associated with lower hazard rate are not necessarily decreasing the risk of death due to gastric cancer. On the other hand, previous investigations showed that cancer patients may adopt healthier lifestyles after diagnosis or treatment [25-27]. This could contribute for differences in survival according to lifestyle changes after gastric cancer diagnosis, but these were not assessed in our study, and their potential confounding effect could not be accounted.

Only two previous reports addressed the effect of dietary exposures on the survival of gastric cancer patients [28-29], and our investigation provides new evidence on these potential determinants of prognosis. In addition to using valid methods to assess dietary intake prior to cancer diagnosis or symptoms, we analysed the potential effect of the exposure to food groups known to be associated with the risk of gastric cancer, as well as the effect of dietary patterns. The latter provides an additional tool to understand the impact of diet in cancer survival.

Our study also adds to previous research on this topic the subgroup analyses according to anatomic site and histological type. Although these clinical characteristics influence survival, no differences were observed according to pre-diagnosis exposures within each of these groups of patients.

In conclusion, pre-diagnosis lifestyles have a small impact in the survival of gastric cancer patients.

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**Conflicts of interest**

There are no conflicts of interest.

Table 1. Observed survival of gastric cancer patients at one-, three- and five-years according to socio-demographic and clinical characteristics

| | n (%)[b] | Deaths during follow-up (n) | Observed survival (%)[b] | | | |
|---|---|---|---|---|---|---|
| | | | 1 year | 3 years | 5 years | *P* value |
| Sex | | | | | | 0.016 |
| Women | 215 (37.9) | 142 | 65.6 | 43.3 | 35.8 | |
| Men | 353 (62.1) | 203 | 75.9 | 52.7 | 44.2 | |
| Age (years) | | | | | | 0.001 |
| ≤50 | 131 (23.1) | 65 | 79.4 | 57.3 | 51.9 | |
| 51-60 | 120 (21.1) | 66 | 78.3 | 56.7 | 45.0 | |
| 61-70 | 156 (27.5) | 98 | 66.0 | 44.2 | 38.5 | |
| 71-80 | 129 (22.7) | 92 | 66.7 | 39.5 | 31.0 | |
| ≥81 | 32 (5.6) | 24 | 68.8 | 50.0 | 34.4 | |
| Education (years) | | | | | | 0.027 |
| 0 | 65 (11.4) | 46 | 60.0 | 40.0 | 33.9 | |
| 1-3 | 98 (17.3) | 67 | 62.2 | 40.8 | 33.7 | |
| 4 | 282 (49.7) | 161 | 76.2 | 51.4 | 44.3 | |
| 5-9 | 89 (15.7) | 49 | 78.7 | 59.6 | 46.0 | |
| ≥10 | 34 (6.0) | 22 | 70.6 | 44.1 | 35.3 | |
| Anatomic site | | | | | | <0.001 |
| Cardia | 69 (12.2) | 51 | 62.3 | 37.7 | 29.0 | |
| Non-cardia | 447 (78.6) | 248 | 79.0 | 55.3 | 46.3 | |
| Not-classified | 52 (9.2) | 46 | 25.0 | 11.5 | 11.5 | |
| Histological type [a] | | | | | | 0.001 |
| Intestinal | 244 (55.0) | 113 | 86.5 | 65.2 | 56.6 | |
| Diffuse | 127 (28.6) | 82 | 78.0 | 47.2 | 36.2 | |
| Mixed | 73 (16.4) | 42 | 78.1 | 52.1 | 43.8 | |
| Extent of disease | | | | | | <0.001 |
| Localised | 112 (19.7) | 11 | 96.4 | 92.7 | 91.1 | |
| Local spread | 37 (6.5) | 11 | 97.3 | 81.1 | 73.0 | |
| Regional spread | 181 (31.9) | 121 | 86.2 | 54.7 | 36.4 | |
| Advanced | 142 (25.0) | 137 | 32.4 | 7.0 | 4.9 | |
| Unknown | 96 (16.9) | 65 | 66.6 | 37.5 | 32.3 | |

[a] This information is available from 444 patients that underwent surgical resection of the stomach; [b] The sum of percentages may be different from 100% due to rounding.

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Table 2. Observed survival of gastric cancer patients at one-, three- and five-years according to lifestyle characteristics

| | n (%)[a] | Deaths during follow-up (n) | Observed survival (%)[a] 1 year | 3 years | 5 years | *P* value |
|---|---|---|---|---|---|---|
| Smoking status | | | | | | 0.039 |
| Never smokers | 318 (56.0) | 209 | 70.1 | 45.9 | 36.8 | |
| Ex-smokers | 138 (24.3) | 73 | 76.1 | 55.1 | 48.6 | |
| Current smokers | 112 (19.7) | 63 | 72.3 | 50.9 | 43.7 | |
| Alcohol status | | | | | | 0.822 |
| Never drinkers | 72 (12.7) | 41 | 70.8 | 51.4 | 44.4 | |
| Ex- drinkers | 82 (14.4) | 51 | 69.5 | 45.1 | 39.0 | |
| Current drinkers | 414 (72.9) | 253 | 72.7 | 49.5 | 40.8 | |
| Fruits and vegetables | | | | | | 0.663 |
| 1st third | 189 (33.3) | 114 | 71.4 | 50.3 | 41.8 | |
| 2nd third | 190 (33.4) | 120 | 71.6 | 46.8 | 38.9 | |
| 3rd third | 189 (33.3) | 111 | 73.0 | 50.3 | 42.3 | |
| Red/processed meat | | | | | | 0.235 |
| 1st third | 192 (33.8) | 120 | 67.7 | 46.9 | 39.6 | |
| 2nd third | 188 (33.1) | 120 | 72.9 | 47.3 | 38.3 | |
| 3rd third | 188 (33.1) | 105 | 75.5 | 53.2 | 45.2 | |
| Sodium intake | | | | | | 0.166 |
| 1st third | 190 (33.4) | 119 | 71.1 | 45.8 | 40.0 | |
| 2nd third | 189 (33.3) | 119 | 69.3 | 43.9 | 37.6 | |
| 3rd third | 189 (33.3) | 107 | 75.7 | 57.7 | 45.5 | |
| Dietary patterns | | | | | | 0.400 |
| Pattern I | 229 (40.3) | 141 | 70.3 | 48.0 | 39.7 | |
| Pattern II (high-risk) | 270 (47.5) | 168 | 73.0 | 48.2 | 40.0 | |
| Pattern III | 69 (12.2) | 36 | 73.9 | 56.5 | 49.3 | |

[a] The sum of percentages may be different from 100% due to rounding.

Table 3. Adjusted Hazard Ratios and corresponding 95% Confidence Intervals for lifestyle characteristics using multivariate Cox regression model

| | | Anatomic site | | Histological type | | Extent of disease | | |
|---|---|---|---|---|---|---|---|---|
| | | Cardia | Non-cardia | Intestinal | Diffuse | Localised and local spread | Regional spread | Advanced |
| | HR [a] (95% CI) | HR [b] (95% CI) | HR [b] (95% CI) | HR [b] (95% CI) | HR [b] (95% CI) | HR [c] (95% CI) | HR [c] (95% CI) | HR [c] (95% CI) |
| Smoking status | | | | | | | | |
| Never smokers | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Ex-smokers | 0.90 (0.66-1.23) | 0.76 (0.31-1.89) | 0.83 (0.57-1.21) | 0.88 (0.50-1.54) | 1.01 (0.56-1.82) | 0.48 (0.13-1.73) | 1.14 (0.71-1.83) | 1.14 (0.65-2.01) |
| Current smokers | 1.00 (0.72-1.38) | 1.31 (0.62-2.77) | 0.96 (0.64-1.44) | 1.16 (0.66-2.05) | 1.54 (0.74-3.22) | 2.17 (0.51-9.23) | 1.01 (0.56-1.85) | 1.30 (0.75-2.25) |
| Alcohol status | | | | | | | | |
| Never drinkers | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Ex-drinkers | 0.97 (0.63-1.48) | 1.93 (0.51-7.37) | 0.92 (0.55-1.52) | 0.82 (0.36-1.84) | 0.99 (0.41-2.38) | (N/A) | 1.84 (0.89-3.79) | 0.87 (0.44-1.74) |
| Current drinkers | 0.87 (0.61-1.25) | 1.37 (0.40-4.63) | 0.92 (0.62-1.38) | 0.97 (0.51-1.84) | 0.61 (0.28-1.30) | 0.63 (0.21-1.89) | 1.04 (0.55-1.98) | 0.81 (0.46-1.42) |
| Fruits and vegetables | | | | | | | | |
| 1st third | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2nd third | 1.18 (0.91-1.52) | 1.52 (0.73-3.19) | 1.89 (0.80-1.48) | 1.04 (0.66-1.62) | 0.84 (0.46-1.54) | 1.55 (0.53-4.54) | 1.04 (0.66-1.64) | 1.25 (0.83-1.89) |
| 3rd third | 0.98 (0.75-1.28) | 1.83 (0.86-3.91) | 0.93 (0.68-1.28) | 0.82 (0.50-1.34) | 0.96 (0.55-1.65) | 2.30 (0.78-6.74) | 1.01 (0.63-1.62) | 0.88 (0.56-1.39) |
| Red/processed meat | | | | | | | | |
| 1st third | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2nd third | 0.97 (0.75-1.26) | 0.86 (0.41-1.77) | 1.00 (0.73-1.37) | 1.21 (0.77-1.91) | 0.97 (0.51-1.83) | 0.67 (0.20-2.22) | 0.99 (0.63-1.54) | 0.94 (0.62-1.41) |
| 3rd third | 1.00 (0.75-1.35) | 0.85 (0.37-1.96) | 1.11 (0.78-1.60) | 0.94 (0.56-1.58) | 1.27 (0.69-2.35) | 2.03 (0.66-6.24) | 0.85 (0.52-1.39) | 1.00 (0.61-1.63) |
| Sodium intake | | | | | | | | |
| 1st third | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2nd third | 0.90 (0.69-1.16) | 0.78 (0.38-1.63) | 0.88 (0.64-1.22) | 1.22 (0.76-1.97) | 0.66 (0.37-1.18) | 0.47 (0.13-1.78) | 1.23 (0.79-1.92) | 0.79 (0.52-1.19) |
| 3rd third | 0.93 (0.71-1.22) | 0.62 (0.28-1.34) | 1.04 (0.75-1.46) | 1.50 (0.91-2.46) | 0.84 (0.46-1.52) | 0.91 (0.53-3.32) | 1.07 (0.65-1.76) | 0.71 (0.45-1.11) |
| Dietary patterns | | | | | | | | |
| Pattern I | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Pattern II | 0.94 (0.75-1.19) | 0.77 (0.38-1.53) | 0.97 (0.73-1.28) | 1.25 (0.83-1.89) | 0.72 (0.42-1.24) | 0.97 (0.39-2.38) | 0.80 (0.54-1.17) | 0.95 (0.63-1.43) |
| Pattern III | 0.79 (0.55-1.15) | 0.78 (0.30-2.02) | 0.85 (0.56-1.31) | 0.90 (0.45-1.79) | 0.46 (0.21-1.05) | 0.51 (0.06-4.47) | 0.45 (0.22-0.93) | 1.10 (0.64-1.90) |

Abbreviations: HR – Hazard Ratios; CI – Confidence Intervals; N/A – not applicable (there is no ex-drinkers patients with an extent of disease as localised and/or local spread).

[a] Adjusted to age, sex, education (continuous), extent of disease (grouped in localised and local spread; regional spread; advanced; unknown) ;[b] Adjusted to age, sex, education (continuous), extent of disease (grouped in localised, local spread and regional spread; advanced; unknown); [c] adjusted to age, sex, education (continuous).

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Figure 1. Survival probability according to age of gastric cancer patients using Kaplan-Meier method

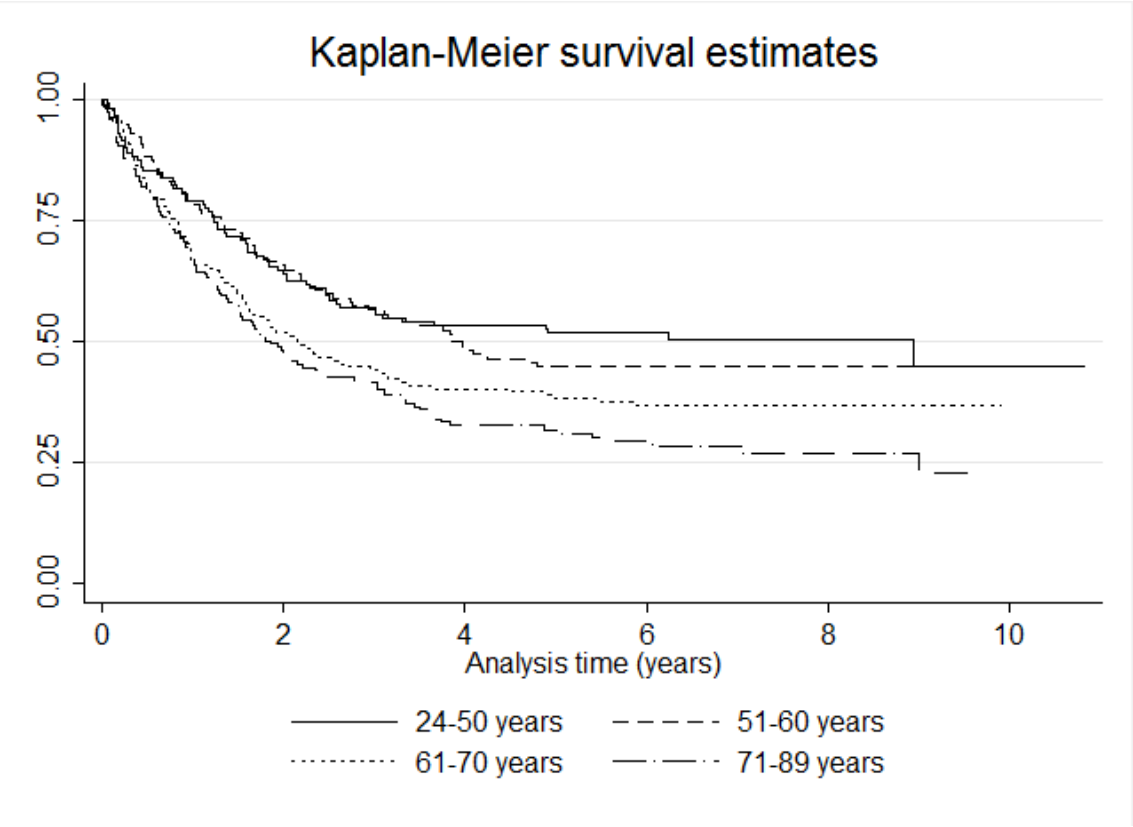
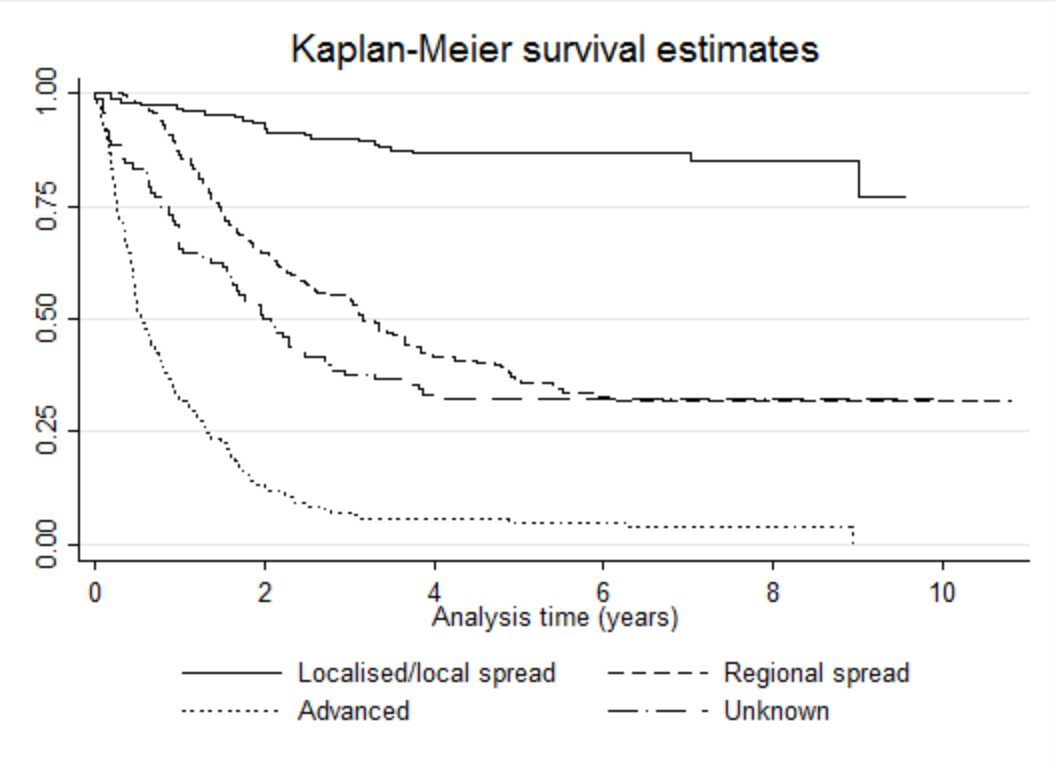


Figure 2. Survival probability according to extent of disease of gastric cancer patients using Kaplan-Meier method



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## 5. General discussion and conclusions

The present dissertation contributes to the understanding of the relationship between pre-diagnosis lifestyles and the survival of gastric cancer patients, taking into account the systematic review of the published articles addressing this topic and a large study with a long follow-up conducted in a high-risk Portuguese population.

The meta-analysis is based in the most comprehensive systematic review on this topic, and provides a summary of the best available evidence on the relation between pre-diagnosis lifestyles and gastric cancer survival.

The results from the cohort study are similar with the conclusions from the systematic review and meta-analysis. Most of the previous research [79-80] has addressed the relationship between foods or nutrients separately without taking into account the effect of dietary patterns. Our study adds the analysis also by dietary patterns. The present study also adds to previous investigations [79-85] the analysis of the pre-diagnosis determinants in relation with the extent of disease, which is an important factor for survival.

Our findings suggest that only dietary pattern III, related with high consumptions of most food groups and low vegetable soup intake, was significantly associated with a better relative survival, but only for patients identified with an extent of disease as regional spread. The dietary patterns are population-dependent and therefore these results may not be generalizable to other settings, particularly to populations with different dietary habits.

In conclusion, this dissertation showed no consistent effects of pre-diagnosis behaviours in the survival of gastric cancer patients, even among the subjects with clinical characteristics at diagnosis that are associated with a better prognosis.

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## 7. Summary

### Pre-diagnosis lifestyle exposures and the survival of gastric cancer patients

Gastric cancer is the fourth most common malignancy in the world and although is frequency has been declining for decades it remains the second leading cause of cancer mortality and ranks second among the cancers accounting for the highest number of disability-adjusted life years (DALYs). In Europe, the average 5-year relative survival rate of patients diagnosed between 2000 and 2002 was estimated in 24.9%, varying widely across countries.

The geographical and temporal differences in gastric cancer survival may be explained by a heterogeneous distribution of the access to early diagnosis, and treatment across populations as well as differences in the socioeconomic status of the patients. The latter may also be associated with environmental exposures with potential impact both in the risk of gastric cancer and the patients' prognosis.

The understanding of the relation between pre-diagnosis lifestyles and survival may contribute to a more accurate characterization of the burden associated with these exposures.

The aim of the present dissertation was to study the relationship between pre-diagnosis behaviours and the survival of gastric cancer patients. It includes two studies, with the following specific objectives:

- To review systematically the published studies assessing the association between pre-diagnosis lifestyle exposures and the survival of gastric cancer patients (Manuscript I).
- To quantify the association between pre-diagnosis lifestyle exposures and survival of gastric cancer patients in a Portuguese setting (Manuscript II).

### Manuscript I – Pre-diagnosis lifestyle exposures and survival of gastric cancer patients: systematic review and meta-analysis

Published studies quantifying the association between pre-diagnosis smoking and alcohol intake and the survival of gastric cancer patients were identified through systematic review and meta-analysis in Pubmed® and EMBASE® up to April 2011. Summary Hazard ratio (HR) estimates and respective 95% confidence intervals (95%CI) were computed through by random-effects meta-analysis (DerSimonian and

Laird) with current vs. never for smoking and drinkers vs. non-drinkers for alcohol consumption. Heterogeneity was quantified using the $I^2$ statistic.

Seven articles, providing data from 6856 cases evaluated in seven countries (Canada, Japan, Italy, USA, Korea, Iran and Sweden), were eligible for meta-analysis.

The summary HR was 1.08 (95%CI: 0.90-1.30) for smoking (current vs. never smokers; 9 estimates from 7 studies; $I^2$=56.2%) and 1.13 (95%CI: 1.00-1.28) for alcohol consumption (drinkers vs. non-drinkers; 6 estimates from 5 studies; $I^2$=13.2%). Only two studies assessed the effect of other dietary factors.

**Manuscript II – Pre-diagnosis lifestyle exposures and survival of gastric cancer patients: a cohort study from Portugal**

Incident cases of gastric cancer admitted to the surgery wards in two hospitals, between June 2001 and December 2006. Patients were interviewed regarding demographic, social, behavioural, and medical characteristics. For the year preceding the diagnosis, smoking habits was assessed and a validated food frequency questionnaire (FFQ) was used to estimate usual food intake.

Survival curves were estimated by the Kaplan-Meier method and Cox proportional hazards regression models were used to estimate age-, sex-, education, extent of disease-adjusted hazard ratios (HRs) and 95% confidence intervals (95%CI). Maximum follow-up: 10 years.

Three dietary patterns were identified: (I) high consumption of fruits and dairy products, and low consumption of alcoholic beverages; (II) low consumption of fruit, salads, vegetables, dairy products, fish and meat; (III) high consumptions of most food groups and low vegetable soup intake.

Only dietary pattern III was correlated significantly with a better 5-year survival and just for an extent of disease as regional spread (HR, 0.45, 95%CI, 0.22-0.93). The results were not significant for other variables (alcohol, smoking, consumption of fruits and vegetables, ingestion of red and processed meat and ingestion of food with the highest contribution of sodium intake).

**Conclusions**

- According to a systematic review and meta-analysis from the literature, a lower survival of gastric cancer patients was related with alcohol

consumption, for smoking there is no association and there is almost no information on the effects of dietary factors.

- The results from a cohort study conducted in Portugal confirm that pre-diagnosis lifestyles have a small impact in the survival of gastric cancer patients.

## 8. Sumário

### Estilos de vida antes do diagnóstico e sobrevivência dos doentes com cancro gástrico

O cancro gástrico é a quarta neoplasia maligna mais frequente e embora a sua incidência tenha vindo a diminuir ao longo de décadas, continua a ser a segunda principal causa de mortalidade por cancro e ocupa a segunda posição entre os cancros que contabilizam o maior número de anos de vida potencialmente perdidos (AVPP). Na Europa, a sobrevivência relativa média nos doentes diagnosticados entre 2000 e 2002 foi estimada em 24,9%, variando largamente entre os países.

As diferenças geográficas e temporais na sobrevivência de doentes com cancro gástrico pode ser explicada por uma distribuição heterogénea do acesso ao diagnóstico precoce e tratamento entre as populações, bem como diferenças no estatuto socioeconómico dos doentes. Também pode ser associada com as exposições ambientais com impacto potencial tanto no risco de cancro gástrico como no prognóstico dos doentes.

A compreensão da relação entre os estilos de vida antes do diagnóstico e sobrevivência podem contribuir para uma caracterização mais precisa da carga associada a estas exposições.

O objectivo desta dissertação foi estudar a relação entre estilos de vida antes do diagnóstico e a sobrevivência dos doentes com cancro gástrico, através consecução dos seguintes objectivos específicos:

- Revisão sistemática dos estudos publicados que avaliam a associação entre a exposição pré-diagnóstica e a sobrevivência de doentes com cancro gástrico (Manuscrito I).
- Quantificar a associação entre estilos de vida antes do diagnóstico e a sobrevivência dos doentes com cancro gástrico numa população portuguesa (Manuscrito II).

### Manuscrito I – Estilos de vida antes do diagnóstico e sobrevivência dos doentes com cancro gástrico: revisão sistemática e meta-análise

Os estudos publicados que quantificavam a associação entre a história pré diagnostica do consumo de tabaco e de bebidas alcoólicas e a sobrevivência de doentes com cancro gástrico foram sistematicamente revistos na Pubmed® e

EMBASE® até Abril de 2011. Foi usado um modelo de efeitos aleatórios (DerSimonian e Laird) para calcular estimativas conjuntas de Hazard Ratio (HR) e respectivos intervalos de confiança de 95% (IC 95%) referentes à comparação dos níveis de exposição mais elevados com os mais baixos (fumadores versus não fumadores para o tabaco e para o consumo de álcool, consumidores de álcool versus não consumidores de álcool). A heterogeneidade foi quantificada através da estatística $I^2$. Sete artigos foram elegíveis para meta-análise, fornecendo dados a partir de 6856 casos avaliados em sete países (Canadá, Japão, Itália, EUA, Coreia, Irão e Suécia).

O HR foi 1,08 (IC 95%: 0,90-1,30) para fumadores (fumadores versus não fumadores; 9 estimativas de 7 estudos; $I^2$ = 56,2%) e 1,13 (IC 95%: 1,00-1,28) para o consumo de álcool (consumidores de álcool versus não consumidores de álcool, 6 estimativas de cinco estudos, $I^2$ = 13,2%). Apenas dois estudos avaliaram o efeito de outros factores dietéticos.

**Manuscripto II – Estilos de vida antes do diagnóstico e a sobrevivência dos doentes com cancro gástrico: um estudo de coorte de Portugal**

Foram avaliados casos incidentes de cancro gástrico internados nos serviços de cirurgia de dois hospitais, entre Junho de 2001 e Dezembro de 2006. Os doentes foram entrevistados sobre as suas características demográficas, sociais, comportamentais e médicas. O consumo de tabaco foi avaliado, assim como ingestão habitual de alimentos por um questionário de frequência alimentar (QFA) validado, com base em informação relativa ao ano anterior ao diagnóstico.

As curvas de sobrevivência foram estimadas pelo método de Kaplan-Meier. Foram utilizados modelos de regressão de Cox para calcular Hazard Ratio ajustados para a idade, sexo, educação, extensão da doença, com os respectivos intervalos de confiança de 95% (IC 95%). O tempo máximo de seguimento foi de 10 anos.

Três padrões alimentares foram identificados: (I) alto consumo de frutas e produtos lácteos, e baixo consumo de bebidas alcoólicas; (II) baixo consumo de frutas, saladas, legumes, lacticínios, peixe e carne; (III) consumos elevados da maioria dos grupos alimentares e baixa ingestão de sopa.

Somente o padrão alimentar III foi correlacionado significativamente com uma melhor sobrevivência relativa a 5 anos, mas apenas para uma extensão da doença caracterizada por disseminação regional (HR, 0,45, 95% IC, 0,22-0,93). Os resultados não foram significativos para as outras variáveis (álcool, tabaco, consumo de frutas e

verduras, ingestão de carnes vermelhas e processadas e ingestão de alimentos com a elevada contribuição de sódio).

**Conclusões**

- De acordo com a revisão sistemática e meta-análise, o consumo de álcool está associado a uma menor sobrevivência dos doentes com cancro gástrico, não se observou uma relação significativa com o tabaco e a informação sobre os efeitos das exposições alimentares é escassa.
- Os resultados de um estudo de coorte realizado em Portugal confirmam que os estilos de vida pré-diagnósticos têm um pequeno impacto na sobrevivência dos doentes com cancro gástrico.