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Risk and survival of third primary cancers in a population-based cohort of gastric cancer patients

Samantha Morais [a], Luís Antunes [b], Maria José Bento [b], Nuno Lunet [a,c,*]

[a] EPIUnit — Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal
[b] Serviço de Epidemiologia — Instituto Português de Oncologia do Porto, Porto, Portugal
[c] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

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ABSTRACT

Background: The growing number of gastric cancers together with improved survival resulted in an increasing population of survivors at risk of multiple primary cancers.
Aims: To estimate the 10-year risk and survival of third primary cancers (TPCs) among gastric first primary cancers (FPCs).
Methods: Gastric FPCs from the Portuguese North Region Cancer Registry, diagnosed in 2000-2006 (n = 7409), were followed for a TPC (31/12/2012), and for all-cause death (31/12/2017). The cumulative incidence of TPCs was estimated. Patients with a TPC were matched (1:1, by sex, age group, years between FPC and second primary cancer [SPC] diagnosis, and SPC location) to FPC + SPC patients without a TPC.
Results: Overall, 25 (0.3% of FPCs and 6.8% of SPCs) TPCs were diagnosed. The most common sites were tobacco-related, mainly including digestive organs. Among all FPCs, 10-year cumulative incidence (95% confidence interval [CI]) of a TPC was 0.4% (0.2–0.5%) and among SPCs 7.6% (4.4–10.8%). For TPCs, compared to matched patients, age-adjusted hazard ratio (95%CI) for death was 1.68 (0.77–3.67). The 10-year cumulative mortality of TPCs and matched patients was 92.6% and 67.9%, respectively.
Conclusions: A clustering of tobacco-related cancers was observed in TPCs, with a 10-year cumulative incidence of 0.4% among FPCs. TPCs had worse survival than patients without a TPC.

1. Introduction

Gastric cancer is the fifth most common malignancy in the world and the third leading cause of death from cancer [1]. Though the survival of these patients remains poor [2], an increase has been observed as a result of gradual improvements in diagnosis and treatment [3], leading to a growing number of gastric cancer survivors. These patients are at higher risk of long-term sequelae, including cardiovascular diseases and multiple primary cancers (MPCs) [4]. Although many studies have described the epidemiological and clinical characteristics of patients with second primary cancers (SPCs) [4–7], there is a lack of published data addressing the risk and survival of patients with higher order primary cancers [8]. Despite this, there are studies that show that they are not that uncommon [4,9,10]; in particular, a previous study in Northern Portugal found that 4% of all MPCs were third tumours [5]. However, the risk and survival of TPCs has not been previously investigated among population-based survivors of gastric cancer.

Therefore, considering gastric cancer as a model of a cancer with low 5-year survival [2] but which is frequent in Northern Portugal [11] and responsible for a high proportion of SPCs [5], this study aimed to estimate the 10-year risk and survival of third primary cancers (TPCs) among gastric first primary cancer (FPC) patients.

2. Methods

A population-based cohort of gastric (International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] C16 [12]) FPCs (n = 7409) from the North Region Cancer Registry of Portugal (RORENO), diagnosed in 2000-2006 was followed for the diagnosis of MPCs (31/12/2012) and vital status (31/12/2017). MPCs were defined as proposed by the International Association of Cancer Registries and International Agency for Research on Cancer [13]. These were considered to be SPCs

* Corresponding author at: Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal.
E-mail address: nlunet@med.up.pt (N. Lunet).

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(n = 369) when two primary cancers were diagnosed in the same individual, TPCs (n = 25) when three primary cancers were diagnosed in the same individual, and fourth or higher order primary cancers (n = 5) when more than three primary cancers were registered.

Cumulative incidence and corresponding 95% confidence intervals (CIs) for the occurrence of TPCs from the date of diagnosis of the gastric FPC and of the SPC were estimated separately using the method of Kalbfleisch and Prentice [14], which accounts for the competing event of death.

In order to estimate the survival of TPCs, a matched-sample analysis was conducted. Individuals with TPCs (SPC + TPC; i.e., those diagnosed with fourth or higher order primary cancers [n = 5] were disregarded) were matched 1:1 to individuals with an SPC but without TPCs (SPC only) who were alive when the corresponding TPC was diagnosed, by sex, age groups (<55, 55–74 and ≥75 for 16 matches; <65 and ≥65 for one match; <75 and ≥75 for one match), number of years between FPC and SPC diagnoses (single year [from 1 to 12 years] for 12 matches; two year groups [from 1–2 years to 11–12 years] for three matches; and three year groups [from 1–3 years to 10–12 years] for three matches), and SPC location (lip, oral cavity and pharynx [ICD-10 C00–C14], digestive organs [ICD-10 C15–C26], respiratory and intrathoracic organs [ICD-10 C30–C39], female breast [ICD-10 C50], female genital organs [ICD-10 C51–C58], male genital organs [ICD-10 C60–C63], urinary tract [ICD-10 C64–C68], and lymphoid, haematopoietic and related tissue [ICD-10 C81–C96] [12]). After excluding two individuals with a TPC, as no match was available, 18 FPC + SPC patients with a TPC were included.

For TPC patients, survival time was considered as the time between TPC diagnosis and death from any cause or end of study period (31/12/2017), whichever occurred first. Survival time for SPC only patients was considered as the time between SPC diagnosis and death or end of study period (31/12/2017), whichever occurred first, minus the time between the TPC diagnosis and the SPC diagnosis of the matched TPC patient.

Cox-proportional hazards regression analyses were used to compute hazard ratios (HR) for all-cause mortality adjusted for age (continuous) with the corresponding 95% CI. The proportional hazards assumption was evaluated using Schoenfeld residuals. The observed cumulative all-cause mortality was estimated using 1-Kaplan–Meier [15].

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

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 173/2015).

3. Results

During follow-up, 369 patients developed an SPC (5.0% of gastric FPCs) and 25 patients a TPC (0.3% of all gastric FPCs and 6.8% of FPC + SPC) (Table 1).The median age at gastric FPC diagnosis for all patients was 68 years. SPCs and TPCs occurred more often among males (66.3% and 80.0%, respectively). For patients diagnosed with an SPC only, the median (percentile 25-percentile 75 [P25-P75]) time between the FPC and the SPC was 1.6 (0.2–4.9) years; the corresponding time for patients with a TPC was 3.2 (0.2–4.3) years. The median (P25–P75) time between an SPC and a TPC was 1.8 (0.1–3.8) years.

As shown in Fig. 1, the SPC (n = 369) distribution among gastric FPC patients showed that the most common sites were digestive organs (n = 187; 50.7%), followed by male genital organs (n = 42; 11.4%), and respiratory and intrathoracic organs (n = 33; 8.9%). Only seven gastric SPCs (1.9%) were diagnosed following a previous gastric cancer diagnosis, and none of these went on to be diagnosed with a TPC. For all 25 patients who developed a TPC, over two-thirds occurred in tobacco-related cancer sites (e.g., lip, oral cavity and pharynx, larynx, kidney, bladder, and colon and rectum) and 56% of TPCs occurred in patients with a previous tobacco-related SPC; the corresponding estimates for digestive organs were 52% and 40% (Fig. 2). There were no gastric TPCs diagnosed in patients with an SPC. In males, another common MPC was prostate cancer, accounting for 20.0% and 10.0% of SPCs and TPCs, correspondingly. Among patients with a gastric FPC, the 10-year cumulative incidence (95% CI) of TPC was 0.4% (0.2–0.5%) (Fig. 3A); while among gastric FPC patients with an SPC diagnosis, the 10-year cumulative incidence (95% CI) of TPC was 7.6% (4.4–10.8%) (Fig. 3-B).

For the SPC + TPC patients, compared to the matched SPC only patients, the crude and age-adjusted hazard ratio (95% CI) for death were 1.76 (0.81–3.83) and 1.68 (0.77–3.67), respectively. The 5-year cumulative all-cause mortality of the SPC + TPC patients and matched SPC only patients were 77.8% and 46.5%, respectively, whereas the corresponding risk at 10-years was 92.6% and 67.9% (Fig. 4).

4. Discussion

Overall, we found that most of the TPCs diagnosed were tobacco-related cancers, mainly in digestive organs, with a 10-year cumulative incidence of 0.4% among all gastric FPC patients. SPC + TPC patients had a substantially increased probability of all-cause death over 10 years compared to patients with an SPC only, highlighting that a TPC is a major contributor to the mortality of these patients.

Table 1
Characteristics of gastric first primary cancer patients with and without a subsequent primary cancer.

N (%)	Total	Patients without any subsequent primary	Patients with an SPC	
	7409 (100.0)	7040 (95.0)	369 (5.0)	
			Patients without a TPC 344 (93.2)	Patients with a TPC 25 (6.8 of SPCs; 0.3 of FPCs)
Age at diagnosis of GC, years (median [P25–P75])	68 (56–76)	68 (56–76)	67 (58–74)	65 (58–76)
Sex (N [%])				
Males	4393 (59.3)	4145 (58.9)	228 (66.3)	20 (80.0)
Females	3016 (40.7)	2895 (41.1)	116 (33.7)	5 (20.0)
GC tumour location (N [%])				
Cardia	436 (5.9)	418 (5.9)	17 (4.9)	1 (4.0)
Non-cardia	2066 (27.9)	1969 (28.0)	85 (24.7)	12 (48.0)
Gastric NOS	4907 (66.2)	4653 (66.1)	242 (70.4)	12 (48.0)
Time to diagnosis, years (median [P25–P75])			1.6 (0.2–4.9) FPC to SPC	3.2 (0.2–4.3) FPC to SPC 1.8 (0.1–3.8) SPC to TPC

FPC first primary cancer, GC gastric cancer, NOS not otherwise specified, P25 percentile 25, P75 percentile 75, SPC second primary cancer, TPC third primary cancer.

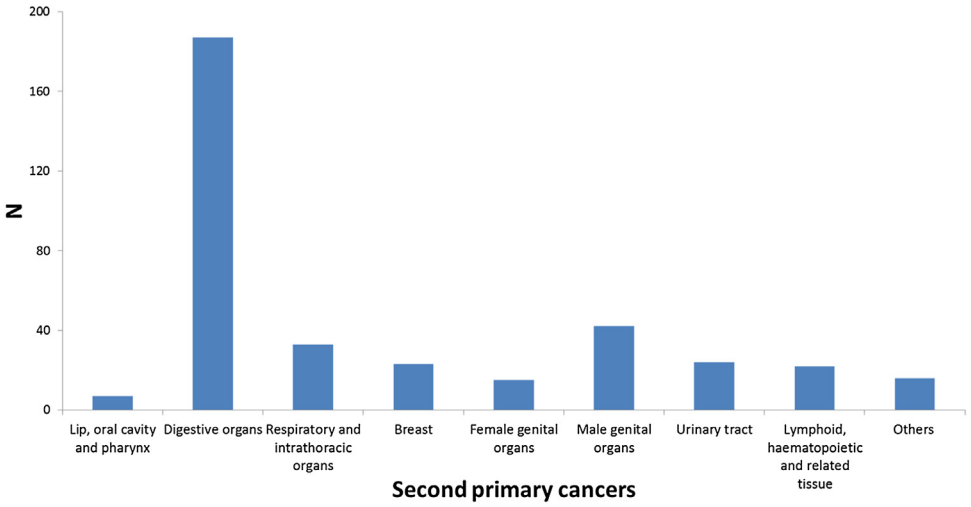

Fig. 1. Distribution of second primary cancers[a] among gastric first primary cancer patients.
[a]Lip, oral cavity and pharynx (C00–C14), digestive organs (C15–C26), respiratory and intrathoracic organs (C30–C39), breast (C50), female genital organs (C51–C58), male genital organs (C60–C63), urinary tract (C64–C68), lymphoid, haematopoietic and related tissue (C81–C96), and others: melanoma and other malignant neoplasms of skin excluding skin non-melanoma (C43–C44), eye, brain and other parts of central nervous system (C69–C72), and thyroid and other endocrine glands (C73–C75) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [12].

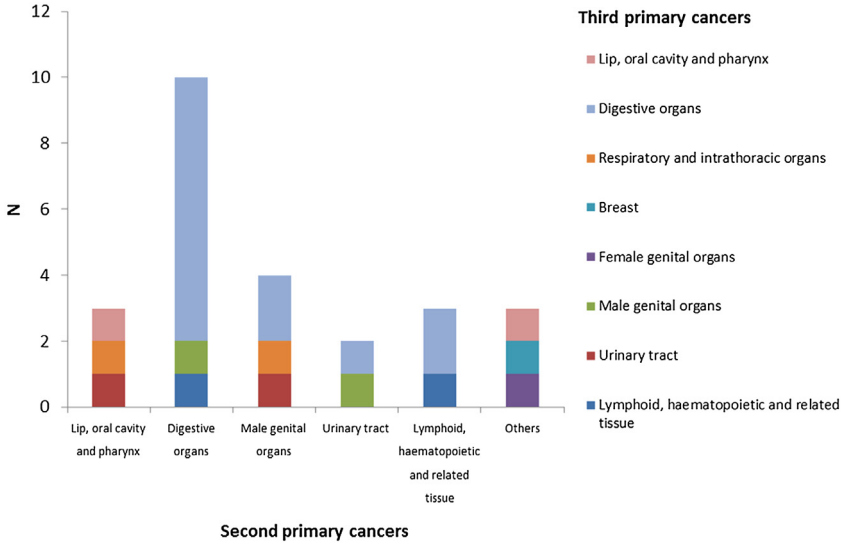

Fig. 2. Distribution of third primary cancers[a] among second primary cancers in gastric first primary cancer patients.
[a]Lip, oral cavity and pharynx (C00–C14), digestive organs (C15–C26), male genital organs (C60–C63), urinary tract (C64–C68), lymphoid, haematopoietic and related tissue (C81–C96), and others: breast (C50), female genital organs (C51–C58), and thyroid and other endocrine glands (C73–C75) defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [12].

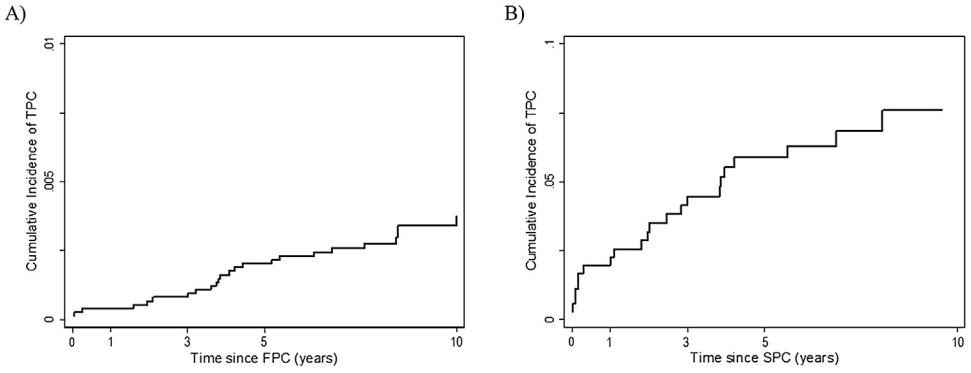

Fig. 3. Cumulative incidence of third primary cancers, among (A) gastric first primary cancers and (B) second primary cancers following a gastric first primary cancer, taking into account the competing event of death.
FPC first primary cancer, SPC second primary cancer, TPC third primary cancer.
*Note that a different scale is used for the two graphs.

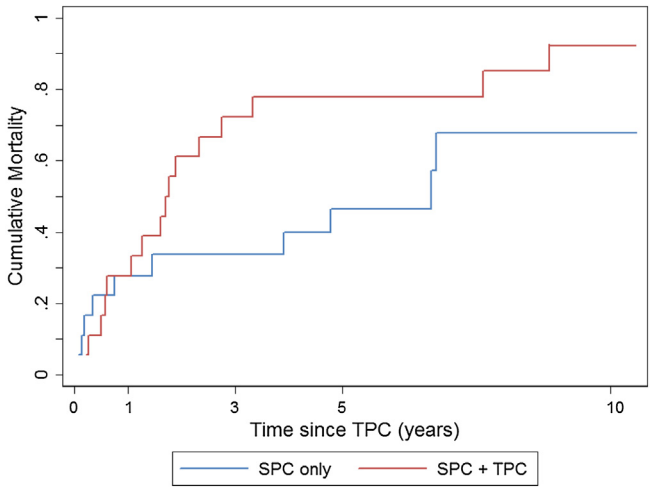

Fig. 4. Observed cumulative all-cause mortality[a] of gastric first primary cancers with a second primary cancer, and with and without a third primary cancer.
SPC second primary cancer, TPC third primary cancer.
[a]Calculated using 1-Kaplan Meier [15].

Although a few national studies on MPCs have been conducted in Italy [9], the Netherlands [10] and the United States of America [4], no population-based study has focused on the risk and survival of TPCs among survivors of gastric cancer specifically. Generally, the proportion of TPCs is small ranging from 0.0% to 2.0% of all cancer diagnoses [8]. In Italy, among cancers diagnosed between 1976 and 2010, and followed to 31 December 2012, 0.3% of patients were diagnosed with TPCs with a 3:1 male to female ratio. Specifically, the sequence of stomach, prostate and urinary bladder cancers was the fifth most common among males [9]. The Surveillance, Epidemiology, and End Results monograph on new malignancies among cancer survivors diagnosed between 1973 and 2000 in the United States of America found that 0.3% of patients with an initial gastric cancer diagnosis had a TPC [4]. A previous hospital-based study from the North of Portugal found 0.5% TPCs diagnosed in 2668 patients with a gastric cancer diagnosed between July 1974 and December 1999 [16].

Cancer survivors may be at increased risk of developing an MPC due to a variety of factors including lifestyles (i.e., tobacco smoking and alcohol intake) as well as host factors (i.e., personal or familial hereditary cancer history) [17]. Tobacco smoking is a major cause of cancer [18], and together with alcohol intake, has been estimated to account for approximately 35% of all excess risk for MPCs [4]. Likewise, we found that most TPCs occurred in tobacco-related cancer sites, particularly in other digestive organs. This may occur as a result of the common carcinogenic process and the same risk factors that affect the gastrointestinal tract (e.g., contaminants such as N-nitroso compounds found in smoked foods, preserved meats, and some alcoholic beverages, diet, and smoking) [19,20]. Additionally, the follow-up of cancers in the gastrointestinal tract may have contributed to the clustering of digestive cancers among these patients as they are under closer examination than the general population [21].

Hereditary cancer syndromes account for an estimated 5–10% of all cancers [22,23]; and it has been shown that individuals with certain hereditary disorders have an increased risk of MPCs [17]. However, due to the overall low frequency of hereditary syndromes, they only account for a small proportion of MPCs [17], and the increased risk of MPCs in an individual is likely influenced by not only a single-gene mutation but also by the cumulative effect of other risk factors [17,24].

The survival of gastric cancer patients who develop a TPC has been seldom described. A previous hospital-based study from Germany found that the 5-year survival rate for gastric cancer patients with multiple malignancies was 33.3% calculated from the time of diagnosis of the TPC, as compared to 28.1% in patients from the same hospital with gastric cancer alone [25]. However, this study did not account for the time patients must survive to develop a TPC as it considered the FPC date of diagnosis for patients with a gastric cancer only.

A recent study, using the same gastric FPC cohort described here, found that the survival of gastric FPCs who survive at least one year to be diagnosed with an SPC was primarily influenced by the second cancer [26]. Similarly, the estimates provided here highlight that gastric cancer survivors diagnosed with a TPC have a worse survival. Consequently, the occurrence of MPCs should be considered by clinicians when establishing a prognosis and treatment plan for these particular patients.

This study is based on data obtained from RORENO, which is representative of cancer survivors from Northern Portugal; however, extrapolating these results to all Portuguese cancer survivors should be done cautiously, since the North has higher incidence, mortality and survival of gastric cancer than the rest of the country [2,11,27]. Regardless, the sample is population-based and the results may be generalized to settings where the overall patterns of cancer incidence and access to health care are not markedly different. Further, we present observed all-cause mortality instead of net survival as we aimed to evaluate patients with a TPC and consequently, net survival would not be reliable estimate of survival of these patients unless lifetables specifically constructed for the populations under study were constructed. Finally, a merely descriptive analysis is presented, as an evaluation according to SPC or TPC cancer site combinations was not feasible due to the small number of TPCs, nevertheless, these results are useful and exhaustive since the occurrence and survival of TPCs among gastric FPCs has yet to be explored in population-based studies.

To conclude, the cumulative incidence of TPCs among all gastric FPC patients was 0.4% over a 10-year period. A clustering of tobacco-related cancers was observed, particularly in other digestive organs, calling attention to lifestyle changes which may potentially prevent the occurrence of MPCs in the long term. Further, gastric FPC patients who develop a TPC have a worse survival compared to those with an SPC only. Taken together, our findings show that additional research is necessary to further quantify the burden and survival of TPCs among patients previously diagnosed with an FPC + SPC to determine the best treatment strategy and prognosis considering all MPCs.

Conflict of interest

None declared.

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