Cancer Epidemiology 50 (2017) 85–91

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Risk of second primary cancers among patients with a first primary gastric cancer: A population-based study in North Portugal

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

[a] EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, no 135, 4050-600 Porto, Portugal
[b] Registo Oncológico Regional do Norte (RORENO) – Instituto Português de Oncologia do Porto, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal
[c] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

ARTICLE INFO

Keywords:
Epidemiology
Gastric neoplasms
Population register
Second primary neoplasm

ABSTRACT

Background: The growing number of incident cases of gastric cancer along with improved survival result in a rising population of survivors at risk of second primary cancers (SPC). We estimated the cumulative incidence of metachronous (diagnosed > 2 months after first primary cancer [FPC]) SPC in gastric FPC patients and compared the incidence of metachronous SPC with that expected in the general population.
Methods: A cohort of gastric FPC patients from the North Region Cancer Registry of Portugal, diagnosed in 2000–2006 (n = 7427) was followed to 31 December 2010 for synchronous and metachronous SPCs. Cumulative incidence of metachronous SPCs taking into account death as a competing event and standardized incidence ratios (SIR) of metachronous SPCs were estimated.
Results: Overall, 331 (4.5%) patients developed an SPC (26.9% synchronous and 73.1% metachronous). Over half of the SPCs occurred in digestive organs. Among men, the most frequent were colon, prostate, and trachea, bronchus and lung; in women, colon, breast and thyroid were the most common. The 10-year cumulative incidence of metachronous SPC for males was 5.7% and for females 3.5%. The SIR for all cancers was 1.30 in males and 1.20 in females. Among both sexes, significantly higher SIRs were observed for cancers of the oesophagus (males: 4.99; females: 8.03), small intestine (males: 11.04; females: 13.09) and colon (males: 2.42; females: 2.58).
Conclusions: Patients with a gastric FPC were found to be at increased risk of developing SPC, mainly in digestive organs, when compared to the general population. Close surveillance of these patients may allow early detection of SPC.

1. Introduction

Gastric cancer is the fifth most common and third leading cause of cancer death worldwide [1]. Downward trends in mortality have been observed, however, the declines have become gradually smaller in some countries and a levelling off may be expected in high-income settings [2]. In Portugal, gastric cancer ranks fifth in incidence and mortality [1]. Despite the latter showing a decreasing trend in the past few decades [3], Portugal continues to present the highest mortality rates in Western Europe [4] and there is a large variation within the country; in the North region, incidence and mortality are much higher [3,5].

Though survival from gastric cancer remains poor [6], an increase has been observed due to gradual improvements in diagnosis and treatment [7]. These survivors are at increased risk for several adverse health events, including recurrence of first primary cancer (FPC), cardiovascular diseases or second primary cancer (SPC) [8]. Between 1995 and 1999, the stomach was the fifth most frequent FPC site of multiple tumours, accounting for 4.1% of all subsequent cancers in Europe [9]. In the United States of America (USA), 4.0% of patients with an initial diagnosis of stomach cancer from 1973 to 2000 and a maximum follow-up of 27-years developed a subsequent primary cancer [8]. In Northern Portugal, stomach cancer has been shown to be the third most common FPC for patients diagnosed with a subsequent tumour between 2000 and 2003, contributing to an estimated 9.5% of all multiple primary cancers [10].

In the present study, we expanded previous observations in the North of Portugal, by following for a maximum of 10-years a population-based cohort of patients with a gastric FPC, diagnosed between

* Corresponding author at: Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200–319 Porto, Portugal.
E-mail address: nlunet@med.up.pt (N. Lunet).

http://dx.doi.org/10.1016/j.canep.2017.08.007
Received 24 February 2017; Received in revised form 12 July 2017; Accepted 10 August 2017
Available online 23 August 2017
1877-7821/

2000 and 2006, for the occurrence of synchronous and metachronous SPCs. Our aim was to estimate the 10-year cumulative incidence of metachronous SPC, taking into account the competing event of death, and to compare the incidence of metachronous SPC in gastric FPC patients with the expected incidence in a sex-, age- and calendar year-matched population.

2. Methods

2.1. Study setting

Cancer data were provided by the North Region Cancer Registry (RORENO), a population-based cancer registry established in 1988. The registry covers the Northern region of Portugal, corresponding to approximately 3.3 million inhabitants, which is nearly one-third of the Portuguese population. All incident cancers occurring in the area are recorded by the registry, either directly from the main public hospitals through a web-based platform, or based on hard copies of medical reports from private hospitals and pathology laboratories. RORENO calculates cancer incidence using estimates of the resident population in the area covered by the registry each year, according to Statistics Portugal. The results are expressed as an annual rate per 100000 person-years. Registration follows the International Agency for Research on Cancer (IARC) rules which include four quality dimensions: comparability, validity, timeliness and completeness. Registries maintain quality through regular screening with pre-defined algorithms for validity and consistency [11]. From 1998 to 2002, RORENO fulfilled IARC indices of data quality, which indicates a high degree of completeness of ascertainment [12,13].

2.2. Tumour classification and definition of multiple primary cancers

Tumour topography and morphology were classified according to the International Classification of Diseases for Oncology, Third Edition [14], and then recoded to the International Statistical Classification of Diseases and Related Health Problems 10th Revision [15].

SPC is a new primary cancer in a person with a history of malignancy [16]. Multiple primary cancers were defined according to the guidelines proposed by the International Association of Cancer Registries (IACR) and IARC [17]. Briefly, these guidelines consider primary cancers those that originally developed in an organ or tissue, not being an extension, recurrence or metastasis. Different morphologies (even with the same topography) or dissimilar topographies should be regarded as multiple primary cancers, regardless of the time between diagnoses, unless they correspond to systemic cancers, which are considered the same cancer.

2.3. Study design

All primary invasive tumours of the stomach (C16) diagnosed in adults resident in the North of Portugal between 1 January 2000 and 31 December 2006 were identified (n = 8174).

We excluded patients who had a diagnosis of an FPC, except skin non melanoma, previous to a stomach cancer (n = 428) and those which could not be linked to the National Health System for assessment of vital status (n = 319). The latter were not significantly different from included participants regarding sex (men: 64.3% vs. 59.3%; p = 0.075) but were significantly older at diagnosis of FPC (median: 72 vs. 68; p = 0.002), and had significantly more gastric not otherwise specified and less non-cardia tumours (90.6% vs. 66.3% and 5.6% vs. 27.9%, respectively; p < 0.001).

The remaining patients (n = 7427) were followed to 31 December 2010, allowing for over 10-years of potential follow-up, until the diagnosis of an SPC or death, whichever occurred first. The occurrence of any subsequent cancer was ascertained by means of record linkage with the list of cases registered by RORENO. Patients known to have died but with an unknown date of death (n = 18), were imputed a follow-up time equal to the median follow-up of the corresponding sex, 5-year age group (from 15–19 to 70–74, and ≥75) and year of diagnosis.

Whenever more than two primary cancers were observed in the same patient, only the first was considered; third and subsequent primaries were disregarded for the present analysis. Due to the thorough evaluation of cancer patients during the initial medical work-up [8], we classified SPCs as synchronous when diagnosed within two months of the gastric FPC or metachronous otherwise, as previous studies on this topic [8,10,18,19].

2.4. Statistical analysis

Patients' characteristics were presented as counts and proportions for categorical variables, and median (percentile 25-percentile 75 [P25-P75]) for quantitative variables. To compare quantitative and categorical variables across groups, the Mann-Whitney test and Chi-square test were used, respectively. Statistical significance was considered when $p < 0.05$. All reported *p*-values are two-sided. These analyses were carried out separately for synchronous and metachronous SPCs.

Cumulative incidence and corresponding 95% confidence intervals (CI), stratified by sex, age and tumour location, for the occurrence of metachronous SPC were calculated, with death as a competing event according to the method introduced by Kalbfleisch and Prentice [20]. Briefly, this method allows for patients who died to no longer be at risk for an SPC by actively removing individuals from the risk sets; thus, it differs from the cumulative incidence estimated by the Kaplan-Meier (KM) method, which treats competing events as censored at the time they occurred. We show plots for metachronous SPCs and mortality [21].

Standardized incidence ratios (SIR) and corresponding 95%CI were computed to compare cancer incidence rates among gastric FPC with those in the general population. SIRs were calculated by dividing the observed number of metachronous SPCs by the expected number of cases, in the same calendar year, if the cancer incidence rates in the general population had been observed among survivors. The latter were estimated by multiplying the cancer incidence in the general population by the person-years at risk (PYAR) in the corresponding stratum; defined according to sex, 5-year age group (from 15–19 to 70–74, and ≥75 years) at FPC diagnosis and each individual calendar year (2000–2010). PYAR were calculated from two months after the diagnosis of FPC until diagnosis of a metachronous SPC, death or end of follow-up (31 December 2010), whichever occurred first. The corresponding stratum incidence of cancer among the general Northern Portuguese population was acquired from RORENO (described in 2.1 Study setting) [22]. The 95%CIs were estimated assuming that the observed number of cancers followed a Poisson probability distribution.

In addition, several sensitivity analyses were performed defining metachronous SPCs as diagnosed one month, six months and one year after the gastric FPC.

Statistical analyses were conducted using STATA®11.2 and R3.3.2 (cmprsk package). The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES IPO: 173/2015) and the analyses were performed according to RORENO guidelines ensuring the anonymity of information used.

3. Results

A total of 7427 cases of gastric FPC diagnosed between 2000 and 2006 were included. During follow-up, we found 331 (4.5%) SPCs, 242 (73.1%) were classified as metachronous (Fig. 1). When the time to define SPCs was changed, the number of metachronous SPCs decreased from 264 (79.8%) to 185 (55.9%) using one month and one year, respectively (Appendix A).

Patients' characteristics are shown in Table 1. The median age at diagnosis of FPC did not differ between patients with and without an