

Evaluation of the frequency of and survival from second primary cancers in North Portugal: a population-based study

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A marked increase in cancer survival and in the frequency of second primary cancers (SPCs) has been observed in the latest decades, propelling the investigation of their burden at a population level. We aimed to quantify the proportion of SPCs among the incident cases in North Portugal and to describe their survival. We identified all SPCs (excluding skin nonmelanoma) registered by the North Region Cancer Registry (RORENO) from 2000 to 2003 according to the International Association of Cancer Registries and the International Agency for Research on Cancer guidelines. We classified tumors diagnosed more than 2 months after a first primary cancer (FPC) as metachronous. The observed survival was computed using vital status in December 2010. A total of 1607 SPCs (3.8% of all cancers) were registered (77.9% metachronous). The most frequent metachronous SPC topographies and the corresponding most frequent FPCs were of the colon (12.2%; FPC: prostate, breast, and stomach), lung (10.5%; FPC: bladder, stomach, and colon), and stomach (9.7%; FPC: prostate, breast, and bladder). The overall 5-year survival of individuals with metachronous SPCs was 47.4%; within the subgroups with higher (63.1%) and lower survival (31.1%), there were no significant differences

across groups of FPCs with expectably different survival. The proportion of SPCs was that anticipated for a registry with approximately one decade of activity. The most common cancers in the general population were also frequent metachronous SPCs, whereas the most frequent FPCs were high incidence and survival cancers. The survival of metachronous SPCs did not vary with the survival expected for the FPCs. *European Journal of Cancer Prevention* 22:599–606 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The improvements in cancer management strategies that have been observed in the past decades, as well as the concomitant decrease in cardiovascular mortality (Allender *et al.*, 2008), also in Portugal (Pereira *et al.*, 2012), have resulted in a marked increase in cancer survival (Stewart and Kleihues, 2003). In 2000, there was an estimated worldwide population of ~22 million cancer survivors (Stewart and Kleihues, 2003).

Cancer survivors have an increased risk for several adverse health events, including the recurrence of first primary cancer (FPC), cardiovascular disease, or a second primary cancer (SPC) (Curtis *et al.*, 2006). After the diagnosis of an FPC, the latter may be determined by iatrogenic causes, genetic characteristics, and persistence of environmental exposures or their effects (Travis, 2006). SPCs represented 6.3% of all incident cancer cases in Europe (1995–1999; Rosso *et al.*, 2009a) and 16% in the USA (2003; Curtis *et al.*, 2006); the proportion of SPCs among all diagnosed tumors is estimated to be similar to that of the sixth most common form of

malignancy in the world (Kosary *et al.*, 1995; Neugut *et al.*, 1999).

In terms of the survival of patients with SPCs, population-based studies frequently disregard these cases because of the difficulties in disentangling the different contributions of the first and second cancers to the survival probability (Berrino *et al.*, 1995; Ries *et al.*, 2006). The few studies that have specifically evaluated the survival of SPC patients have yielded conflicting results (Holmberg *et al.*, 1988; Heron *et al.*, 2000; Liu *et al.*, 2002), largely because of their methodological heterogeneity, namely, in terms of the strategy to account for the contribution of the FPC toward the probability of survival.

This increasing burden of morbidity and mortality associated with SPCs requires an investigation at a population level to obtain epidemiologic data for defining surveillance priorities and planning of health services. Therefore, we aimed to quantify and characterize the SPCs identified among the incident cancer cases registered between 2000 and 2003, in North Portugal,

and to describe their survival according to the characteristics of the FPC.

Methods

Study population

We identified all the SPCs among the cancer cases registered in the North Region Cancer Registry (ROR-ENO) during the period from 2000 to 2003, excluding nonmelanoma skin cancers. This population-based cancer registry was set up in 1988 and covers the entire northern region of Portugal, corresponding to ~3.3 million inhabitants, nearly 30% of the Portuguese population.

Date of diagnosis, birth date, sex, topography, morphology, vital status, and date of death, when applicable, were registered by RORENO.

Tumor topography and morphology were classified according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) categories. For analysis, head and neck topographies (C0.0 to C14.9) were aggregated into a single category, as well as the morphologies corresponding to cases of lymphoma (9590–9729, 9735–9738), leukemia (9800–9950), and other hematologic neoplasms (9731–9734; 9740–9764; 9960–9992).

We assessed the vital status of the SPC patients in December 2010 through linkage with the National Health System database. The median follow-up was 103 months for survivors and 13 months for nonsurvivors.

Definition of multiple primary cancers

The definition of multiple primary cancers (MPCs) followed the guidelines proposed by the International Association of Cancer Registries and the International Agency for Research on Cancer (IARC) (Working Group Report, 2005). Briefly, these criteria consider that: (i) MPCs are those that originally developed in an organ or a tissue, not being an extension, a recurrence, or a metastasis; (ii) different morphologies (even with the same topography) and dissimilar topographies should be considered as MPCs, irrespective of the time between the diagnoses, unless they correspond to systemic cancers that are considered to be the same cancer.

Statistical analysis

We quantified the overall proportion of MPCs among the incident cases of cancer registered within the study period. When each individual had more than one MPC, we considered the first MPC as the SPC, and further analyses were limited to the SPCs, excluding the third or subsequent primary cancers. SPCs were classified as synchronous when diagnosed within 2 months of the FPC or metachronous otherwise, as in previous studies on this topic (Curtis *et al.*, 2006; Youlden and Baade, 2011), and data analyses were carried out separately for synchronous and metachronous SPCs.

We described the 10 most frequent topographies of SPCs in terms of sex, age at diagnosis, topography/morphology of the FPC, and time between the diagnoses of the FPC and the corresponding SPC.

Kaplan–Meier curves and 5-year observed survival were computed for the five most frequent SPCs and by groups of FPCs and SPCs defined according to the expected survival of these cancers in the general population; on the basis of their topographies/morphologies, FPCs and SPCs were grouped into high-survival (e.g. thyroid, prostate, breast), intermediate-survival (e.g. colon, rectum, lymphoma), or low-survival cancers (e.g. stomach, liver, lung) using the tertiles of the distribution of the latest 5-year relative survival estimates in Europe published by EURO CARE (Sant *et al.*, 2009) as cutoffs (thirds of the distribution: <47.4, 47.4–56.3, >56.3%).

The log-rank test was used for the comparison of the Kaplan–Meier curves. All analyses were carried out using STATA software, version 9.2 (StataCorp, College Station, Texas, USA).

Results

Frequency of multiple primary cancers

Between 2000 and 2003, a total of 42 600 new cancer cases were registered in the North Region Cancer Registry. The proportion of MPCs was 4.0% ($n = 1684$), of which 95.0% ($n = 1607$) were second tumors (SPCs), 4.0% ($n = 71$) were third tumors, and 1.0% ($n = 6$) were tumors of fourth or higher order.

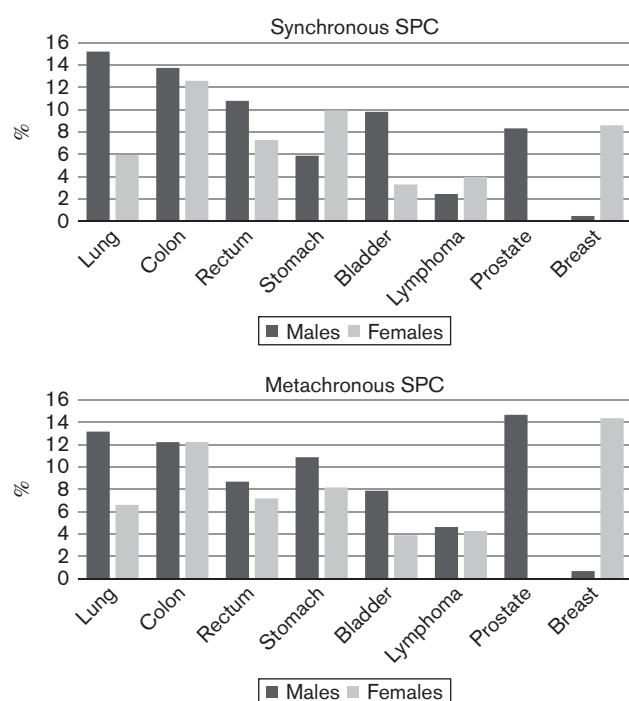
The median age at diagnosis of the 1607 SPCs was 68.9 years, 58.6% ($n = 942$) were men, and the median time between the diagnoses of the FPC and SPC was 21.7 months. The five most frequent SPC topographies were colon ($n = 200$; 12.5%), lung ($n = 171$; 10.7%), stomach ($n = 149$; 9.3%), rectum ($n = 134$; 8.3%), and prostate ($n = 125$; 7.8%). The median age of diagnosis of the FPC was 65.3 years and the five most frequent topographies were colon ($n = 198$; 12.3%), prostate ($n = 190$; 11.2%), stomach ($n = 152$; 9.5%), breast ($n = 139$; 8.7%), and bladder ($n = 113$; 7.0%). The overall proportion of metachronous tumors was 77.9% ($n = 1252$).

The third tumors ($n = 71$) were diagnosed at an older age (71.4 years), 62.0% ($n = 44$) were men, and the median time between the first and the third tumors was 53.6 months. The three most frequent topographies were colon ($n = 13$; 18.3%), lung ($n = 11$; 15.5%), and prostate ($n = 6$; 8.5%).

Among the metachronous SPCs, colon ($n = 153$; 12.2%), lung ($n = 131$; 10.5%), stomach ($n = 122$; 9.7%), prostate ($n = 108$; 8.6%), and rectum ($n = 101$; 8.1%) were the five most commonly observed topographies. There were similar proportions of cases of colon cancer and lymphoma between men and women and a higher proportion of lung, rectum, stomach, and bladder cancers in men.

The proportions of prostate and breast cancer cases were high in men and women, respectively (Fig. 1). The median time between the FPC and SPC diagnoses ranged

Fig. 1



Sex differences in the distribution of the five most frequent second primary cancer (SPC) topographies.

from 26.6 months for corpus uteri SPC to 41.9 months for lung SPC (Table 1). Prostate ($n = 164$; 13.1%), colon ($n = 144$; 11.5%), and breast ($n = 127$; 10.1%) were the three most frequent FPCs among patients with metachronous SPCs (Fig. 2).

Colon ($n = 47$; 13.2%), lung ($n = 40$; 11.3%), rectum ($n = 33$; 9.3%), stomach ($n = 27$; 7.6%), and bladder ($n = 25$; 7.0%) were the five most frequent topographies of synchronous SPCs. The sex distribution of synchronous SPC was similar to that observed for the metachronous SPCs, except for a higher proportion of cases of stomach cancer and lymphoma among women (Fig. 1). The median time between the diagnoses was less than 1 month (Table 1). The frequency of FPC topographies according to the corresponding SPCs had a pattern compatible with the sharing of environmental risk factors (e.g. lung, head and neck, and larynx FPCs associated with lung SPCs) or similar procedures for diagnosis (FPCs in digestive organs associated with colon SPCs; Fig. 2).

Survival of the second primary cancer patients

The 5-year survival of all SPCs was 46.1% [95% confidence interval (CI): 43.7–48.6]; it was 47.4% (44.6–50.1) for the metachronous SPCs and 41.7% (36.5–46.8) for the synchronous SPCs. The 5-year survival was lower among the synchronous SPCs for colon (36.2 vs. 50.3%) and prostate (29.4 vs. 71.0%) cancers; for stomach cancer, the survival was lower among the metachronous SPCs (32.8 vs. 42.9%; Table 2).

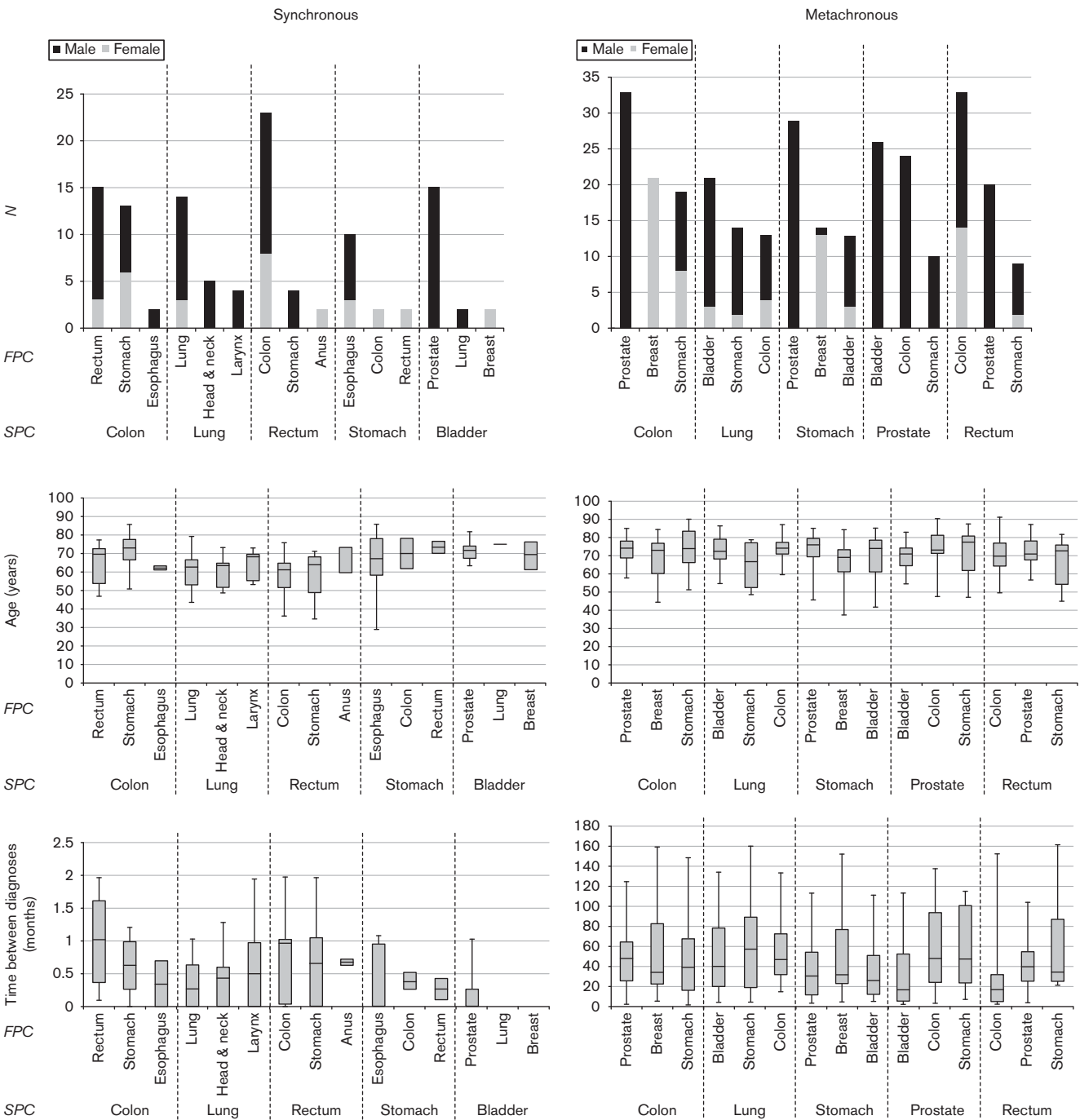
Table 1 General characteristics of the synchronous and metachronous second primary cancers registered in North Portugal between 2000 and 2003

Topography/morphology ^{a,b}	N (%)	Sex (male) [n (%)]	Age (years), median (P25–P75)	Time between diagnoses (months), median (P25–P75)
Synchronous				
Colon	47 (13.2)	29 (61.7)	69.6 (60.1–75.5)	1.0 (0.3–1.1)
Lung	40 (11.3)	31 (77.5)	63.3 (53.1–70.5)	0.5 (0.0–1.0)
Rectum	33 (9.3)	22 (66.7)	61.5 (54.4–66.5)	0.9 (0.0–1.0)
Stomach	27 (7.6)	12 (44.4)	67.5 (51.0–76.2)	0.5 (0.0–1.0)
Bladder	25 (7.0)	20 (80.0)	71.3 (65.8–75.2)	0.0 (0.0–0.4)
Prostate	17 (4.8)	17 (100.0)	69.9 (67.5–78.1)	0.1 (0.0–1.1)
Head and neck	16 (4.5)	14 (87.5)	56.4 (67.3–78.0)	0.8 (0.1–1.1)
Breast	14 (3.9)	1 (7.1)	51.2 (44.3–69.4)	0.6 (0.0–0.7)
Lymphoma	11 (3.1)	6 (54.6)	66.7 (43.7–72.6)	1.0 (0.0–1.3)
Corpus uteri	8 (2.3)	0 (0.0)	67.9 (57.5–74.5)	1.0 (0.6–1.0)
Other	117 (33.0)	53 (45.3)	61.4 (47.5–72.7)	0.5 (0.0–1.0)
Metachronous				
Colon	153 (12.2)	90 (58.8)	71.0 (64.9–77.1)	38.1 (15.9–76.8)
Lung	131 (10.5)	97 (74.1)	70.0 (62.8–75.8)	41.9 (18.1–81.3)
Stomach	122 (9.7)	80 (65.6)	72.2 (67.2–78.0)	29.9 (12.0–78.9)
Prostate	108 (8.6)	108 (100.0)	71.1 (67.7–76.8)	36.9 (13.7–92.0)
Rectum	101 (8.1)	64 (63.4)	70.2 (65.1–76.0)	29.0 (11.0–57.9)
Breast	79 (6.3)	5 (6.3)	66.4 (55.2–74.1)	56.9 (22.4–96.8)
Bladder	78 (6.2)	58 (74.4)	71.5 (67.3–78.0)	43.8 (13.4–71.4)
Lymphoma	56 (4.5)	34 (60.7)	68.9 (55.3–77.2)	40.4 (17.0–75.9)
Head and neck	45 (3.6)	40 (88.9)	66.1 (55.2–72.5)	31.0 (7.0–51.1)
Corpus uteri	34 (2.7)	0 (0.0)	66.7 (56.0–77.8)	26.6 (9.9–61.9)
Other	345 (27.6)	161 (46.7)	67.4 (57.9–74.9)	30.0 (10.0–76.8)

^aOnly the 10 most frequent topography/morphology groups were listed individually.

^bColon – ICD10: C18, lung: C34, rectum: C20, stomach: C16, bladder: C67, prostate: C61, head and neck: C00–C14.9, breast: C50, lymphoma: 9590–9729; 9735–9738, corpus uteri: C54.

Fig. 2



General characteristics of the synchronous and metachronous second primary cancers (SPCs) registered in North Portugal between 2000 and 2003 according to the three most frequent first primary cancer (FPC) topographies/morphologies.

For the metachronous SPCs, the 5-year survival was significantly different across the SPC groups with topographies of expectedly high [63.1% (58.2–67.5)], intermediate [47.2% (42.0–52.2)], and low [31.1% (26.6–35.6)] survival (Table 2). There were no significant differences in

survival according to the groups of FPCs defined by the expected survival, except among the SPCs, with topography/morphology corresponding to an expectedly intermediate survival (Fig. 3). No statistically significant differences were observed according to sex (data not shown).

Table 2 Survival descriptive data of the synchronous and metachronous second primary cancers registered in North Portugal between 2000 and 2003

	5-year observed survival (95% CI)	
	Synchronous SPCs	Metachronous SPCs
All SPCs	41.7 (36.5–46.8)	47.4 (44.6–50.1)
Most frequent SPCs ^a		
Colon	36.2 (22.8–49.7)	50.3 (42.2–57.9)
Lung	24.4 (12.7–38.2)	23.7 (16.8–31.2)
Stomach	42.9 (24.6–60.0)	32.8 (24.9–41.0)
Prostate	29.4 (10.7–51.2)	71.0 (61.4–78.7)
Rectum	45.5 (28.2–61.2)	46.0 (36.0–55.4)
High-survival SPC ^b	41.8 (32.0–51.3)	63.1 (58.2–67.5)
Low-survival FPCs	29.2 (13.0–47.6)	62.1 (51.6–71.0)
Intermediate-survival FPCs	42.9 (24.6–60.0)	56.8 (47.4–65.1)
High-survival FPCs	51.1 (35.5–64.8)	66.5 (59.3–72.7)
Intermediate-survival SPCs ^b	47.5 (38.2–56.1)	47.2 (42.0–52.2)
Low-survival FPCs	40.0 (25.8–53.8)	39.0 (28.5–49.4)
Intermediate-survival FPCs	49.2 (35.9–61.1)	43.4 (33.9–52.6)
High-survival FPCs	69.2 (37.3–87.2)	54.8 (47.2–61.8)
Low-survival SPCs ^b	36.0 (27.7–44.4)	31.1 (26.6–35.6)
Low-survival FPCs	25.4 (15.7–36.2)	30.3 (21.6–39.5)
Intermediate-survival FPCs	38.5 (20.4–56.3)	26.3 (18.6–34.6)
High-survival FPCs	53.6 (33.8–69.8)	35.5 (28.7–42.4)

FPC, first primary cancer; SPC, second primary cancer.

^aOnly the five most frequent topography/morphology groups were listed individually.

^bFPC and SPC topographies/morphologies were grouped by tertiles of the distribution of the latest EUROCARE 5-year relative survival estimates; low-survival group (5-year survival reported <47.4%): melanoma skin cancer – ICD10: C44, breast: C50, vagina and labia: C51–52, cervix uteri: C53, corpus uteri: C54, corpus uteri: C54, penis: C60, prostate: C61, testis: C62, kidney: C64, bladder: C67, thyroid: C73; intermediate survival group (5-year survival reported 47.4–56.3%): colon: C18, rectum: C20, sinuses, middle, and inner ear: C30–31, larynx: C32, bones and joints: C40–41, retroperitoneum: C48, connective and soft tissue: C49, lymphoma: 9590–9729, 9735–9738; high-survival group (5-year survival reported >56.3%): esophagus: C15, stomach: C16, small intestine: C17, liver: C22, gallbladder and extrahepatic bile ducts: C23–C24, pancreas: C25, lung: C34, mediastinum: C38, ovary: C56, brain: C71, head and neck: C0–C14, leukemia: 9800–9950 (Youlten and Baade, 2011).

There were no significant differences in the 5-year survival across the groups of synchronous SPCs defined previously by the expected survival [high: 41.8% (95% CI: 32.0–51.3), intermediate: 47.5% (38.2–56.1), and low: 36.0% (27.7–44.4)] (Table 2). Taking into account the FPC, the pattern observed for the synchronous SPCs was different from that described for the metachronous SPCs. The stratified analysis on the basis of the expected survival groups in FPCs showed a higher survival in individuals belonging to the FPC high-survival group and a lower survival in those belonging to the FPC low-survival group; the latter differences were statistically significant in the SPC intermediate-survival ($P = 0.047$) and low-survival ($P = 0.009$) groups (Table 2 and Fig. 3). There were no statistically significant differences according to sex (data not shown).

Discussion

In North Portugal, between 2000 and 2003, the SPCs represented 3.8% of the incident cancers; nearly 80% were metachronous, and the most frequent topographies were colon, lung, and stomach. Among patients with a metachronous SPC, the survival seems to be influenced

essentially by the SPC, whereas in patients with a synchronous SPC, the survival varied mainly with the type of FPC.

The proportion of SPCs among incident cancer cases in North Portugal was lower than the most recent overall estimates for Europe (6.3%; Rosso *et al.*, 2009a) and USA (16.7%; Travis, 2006), and higher than those reported previously for South Portugal (2.5%; Rosso *et al.*, 2009a). This heterogeneity observed across population-based registries can be explained by differences in the time elapsed since the onset of cancer registration, as the probability of identifying patients with a primary cancer that had already developed other primary cancer before depends on the number of cases that were registered earlier. The EUROCARE group reported the proportion of SPCs across European cancer registries, showing that it increased with the registry operating time; our results are in agreement with those expected from a cancer registry functioning for ~13 years (Rosso *et al.*, 2009a).

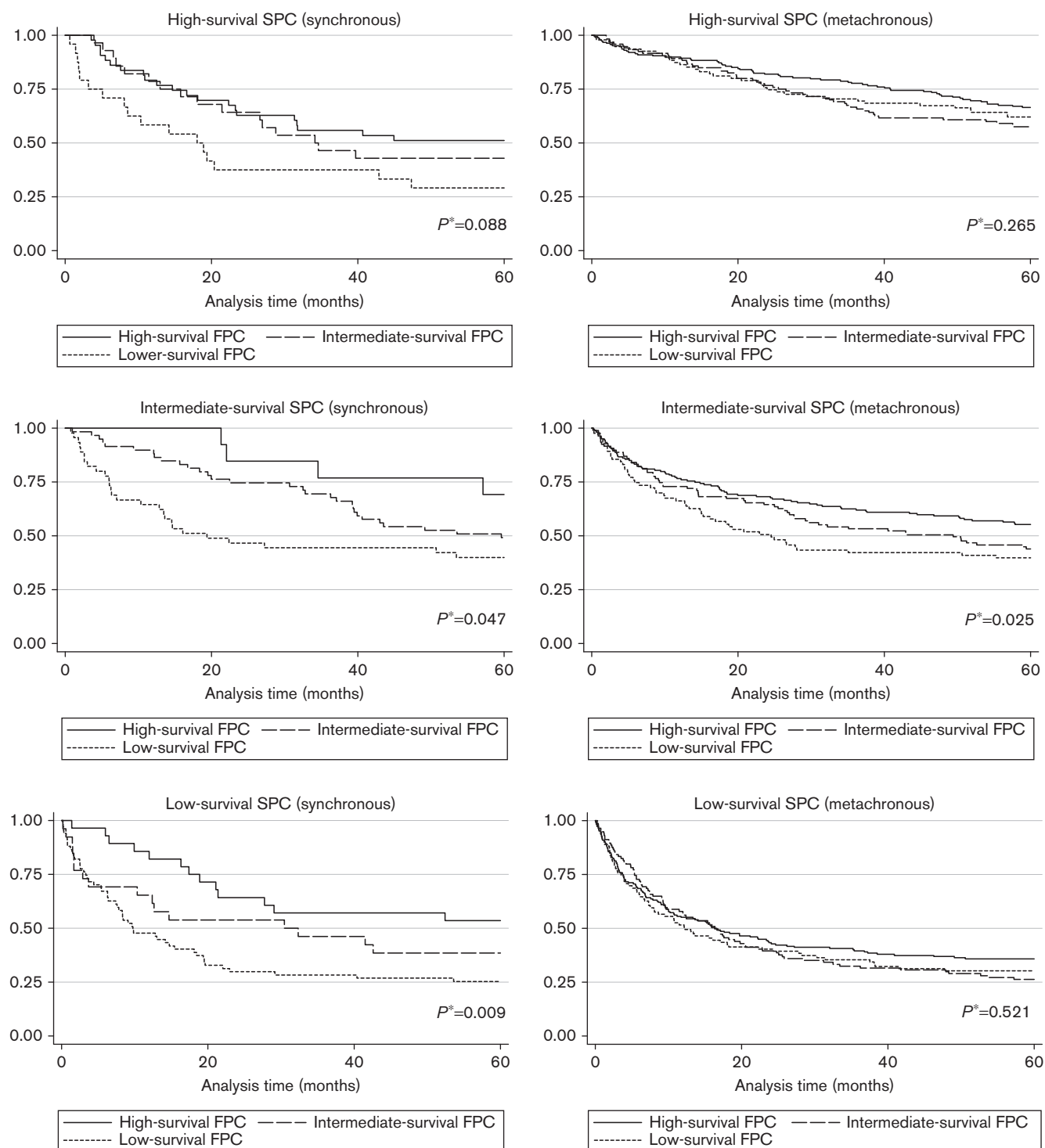
The difference in the frequency of SPCs observed across the cancer registries also depends on the overall and cancer-specific incidence and survival in each setting. In North Portugal, the age-standardized (World reference population) incidence of cancer (249.0/100 000) [Registo Oncologico Regional do Norte (RORENO), 2007] is similar to that estimated for Europe (246.9/100 000 cases) and lower than that in the USA (300.2/100 000; Ferlay *et al.*, 2010). Further, although the five most frequent cancer topographies have a similar 5-year relative survival in Portugal and Europe, it is lower than that in the USA (Coleman *et al.*, 2008).

In terms of the sex distribution of the most frequent SPC topographies/morphologies, SPCs more strongly associated with tobacco exposure had a consistently higher frequency in men, and prostate and breast cancers had expectedly high frequencies among men and women, respectively. The higher proportion of stomach metachronous SPCs among men is in accordance with the known sex differences in the frequency of stomach cancer, whereas the higher proportion of stomach synchronous SPCs among women is possibly better explained by the imprecision of the estimates.

In our study, the proportion of the five most frequent SPC topographies was similar to that observed when considering all cancer cases registered in RORENO within the same period, except for a higher frequency of lung cancer (metachronous SPC vs. all cancers: 10.5 vs. 7.5%) and a lower frequency of breast cancer (metachronous SPC vs. all cancers: 6.3 vs. 12.5%).

The comparison of the proportion of the most frequent SPC topographies observed in our study against data from European population-based cancer registries with a similar working time (Table 3) showed that: (a) there was a higher frequency of stomach SPCs in our study,

Fig. 3



Kaplan-Meier curves with a stratified analysis of the survival of second primary cancers on the basis of high, intermediate, and low topography survival of the first primary cancers. FPC and SPC topographies/morphologies were grouped by tertiles of the distribution of the latest EURO CARE 5-year relative survival estimates; high-survival group (5-year survival reported $>56.3\%$): melanoma skin cancer – ICD10: C44, breast: C50, vagina and labia: C51–52, cervix uteri: C53, corpus uteri: C54, corpus uteri: C54, penis: C60, prostate: C61, testis: C62, kidney: C64, bladder: C67, thyroid: C73; intermediate-survival group (5-year survival reported 47.4–56.3%): colon: C18, rectum: C20, sinuses, middle, and inner ear: C30–31, larynx: C32, bones and joints: C40–41, retroperitoneum: C48, connective and soft tissue: C49, lymphoma: 9590–9729, 9735–9738; low survival group (5-year survival reported $<47.4\%$): esophagus: C15, stomach: C16, small intestine: C17, liver: C22, gallbladder and extrahepatic bile ducts: C23–C24, pancreas: C25, lung: C34, mediastinum: C38, ovary: C56, brain: C71, head and neck: C0–C14, leukemia: 9800–9950 (Youlten and Baade, 2011). *Log-rank test. FPC, first primary cancer; SPC, second primary cancers.

Table 3 Proportion of second primary cancers of selected topographies among cancer patients with age at diagnosis between 15 and 99 years, diagnosed during the period from 1995 to 1999 on the basis of data from European population-based cancer registries, with the starting year of registration between 1982 and 1988 (Travis, 2006)

Country	Registry	Date of onset	Colon/rectum (%) ^a	Lung (%) ^a	Stomach (%) ^a	Prostate (%) ^a	Breast (%) ^a	Total [n (%)] ^b
Austria	Austria	1983	14.9	10.9	4.7	14.4	9.2	8702 (5.0)
England	Thames	1985	14.5	16.6	3.8	10.2	7.1	13582 (4.7)
France	Herault	1987	13.0	9.3	2.8	20.9	5.6	215 (2.1)
	Somme	1982	14.9	13.0	3.8	11.4	3.8	316 (4.9)
	Tarn	1982	17.0	7.4	3.9	13.5	6.4	311 (6.3)
Italy	Firenze	1985	17.0	15.6	8.9	9.2	6.1	2108 (6.0)
	Genova	1986	15.7	15.3	3.9	10.5	5.9	1955 (6.2)
	Romagna	1986	14.1	15.1	9.3	11.7	5.7	2062 (6.6)
	Torino	1985	13.4	17.2	4.6	10.3	7.0	1560 (6.0)
	Veneto	1987	11.4	17.9	5.2	11.5	5.9	4226 (7.2)
Spain	Basque country	1986	14.0	16.8	5.2	9.4	4.4	2440 (5.5)
	Tarragona	1985	12.3	15.3	5.1	10.1	5.1	653 (5.3)
Portugal ^c	North	1988	20.9	10.9	9.1	7.8	5.8	1684 (4.0)

^aProportion of each topography among all multiple primary tumors.^bNumber of identified multiple primary tumors and its proportion among the incident cancer cases.^cSecond primary cancer cases diagnosed between 2000 and 2003, with age at diagnosis of 0–99 years.

which may be explained by the high gastric cancer rates observed in Portugal, and specifically in the North, where the incidence and mortality rates of gastric cancer are among the highest in Europe (Lunet *et al.*, 2004; Lunet, 2011); (b) there was a higher frequency of colon/rectum SPCs in our study, only similar to those observed in cancer registries that also had a high incidence of stomach cancer, which probably reflects the effect of common diagnostic and follow-up procedures; and (c) the frequencies of breast SPCs were low across the different cancer registries, despite the high frequency of breast FPC cases within the same cancer registries (IARC, 1999). Although the cancer registries had similar working times, our cases were diagnosed in a later period (2000–2003 vs. 1995–1999) and were not limited to patients older than 15 years of age; however, this is not expected to compromise these comparisons as in our study there was only one case of an SPC in a patient younger than 15 years of age.

In terms of the FPC more frequently associated with a subsequent diagnosis of a primary cancer, among the metachronous SPCs, there was an underrepresentation of FPC topographies expected to have a low survival. For example, although lung cancer is among the most frequent cancers in this setting, it has an expectedly low survival (Sant *et al.*, 2009) and is seldom observed as an FPC preceding a metachronous SPC. Some of the associations observed frequently between FPC and SPC topographies/morphologies may be explained by the sharing of exposures associated with cancer, including environmental factors and genetic profile, or the iatrogenic outcome of the FPC treatment (Travis, 2002; Travis *et al.*, 2006), as well as by the use of common diagnostic procedures or enhanced clinical surveillance after an FPC (Liu *et al.*, 2011; Nielsen *et al.*, 2012). The high proportion of patients with lung SPCs who had bladder, head and neck, and larynx FPCs most likely reflects the importance

of smoking as a main risk factor for both FPCs and SPCs (Gandini *et al.*, 2008; Nielsen *et al.*, 2012). When the SPCs were synchronous or when there was a short time between the diagnoses of the FPC and metachronous SPC, the overlapping of procedures for clinical investigation and diagnosis may contribute toward the associations observed between FPC and SPC. For example, in our study, there was a high frequency of gastrointestinal (colon SPC with rectum, stomach, and esophagus FPCs; rectum SPC with colon FPC) and urological (prostate SPC with bladder FPC) FPC–SPC pairs (Liu *et al.*, 2011; Nielsen *et al.*, 2012).

The description of the survival of SPC patients provides information on the burden of these cancers. However, the usefulness of these data may be further improved by disentangling the contribution of FPCs and SPCs toward the overall survival. Our analyses, stratified by the expected survival for different topographies/morphologies, showed that among the synchronous tumors, the observed survival was in accordance with that expected for the FPCs, irrespective of the SPC. In contrast, among the metachronous SPCs, the survival curves were similar across groups of FPCs, and the observed survival varied according to that expected for the topographies/morphologies of the SPCs. This may reflect a different contribution of the SPC and FPC toward the overall survival according to the time between the diagnoses (Heinavaara *et al.*, 2002; Rosso *et al.*, 2009b). Patients with SPCs with a large interval between the diagnoses are more likely to be cured of the FPC (Heinavaara and Hakulinen, 2002; Francisci *et al.*, 2009) and, therefore, the survival will not be influenced by it. However, when multiple cancers are diagnosed within a short period, the SPCs are more likely to be discovered because of common diagnostic procedures or surveillance; this may contribute toward an overrepresentation of cases that would not be diagnosed otherwise or would be

diagnosed later on, less likely to influence survival than the FPC, and with a better prognosis.

In terms of methodological limitations, our results may have underestimated the proportion of SPCs because of the fact that the cancer registry has been in operation only since 1988 and because we used the IARC coding rules, which are more restrictive than those issued by the SEER.

We presented observed survival rather than relative survival estimates, as we were evaluating patients with two different cancers, and consequently, the relative survival would not be a reliable surrogate for the cancer-specific survival from SPCs; although the contribution of non-oncological causes of death may vary across the subgroups of SPCs considered, our analyses account for the contribution of FPCs with different characteristics to the observed survival of SPC patients and to disentangling the contribution of FPCs and SPCs toward patient survival.

While the present work is mainly a population-based descriptive study, the absence of tumor staging for a large proportion of cancer cases precluded the stratification of survival estimates by stage and hindered some possible interpretations from the observed differences in survival.

Although the results from our study reflect the epidemiology of SPC in North Portugal, the survival estimates highlight the different contributions of SPCs and FPCs toward the overall survival, and similar patterns are likely to be observed in other settings.

Conclusion

The present work showed a considerable proportion of SPCs among newly diagnosed cancer cases of North Portugal, in accordance with European estimates from cancer registries with a similar operating time. This emphasizes the importance of enhancing surveillance strategies for cancer survivors and better understanding the determinants for the incidence of and survival from SPCs. Moreover, our results showed that the contribution of the FPC toward the observed survival of SPC patients tends to decrease as the time between the diagnoses increases.

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Conflicts of interest

There are no conflicts of interest.

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