LUÍS MANUEL DA CUNHA PACHECO FIGUEIREDO

EPIDEMIOLOGY OF CANCER SURVIVORSHIP IN PORTUGAL

PORTO | 2015

TESE DE DOUTORAMENTO EM SAÚDE PÚBLICA APRESENTADA À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Art.º 48º, § 3º - "A Faculdade não responde pelas doutrinas expendidas na dissertação."

(Regulamento da Faculdade de Medicina da Universidade do Porto – Decreto-Lei nº 19337 de 29 de Janeiro de 1931)

Corpo Catedrático da Faculdade de Medicina do Porto

Professores Catedráticos Efectivos

Doutor Manuel Alberto Coimbra Sobrinho Simões
Doutora Maria Amélia Duarte Ferreira
Doutor José Agostinho Marques Lopes
Doutor Patrício Manuel Vieira Araújo Soares Silva
Doutor Daniel Filipe Lima Moura
Doutor Alberto Manuel Barros da Silva
Doutor José Manuel Lopes Teixeira Amarante
Doutor José Henrique Dias Pinto de Barros
Doutora Maria Fátima Machado Henriques Carneiro
Doutora Isabel Maria Amorim Pereira Ramos
Doutora Deolinda Maria Valente Alves Lima Teixeira
Doutora Maria Dulce Cordeiro Madeira
Doutor Altamiro Manuel Rodrigues Costa Pereira
Doutor Rui Manuel Almeida Mota Cardoso
Doutor António Carlos Freitas Ribeiro Saraiva
Doutor José Carlos Neves da Cunha Areias
Doutor Manuel Jesus Falcão Pestana Vasconcelos
Doutor João Francisco Montenegro Andrade Lima Bernardes
Doutora Maria Leonor Martins Soares David
Doutor Rui Manuel Lopes Nunes
Doutor José Eduardo Torres Eckenroth Guimarães
Doutor Francisco Fernando Rocha Gonçalves
Doutor José Manuel Pereira Dias de Castro Lopes
Doutor António Albino Coelho Marques Abrantes Teixeira
Doutor Joaquim Adelino Correia Ferreira Leite Moreira
Doutora Raquel Ângela Silva Soares Lino

Professores Jubilados ou Aposentados

Doutor Abel Vitorino Trigo Cabral
Doutor Alexandre Alberto Guerra Sousa Pinto
Doutor Álvaro Jerónimo Leal Machado de Aguiar
Doutor Amândio Gomes Sampaio Tavares
Doutor António Augusto Lopes Vaz
Doutor António Carvalho Almeida Coimbra
Doutor António Fernandes Oliveira Barbosa Ribeiro Braga
Doutor António José Pacheco Palha
Doutor António Manuel Sampaio de Araújo Teixeira
Doutor Belmiro dos Santos Patrício
Doutor Cândido Alves Hipólito Reis
Doutor Carlos Rodrigo Magalhães Ramalhão
Doutor Cassiano Pena de Abreu e Lima
Doutor Daniel Santos Pinto Serrão
Doutor Eduardo Jorge Cunha Rodrigues Pereira
Doutor Fernando Tavarela Velloso
Doutor Francisco de Sousa Lé
Doutor Henrique José Ferreira Gonçalves Lecour de Menezes
Doutor Jorge Manuel Mergulhão Castro Tavares
Doutor José Carvalho de Oliveira
Doutor José Fernando Barros Castro Correia
Doutor José Luís Medina Vieira
Doutor José Manuel Costa Mesquita Guimarães
Doutor Levi Eugénio Ribeiro Guerra
Doutor Luís Alberto Martins Gomes de Almeida
Doutor Manuel António Caldeira Pais Clemente
Doutor Manuel Augusto Cardoso de Oliveira
Doutor Manuel Machado Rodrigues Gomes
Doutor Manuel Maria Paula Barbosa
Doutora Maria da Conceição Fernandes Marques Magalhães
Doutora Maria Isabel Amorim de Azevedo
Doutor Mário José Cerqueira Gomes Braga
Doutor Serafim Correia Pinto Guimarães
Doutor Valdemar Miguel Botelho dos Santos Cardoso
Doutor Walter Friedrich Alfred Osswald

Ao abrigo do Art.º 8º do Decreto-Lei n.º 388/70, fazem parte desta dissertação as seguintes publicações:

I. Pacheco-Figueiredo L, Lunet N. Health status, use of healthcare, and socio-economic implications of cancer survivorship in Portugal: results from the Fourth National Health Survey. J Cancer Surviv. 2014 Dec; 8(4):611-7.

II. Pacheco-Figueiredo L, Antunes L, Bento MJ, Lunet N. Health-related behaviours in the EpiPorto study: cancer survivors versus participants with no cancer history. Eur J Cancer Prev. 2011 Jul; 20(4):348-54.

III. Pacheco-Figueiredo L, Antunes L, Bento MJ, Lunet N. Incidence of second primary cancers in North Portugal – a population-based study. [submetido para publicação].

IV. Pacheco-Figueiredo L, Antunes L, Bento MJ, Lunet N. Frequency and survival of second primary cancers in North Portugal – a population-based assessment. Eur J Cancer Prev. 2013 Nov; 22(6):599-606.

Em cumprimento com o disposto no referido Decreto-Lei, declaro que participei ativamente na definição dos objectivos de cada um dos trabalhos apresentados, bem como na análise estatística dos dados. Fui responsável pela redação da versão inicial de todos os manuscritos e colaborei ativamente na preparação das suas versões finais.

Esta investigação foi realizada no Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e no Instituto de Saúde Pública da Universidade do Porto, sob orientação do Professor Doutor Nuno Lunet (Faculdade de Medicina e Instituto de Saúde Pública da Universidade do Porto).

Esta investigação foi financiada pela Fundação para a Ciência e a Tecnologia, através da atribuição de uma bolsa de interno doutorando [SFRH/SINTD/60124/2009].

Tese de Doutoramento em Saúde Pública apresentada à Faculdade de Medicina da Universidade do Porto

Apresentação em Provas Públicas no dia 9 de Abril de 2015, às 14:00

(Aula Magna, Faculdade de Medicina, Universidade do Porto)

JÚRI

Doutora Maria Amélia Duarte Ferreira (Presidente)
Faculdade de Medicina, Universidade do Porto

Doutor Angel Esteve Fernandez Muñoz
Institut Català d'Oncologia, Universitat de Barcelona

Dr. Nuno Augusto Alberto de Miranda
Instituto Português de Oncologia de Lisboa de Francisco Gentil

Doutor José Henrique Dias Pinto de Barros
Faculdade de Medicina, Universidade do Porto

Doutor Francisco José Miranda Rodrigues da Cruz
Faculdade de Medicina, Universidade do Porto

Doutora Maria do Rosário Oliveira Martins
Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa

Doutora Bárbara Neves Peleteiro
Faculdade de Medicina, Universidade do Porto

Doutor Nuno Miguel de Sousa Lunet (Orientador)
Faculdade de Medicina, Universidade do Porto

À Cláudia

À Mafalda

Agradecimentos

Ao Sr. Professor Nuno Lunet, pela forma dedicada como sempre exerceu a sua orientação, pelas excelentes condições de trabalho que me proporcionou, pela sua notável contribuição para o meu enriquecimento científico e académico e pelas palavras de estímulo que me dispensou.

Ao Sr. Professor Henrique Barros, pelo modo exemplar como me acolheu no Serviço de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e pelo elevado nível científico com que coordenou as atividades formativas e científicas do Programa Doutoral de Saúde Pública, no qual tive o privilégio de participar.

Ao Sr. Professor Jaime Correia de Sousa, pelo apoio pessoal e institucional que me concedeu enquanto coordenador da Área Científica de Saúde Comunitária da Escola de Ciências de Saúde da Universidade do Minho, local onde exerço a minha atividade académica.

Ao Sr. Professor Francisco Cruz, pela sua contribuição ativa na conciliação das atividades do Programa Doutoral em Saúde Pública com as minhas tarefas clínicas enquanto interno do Serviço de Urologia do Centro Hospitalar São João.

Ao Sr. Professor Nuno Tomada, pelo modo como sempre incentivou e valorizou as minhas atividades científicas como parte integrante do meu internato médico em Urologia.

À Sra. Dra. Maria José Bento, ao Luís Antunes e à Clara Castro, pelo apoio inexcedível que prestaram no desenvolvimento dos trabalhos da tese, através da disponibilização de dados do Registo Oncológico Regional do Norte e da análise crítica dos resultados obtidos.

À Sra. Dra. Isabel Carvalho, responsável do Registo Oncológico do Centro Hospitalar São João, pelas palavras de simpatia e incentivo, assim como pela disponibilização dos dados do registo hospitalar, que ajudaram na concepção dos objectivos da tese.

Aos colegas do Programa Doutoral em Saúde Pública, em especial ao amigo Jean-Pierre, pelo companheirismo e pela forma entusiasmada como contribuíram para o meu enriquecimento, com a frequente partilha de experiências, e por tornarem este percurso aprazível.

Aos meus pais, pela educação que me proporcionaram, pelo espírito de conquista e aprendizagem constante que me incutiram e pelo exemplo de trabalho que me concederam, constituindo ingredientes indispensáveis para esta caminhada.

À Cláudia, pelo apoio incondicional e compreensão durante esta exigente etapa do meu desenvolvimento profissional, que se traduziu em períodos de menor convívio familiar.

À Mafalda, pela alegria que sempre emprestou à família, mesmo nos momentos de menor presença do pai, constituindo uma importante fonte de motivação durante este percurso.

Aos meus sogros, pelo modo dedicado e inexcedível como sempre se mostraram disponíveis para auxiliar no que fosse necessário, de modo a suavizar as minhas ausências.

Table of contents

Acronyms and abbreviations

ASR – Age-standardized rate
CAD – Coronary artery disease
CHF – Congestive heart failure
CNS – Central nervous system
CI – Confidence interval
CS – Cancer survivor
DALY – Disability-adjusted life year
FAP – Familial adenomatous polyposis
FPC – First primary cancer
HDI – Human development index
HNPCC – Hereditary non-polyposis colorectal cancer
HSCT – Hematopoietic stem cell transplantation
IACR – International Association of Cancer Registries
IARC – International Agency for Research on Cancer
IC 95% – Intervalo de confiança a 95%
ICSS – International cancer survival standard
LC – Latent cancer participant
MEN – Multiple endocrine neoplasia
NC – No-cancer participant
NCI – National Cancer Institute
NHS – National Health System
PYAR – Person-year at risk
RORENO – North Region Cancer Registry
SEER – Surveillance, Epidemiology and End Results program
SIR – Standardized incidence ratio
SPC – Second primary cancer
VHL – Von Hippel-Lindau syndrome
WHO – World Health Organization
YLL – Years of life lost
YLD – Years lived with disability
95% CI – 95% confidence interval

LUÍS MANUEL DA CUNHA PACHECO FIGUEIREDO

EPIDEMIOLOGY OF CANCER SURVIVORSHIP IN PORTUGAL

PORTO | 2015

U.PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Resumo

1. Resumo

Durante as últimas décadas tem-se assistido a um aumento na incidência de cancro conjuntamente com uma melhoria na sobrevivência, resultando num número crescente de sobreviventes de cancro a nível mundial. Estes fatos sugerem a importância de se proceder a uma caraterização epidemiológica detalhada, em diferentes contextos demográficos, assim como efetuar uma monitorização frequente da evolução dos dados epidemiológicos. Neste contexto, a presente tese de doutoramento pretende contribuir para um melhor conhecimento da epidemiologia dos sobreviventes de cancro em Portugal durante a última década. De forma a atingir esse objectivo, foram desenvolvidos quatro trabalhos, com diferentes desenhos de estudo. Os parágrafos seguintes descrevem de forma resumida os objetivos específicos associados a cada um dos estudos, assim como a metodologia adotada e os resultados obtidos.

a) Avaliar o estado de saúde e as condições socioeconómicas dos sobreviventes de cancro em Portugal, assim como a sua utilização de recursos de saúde (Artigo I)

Comparou-se o estado de saúde, a utilização de recursos de saúde e as condições socioeconómicas entre os sobreviventes de cancro (CS) e a população em geral, utilizando dados de uma amostra representativa da população Portuguesa com idade ≥15 anos (n=35 229). Foram definidos três grupos de sobreviventes de cancro, de acordo com o tempo desde o diagnóstico e do último tratamento: CS1 – diagnóstico nos últimos 12 meses; CS2 – diagnóstico há mais de 12 meses e tratamentos nos últimos 12 meses; CS3 – diagnóstico e tratamento há mais de 12 meses. A comparação destes grupos com a população em geral foi ajustada para as variáveis idade, sexo e área de residência.

A prevalência de CS foi de 2,2% (CS1: 0,2%; CS2: 0,9%; CS3: 1,1%). Verificou-se que os CS reportavam mais frequentemente um pior estado de saúde e incapacidade temporária, fundamentalmente nos grupos CS1 e CS2. Constataram-se níveis mais elevados de despesas de saúde e rendimentos familiares mais baixos nos estádios iniciais de sobrevivência da doença. A frequência de dificuldades financeiras reportadas foi superior nos indivíduos do sexo masculino pertencentes ao grupo CS3.

b) Comparar a frequência de exposição a factores de risco para doenças crónicas, entre sobreviventes de cancro e indivíduos sem antecedentes de neoplasia, utilizando uma coorte de base populacional Portuguesa (Artigo II)

Com recurso a uma coorte de adultos, representativa da população da cidade do Porto (recrutamento: 1999-2003; seguimento de casos novos de cancro: até 2009), comparou-se, na avaliação inicial, a exposição ao tabaco e álcool, os hábitos alimentares e o nível de atividade física entre os seguintes grupos: a) sobreviventes de cancro (CS) – indivíduos com diagnóstico de cancro previamente à avaliação inicial (n=53); b) participantes sem cancro (NC) – indivíduos sem diagnóstico de cancro na avaliação inicial ou durante o seguimento (n=2261); c) participantes com cancro latente (LC) – indivíduos sem diagnóstico de cancro na avaliação inicial, mas com posterior diagnóstico durante o seguimento (n=139).

A prevalência de fumadores activos foi de aproximadamente 20% entre os grupos CS e NC (média de consumo: 4 cigarros/dia) e de cerca de 30% no grupo LC (média de consumo: 7 cigarros/dia). Observou-se um consumo médio de álcool mais elevado no grupo LC (25,5 g/dia) e menor no grupo NC (17,0 g/dia). A proporção de indivíduos a praticar actividade física foi superior no grupo CS (≈50%), comparativamente com os grupos NC ou LC (≈33%). Os grupos CS e NC apresentaram níveis médios mais elevados de consumo de frutas e vegetais do que o grupo LC (4,2 e 4,4 vs. 3,8 porções/dia). O nível médio de pontuação do índice integrado de comportamentos saudáveis (inclui tabagismo, actividade física e consumo de álcool, frutas e vegetais) foi mais elevado no grupo NC (1,74) e menor no grupo LC (1,52), enquanto no grupo CS foi de 1,63.

c) Estimar a incidência de segundos tumores primários (SPC) numa coorte de base populacional de sobreviventes de cancro do norte de Portugal (Artigo III)

Quantificou-se a taxa de incidência e a incidência cumulativa de SPC, assim como a razão de taxas de incidência padronizada (SIR), numa coorte de base populacional de indivíduos com o diagnóstico de um primeiro tumor primário (FPC) durante o período 2000-2003, utilizando dados do Registo Oncológico da Região Norte (RORENO).

Verificou-se uma taxa de incidência aproximadamente cinco vezes superior nos primeiros dois meses de seguimento (SPC síncronos), comparativamente com os restantes 58 meses (SPC metácronos), ao longo dos quais esta se manteve relativamente estável. Os sobreviventes de cancro revelaram uma taxa de incidência de cancro superior à população em geral (SIR=1,31; IC 95%: 1,25-1,38), apesar das diferenças se atenuarem quando apenas se consideraram os SPC metácronos (SIR=1,02; IC 95%: 0,96-1,08). A taxa de incidência de cancro nas mulheres sobreviventes de cancro do pulmão foi superior ao observado na população em geral, enquanto nos sobreviventes de cancro da próstata se verificou o oposto. A incidência cumulativa aos cinco anos de SPC metácronos foi de cerca de 3%, atingindo valores próximos de 5% nos sobreviventes de FPC com risco menor de morte aos cinco anos.

d) Quantificar e caracterizar os SPC identificados num grupo de casos incidentes de cancro do norte de Portugal e descrever a sua sobrevivência de acordo com as características do FPC (Artigo IV)

Pretendeu-se quantificar a proporção de SPC entre os casos incidentes de cancro registados no RORENO durante o período 2000-2003 e descrever a sua sobrevivência com base na informação do estado vital em Dezembro de 2010.

Identificaram-se 1607 SPC (3,8% do total de casos incidentes), sendo a proporção de síncronos de 22,1%. As três topografias mais frequentes de SPC metácronos, assim como as respectivas topografias mais comuns de FPC foram: cólon (12,2%; FPC: próstata, mama e estômago), pulmão (10,5%; FPC: bexiga, estômago e cólon) e estômago (9.7%; FPC: próstata, mama e bexiga). A sobrevivência global aos cinco anos dos SPC metácronos foi de 47,4%; entre os subgrupos de alta (63,1%) e baixa sobrevivência (31,1%), não se verificaram diferenças estatisticamente significativas com base nas topografias dos FPC.

Em conclusão, a frequência de sobreviventes de cancro em Portugal, conjuntamente com as suas co-morbilidades e constrangimentos socioeconómicos, constituem um importante de problema saúde com uma relevância cada vez maior no contexto nacional. Simultaneamente, os níveis elevados de exposição a factores de risco para doenças crónicas no grupo de sobreviventes de cancro, alertam para a necessidade de encetar esforços para reverter esta situação, tanto numa

dimensão clínica como no âmbito da saúde pública. O aumento do número de segundos tumores primários observado na última década, conjuntamente com taxas de incidência de cancro entre os CS superiores às observadas na população em geral, evidencia outra vertente igualmente relevante da carga de doença associada à crescente melhoria do prognóstico dos doentes com cancro.

Abstract

2. Abstract

The worldwide growing number of cancer survivors, due to the increase in cancer incidence along with better survival rates, highlights the health and socio-economic burden associated with survivorship. This demands an epidemiologic characterization within different settings, as well as a continuous monitoring of the evolving trends. Therefore, this thesis aimed to contribute to a better understanding of the epidemiology of cancer survivorship in Portugal, during the last decade. To accomplish this main goal, four studies were performed following different designs. The next paragraphs briefly describe the specific objective pursued in each study, as well as the methodology adopted and the main results.

a) To assess cancer survivors' health status, use of healthcare resources and socio-economic conditions, in Portugal (Paper I)

We compared cancer survivors (CS) with the general population regarding health status, use of healthcare resources and socio-economic condition, using data from a representative sample of the Portuguese population aged ≥15 years (n=35 229). Three groups of CS were defined, according to the time since diagnosis and the latest cancer treatment: CS1 – diagnosis within 12 months of interview; CS2 – diagnosis more than 12 months before and treatment in the previous 12 months; CS3 – diagnosis and treatment more than 12 months before. These were compared with the general population, adjusting for differences in sex, age and place of residence.

The prevalence of CS was 2.2% (CS1: 0.2%; CS2: 0.9%, CS3: 1.1%). Self-perceived health-status was worse among CS and short-time incapacity was more frequent among CS1 and CS2. Health expenses were higher in the early stages of survivorship. Lower household income and financial difficulties were more frequent in CS1 and CS3 men, respectively.

b) To compare the frequency of exposure to environmental risk factors for chronic diseases between cancer survivors and individuals with no previous cancer diagnosis, within a Portuguese cohort (Paper II)

In a cohort of adults (recruitment: 1999–2003; follow-up, through linkage with population-based cancer registry: up to 2009) from Porto, we compared the baseline exposure to smoking, alcohol

and dietary intake, as well as the physical activity level between: cancer survivors (CS) – cancer diagnosis before baseline (n=53); no-cancer participants (NC) – without cancer diagnosis at baseline or during follow-up (n=2261); latent cancer participants (LC) – participants with no cancer diagnosis at baseline but diagnosed during follow-up (n=139).

The prevalence of current-smoking was nearly 20% among CS and NC (average consumption: 4 cigarettes/day) and 30% in LC (average consumption: 7 cigarettes/day). LC had the highest average alcohol intake (25.5 g/day) and NC the lowest (17.0 g/day). The proportion of subjects reporting sports practice was higher for CS (≈50%) than for NC or LC (≈33%). CS and NC had higher fruit/vegetables consumptions than LC (mean number of servings/day: 4.2 and 4.4 vs. 3.8). In a composite index on health behaviors (including smoking, physical activity, and alcohol and fruit/vegetables intake) the highest and lowest average scores were observed in the NC (1.74) and LC (1.52) groups, respectively, whereas CS scored 1.63.

c) To estimate the dynamics of SPC incidence in a population-based cohort of cancer survivors from North Portugal (Paper III)

We quantified the incidence rate and cumulative incidence of second primary cancers (SPC) and standardized incidence ratios (SIR) in a population-based cohort of subjects diagnosed with a first primary cancer (FPC) during the 2000-2003 period (n=39451), using data from the Portuguese North Region Cancer Registry (RORENO).

The incidence rate of SPC was more than 5-fold higher in the first two months of follow-up (synchronous SPC) than in the period between two months and five years (metachronous SPC), across which the incidence rates were relatively stable. Cancer survivors had an overall higher incidence rate of cancer than the general population (SIR=1.31; 95% CI: 1.25-1.38), although that difference faded when only metachronous SPC were considered (SIR=1.02; 95% CI: 0.96-1.08). Cancer incidence rates were higher among female lung FPC survivors and lower in prostate FPC cancer survivors than in the general population. The 5-year cumulative risk of developing a metachronous SPC was approximately 3%, and reached nearly 5% among patients with FPC associated with lower risk of death.

d) To quantify and characterize the SPC identified among the incident cancer cases from North Portugal, and to describe their survival according to the characteristics of the FPC (Paper IV)

We aimed to quantify the proportion of SPC among the incident cases registered by the North Region Cancer Registry (RORENO) during 2000-2003, and to describe their survival using vital status at December 2010.

A total of 1607 SPC (3.8% of all cancers) were registered (22.1% of synchronous). The most common metachronous SPC topographies and corresponding most frequent FPC were: 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 metachronous SPC was 47.4%; within the subgroups with higher (63.1%) and lower survival (31.1%) there were no significant differences across groups of FPC with expectably different survival.

In conclusion, the frequency of cancer survivors in Portugal and their associated health and socio-economic concerns are becoming increasing meaningful, as well as their exposure to chronic disease risk factors has still an ample scope for improving. Moreover, the incidence of SPC is higher than the cancer incidence in the general population, mainly in the first months of follow-up, constituting another relevant concern within the whole burden associated with the longer cancer survival.

Public Health relevance of cancer survivorship

3. Public Health relevance of cancer survivorship

The increase in cancer incidence due to population aging [1, 2], the decline in cardiovascular mortality [3, 4] and higher levels of screening, concomitantly with improvements in cancer management strategies, resulted in a dramatic increase in the number of cancer survivors during the last decades [5, 6]. In 2012, there was an estimated worldwide population of approximately 32 million cancer survivors [6] and the projections anticipate a 75% rise until 2030 [7]. As a result, the burden associated with cancer survivorship is growing, which includes the management of comorbidities and late effects of treatments [8, 9], the higher risk of developing a second primary cancer (SPC) [10], the social-economic consequences for the patient and for the society [11], as well as the financial concerns associated with the cost of care [12].

The health-status impairment and the socio-economic effects of cancer diagnosis and treatment are important concerns among the growing population of living persons ever diagnosed with cancer [8, 13]. Cancer survivors often suffer from persistent symptoms (pain, distress, fatigue or cognitive impairment), as well as employment changes and financial difficulties, that could affect not only the patient but also their families, among other short and long term effects [8, 13]. Assessing the impact of these phenomena in different settings is needed to support a more comprehensive management of oncological diseases.

Cancer survivors also have a nearly 14% higher risk of developing a new malignancy than the general population [10]. SPC represented 6% of all incident cancer cases in Europe (1995-1999) [14] and 18% in the USA (2007) [15]; in some settings the proportion of SPC among all diagnosed tumors is estimated to be higher than breast, lung or prostate first primary cancers (FPC) [15]. The occurrence of SPC is mostly related to genetic characteristics, deleterious environmental exposures and late effects of FPC treatment [15, 16]. It is therefore important to characterize cancer survivors regarding the exposure to amendable risk factors such as treatment modalities of the FPC as well as lifestyle behaviors modifiable by health promotion activities like smoking, alcohol consumption, diet and physical inactivity [17-21]. On other hand, since SPC are a problem increasingly encountered in routine medical practice, descriptive data concerning the incidence of SPC should be available, to provide local clinicians with a benchmark to estimate the probability of cancer survivors developing another cancer within the next years.

These challenges, among others, contributed to the worldwide trend of increasing number of cancer survivorship research publications [13]. This represents a major change in the cancer research focus, which used to be centered on cure, to one including longer term issues such as morbidity and the quality of life of cancer survivors. Nevertheless, in Portugal, apart from the regular reports of the population-based cancer registries, the number of publications describing the several domains related to the burden of cancer survivorship is scarce.

Trends in cancer incidence, mortality and survival

4. Trends in cancer incidence, mortality and survival

There is an increasing burden of non-communicable diseases, which nowadays are responsible for the majority of deaths worldwide, killing more people each year than all other causes combined [22]. Cancer is already the leading cause of death in many high-income countries and is expected to become a main cause of morbidity and mortality in the next few decades in every region of the world, irrespective of resource level [6].

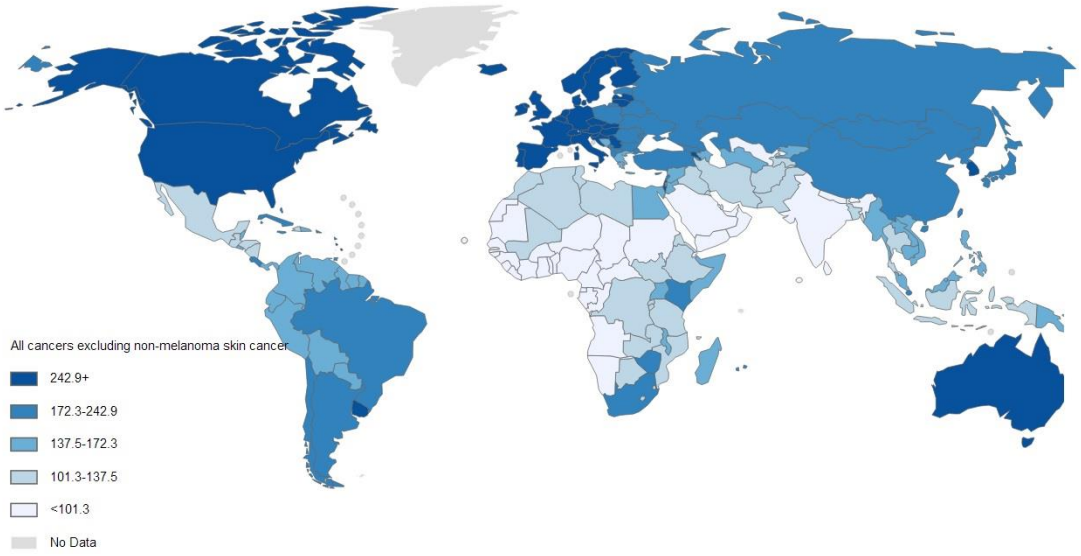
4.1. Incidence and mortality

4.1.1. Worldwide

Worldwide, about 14.1 million new cancer cases and 8.2 million cancer deaths are estimated to have occurred in 2012. Forty-three percent of the new cancer cases and 35% of the cancer deaths occurred in the more developed regions. The overall estimated age-standardized incidence rate (ASR) of cancer was 182.3 cases per 100 000 persons per year (figure 1) [6]. It was almost 25% higher in men than in women, with rates of 205 and 165 per 100 000, respectively. Male incidence rates varied almost five-fold across the different regions of the world, with rates ranging from 79 per 100 000 in Western Africa to 365 per 100 000 in Australia/New Zealand (with high rates of prostate cancer representing a significant driver of the latter) [6]. There was less variation in female incidence rates (almost three-fold) with rates ranging from 103 per 100 000 in South-Central Asia to 295 per 100 000 in Northern America [6].

Regarding mortality, there was less regional variability than for incidence. The rates were 15% higher in more developed than in less developed regions among men, and 8% higher in women. In men, the rates were highest in Central and Eastern Europe (173 per 100 000) and lowest in Western Africa (69 per 100 000) [6]. In contrast, the highest rates in women were in Melanesia (119 per 100 000) and Eastern Africa (111 per 100 000), and the lowest in Central America (72 per 100 000) and South-Central Asia (65 per 100 000) [6].

Figure 1 – Worldwide distribution of estimated age-standardized cancer incidence rates (per 100 000 cases) in 2012

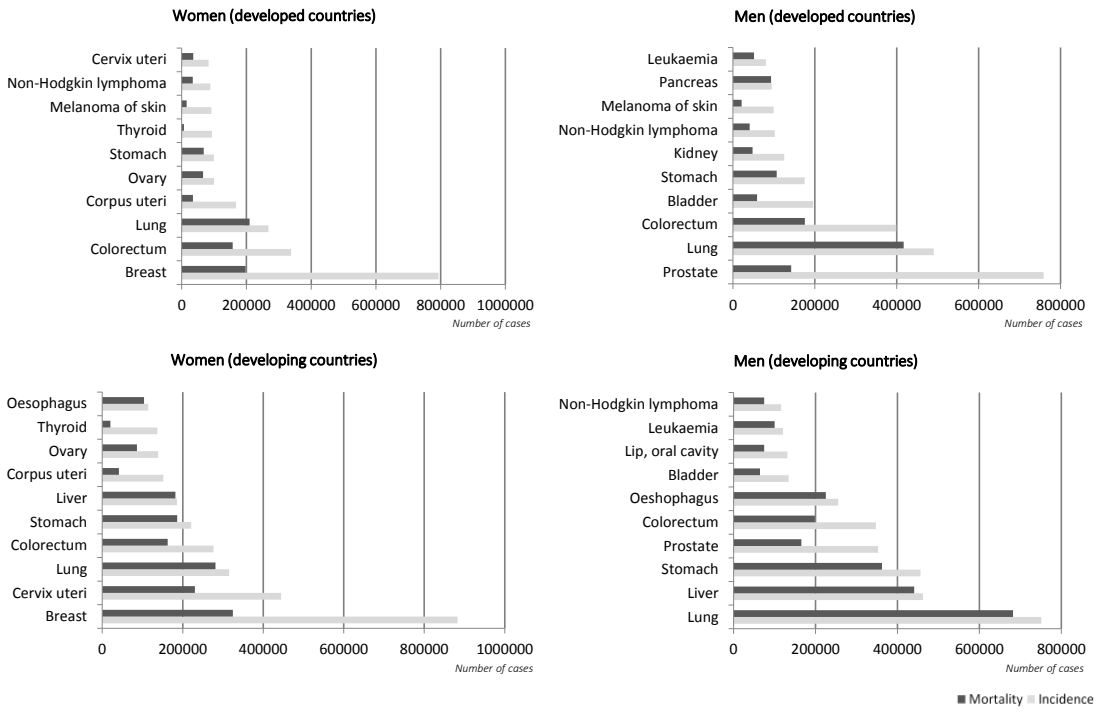


Source: GLOBOCAN 2012 [6]

Lung (13.0%), breast (11.9%), colorectum (9.7%), prostate (7.9%) and stomach (6.8%) tumors were the most frequent incident cancer cases, regarding worldwide data [6]. However, this distribution differed across the geographical regions; lifestyle-related cancers were more frequent in developed countries and the proportion of infection-related cancers was higher in developing countries, both for incidence and mortality (figure 2) [6].

The pattern of cancer incidence rates has been evolving during the last decades, showing a clear trend towards an increase of new cancer cases, both in developed and developing countries (figure 3), although the estimates of age-standardized incidence rate (ASR) have been rising mainly in the developing countries (figure 4) [23].

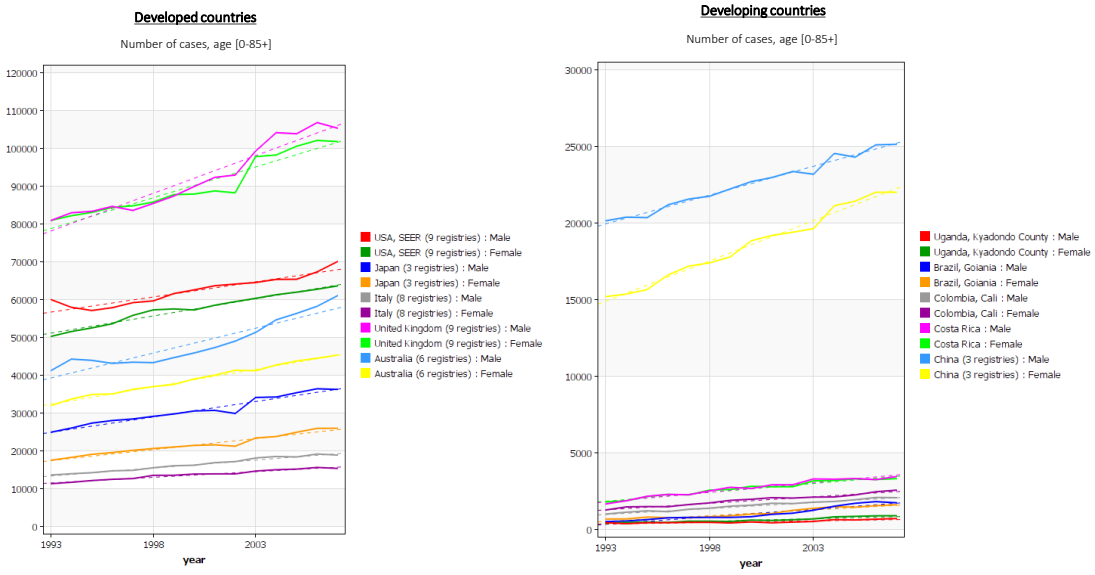
Figure 2 – Top ten incident cancers in developed and developing countries



Data source: GLOBOCAN 2012 [6]

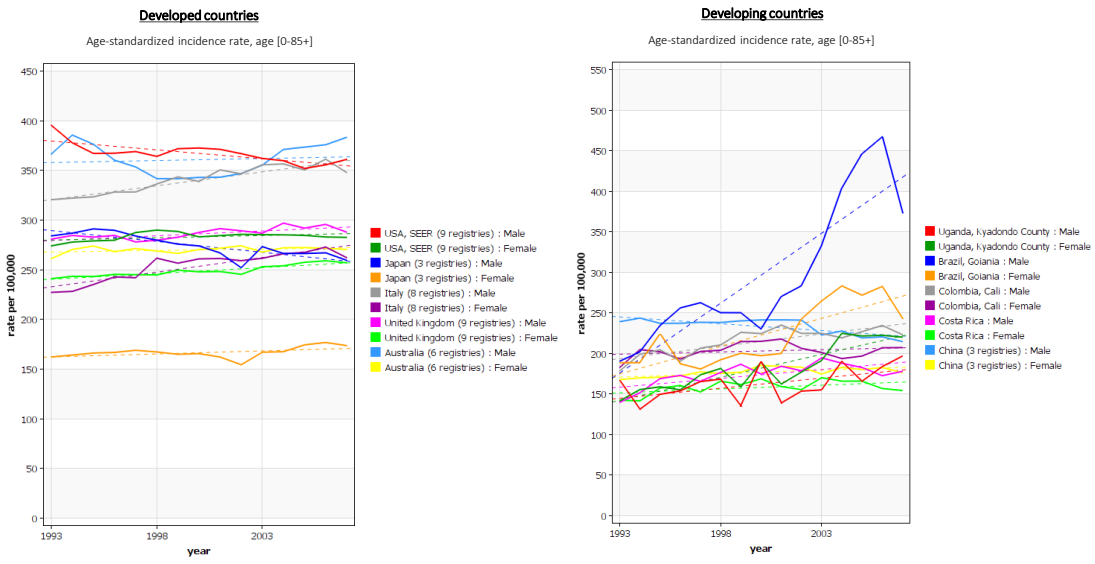
The increase in the absolute number of cancer cases in the developed countries despite the stable ASR's, mainly reflects the effect of population aging and the reduction in cardiovascular mortality [2, 3, 5]. Among developing countries, although the rapid societal and economic evolution contributed to reductions in infection-related cancers, they were offset by an increasing number of new cancer cases associated with tobacco consumption, diet, obesity and sedentary behaviors, showing a clear "epidemiologic transition" [7, 24]. Rising levels of screening at the population level might have also contributed to the increase of the cancer incidence burden in many settings, especially within those countries where the screening procedures used to be less frequent [7].

Figure 3 – Trends in the absolute number of cancer cases (all sites, except non-melanoma skin cancer) in selected countries



Source: CI-5 Plus [23]

Figure 4 – Trends in age-standardized incident rate (world) of cancer (all sites, except non-melanoma skin cancer) in selected countries



Source: CI-5 Plus [23]

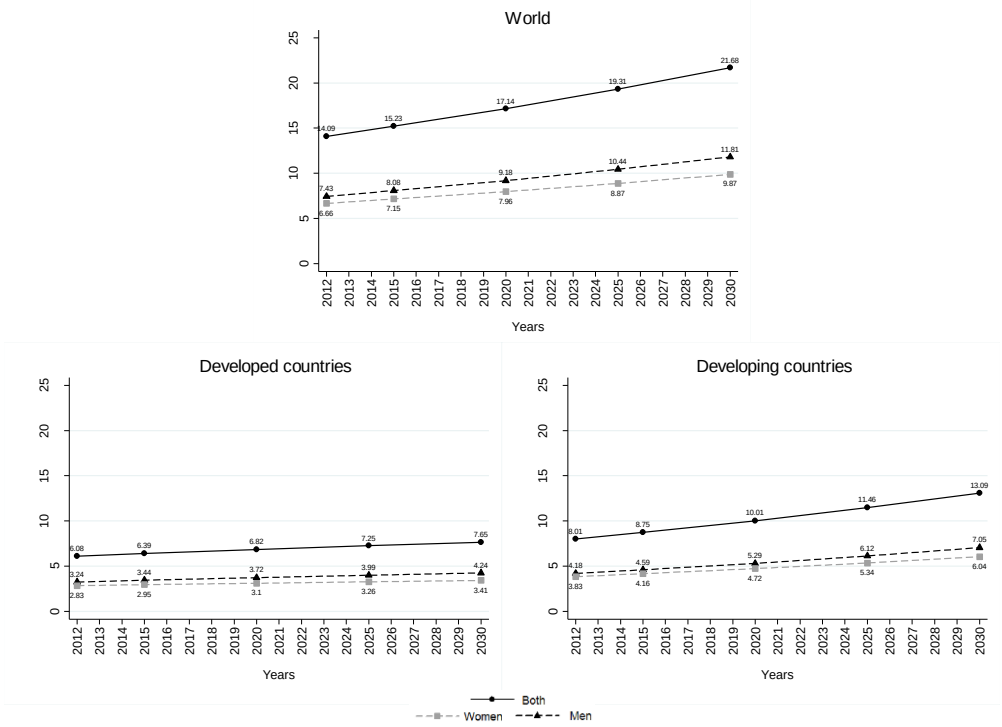
Bray et al. [7], using worldwide data from GLOBOCAN and CI-5, evaluated the trends in age-adjusted incidence rates of lung, female breast, colorectal, stomach, prostate, liver and cervical cancer, within the 1988–2002 period, stratified by sex, among 101 cancer registries from countries in medium, high or very high Human Development Index (HDI). A tendency towards increases in breast, colorectal and prostate cancers was observed in the very high HDI, high HDI and medium HDI regions. In very high HDI countries these trends seemed to be stronger, suggesting the contribution of high levels of cancer screening, and they might be indicative that an incidence plateau is closely to be reached, like it happened with colorectal cancer that stabilized or decreased its incidence rates in the last years. Among the high and medium HDI regions, the improvement in the social and economic conditions was accompanied by a rising prevalence of several reproductive, dietary, metabolic and hormonal risk factors (towards levels more similar to those commonly seen in very high HDI countries) which might have contributed to increase the incidence of those cancers [7]. Moreover, in some geographical areas with high or medium HDI, along with this westernization effect, the increasing levels of screening might have independently contributed to the observed rise in cancer incidence estimates [7].

Decreases in the incidence of stomach and cervical cancers were consistently seen in populations with very high, high and medium HDI levels. The reduction in cervical cancer burden has been attributed to the progressive lowering levels of HPV infection in older generations of women and, within higher-resource settings, the beneficial effects of mass screening cytology programs [7, 25]. The uniform reductions of stomach cancer incidence rates during the past 50 years were commonly endorsed to both a decline in the prevalence of *Helicobacter pylori* infection in successive birth cohorts related to changing childhood environment, and to improved food preservation practices and better nutrition [7, 25]. The onset of refrigeration for food transport and storage could have been vital in reduction of salt consumption by largely eradicating the need for salting, smoking, and pickling of foods [7, 25].

Despite these worldwide evolving changes in the frequency of the different tumors, the overall burden of cancer is expected to continue rising. According to worldwide projections, there will be approximately 21.7 million new cancer cases (9.9 and 11.8 million, respectively among women and

men) in 2030, and the larger increases are anticipated to take place across the developing countries (figure 5).

Figure 5 – Worldwide predictions of new cancer cases until 2030



Data source: GLOBOCAN 2012 [6]

4.1.2. Portugal

In Portugal, the estimated number of new cases of cancer and cancer deaths was 492 000 and 241 000, respectively, corresponding to an age-standardized incidence rate of 246.2 cases per 100 000 and an age-standardized mortality rate of 99.0 cases per 100 000 [6]. These estimates indicate that in Portugal, as in other developed countries, there is a high burden of disease related to cancer, especially among men (table 1).

National data from the Portuguese population-based cancer registries, between 2001-2007, showed an increase from 33 052 (women: 15 026; men: 18 026) to 42 374 (women: 18 634; men: 23 740) new cancer cases, as well as a trend of rising age-standardized incidence rates from 198.0 (women: 173.9 per 100 000; men: 231.1 per 100 000) to 225.5 per 100 000 (women: 190.6 per 100 000; men: 271.4 per 100 000). In North Portugal, although we can observe higher incidence rates, the trends were similar, showing an increase of age-standardized incidence rate from 211.5 (women: 183.8 per 100 000; men: 250.9 per 100 000) to 249.0 per 100 000 (women: 190.6 per 100 000; men: 271.4 per 100 000) (figure 6).

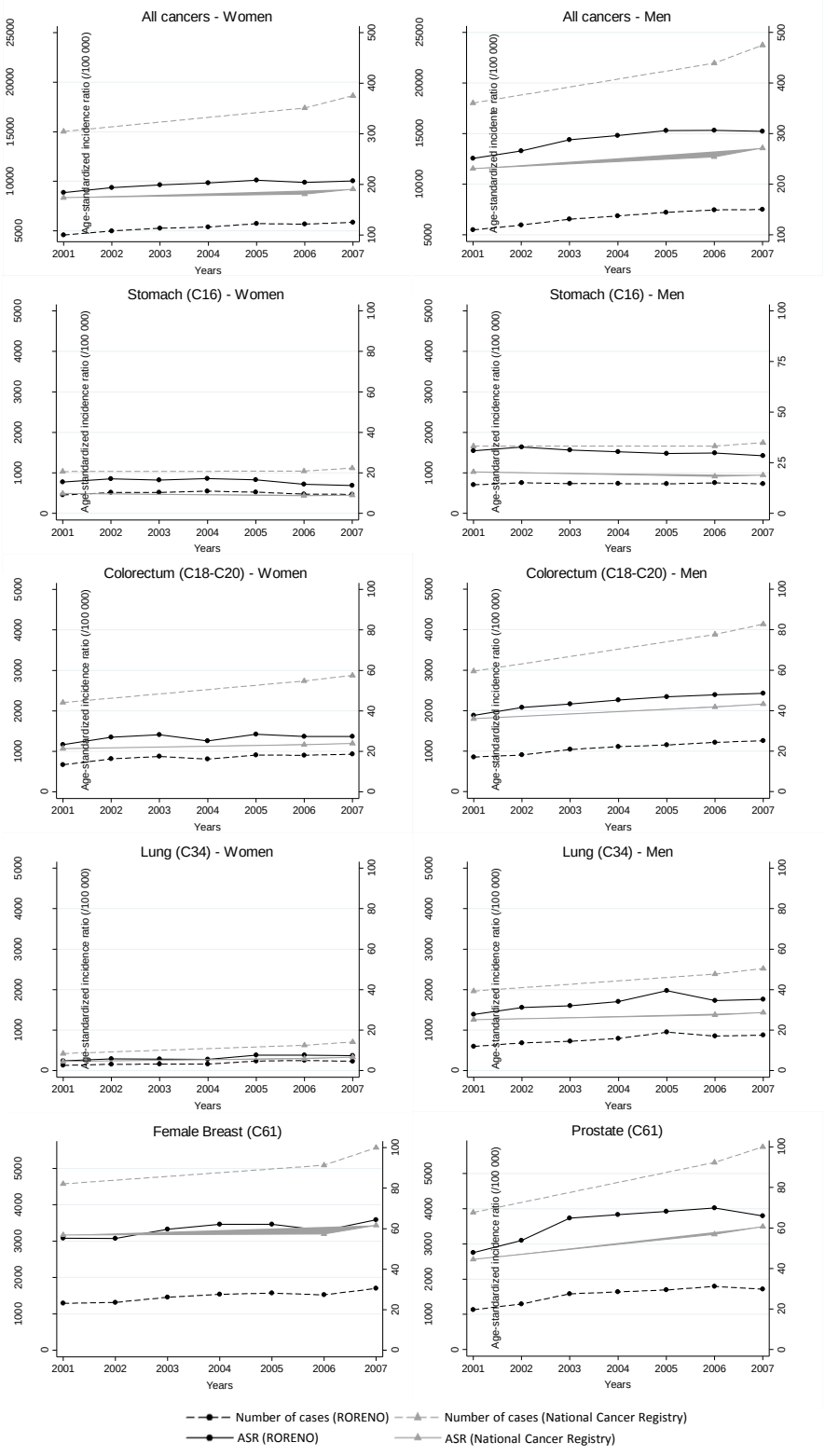
Table 1 – Cancer incidence and mortality estimates for 2012

Region	Age-standardized rates, all ages (world reference population)			
	Incidence rate/100 000		Mortality rate/100 000	
	Women	Men	Women	Men
World	165.3	205.4	82.9	126.3
Developed countries	240.6	308.7	86.2	138.0
Developing countries	135.8	163.0	79.8	120.1
Portugal	198.1	306.3	70.1	134.7

Data source: GLOBOCAN 2012 [6]

The trends of cancer incidence across the most frequent tumors also showed an increase during the same period (2001-2007), both in National [26-28] and North Portugal data [29-35], although with a stabilization or even a slight decrease in the more recent years. The more noticeable rises were observed among female breast and prostate cancers, possibly due to an increase in cancer screening (figure 6).

Figure 6 – Cancer incidence trends in Portugal: data from Portugal and North Portugal (RORENO)



Data source: Portuguese National Cancer Registry [26-28] and North Region Cancer Registry (RORENO) [29-35]

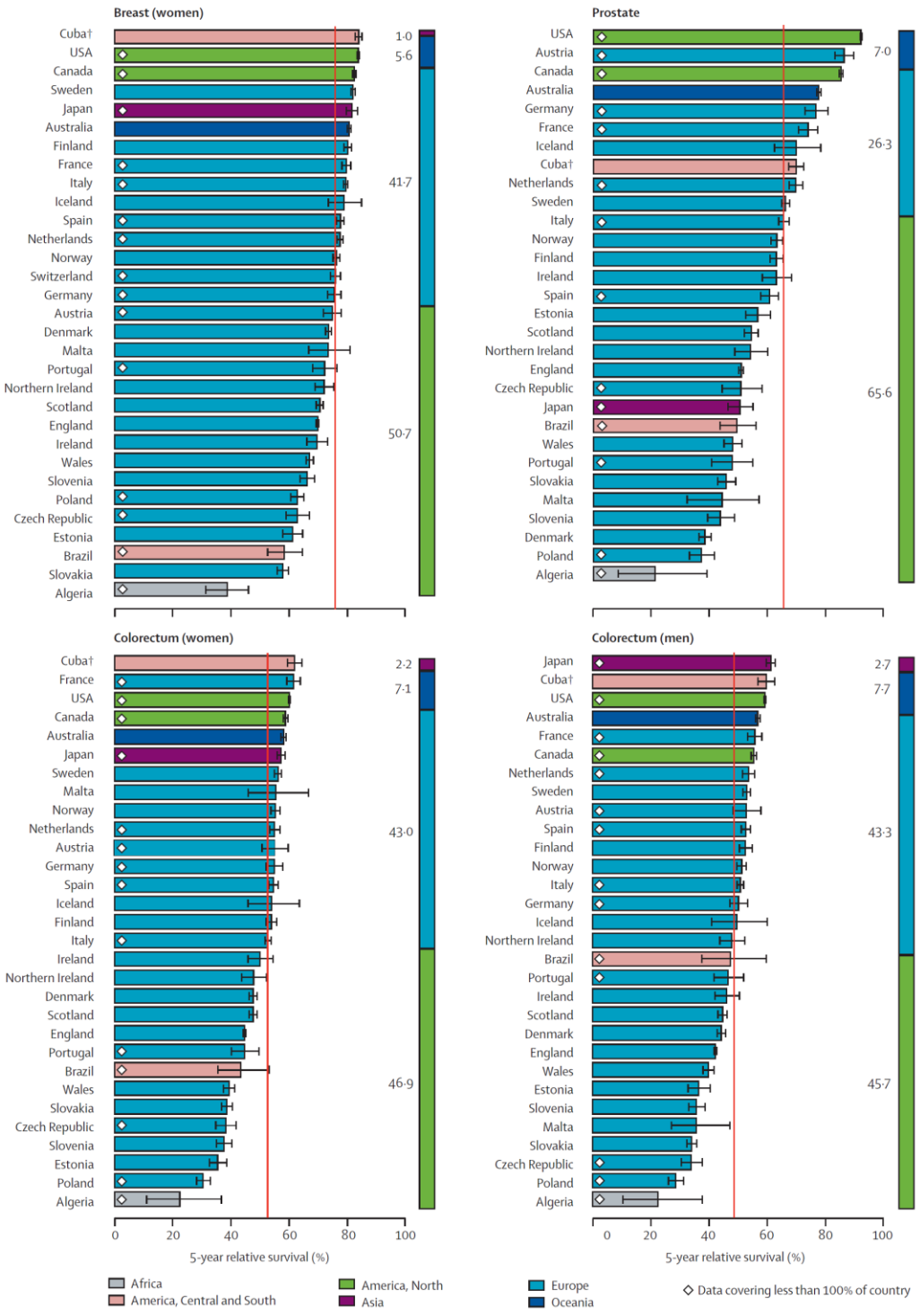
4.2. Survival

The worldwide heterogeneity of cancer incidence and mortality estimates is also observed for cancer survival. Coleman et al. [36] using data from the CONCORD project, provided the survival estimates for 1.9 million adults (aged 15–99 years) diagnosed with a first, primary, invasive cancer of the breast (women), colon, rectum or prostate during 1990–94, and followed up until 1999, across 31 countries on five continents, in a first attempt to directly compare cancer survival from many countries around the world. The study main findings showed that global variation in cancer survival was very wide. Five-year relative survival estimates [age-standardized for the International Cancer Survival Standard (ICSS) weights] for breast, colorectal and prostate cancer were generally higher in North America, Australia, Japan, and northern, western, and southern Europe, and lower in Algeria, Brazil and eastern Europe (figure 7).

In Europe, over the past 20 years, EUROCARE studies have provided data showing that survival has improved, although at different paces depending of time analysis and geographical settings. The EUROCARE-5 study [37], the largest cooperative study of population-based cancer survival in Europe, using the more recent data from 107 cancer registries within 29 European countries (2000-2007), revealed an overall age-standardized 5-year relative survival estimate of 54.2% (women: 58.0%; men: 50.2%), ranging from 6.9% in pancreatic cancer (women: 7.9%; men: 6.3%) to 88.6% in testicular cancer. About a third of all cancer cases had a survival greater than 80%, whereas a quarter had survival below 30% [37].

Survival in Eastern Europe was commonly lower and below the European mean, particularly for cancers with good or intermediate prognosis (such as prostate, female breast, rectum or non-Hodgkin lymphoma). Survival was highest for northern, central, and southern Europe.

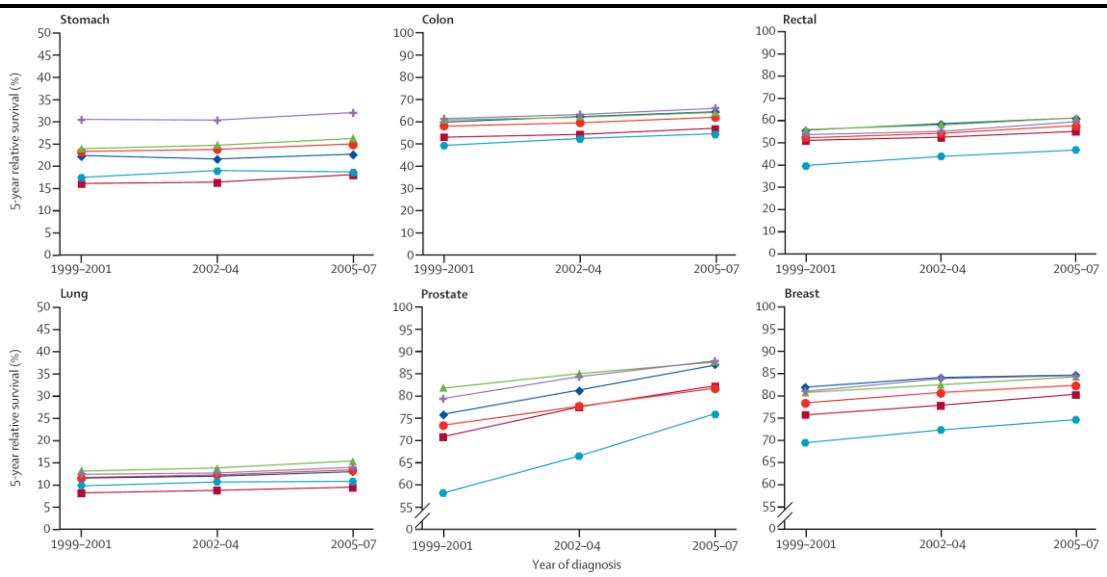
Figure 7 – Age-standardized [International Cancer Survival Standards (ICSS) population weights] 5-year relative survival for adults (aged 15–99 years) diagnosed with cancer of the breast, colorectum or prostate during 1990-94 and followed up to 1999



Reproduced from Coleman M et al. [36]

During the recent decades, cancer diagnosis and treatment have changed greatly. Cancer screening practices have been widely adopted, especially for breast, cervical, colorectal and prostate cancers, as well as early diagnosis initiatives to melanoma, thyroid and lung cancer have become frequent [38]. On other hand, there have been advances in diagnostic imaging, genetic profiling, and treatments, including the introduction of targeted drugs, multidisciplinary care, and a growing concentration of treatment in specialist centers [39-41]. As a result, the trends of cancer survival in Europe, considering data from EUROCARE-4 (1995-1999) and EUROCARE-5 studies (2000-2007), showed an overall increase of age-standardized 5-year relative survival from 50.4% to 53.2%. The trends within the EUROCARE-5 across the most frequent tumors showed a rise of age-standardized 5-year relative survival, which was more noticeable in prostate, breast and rectal cancer survivors (figure 8) [37].

Figure 8 – Trends in age-standardized (ICSS population weights) 5-year relative survival for adults (aged 15–99 years) diagnosed with cancer and followed up in the 1999–2001, 2002–04 and 2005–07 periods



Reproduced from De Angelis R et al. [37]

The latest survival estimates from National Cancer Institute (NCI) in the USA, using data from SEER registries (2004-2010), showed a 5-year relative survival for all cancer sites of 68.3% (women: 67.6%; men: 69.0%) [42]; in the past (1975-1977) the rates were lower [48.9% (women: 55.9%; men: 41.7%)], although a direct comparison between the two periods is limited since the rates were not age-standardized.

In Portugal, the 5-year age-standardized relative survival estimate (2000-2007) for all cancer sites was 56.4% (women: 60.8%; men: 52.1%) [37]. Data from North Portugal population-based cancer registry (RORENO) within the 2005-2006 period, revealed a 5-year age-standardized relative survival of 61.9% (women: 67.4%; men: 57.8%) [43].

Burden of cancer survivorship

5. Burden of cancer survivorship

As previously described, during the last decades the number of new cancer patients has been increasing, mainly as a consequence of population growth, aging and screening; concurrently, the early diagnosis and more effective cancer treatments contributed to a better cancer survival leading to a growing number of cancer survivors, mostly in the more developed countries. Although these data reflect an improvement of healthcare in those settings, they also underline the growing burden of disease associated with cancer survivorship, especially regarding the management of comorbidities and late effects of cancer treatments, higher risk of developing a SPC and cost of care.

5.1. Cancer survivors: definition and frequency

The definition of cancer survivor has not been the same during the previous decades. In the past, cancer survivors used to be defined as those who remained disease-free for a minimum of 5 years [13]. In 1985, a publication in the New England Journal of Medicine by a young physician – Dr. Fitzhugh Mullan – describing his journey with cancer, revolutionized the concept of "cancer survivor", proposing that any person should be considered a survivor from the time of diagnosis onward [44]. The National Cancer Institute (NCI) stated: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience and are therefore included in this definition" [13]. For statistical purposes, cancer survivors are prevalent cases and are often estimated by the 5-year cancer prevalence. However, since the latter is computed based on incidence and survival information of the population-based cancer registries [13] during the last 5 years, it is expected that this measure underestimate the real prevalence of cancer survivors.

Data from the GLOBOCAN 2012 [6] revealed an estimated 5-year prevalence of over 32.5 million cancer cases (women: 17.2 million cancer cases; men: 15.3 million cancer cases). Among the more developed countries there were 16.9 million cancer cases and 15.6 million were estimated within the developing countries [6]. The 5-year prevalence estimates for USA and Europe during the same

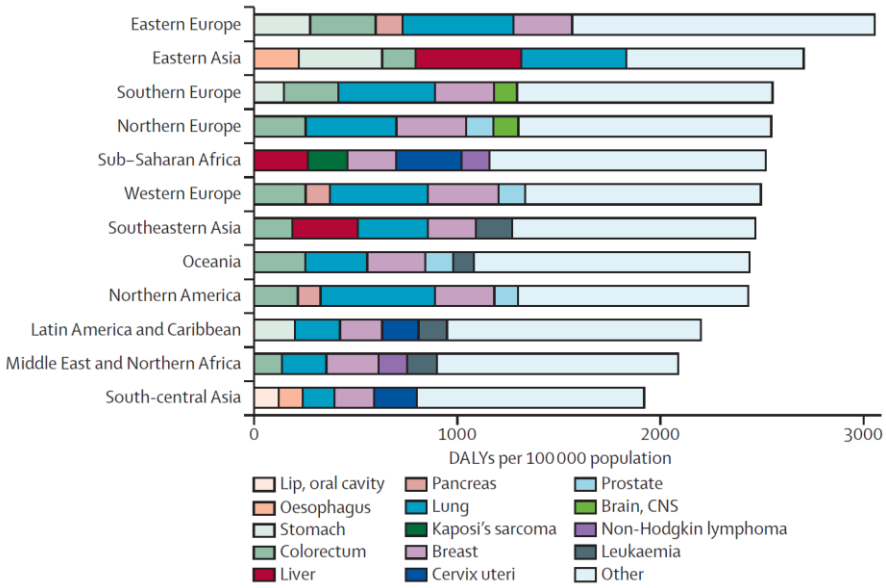
period were 4.7 and 9.8 million cancer cases, respectively; 134 300 cancer cases were estimated to be alive in Portugal in 2012 [6].

However, to understand the overall burden of cancer survivorship, it is important to have information concerning other outcomes, apart from cancer frequency. Nowadays when more than half of cancer patients are expected to be alive after five years from the diagnosis, interest has grown in evaluating other domains, such as quality of life of cancer survivors and cancer-related sequelae that lead to disability. Therefore, information about fatal and non-fatal cancer-related outcomes is needed to aid establishing priorities in cancer control. Disability-adjusted life-years (DALYs) are a key measure for such purposes, since their two dimensions - years of life lost (YLLs) and years lived with disability (YLDs) - link the burden of cancer mortality with the degree of illness and disability in patients and long-term survivors [45].

Worldwide, more than 169 million healthy life-years were lost due to cancer in 2008, with differences across the several countries [45]. Colorectal, lung, breast, and prostate cancers were the most frequent contributors to total DALYs, being responsible for 18–50% of the overall estimates [45]. In sub-Saharan Africa and eastern Asia, respectively 25% and 27% of the total burden was associated with the infection-related cancers (liver, stomach and cervical) (figure 10).

YLLs were the most important component of DALYs in all countries and for all cancers, contributing with more than 90% of the total burden [45]. Nonetheless, there were differences in the weight of YLLs as a proportion of DALYs across the different geographical settings, since higher rates of YLDs were observed in the more developed areas (figure 11), suggesting that the management of quality of life, disability and other late effects of cancer treatment is becoming increasingly relevant in these countries [45].

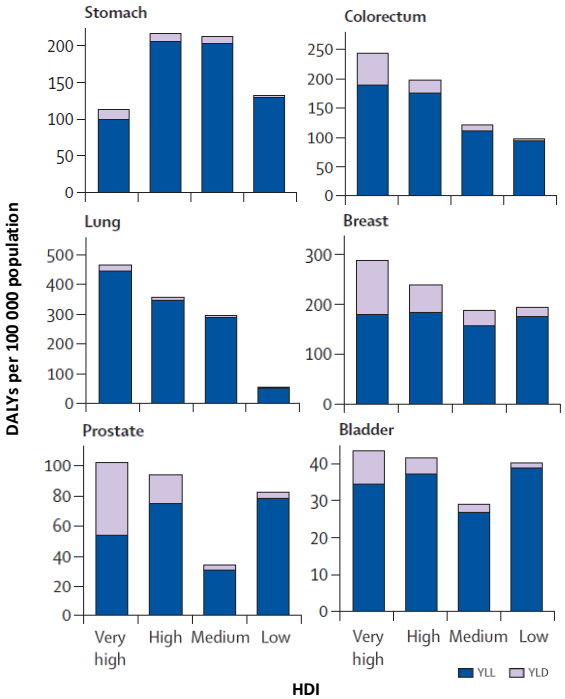
Figure 10 – Age-adjusted DALYs by world region for the five cancers most frequent in each region



DALYs=Disability-adjusted life-years; CNS - Central Nervous System

Reproduced from Soerjomataram I et al. [45]

Figure 11 – Age-adjusted DALYs per 100 000 population by cancer site and level of Health Development Index (HDI)



DALYs=Disability-adjusted life-years; YLL=years of life lost; YLD=years of life lived with disability

Adapted from Soerjomataram I et al. [45]

5.2. Health-status of cancer survivors

The impact of cancer and cancer treatment on the short- and long-term health of cancer survivors is substantial. Late effects include not only the organ damage and functional disabilities that result from the disease, the treatment, or both, but also the development of second malignancies. Several psychosocial issues that adult cancer survivors have to face are also a matter of concern.

5.2.1. Comorbidities

The benefit of a longer life is offset for many survivors, by multiple persistent symptoms, including fatigue, distress, pain, and cognitive impairment [9, 13]. While some survivors remain on anticancer treatment and, thus, continue to experience treatment-related symptoms, others who have completed treatment will experience residual symptoms of both the disease and the treatment. In either case, symptoms cause a significant burden that diminishes their quality of life. More than 1 in 4 cancer survivors have high symptom burden one year after the diagnosis, even after treatment termination [9]. Metastatic cancer, the number of comorbid conditions, remaining on active chemotherapy, younger age, lacking of medical insurance, lower income, being unemployed and being less educated are some of the characteristics of the cancer survivors that had demonstrated to be associated with high symptom burden [9]. Depression, fatigue and pain constitute some of the complaints with greatest impact on health-related quality of life [9].

Beside the symptoms, that are more frequent in the first months of survivorship or during the active treatment phase, cancer survivors have a higher prevalence of chronic conditions compared to individuals without cancer [13]. These could be the result of long-term effects of cancer treatment or comorbid conditions not related to survivorship.

Long-term cancer survivors are at risk for a variety of comorbidities, being the cardiovascular and pulmonary late effects some of the most frequent [46]. Chemotherapy-induced cardiovascular toxicity may include cardiomyopathy with or without overt congestive heart failure (CHF), endothelial dysfunction and arrhythmias [47]. Doxorubicin-induced cardiomyopathy is the most

studied chemotherapy-induced cardiovascular toxicity. A similar entity is associated with the anthracyclines and mitoxantrone and may also be associated with high-dose cyclophosphamide [47]. Radiotherapy-induced cardiovascular toxicity may include coronary artery disease (CAD), valvular disease, chronic pericardial disease, arrhythmias and conduction disturbances, cardiomyopathy or carotid artery stenosis [47].

Pulmonary toxicity may be secondary to either chemotherapy or radiotherapy; these toxicities can include radiation pneumonitis, pulmonary fibrosis and an overall decrease in pulmonary function [47]. Stem-cell transplantation may also be associated with long-term pulmonary complications, including idiopathic pneumonia syndrome and bronchiolitis obliterans [47]. Although a variety of chemotherapeutic agents may cause pulmonary toxicity, bleomycin has been the most studied.

Of particular concern for cancer survivors are also the psychological side effects of cancer diagnosis and treatment. They often report cancer-specific concerns, such as fear of recurrence, as well as more generalized symptoms regarding their future, the possibility of death, trouble sleeping, fatigue and concentration difficulties [48]. Individuals with cancer may also experience a mental disorder or an exacerbation of a prior psychiatric disease (e.g. recurrent depression). Major depression and depressive symptoms occur frequently in cancer patients, and the prevalence varied from 10 to 25%, which was at least four times higher than the observed in the general population [13, 49].

5.2.2. Second primary cancer

Second primary cancers (SPC) have become an increasingly important concern in cancer epidemiology during the last two decades, as their proportion among the incident cancer cases is rising, comprising about 18% of all incident cases in the USA, superseding breast, lung and prostate first cancers [15, 50].

What was formerly a problem primarily in pediatric cancer survivors and for the survivors of the more curable adult cancers, has become a more universal concern in the practice of oncology nowadays. As previously addressed, the number of cancer survivors has steadily increased in the last decades due to advances in early detection, supportive care and treatment [5]. One of the most serious events those individuals can experience is the diagnosis of a new cancer – a SPC [10, 15].

5.2.2.1. Definition of second primary cancers

There are several definitions of SPC in the literature, all of them are around the concept that it should correspond to a second neoplasm that differs histologically or molecularly from the original cancer, not being a recurrence or a metastasis. Although the term "second primary cancers" is frequently used when considering multiple primary cancers (MPC), sometimes when more than two multiple primary cancers are observed in the same patient, only the second cancer is classified as a SPC [51]. The cancer registries worldwide mainly classify the SPC using the rules proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) [52] or those defined by the Surveillance Epidemiology and End Results program (SEER).

The IARC/IACR guidelines have the following recommendations:

1. The recognition of the existence of two or more primary cancers does not depend on time;
2. A primary cancer is one that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis;

3. Only one tumor shall be recognized as arising in an organ or pair of organs or tissue. Some groups of codes are considered to be a single organ for the purposes of defining multiple tumors (these topography code groups are shown in table 2). Multifocal tumours – that is, discrete masses apparently not in continuity with other primary cancers originating in the same primary site or tissue – are counted as a single cancer;
4. Rule 3 does not apply in two circumstances:
    4.1. Systemic (or multicentric) cancers potentially involving many different organs are only counted once in any individual. These are Kaposi sarcoma and tumours of the haematopoietic system.
    4.2. Neoplasms of different morphology should be regarded as multiple cancers (even if they are diagnosed simultaneously in the same site).

If the morphological diagnoses fall into one category in table 3, and arise in the same primary site, they are considered to be the same morphology for the purpose of counting multiple primaries. If the morphological diagnoses fall into two or more of the categories in table 3, even if they concern the same site, the morphology is considered to be different, and two or more cases should be counted. Single tumours containing several different histologies which fall into one histological group in table 3 are registered as a single case, using the numerically highest ICD-O morphology code. If, however, one morphology is not specific [groups (5), (14) and (17)] and a specific morphology is available, the case should be reported with the specific histology and the non-specific diagnosis should be ignored.

Table 2 – Groups of topography codes considered a single site in the definition of SPC

ICD-O-2/3 site code	Label	If diagnosed at different times, code first diagnosis. If diagnosed at the same time use codes given below
C01	Base of tongue	
C02	Other and unspecified parts of tongue	C02.9
C00	Lip	
C03	Gum	
C04	Floor of mouth	
C05	Palate	
C06	Other and unspecified parts of mouth	C06.9
C09	Tonsil	
C10	Oropharynx	
C12	Pyriform sinus	
C13	Hypopharynx	
C14	Other and ill-defined sites in lip, oral cavity and pharynx	C14.0
C19	Rectosigmoid junction	
C20	Rectum	C20.9
C23	Gallbladder	
C24	Other and unspecified parts of biliary tract	C24.9
C33	Trachea	
C34	Bronchus and lung	C34.9
C40	Bones, joints and articular cartilage of limbs	
C41	Bones, joints and articular cartilage of other and unspecified sites	C41.9
C65	Renal pelvis	
C66	Ureter	
C67	Bladder	
C68	Other and unspecified urinary organs	C68.9

Adapted from "International rules for multiple primary cancers (ICD-0 third edition)"[52]

SEER multiple primary coding rules are more liberal than IACR rules in allowing the registration of multiple primary cancers, particularly cancers that occur at the same site including paired organs (breast, kidney) and organs with relatively large surface areas (skin, urinary bladder, colon and rectum, oral cavity and pharynx) [53]. Therefore, based on SEER multiple primary rules, which are used by cancer registries in the United States and in the majority of provincial registries in Canada, the estimates of SPC tend to be systematically higher than if the IACR rules are applied [53].

Table 3 – Groups of malignant neoplasms considered to be histologically 'different' for the purpose of defining SPC

Group	
Carcinomas	
1. Squamous and transitional cell carcinoma	8051-8084, 8120-8131
2. Basal cell carcinomas	8090-8110
3. Adenocarcinomas	8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941
4. Other specific carcinomas	8030-8046, 8150-8157, 8170-8180, 8230-8255, 8340-8347, 8560-8562, 8580-8671
5. Unspecified carcinomas (NOS)	8010-8015, 8020-8022, 8050
6. Sarcomas and soft tissue tumours	8680-8713, 8800-8921, 8990-8991, 9040-9044, 9120-9125, 9130-9136, 9141-9252, 9370-9373, 9540-9582
7. Mesothelioma	9050-9055
Tumours of haematopoietic and lymphoid tissues	
8. Myeloid	9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987
9. B-cell neoplasms	9670-9699, 9728, 9731-9734, 9761- 9767, 9769, 9823-9826, 9833, 9836, 9940
10. T-cell and NK-cell neoplasms	9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948
11. Hodgkin lymphoma	9650-9667
12. Mast-cell Tumours	9740-9742
13. Histiocytes and Accessory Lymphoid cells	9750-9758
14. Unspecified types	9590-9591, 9596, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989
15. Kaposi sarcoma	9140
16. Other specified types of cancer	8720-8790, 8930-8936, 8950-8983, 9000-9030, 9060-9110, 9260-9365, 9380-9539
17. Unspecified types of cancer	8000-8005

Adapted from "International rules for multiple primary cancers (ICD-0 third edition)"[52]

The SPC may also be classified as synchronous or metachronous, according to time interval between the FPC and the SPC. The most frequently adopted criteria classifies the SPC as synchronous if the difference between the FPC and SPC was less than two months; metachronous SPC are those diagnosed at two months of follow-up of the FPC or posteriorly [54]. Although less

frequently, some studies adopted three, six or twelve months as the cutoff to classify synchronous and metachronous SPC.

5.2.2.2. Frequency of SPC

Information from the Eurocare-4 collaborative study using data from 69 European cancer registries, during the period 1995–1999, revealed that 6.3% of the incident cancer cases were SPC, ranging from 0.4% in the Naples registry (Italy) to 12.9% in the Icelandic registry [14]. The most frequent localizations of the SPC were colorectal (15.1%), lung (13.4%), female breast (11.5%) and prostate (10.3%), which corresponded to high incidence localizations when the overall cancer incidence is considered [14].

Reports in USA using data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program (SEER), showed that 18% of the newly diagnosed cancers in 2007 were SPC [55]. Prostate (16.9%), female breast (15.6%), colorectal (14.2%) and urinary bladder (9.6%) cancers were the most frequent FPC topographies among cancer survivors that developed a SPC, corresponding to localizations with high frequency and survival [55].

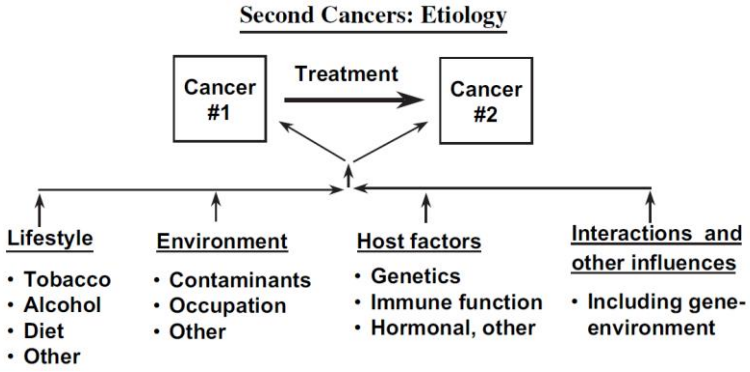
5.2.2.3. Etiology of SPC

According to the model proposed by Travis et al. [16], SPC can reflect host factors (high- and low-penetrant genetic modifications), lifestyle environmental exposures and late consequences of FPC treatment (figure 12).

The contribution of genetics to the etiology of SPC is complex and characterized by the penetrance of individual genetic variants and how these are modified by interaction with other risk factors for SPC. Some syndromic cancers are associated with nonmalignant phenotypes that identify individuals at increased risk, such as Fanconi anemia or Cowden disease, whereas others exhibit only malignant phenotypes, such as BRCA1- and/or BRCA2-related breast and/or ovarian cancer or Li Fraumeni syndrome [56]. Some syndromes are autosomal dominant (e.g., Li Fraumeni syndrome

and Cowden disease); others are autosomal recessive (e.g., Fanconi anemia, Bloom syndrome, and xeroderma pigmentosum). Usually they are most frequently observed in familiar setting, and the major susceptibility genes for many of these syndromes have already been identified. Although hereditary susceptibility explains only a small proportion of all second cancers, an increased risk of primary tumors arising in multiple sites is a distinguishing feature of kindreds carrying germline genetic predispositions and can provide unique insights into underlying mechanisms [56].

Figure 12 – Schematic illustration of risk factors for SPC



Reproduced from Travis LB et al. [16]

The overall burden of the risk of SPC associated with the common hereditary breast and colon cancer syndromes is remarkable, since they are frequent cancer localizations with good survival [16, 37], and 5% – 10 % may be caused by genetic factors [57]. The hereditary breast cancer survivors have a two to fivefold increased risk of developing cancers of the ovary, thyroid, and connective tissue, due to syndromic association of these tumors with inherited mutations of BRCA1, BRCA2, PTEN, and p53 [57]. By far the largest cumulative risk of a secondary cancer in BRCA mutation carriers is associated with cancer in the contralateral breast, which may reach a risk of 29.5% at 10 years [58]. The Breast Cancer Linkage Consortium [59] also documented threefold to fivefold increased risks of subsequent cancers of prostate, pancreas, gallbladder, stomach, skin (melanoma), and uterus in BRCA2 mutation carriers and twofold increased risks of prostate and pancreas cancer in BRCA1 mutation carriers [59-61].

Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are frequent inherited colorectal cancer syndromes. FAP has an incidence of 1 in 6000-13000, with

autosomal-dominant transmission and 100% penetrance [62]. It is characterized by the presence of 100 or more adenomatous polyps in the colon. Colorectal cancer invariably occurs by 40–50 years of age unless prophylactic colectomy is performed [63]. FAP is also associated with colorectal, gastric, periampullary, small intestinal and thyroid cancers. HNPCC or Lynch II syndrome is the most frequent form of hereditary colorectal cancer, accounting for 6–10% of all colorectal cancers [63]. Synchronous and metachronous colorectal cancers are common, with most occurring proximal to the splenic flexure [63]. Lynch II syndrome is frequently associated with endometrial and ovarian cancers. Turcot syndrome is a combination of colonic polyps and a CNS neoplasm. In Turcot syndrome, medulloblastoma is usually associated with FAP, and glioblastoma is associated with HNPCC [62].

Although the cancer genetic syndromes that were previously described correspond to those most frequently associated with the total burden of SPC, Li Fraumeni, multiple endocrine neoplasia (MEN 1 and MEN 2), neurofibromatosis and von Hippel–Lindau (VHL) syndromes are other frequent cancer hereditary syndromes which predispose the individuals with the genetic alterations to a higher risk of developing several tumors.

However, high-penetrance mutations in cancer susceptibility genes make only a small contribution to the SPC burden, owing to their low frequency [15]. The prevailing model is that genetic risk of both first and subsequent primary cancers is defined by the cumulative effect of multiple low-penetrance and intermediate-penetrance risk alleles for cancer, where each individual genetic variant confers a modest increase in risk, but which collectively increase risk substantially when co-inherited in an individual [15].

Although there are scarce data evaluating the contribution of certain lifestyle factors (for example, diet, dietary supplements, physical activity, weight management, and sun exposure) to SPC development, for alcohol and tobacco consumption there is enough evidence suggesting their role as risk factors.

Smoking increases the risk of several cancer types, mainly lung and esophagus, and is regarded as the cause of 25–30% of all deaths from cancer and 87% from lung cancer [64]. Tobacco smoke is proved to contain carcinogenic mutagens and alters a number of cell signaling pathways

predominantly by activation of nuclear transcription factor (NF-κB) that induces tumorigenesis, via inflammation and other gene products [21].

The causal association between drinking alcohol and cancer development has been definitely established to oral, esophageal, liver and other head and neck cancers [21]. Although with a lower level of evidence, there is data demonstrating the carcinogenic role of alcohol in breast, colon and rectal cancers [21]. Several works have documented that there is a dose-response relationship between alcohol consumption level and cancer risk. The carcinogenic mechanisms associated with alcohol consumption are not yet completely understood. Among hypotheses proposed to explain the increased cancer risk are: a) a carcinogenic effect of chemicals other than ethanol present in alcoholic beverages (such as N-nitrosamines); b) a solvent action which facilitates absorption of other carcinogens; c) a carcinogenic role for acetaldehyde, the major metabolite of ethanol [65]. Alcohol drinking and tobacco smoking show a synergistic interaction in the etiology of cancers of the oral cavity, pharynx, larynx and oesophagus [21].

Consumption of high-caloric and fatty food often combined with a sedentary lifestyle and hence energy imbalance, increases the risk of colon, breast, prostate, endometrial and other cancers [21]. Chronic infections, such as those with hepatitis B and C viruses, human papilloma viruses or *Helicobacter pylori*, are well-known risk factors for specific cancers, and it was estimated that almost 18% of neoplasms are attributable to an infection [66, 67].

Another risk factor for development of SPC is the treatment of the FPC. A USA nationwide study using the SEER registries concluded that cancer treatment may only cause a minor proportion of all SPC when all adult-onset cancers are considered together (a noticeably larger role was observed among survivors of childhood cancer); however, in long-term survivors of certain adult onset cancers (for example, Hodgkin lymphoma), SPC are one of the most common causes of death [10].

Radiotherapy is used to treat over 50% of patients with cancer, either as definitive, adjuvant or palliative treatment, resulting in an improvement in disease control, overall survival, and quality of life [15]. In a SEER study, the attributable risk of SPC related to radiotherapy ranged from 4% to 24%, being especially evident among survivors of testicular seminoma [68]. The majority of radiotherapy-related SPC are solid tumors that frequently arise within or near irradiated fields and

are associated with latency periods of at least 5–10 years, with risk varying by age at exposure and attained age [15].

Among chemotherapy-associated SPC, a substantial amount of data has been published about therapy-related myeloid neoplasms, which are now classified as a distinct disease entity by World Health Organization (WHO) [15]. Several classes of chemotherapeutic agents have been associated with therapy-related myeloid neoplasms, including alkylating agents, topoisomerase II inhibitors and antimetabolites [69]. Tamoxifen is used as an adjuvant therapy in women with estrogen-receptor (ER)-positive breast cancer, with an associated reduction in breast cancer recurrence and increased survival. However, studies have also demonstrated a two to four-fold increased risk of endometrial cancer after treatment with tamoxifen, especially among post-menopausal women [70]. Survivors of haematopoietic stem-cell transplantation (HSCT) are at increased risk of developing a SPC, mainly myeloid neoplasms and lymphoproliferative disorders, as well as solid tumors in young survivors [15].

5.3. Social and economic burden

Beside the comorbidities and the late-effects of cancer and its treatment on the physical and mental health status of the cancer patients, the social and economic burden of survivorship is also a matter of concern to the patients and to the society.

5.3.1. Patients

Several studies have demonstrated the profound financial consequences of a cancer diagnosis [71]. The cost of cancer diagnosis and treatment can present a barrier to obtaining high-quality care and adequate screening for cancer recurrence or SPC, which may result in worse survival [72]. Even for patients with insurance in the North American model and for European survivors with national health system support, out-of-pocket expenses associated with cancer treatment may still be substantial and lead to delay in treatment, noncompliance, exhaustion of savings, and personal bankruptcy [72, 73]. Moreover, these expenses often have a disproportionate effect on those with lower incomes [71].

In addition to its financial impact, increasing cancer care costs can affect the psychosocial well-being of patients, as well as their ability to make optimal treatment decisions and implement them. Since these patients face a life-threatening illness they often have difficulty determining whether some treatment represents good value, as they perceive high-cost treatments to be more valuable than the other ones [74]. These patients may feel pressure to fight the battle against cancer at any cost, and they and their families may subjugate financial concerns to medical ones [71].

The cancer diagnosis may also represent a relevant financial burden for the patients due to changes in their employment status as well as in their families [11]. A recent meta-analysis of 36 studies, predominantly from the USA and Europe, found that cancer survivors were 37% more likely to be unemployed compared with healthy controls [75]. In addition, only 60 % of individuals (on average) who are diagnosed with cancer have returned to work 1–2 years following cancer treatment [76]. This is problematic as many individuals who experience cancer may still be in the

prime of their working lives, and if unable to return to work, pose significant cost to the health care system and financial losses at the individual, family, and societal levels.

Roelen et al. [77] demonstrated that, 2 years after a cancer diagnosis, the highest percentage of patients who had fully returned to work were those who had female genital cancer, male genital cancer and skin cancer. The lowest percentage of patients returning to work was observed among those with breast, lung and gastrointestinal tumors [77].

5.3.2. Society

Cancer is a major economic expenditure for all developed countries and the ability to deliver affordable care is becoming challenging. The total costs of cancer care in the USA were estimated to be more than 124 billion dollars for 2010, representing roughly 5% of total health-care spending [78]. The UK National Health System (NHS) reports that total cancer spending was 5.9 billion pounds in 2009–10, representing 5.6% of total health spending for the year [72]. Despite diverse health-care systems, the USA figure is remarkably consistent with data (2004) from Europe, Canada, Australia, and New Zealand, where cancer costs as a percentage of total health-care spending ranged from 4.1% in the Netherlands to 7% in Sweden [72]. In Japan, cancer costs accounted for a slightly higher percentage of total health-care spending, at 9.3% in 2004 [72]. Data from 2006 revealed that in Portugal, the cancer care expenditures were 565 million euros, corresponding to 3.9% of total health-care spending [79].

The issue that concerns economists and policy makers is not just the amount of money currently spent on health care, but also the rate of increase in spending. Data from the USA revealed that total spending on cancer is estimated to have grown from 27 billion dollars in 1990 to 90 billion dollars in 2008. It is projected to reach 157 billion dollars by 2020, roughly a 600% increase in 30 years [78]. This trend of rising spending with cancer care is justified by a higher number of patients to be treated (as addressed in the previous chapters) but also to an increase in the cost to treat an individual patient. The latter is driven by innovation in cancer diagnostic and treatment procedures, overutilization of resources such as routine surveillance studies that have no evidence to support them, and also by futile disease-directed care provided in the last weeks of life, that has

financial consequences for the patient's family and to the society, compromising the patient's quality of life without a meaningful increase in overall survival [72].

Beyond the direct costs of cancer to individuals and health-care budgets, the economic and societal effect of cancer on family income and overall productivity is large, though not widely acknowledged in economic discussions of health-care expenditure. In Europe, the indirect costs of cancer in terms of lost productivity are estimated to be around 30% higher than the direct costs associated cancer treatments [72]. Although many European countries have employment discrimination laws and employment regulation to support disabled people, there is no legislation for chronically sick people. Therefore, many patients with cancer are permanently lost to the labor market, who could return to their jobs if given a chance and the time to overcome their disease. As a consequence, the financial effect of cancer in terms of social costs and reduced productivity is evident. Furthermore, vulnerable groups — such as people in poverty, migrants, ethnic minority groups, and disabled or elderly people — are often more affected by cancer in the economic and social domains, because their environment is less capable of compensating the strains of a cancer diagnosis [72].

Aims

6. Aims

The worldwide growing number of cancer survivors with the associated health and socio-economic burden, demands an accurate epidemiologic characterization within different settings, as well as a continuous monitoring of the evolving trends. Therefore, this thesis aimed to contribute to a better understanding of the epidemiology of cancer survivorship in Portugal, during the last decade.

The main research question was applied, through the following specific objectives:

1. To assess cancer survivors' health status, use of healthcare resources and socio-economic conditions, in Portugal;
2. To compare the frequency of exposure to environmental risk factors for chronic diseases between cancer survivors and individuals with no previous cancer diagnosis, within a Portuguese cohort;
3. To estimate the dynamics of SPC incidence in a population-based cohort of cancer survivors from North Portugal;
4. To quantify and characterize the SPC identified among the incident cancer cases from North Portugal, and to describe their survival according to the characteristics of the FPC.

The methods and results are presented in each of the following papers:

Paper I. Health status, use of healthcare, and socio-economic implications of cancer survivorship in Portugal: results from the Fourth National Health Survey.

Paper II. Health-related behaviours in the EpiPorto study: cancer survivors versus participants with no cancer history.

Paper III. Incidence of second primary cancers in North Portugal – a population-based study.

Paper IV. Frequency and survival of second primary cancers in North Portugal – a population-based assessment.

PAPER I

Health status, use of healthcare, and socio-economic implications of cancer survivorship in Portugal: results from the Fourth National Health Survey.

J Cancer Surviv. 2014 Dec; 8(4):611-7

J Cancer Surviv
DOI 10.1007/s11764-014-0370-6

Health status, use of healthcare, and socio-economic implications of cancer survivorship in Portugal: results from the Fourth National Health Survey

Luís Pacheco-Figueiredo · Nuno Lunet

Received: 4 February 2014 / Accepted: 19 May 2014

Abstract
Purpose Understanding the morbidity and socio-economic implications of cancer survivorship is essential for a comprehensive management of oncological diseases. We compared cancer survivors (CS) with the general population regarding health status, use of healthcare resources and socio-economic condition.
Methods We analyzed data from a representative sample of the Portuguese population aged ≥15 years (n=35,229). We defined three groups of CS, according to the time since diagnosis and the latest cancer treatment: CS 1 diagnosis within 12 months of interview; CS 2 diagnosis more than 12 months before and treatment in the previous 12 months; CS 3 diagnosis and treatment more than 12 months before. These were compared with the general population, adjusting for differences in sex, age, and place of residence.
Results The prevalence of CS was 2.2 % (CS 1: 0.2 %; CS 2: 0.9 %, CS 3: 1.1 %). Self-perceived health status was worse among CS and short-time incapacity more frequent among CS 1 and CS 2. Health expenses were higher in the early stages of survivorship. Lower household income and financial difficulties were more frequent in CS 1 and CS 3 men, respectively.
Conclusion This study confirmed the higher consumption of healthcare resources and worse financial situation among CS.
Implications for Cancer Survivors Our study provides valuable information for understanding the global impact of cancer survivorship.

Keywords Neoplasms · Survival · Health survey · Portugal

L. Pacheco-Figueiredo · N. Lunet (✉)
Department of Clinical Epidemiology, Predictive Medicine and Public Health, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
e-mail: nlunet@med.up.pt

L. Pacheco-Figueiredo · N. Lunet
Institute of Public Health, University of Porto (ISPUP), Porto, Portugal

L. Pacheco-Figueiredo
Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal

Published online: 06 June 2014

Introduction

An increasing number of cancer patients has been observed in the last decades, especially due to population growth, aging and screening [1–5]; in 2012, over six million new cases were estimated to have occurred in the more developed regions [6]. Concurrently, early diagnosis and effective treatment resulted in improved survival [7]; the 5-year relative survival for all cancers was 52.0 % among cases diagnosed in Europe between 1995 and 1999 [8], and 68.1 % in the USA in 2003–2009 [9]. In Portugal, almost 50,000 new cancers are diagnosed each year [6]; among patients diagnosed in the North during 2005–2006, the 5-year relative survival was above 60 % [10].

The morbidity and socio-economic effects of cancer diagnosis and treatment are important components of its overall burden among the growing population of living persons ever diagnosed with cancer [11, 12]. Cancer survivors often suffer from persistent symptoms (pain, distress, fatigue or cognitive impairment), as well as employment changes and financial difficulties, that could affect not only the patient but also their whole families, among other short and long term effects [13, 11]. Assessing the impact of these phenomena in different settings is needed to support a more comprehensive management of oncological diseases.

Therefore, we aimed to assess the impact of cancer survivorship on health status, use of healthcare and socio-economic

condition, using data from the latest Portuguese National Health Survey.

Methods

The present analysis is based on data collected as part of the fourth National Health Survey (IV-NHS), which is a nationwide community-based cross-sectional study [14].

Population sampling and data collection

A sample of households was defined, using data from the 2001 Population and Housing Census, to be used as the sampling frame for household surveys conducted by the National Institute of Statistics (INE). It included 1,408 geographical units with at least 240 households each, selected systematically within larger geographical strata, with a probability proportional to the number of households in each unit. A random sample of the households was then selected and all dwellers were eligible.

During a total of 52 weeks, between February 2005 and January 2006, 41,193 persons from 15,239 households were evaluated. All the information was collected directly from the individuals or from proxies, through computer-assisted interviews performed by trained interviewers.

The participants that reported a previous cancer diagnosis (medically confirmed) were considered cancer survivors (CS) and were further divided in three groups: (a) those with the diagnosis in the previous 12 months (CS 1); (b) those with a diagnosis more than 12 months before the interview, but having been submitted to a cancer treatment in the previous 12 months (CS 2); (c) those with cancer diagnosis and treatment more than 12 months before (CS 3).

A detailed description of the assessment of the participants' health status, healthcare consumption, and socio-economic characteristics is presented in footnotes in the tables and figures depicting the results.

Statistical analysis

Data analysis was restricted to participants aged ≥15 years, corresponding to a sample of 35,229 respondents. The evaluation of the use of preventive care procedures and the financial status of the respondents was accomplished only in subsamples of approximately one quarter of the total sample, evaluated in weeks of data collection 27 to 39 and 40 to 52, respectively. Data on the general health status and quality of life domains of the questionnaire were collected only from non-proxy respondents (approximately two thirds of the sample). All analyses were conducted with STATA®, version 11.1 (StataCorp LP, College Station, TX, USA), using sampling weights, calculated based on the inverse of the probability of selection of each sampling unit, further corrected for nonresponses and for the effective number of subjects evaluated, regarding the age and sex structures.

We computed weighted prevalences and corresponding 95 % confidence intervals (95%CI), as well as age-, region-, and education-adjusted prevalence ratios (PR), using Poisson regression [15] to compare each group of CS, namely CS 1, CS 2, and CS 3, with the participants not reporting a previous diagnosis of cancer (NC). To analyze data on family income we assigned to each category the corresponding midpoint and treated the variable as continuous; data were described with box-and-whisker plots and different groups were compared using multivariable linear regression.

Results

A total of 784 participants were cancer survivors, corresponding to a weighted prevalence of 2.2 % (95%CI: 1.9–2.4), from which 71 (0.2 %, 95%CI: 0.1–0.2) reported a cancer diagnosis in the last 12 months (CS 1), 321 (0.9 %, 95%CI: 0.7–1.1) were diagnosed a cancer more than 12 months before, but had been treated during the preceding 12 months (CS 2), and 392 (1.1 %, 95%CI: 0.9–1.3) had been diagnosed and treated for cancer more than 12 months before (CS 3).

The percentage of men was lowest in CS 3 (28.9 %) and ranged between 48.0 % and 57.4 % in NC and CS 1, respectively. CS were more frequently aged above 65 years (percentage ranging from 52.7 % of CS 1 to 43.7 % of CS 3) than NC (19.7 %). Less educated participants were more prevalent among CS (Table 1).

Participants' health status and healthcare consumption

Compared to NC, CS reported an approximately 30 % higher prevalence of bad perceived health status, regardless of the time since the diagnosis, while significantly higher levels of short-term incapacity were observed only in CS 1 (PR=3.7) and CS 2 (PR=2.0) (Fig. 1). CS had a 20 % higher prevalence of medication consumption, though the PR for medical consultations decreased from 1.5 in CS 1 to 1.2 in CS 3 (Fig. 1). Regarding preventive care, CS reported an approximately 20 % higher prevalence of cholesterol evaluation, and smaller differences were observed for blood pressure assessment, which was significantly more frequent only in CS 1 and CS 2 (PR=1.1). All groups reported a low frequency of flu vaccination, though a non-significantly 20 % higher prevalence was observed among CS 2 and CS 3 (Fig. 1). The results were similar when data were analyzed separately for men and women (data not shown).

Table 1 Socio-demographic characteristics of cancer survivors and non-cancer individuals

	NC	Cancer survivor		
	% (95%CI)[a]	CS 1 % (95%CI)[a]	CS 2 % (95%CI)[a]	CS 3 % (95%CI)[a]
Gender				
Female	52.0 (51.0–53.0)	42.6 (20.2–65.0)	47.1 (36.7–57.5)	71.1 (63.5–78.8)
Male	48.0 (47.0–49.0)	57.4 (35.0–79.8)	52.9 (42.5–63.2)	28.9 (21.2–36.5)
Age (years)				
15–34	33.8 (32.7–34.8)	4.3 (0.0–11.0)	2.1 (0.0–4.6)	12.6 (5.4–19.8)
35–64	46.6 (45.6–47.6)	42.9 (19.4–66.5)	50.2 (39.8–60.7)	43.7 (35.2–52.2)
≥65	19.7 (18.9–20.4)	52.7 (29.2–76.2)	47.6 (37.2–58.0)	43.7 (35.4–52.0)
Education (years)				
None	11.8 (11.1–12.4)	21.3 (4.7–37.9)	21.3 (13.1–29.4)	18.4 (12.1–24.7)
1–4	31.6 (30.7–32.5)	51.3 (28.0–74.6)	56.2 (46.0–66.5)	43.6 (35.1–52.1)
5–6	14.9 (14.1–15.7)	14.9 (0.0–33.6)	5.5 (1.2–9.8)	13.1 (6.9–19.3)
7–9	14.7 (14.0–15.5)	5.3 (0.0–10.7)	7.1 (1.9–12.3)	10.3 (4.6–16.0)
10–12	14.7 (14.0–15.4)	5.4 (0.0–10.8)	6.1 (0.7–11.5)	7.3 (3.7–10.8)
>12	12.3 (11.6–13.0)	1.9 (0.0–4.5)	3.8 (0.0–7.9)	7.3 (3.0–11.6)

NC Participants not reporting a previous diagnosis of cancer, *CS 1* Cancer survivors with a cancer diagnosis in the previous 12 months, *CS 2* Cancer survivors with a cancer diagnosis with more than 12 months, but have been submitted to treatment in the 12 months before, *CS 3* Cancer survivors with a cancer diagnosis or treatment with more than 12 months

[a] Weighted prevalence

Among women, mammography use was more frequent in cancer survivors, being especially higher in the CS 1 group (PR=4.3). The use of cervical cytology was more frequent only in CS 1 (PR=5.3) (Fig. 1).

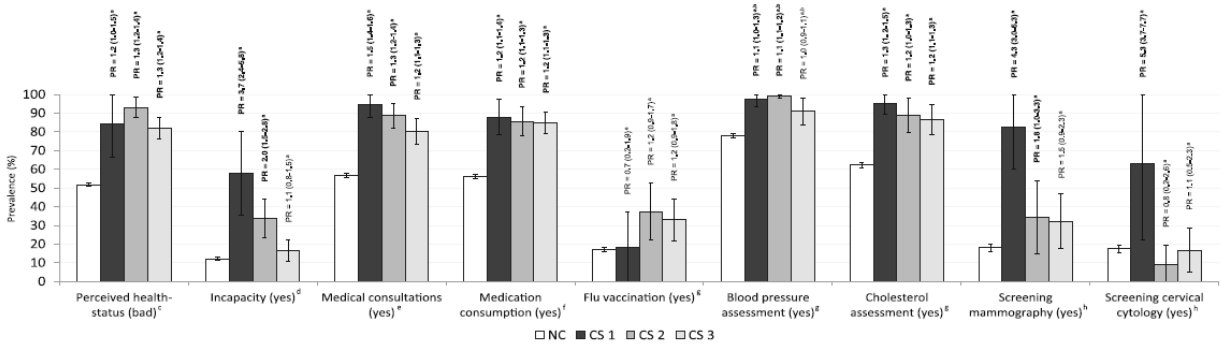


Fig. 1 Participant's health status and healthcare consumption, in non-cancer participants and cancer survivors. (*a*) Age-, region-, and education-adjusted prevalence ratio and corresponding 95 % confidence interval: PR (95%CI). (*b*) Poisson regression model also included a variable on the history of hypertension. (*c*) Perceived health status was evaluated with a question asking how the participants classify their health status. They could answer: "very good", "good", "reasonable", "bad" and "very bad". For further analysis the answers were aggregated within "good" (the first three options) and "bad" categories (the last two options). (*d*) Incapacity was evaluated with the question: "During the last 2 weeks, how many days did you have your ability to accomplish regular activities compromised due to disease, accident, violence or other health problem?"; those respondents that reported at least 1 day were considered to have incapacity. (*e*) Participants were asked about the number of medical consultations in the previous 3 months. (*f*) Participants were asked about the consumption of any medicines in the past 2 weeks. (*g*) Participants were asked about the use of preventive care measures during the previous year: flu vaccination, blood pressure measurement and cholesterol evaluation. (*h*) Mammography and cervical cytology were evaluated by asking the participants if they had been submitted to the procedure in the previous 12 months, and it was restricted to women evaluated during the weeks 27 to 39. *NC* Participants not reporting a previous diagnosis of cancer. *CS 1* Cancer survivors with a cancer diagnosis in the previous 12 months. *CS 2* Cancer survivors with a cancer diagnosis with more than 12 months, but have been submitted to treatment in the 12 months before. *CS 3* Cancer survivors with a cancer diagnosis or treatment with more than 12 months

Socio-economic implications

A higher proportion of CS reported health expenditures in the last 2 weeks, especially in the CS 1 group (PR=1.4), though differences were not statistically significant. The level of health expenditures was nearly twice higher among CS 1 than in NC; smaller and non-statistically significant differences were observed between CS 2 or CS 3 and NC (Fig. 2). Results were similar when gender stratified analyses were conducted (data not shown).

The household income was lower among male cancer survivors, mainly in the CS 1 group (β=−304.3; −431.3, −117.3), but no significant differences were observed among women (Fig. 3).

We found a higher prevalence of financial difficulties among cancer survivors, only among men, which was statistically significant in the CS 3 group (PR=2.2) (Fig. 4).

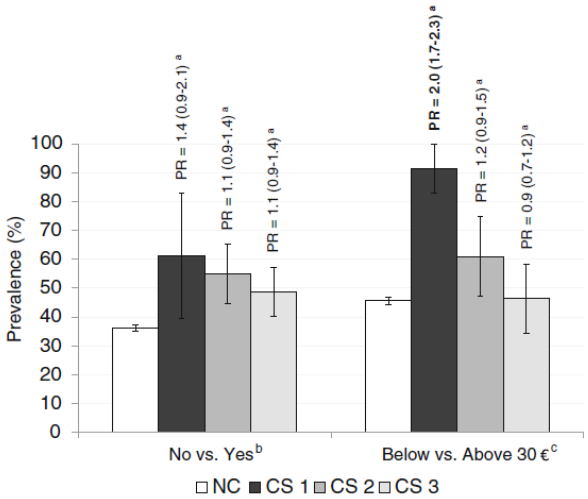


Fig. 2 Health-related expenditures by household members in the previous 2 weeks, in non-cancer participants and cancer survivors. (*a*) Age-, region-, and education-adjusted prevalence ratio and corresponding 95 % confidence interval: PR (95%CI). (*b*) Participants were asked about the health-related expenditures by household members in the previous 2 weeks (including medical consultations, medications, diagnostic procedures and other treatments). (*c*) Median (30 €) of the level of expenses, among those that reported health-related expenditures. *NC* Participants not reporting a previous diagnosis of cancer. *CS 1* Cancer survivors with a cancer diagnosis in the previous 12 months. *CS 2* Cancer survivors with a cancer diagnosis with more than 12 months, but have been submitted to treatment in the 12 months before. *CS 3* Cancer survivors with a cancer diagnosis or treatment with more than 12 months

Discussion

The prevalence of CS in the Portuguese adult population was 2.2 % in 2005/2006. CS reported worse health status and a higher consumption of healthcare resources, both for men and women, whereas financial consequences were more frequent in male CS.

The recent estimates of cancer prevalence in the USA (2007) [16] and in the UK (2008) [17], based on data from cancer registries, were 3.9 % and 3.3 %, respectively. The lower prevalence observed in our study may reflect the lower crude incidence rates in the Portuguese setting (405.4/100,000 vs. 461.1/100,000 in the USA and 496.9/100,000 in the UK) [18], as well as worse survival among Portuguese cancer patients in comparison with those in the USA and similar to those observed in the UK [7]. On other hand, the present study assessed the prevalence of CS using cross-sectional self-reported data, which may contribute to an overestimation of cancer survivorship due to misclassification of diagnoses of benign conditions as cancer [19].

According to our results the estimated number of CS in Portugal would be approximately 220,000, whom may be expected to suffer several physical and psychological adverse effects of diagnosis and treatment [12, 11]. Our results highlight a worse perceived health status among cancer survivors, independently of the survivorship period, in accordance with previous observations in other settings, probably reflecting high levels of bothering symptoms, such as persistent pain, fatigue, distress and cognitive impairment [13, 20, 21].

The first 12 months after the diagnosis are often associated with a high symptom burden, especially as a consequence of treatment, which frequently impairs the ability to maintain the regular activities [13]. In accordance, we found the highest prevalence of short-term incapacity among the CS diagnosed more recently.

Despite some heterogeneity across different studies from several countries, cancer survivors often have a greater utilization of healthcare services, which mainly correspond to consultations with the primary care physician and/or the oncologist [22]. The frequency of those contacts with the healthcare system is higher in the first year, mostly related to diagnosis and treatment, and tends to decrease to nearly half during the three subsequent years [22, 23]. Similarly, in our study CS reported a higher frequency of medical consultations during the first 12 months. However, they maintained a pattern of high consumption of medicines for a longer period, possibly reflecting the bothering symptoms and chronic conditions that persist after cancer diagnosis and primary treatment.

Preventive care assumes an important role among cancer survivors, due to their poorer health condition, which is commonly associated with a higher prevalence of comorbidities and an increased risk of second primary tumors [12, 24, 25]. Several studies comparing the use of preventive care between CS and the general population yielded inconsistent results [26, 23, 27–30], which may reflect the fact that these studies were performed in different settings, with heterogeneous models of health financing and accessibility to healthcare services.

Moreover, there were also differences regarding age and tumor topography distributions, as well as several lengths of time since the diagnosis, which are important determinants of preventive care use [30]. In our study, CS reported a higher frequency of blood pressure and cholesterol evaluations, as well as cancer screening (cervical cytology and mammography) among subjects with a more recent cancer diagnosis; however, the latter may reflect, at least partially, the misclassification of diagnosis mammography exams as screening.

Regarding flu vaccination, we should emphasize the lower proportion of CS undergoing immunization as a public health concern, namely in comparison with observations from other settings [11]. This is especially relevant in our sample since we had more than 20 % of the individuals with age above 65 years and a large percentage of the CS were probably under immunosuppressant treatments, which are some of the established criteria to perform the immunization [31].

Several studies have illustrated the financial impact that comes with the variety of problems posed by a cancer diagnosis [32]. Although in Portugal the payment of cancer treatments is mostly supported by the National Health System, there are studies performed in other settings, mainly in the USA, showing that even for insured patients the cost of cancer diagnosis and treatment can represent a barrier to high-quality care [33]. Out-of-pocket expenses associated with cancer treatment may still be substantial and lead to delay in treatment, noncompliance, exhaustion of savings and personal bankruptcy [34]. In our sample, we found a higher level of health expenditures among cancer survivors, mostly in the first stages of survivorship.

CS also reported lower levels of family income after the cancer diagnosis, which were particularly relevant among male survivors. This decrease is in accordance with the known changes in the working situation among cancer patients, such as unemployment due to incapacity, switch to part-time activities and early-retirement [35]. The high level of health expenditures among CS, concurrently with these lower levels of family income in men, may explain the higher frequency of financial difficulties that we found in male CS, mostly among those surviving for longer periods.

The follow-up of the growing population of CS, which reveals a higher consumption of healthcare resources, may need to be reassigned to primary care services with well-established standard protocols of clinical surveillance, in order to decentralize services and facilitate the access of these individuals to healthcare. Policy makers might also have to consider setting up effective supportive programs to help the most socially disadvantaged CS, with the perspective of minimizing the financial difficulties and their negative impact in the quality of life and in the disease survival [36], namely through multidisciplinary interventions to enhance return-to-work for CS [37].

Despite the strengths of using a large nationally representative sample with data from the latest Portuguese National

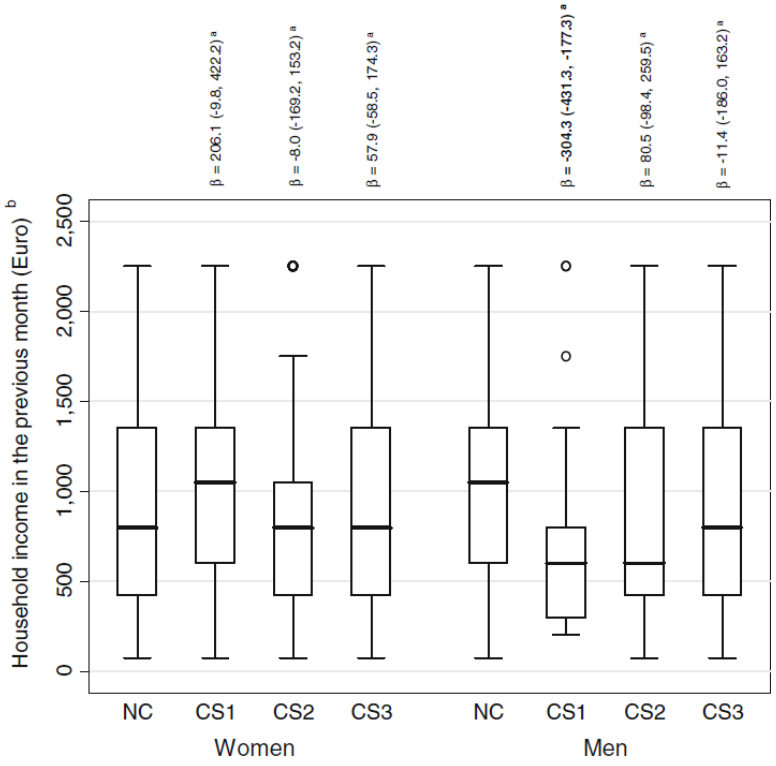


Fig. 3 Household income in the previous month in non-cancer participants and cancer survivors, for women and men. (*a*) Age-, region-, and education-adjusted coefficients of a linear regression model and corresponding 95 % confidence intervals: β (95%CI). (*b*) Overall income of the household in the previous month, by selecting one of ten given categories of income. *NC* Participants not reporting a previous diagnosis of cancer. *CS 1* Cancer survivors with a cancer diagnosis in the previous 12 months. *CS 2* Cancer survivors with a cancer diagnosis with more than 12 months, but have been submitted to treatment in the 12 months before. *CS 3* Cancer survivors with a cancer diagnosis or treatment with more than 12 months

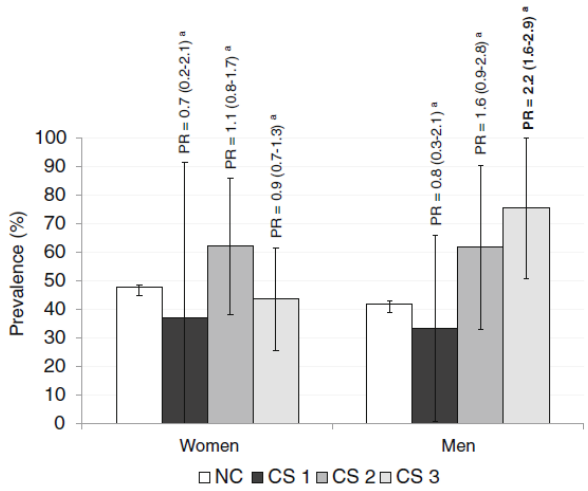


Fig. 4 Reported financial difficulties[b] in non-cancer participants and cancer survivors, for women and men. (*a*) Age-, region-, and education-adjusted prevalence ratio and corresponding 95 % confidence interval: PR (95 %CI). (*b*) Participants were asked if they have enough money to fulfill their basic needs. They could answer: "not at all", "little", "some", "usually have" and "always have". For further analysis the answers were aggregated within "have financial difficulties" (the first three options) and "do not have financial difficulties" categories (the last two options). *NC* Participants not reporting a previous diagnosis of cancer. *CS 1* Cancer survivors with a cancer diagnosis in the previous 12 months. *CS 2* Cancer survivors with a cancer diagnosis with more than 12 months, but have been submitted to treatment in the 12 months before. *CS 3* Cancer survivors with a cancer diagnosis or treatment with more than 12 months

Health Survey, constituting an important piece of information for understanding the dimension of this problem in Portugal, the present study has some limitations. CS were identified by self-report, and data about stage at diagnosis, treatment, recurrence, or other clinical characteristics were not available. The accuracy of information on a previous cancer diagnosis was improved by considering only those reported to be medically confirmed, but the lack of additional information on these events precluded a finer assessment of the burden of cancer survivorship in Portugal. Data on some variables was available only for subsamples of the participants in the national Health Survey, which compromised the statistical power of the study, but this is not expected to compromise the validity of the conclusions. Also, for some variables proxy respondents were allowed, which may contribute to information bias; however, we conducted sensitivity analyses excluding data obtained from proxies and the conclusions remained essentially the same (data not shown). Although we excluded from our analyses the participants aged <15 years, because only 6 CS were observed in this age group, the small proportion of subjects aged 15–34 years among CS 1 and CS 2 could have contributed for spurious age-adjusted estimates; however, a sensitivity analysis including only the participants aged ≥35 years yielded essentially the same results (data not shown). The establishment of causal relationships between the onset of comorbid conditions and the cancer diagnosis or treatment is limited by the cross-sectional design of the study, which also leads to an underrepresentation of newly diagnosed cancers and those with a short survival. Nevertheless, to our knowledge, this is the first study addressing this topic in a representative sample of the Portuguese population and provides valuable information for understanding a different dimension of the burden of cancer survivorship, in addition to increasing the awareness to this growing public health concern, which brings new challenges to healthcare provision and social security.

Acknowledgments The authors thank the National Health Systems Observatory (Observatório Nacional de Saúde), National Institute of Health Dr. Ricardo Jorge (INSA), Ministry of Health and the National Institute of Statistics (INE) for providing the data (Ministério da Saúde, Instituto Nacional de Saúde Dr. Ricardo Jorge; IP, Departamento de Epidemiologia/Instituto Nacional de Estatística: Inquérito Nacional de Saúde 2005/2006). Luís Pacheco-Figueiredo received a grant from the Fundação para a Ciência e a Tecnologia (SFRH/SINTD/60124/2009).

Conflict of interest Luís Pacheco-Figueiredo and Nuno Lunet declare that they have no conflicts of interest.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403. doi:10.1016/j.ejca.2012.12.027.
2. Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, Yancik R, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. Cancer. 2002;94(10):2766–92.
3. Araujo F, Gouvinhas C, Fontes F, La Vecchia C, Azevedo A, Lunet N. Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980–2010). Eur J Prev Cardiol. 2013. doi:10.1177/2047487313497864.
4. Amaro J, Severo M, Vilela S, Fonseca S, Fontes F, La Vecchia C, et al. Patterns of breast cancer mortality trends in Europe. Breast. 2013;22(3):244–53. doi:10.1016/j.breast.2013.02.007.
5. Fontes F, Severo M, Castro C, Lourenco S, Gomes S, Botelho F, et al. Model-based patterns in prostate cancer mortality worldwide. Br J Cancer. 2013;108(11):2354–66. doi:10.1038/bjc.2013.217.
6. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide [database on the Internet]. Lyon, France: International Agency for Research on Cancer. 2013. Available from: http://globocan.iarc.fr. Accessed 11 Nov 2013.
7. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9(8):730–56. doi:10.1016/S1470-2045(08)70179-7.
8. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer. 2009;45(6):931–91.
9. SEER Cancer Statistics Review, 1975–2010 [database on the Internet]. National Cancer Institute. 2013. Available from: http://seer.cancer.gov/csr/1975_2010/. Accessed 11 Nov 2013.

10. RORENO. Sobrevivência Global, Doentes diagnosticados em 2005–06—Região Norte. Registo Oncológico Regional do Norte. 2013;Instituto Português de Oncologia do Porto, ed. Porto, 2013.
11. CDC, Prevention CfDCa. Surveillance of demographic characteristics and health behaviours among adult cancer survivors—behavioral risk factor surveillance system, United States, 2009. MMWR; 2012.
12. Hewitt M, Greenfield S, Stovall E, Editors. From cancer patient to cancer survivor: lost in transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council; 2006.
13. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's studies of cancer survivors. Cancer. 2011;117(12):2779–90. doi:10.1002/cncr.26146.
14. INE, INSA. Inquérito Nacional Saúde 2005/2006. Instituto Nacional Estatística, Instituto Nacional Ricardo Jorge; 2009. p. 1–330.
15. Coutinho LM, Scazufca M, Menezes PR. Methods for estimating prevalence ratios in cross-sectional studies. Rev Saude Publica. 2008;42(6):992–8.
16. Cancer prevalence statistics: approaches to estimation using cancer registry data. [database on the Internet]. Bethesda, MD: National Cancer Institute (NCI). 2010. Available from: http://srab.cancer.gov/prevalence/approaches.html. Accessed: March 4, 2011.
17. Maddams J, Brewster D, Gavin A, Steward J, Elliott J, Utley M, et al. Cancer prevalence in the United Kingdom: estimates for 2008. Br J Cancer. 2009;101(3):541–7. doi:10.1038/sj.bjc.6605148.
18. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide [database on the Internet]. Lyon, France: International Agency for Research on Cancer. 2010. Available from: http://globocan.iarc.fr. Accessed 9 Nov 2013.
19. Desai MM, Bruce ML, Desai RA, Druss BG. Validity of self-reported cancer history: a comparison of health interview data and cancer registry records. Am J Epidemiol. 2001;153(3):299–306.
20. Fu OS, Crew KD, Jacobson JS, Greenlee H, Yu G, Campbell J, et al. Ethnicity and persistent symptom burden in breast cancer survivors. J Cancer Survivorship Res Pract. 2009;3(4):241–50. doi:10.1007/s11764-009-0100-7.
21. Kuhnt S, Ernst J, Singer S, Ruffer JU, Kortmann RD, Stolzenburg JU, et al. Fatigue in cancer survivors—prevalence and correlates. Onkologie. 2009;32(6):312–7. doi:10.1159/000215943.
22. Treanor C, Donnelly M. An international review of the patterns and determinants of health service utilisation by adult cancer survivors. BMC Health Serv Res. 2012;12:316. doi:10.1186/1472-6963-12-316.
23. Snyder CF, Frick KD, Kantsiper ME, Peairs KS, Herbert RJ, Blackford AL, et al. Prevention, screening, and surveillance care for breast cancer survivors compared with controls: changes from 1998 to 2002. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(7):1054–61. doi:10.1200/JCO.2008.18.0950.
24. Yabroff KR, Lawrence WF, Clauser S, Davis WW, Brown ML. Burden of illness in cancer survivors: findings from a population-based national sample. J Natl Cancer Inst. 2004;96(17):1322–30. doi:10.1093/jnci/djh255.
25. Travis LB. The epidemiology of second primary cancers. Cancer Epidemiol, Biomark Prev Publ Am Assoc Cancer Res Am Soc Prev Oncol. 2006;15(11):2020–6. doi:10.1158/1055-9965.EPI-06-0414.
26. Earle CC, Neville BA. Under use of necessary care among cancer survivors. Cancer. 2004;101(8):1712–9. doi:10.1002/cncr.20560.
27. Snyder CF, Frick KD, Peairs KS, Kantsiper ME, Herbert RJ, Blackford AL, et al. Comparing care for breast cancer survivors to non-cancer controls: a five-year longitudinal study. J Gen Intern Med. 2009;24(4):469–74. doi:10.1007/s11606-009-0903-2.
28. Cooper GS, Yuan Z, Chak A, Rimm AA. Patterns of endoscopic follow-up after surgery for nonmetastatic colorectal cancer. Gastrointest Endosc. 2000;52(1):33–8. doi:10.1067/mge.2000.106685.
29. Earle CC, Burstein HJ, Winer EP, Weeks JC. Quality of non-breast cancer health maintenance among elderly breast cancer survivors. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21(8):1447–51. doi:10.1200/JCO.2003.03.060.
30. Yabroff KR, Short PF, Machlin S, Dowling E, Rozjabek H, Li C, et al. Access to preventive health care for cancer survivors. Am J Prev Med. 2013;45(3):304–12. doi:10.1016/j.amepre.2013.04.021.
31. Vieira M, Frutuoso A, Correia AM. Vacinação contra a Gripe Sazonal—Época 2012/2013. Administração Regional de Saúde do Norte; 2013. p. 1–2.
32. Meropol NJ, Schrag D, Smith TJ, Mulvey TM, Langdon Jr RM, Blum D, et al. American society of clinical oncology guidance statement: the cost of cancer care. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(23):3868–74. doi:10.1200/JCO.2009.23.1183.
33. Ward E, Halpern M, Schrag N, Cokkinides V, DeSantis C, Bandi P, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. 2008;58(1):9–31. doi:10.3322/CA.2007.0011.
34. Meropol NJ, Schulman KA. Cost of cancer care: issues and implications. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25(2):180–6. doi:10.1200/JCO.2006.09.6081.
35. Mols F, Thong MS, Vissers P, Nijsten T, van de Poll-Franse LV. Socio-economic implications of cancer survivorship: results from the PROFILES registry. Eur J Cancer. 2012;48(13):2037–42. doi:10.1016/j.ejca.2011.11.030.
36. Mehnert A, de Boer A, Feuerstein M. Employment challenges for cancer survivors. Cancer. 2013;119 Suppl 11:2151–9. doi:10.1002/cncr.28067.
37. de Boer AG, Taskila T, Tamminga SJ, Frings-Dresen MH, Feuerstein M, Verbeek JH. Interventions to enhance return-to-work for cancer patients. The Cochrane database of systematic reviews. 2011(2):CD007569. doi:10.1002/14651858.CD007569.pub2.

PAPER II

Health-related behaviours in the EpiPorto study: cancer survivors versus participants with no cancer history

Eur J Cancer Prev 2011 Jul; 20(4):348-54

Health-related behaviours in the EpiPorto study: cancer survivors versus participants with no cancer history

Luís Pacheco-Figueiredo[a,b,d], Luis Antunes[c], Maria José Bento[c] and Nuno Lunet[a,b]

Cancer survivors are at an increased risk of a second primary cancer, partly due to unhealthy behaviours. In a cohort of adults (recruitment: 1999–2003; follow-up – linkage with population-based cancer registry: up to 2009) we compared the baseline exposure to smoking, alcohol and dietary intake and physical activity between: cancer survivors (CS) – cancer diagnosis before baseline ($n=53$); no cancer (NC) participants – without cancer diagnosis at baseline or during follow-up ($n=2261$); latent cancer (LC) participants – without cancer diagnosis at baseline but diagnosed during follow-up ($n=139$). Age-, sex- and education-adjusted prevalences and means were computed, as applicable.

The prevalence of current smoking was nearly 20% among CS and NC (approximately four cigarettes per day) and 30% in LC (seven cigarettes per day). LC had the highest average alcohol intake (25.5 g/day) and NC the lowest (17.0 g/day). The proportion of participants reporting sports practice was higher for CS (50%) than for NC or LC (approximately 33%). CS and NC had higher fruit/vegetable consumption than LC (4.2 and 4.4 vs. 3.8 servings per day). In a composite index on health behaviours (including smoking, physical activity and alcohol and fruit/vegetable intake) the highest and lowest scores were 1.74 for NC and 1.52 for LC respectively, whereas CS scored 1.63.

The exposure to each risk factor appeared comparable in CS and NC, whereas LC tended to have unhealthier behaviours. This may be partially explained by the acquisition of healthier habits by CS after diagnosis, but there still remains scope for improvement, as revealed by the low scores observed for the joint exposure to the main risk factors. *European Journal of Cancer Prevention* **20:348–354 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Cancer Prevention 2011, 20:348–354

Keywords: alcohol drinking, cancer survivorship, diet, exercise, smoking

[a]Department of Hygiene and Epidemiology, University of Porto Medical School, [b]Institute of Public Health – University of Porto, [c]North Region Cancer Registry – Portuguese Oncology Institute, Porto and [d]School of Health Sciences, University of Minho, Braga, Portugal

Correspondence to Nuno Lunet, Serviço de Higiene e Epidemiologia, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
Tel: +351 225513652; fax: +351 225513653;
e-mail: nlunet@med.up.pt

Received 22 August 2010 Accepted 12 February 2011

Introduction

Cancer survivorship has dramatically increased in the latest decades, with most recent overall 5-year relative survival estimates (age-adjusted and casemix-adjusted) of 49.6% in Europe (Berrino *et al.*, 2009) and 64.4% in the USA (Curtis *et al.*, 2006; Ries *et al.*, 2007). Worldwide, the increasing survival of oncologic patients results in approximately 22 million cancer survivors (CSs) (Stewart and Kleihues, 2003), with a myriad of medical problems, such as recurrence of first cancer, comorbid late effects of treatment and second primary cancers.

Overall, CSs have a risk of developing a new malignancy nearly 14% higher than expected for the general population (Curtis *et al.*, 2006). Second primary cancers were estimated to represent 6.3% (ranging from 0.4 to 12.9% across cancer registries according to date of registration onset) of all incident cancer cases in Europe (1995–1999; Rosso *et al.*, 2009) and 16% in the USA (2003; Travis, 2006).

Second primary cancers are determined by iatrogenic causes, genetic characteristics and persistence of exposure and/or effects of environmental exposures (Travis, 2006) after the diagnosis of a first primary cancer. It is therefore important to characterize CSs regarding risk behaviours modifiable by health promotion activities, namely those related to smoking, alcohol consumption, diet, obesity and physical activity (Hebert *et al.*, 1998; Khuri *et al.*, 2001; Rock and Demark-Wahnefried, 2002; Do *et al.*, 2003; Holmes *et al.*, 2005; Meyerhardt *et al.*, 2006a, 2006b; World Cancer Research Fund, 2007; Sanchez *et al.*, 2008), but research conducted in these specific populations is scarce.

In a cohort study we aimed to compare the baseline frequency of environmental risk factors for chronic diseases between CSs and participants with no previous cancer diagnosis (according to their status regarding cancer diagnosis at the end of follow-up).

Methods

Study population

This study was based on the evaluation of a cohort of adults living in Porto (EPIPorto). The recruitment of the initial sample has been previously described (Lucas *et al.*,

0959-8278 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins

DOI: 10.1097/CEJ.0b013e328345f923

2009). In brief, the assembling of the cohort was conducted between 1999 and 2003 and comprised the evaluation of 2485 individuals, selected by random digit dialling, having households as the sampling unit. When a household was selected, all residents were identified by age and sex, and one resident (aged 18 years or more) was randomly selected as the respondent, without replacement if there was a refusal. The participation rate was 70% (Ramos *et al.*, 2004). A visit to the Department of Hygiene and Epidemiology of Porto Medical School was scheduled by telephone according to the participant's convenience. A personal interview, using a structured questionnaire comprising data on sociodemographic, clinical and lifestyle exposures, and a physical examination was performed by trained interviewers.

Identification of cancer cases

The identification of participants with a cancer diagnosis was accomplished using the North Region Cancer Registry and death certificate information. This population-based cancer registry was set up in 1988 and covers the whole northern region of Portugal (approximately 3.3 million inhabitants; RORENO, 1988). The identification of cohort participants in the cancer registry database was performed using the name and date of birth of each participant, up to December 2009, comprising a median follow-up time of 7.6 years (percentiles 25–75: 5.5–10.7).

We identified 192 first primary cancer cases (excluding 32 nonmelanoma skin cancers), 53 diagnosed before baseline assessment and 139 after the initial cohort evaluation. For analysis, we defined three groups taking into account the existence of a first primary cancer diagnosis and its timing, if applicable: CSs (cancer diagnosis before baseline assessment); participants with no cancer (NC) (without cancer diagnosis at baseline or during the follow-up); participants with latent cancer (LC) at baseline (without cancer diagnosis at the baseline but being diagnosed during the follow-up).

Evaluation of health-related behaviours

Participants were classified as smokers (current consumers of at least one cigarette per day, on average), occasional smokers (current consumers of less than one cigarette per day, on average), ex-smokers (not smoking for more than 6 months) and never-smokers [World Health Organization (WHO), 1997]. Smokers and occasional smokers were grouped for data analysis. With regard to the consumption of alcoholic beverages, participants were classified as drinkers (current consumers of at least one drink per week, on average), occasional drinkers (current consumers of less than a drink per week, on average), ex-drinkers (not drinking for more than 6 months) and never-drinkers. For analysis, occasional drinkers were grouped with drinkers of at least one beverage per week, and a category of drinkers of less than or equal to 1 standard drink per day for women and less than or equal to 2 standard drinks per day for men was also created, according to the cutoff proposed by the American Heart Association (Lichtenstein *et al.*, 2006).

Dietary intake during the previous year was estimated using a validated semi-quantitative food-frequency questionnaire (Lopes, 2000; Lopes *et al.*, 2007) comprising 82 food item/group and beverage categories. For each item, participants were asked to indicate the average frequency of consumption (nine possible responses, ranging from never to six or more times per day), as well as the amount consumed (using a photograph manual with three portion sizes, small, medium and large), and the number of months during which the foods had been consumed in the previous year. Any foods that were not specified in the food-frequency questionnaire but eaten regularly (once a week or more frequently) were listed in an open section.

The consumption of fruit and vegetables was estimated by adding up the frequencies of consumption of medium servings, corrected for seasonality, of the items referring to different fruits (apple or pear, orange or mandarin, banana, kiwi, strawberry, cherry, peach or plum, melon or watermelon, persimmon, fig or loquat or apricot and grapes) and vegetables (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 pepper and onion), as previously described in detail (Lunet *et al.*, 2006). For analysis, the cutoff of five servings per day recommended by the World Cancer Research Fund on 'Food, Nutrition, Physical activity and the Prevention of Cancer' was used to classify participants according to fruit and vegetable consumption (World Cancer Research Fund, 2007).

Energy and nutrient intake were obtained from consumption frequency and portion size data using the software Food Processor Plus R (ESHA Research, Salem, Oregon, USA), based on values from the US Department of Agriculture, further adapted for typical Portuguese foods using the Portuguese tables of food composition (Ferreira and Graca, 1985) and data from other studies that analysed the composition of Portuguese foods (Lopes, 2000).

To calculate energy expenditure, we used standard metabolic energy equivalent task (MET) values. The MET is defined as the rate of energy expenditure in the activity compared with the resting metabolic rate (Blair *et al.*, 1985). Participants reported the average time spent on the following types of activity: rest (sleeping/lying awake); transport (to and from work); work; household activities; sedentary and leisure-time exercise. The activities were categorized as very light, light, moderate and heavy intensity, corresponding to an average of 1.5, 2.5, 5.0 and 7.0 MET, respectively (National Research Council, 1989). Energy expenditure was estimated by

multiplying the corresponding MET value by the time spent in each activity. The sum of the energy expenditure in each activity was computed to estimate the full-day energy expenditure.

Health behaviour score

To synthesize the joint exposure to the most important health behaviours, we adopted a previously published health behaviour score (Khaw *et al.*, 2008). In brief, the participants scored one point for each of the following health behaviours: current nonsmoking, not physically inactive (considering sedentary those with less than 10% of energy expenditure at a moderate or high intensity level – four METs – during occupational activities, leisure time or throughout the day), moderate alcohol intake (1–14 units per week) and at least five servings of fruit and vegetables per day. For data analysis, we considered the score as a continuous variable and dichotomized (the median was used as cutoff).

Anthropometrics

Anthropometric measurements were obtained after a 12-h overnight fast, with the participant wearing light clothing and no footwear. Body weight was measured to the nearest 0.1 kg using a digital scale, and height was measured to the nearest centimetre in the standing position using a wall stadiometer. Body mass index (BMI) was calculated as weight (kilograms) divided by squared height (metres), and further divided into two categories: overweight or obesity ($\geq 25.0\,kg/m^2$); normal and underweight ($< 24.9\,kg/m^2$; National Institutes of Health, 1998).

Statistical analysis

The sociodemographic characteristics of the participants were compared using the χ^2 and the Kruskal–Wallis tests, respectively for categorical and continuous variables. Multiple logistic and multiple linear regression analyses were used to compute age-, sex- and education-adjusted prevalences and mean values, respectively, and to conduct hypothesis tests for the comparisons between the groups of participants, considering the differences statistically significant when the *P* value was less than 0.05. All data analyses were performed using STATA Software, version 9.2 (College Station, Texas, USA).

Results

Sample characteristics

CSs were more frequently male and older than participants with LC or not having a cancer diagnosis (percentage of men: CSs, 60.4 vs. LC, 49.6 vs. NC, 36.6; median age: CSs, 67.1 years vs. LC, 61.8 years vs. NC, 52.5 years). Their level of education was lower than the participants with NC but equal to the participants with LC (median education: CSs, 5.0 vs. LC, 5.0 vs. NC, 8.0 years; Table 1).

Most CSs had had a female reproductive system (47.6% among women), breast (42.8% among women), prostate (28.1% among men), bladder (22.0% among men) or colorectal (18.6% among men and 4.8% among women) cancer. The overall median time from diagnosis to baseline assessment was 27.4 and 55.7 months, respectively for men and women (Table 2).

With regard to participants with LC, the neoplasms that were more frequently diagnosed during the follow-up

Table 1 Sociodemographic characteristics of the cancer survivors and participants with no cancer diagnosis at baseline evaluation (according to their status regarding cancer diagnosis at the end of follow-up)

	Participants with no cancer diagnosis at baseline					
	Participants with no cancer[a] (*N*=2261)	Participants with latent cancer[b] (*N*=139)	Cancer survivors[c] (*N*=53)	*P*[d]	*P*[e]	*P*[f]
Age (years), median (P25–P75)	52.5 (41.9–64.5)	61.8 (54.2–69.5)	67.1 (56.9–72.9)	<0.001	<0.001	0.069
Age (years), *n* (%)						
≤40	478 (21.1)	5 (3.6)	2 (3.8)			
41–65	1241 (54.9)	76 (54.7)	20 (37.7)	<0.001	<0.001	0.104
>65	542 (24.0)	58 (41.7)	31 (58.5)			
Sex, *n* (%)						
Men	828 (36.6)	69 (49.6)	32 (60.4)	0.013	<0.001	0.119
Women	1433 (63.4)	70 (50.4)	21 (39.6)			
Education (years), median (P25–P75)	8.0 (4.0–14.0)	5.0 (4.0–9.0)	5.0 (4.0–10.0)	0.001	0.102	0.829
Education (years), *n* (%)						
<4	224 (9.9)	8 (5.8)	4 (7.6)			
4	633 (28.0)	61 (43.9)	22 (41.5)			
5–9	487 (21.5)	39 (28.1)	13 (24.5)	<0.001	0.167	0.849
10–12	296 (13.1)	15 (10.8)	5 (9.4)			
≥13	621 (27.5)	16 (11.5)	9 (17.0)			

P25–P75, 25th percentile–75th percentile.
[a]Participants with no cancer diagnosis at baseline or during follow-up.
[b]Participants with no cancer diagnosis at the baseline but diagnosed with a cancer during follow-up.
[c]Participants with a cancer diagnosis before baseline assessment.
[d]Participants with no cancer versus participants with latent cancer.
[e]Participants with no cancer versus cancer survivors.
[f]Participants with latent cancer versus cancer survivors.

were prostate (23.2% among men) and breast (34.3% among women) cancers. The overall median time from baseline assessment to diagnosis was 72.3 and 52.2 months, respectively for men and women.

Health-related behaviours and anthropometric characteristics

At baseline evaluation, the prevalence of smoking was nearly 20% among the CSs and participants with NC at baseline or after the follow-up, and approximately 30% among the participants with LC. The latter also reported the highest cigarette consumption, and the NC participants the lowest, although the differences were statistically significant only when comparing NC participants with those with LC. The proportion of former smokers was similar across the three groups. No meaningful or statistically significant differences in the prevalence of current or former alcohol consumption were observed. However, LC participants had the highest average alcohol consumption (25.5 g/day) and NC participants the lowest (17.0 g/day). The proportion of CSs reporting sports practice was nearly 50% higher than for NC or participants with LC. Total physical activity was lower in the participants with LC, close to statistical significance, but the magnitude of the differences was small. With regard to dietary habits, CSs had a consumption of fruit and vegetables, fibre and vitamin C similar to that observed for NC participants and higher than that reported by participants with LC.

The assessment of the joint exposure to the main risk factors using a health behaviour score revealed higher scores (higher scores reflect the exposure to a smaller number of risk factors) among the group of subjects with NC diagnosis in comparison with participants with LC or CSs (1.74 vs. 1.52 vs. 1.63, respectively).

As expected, overweight and obesity were substantially less frequent and mean BMI lower in CSs than in the remaining groups (Table 3).

The same analyses were conducted separately for women and men, reaching the same conclusions (data not shown).

Discussion

Participants with LC showed a higher frequency of unhealthy behaviours, especially regarding smoking, alcohol intake and dietary habits, contrasting with an analogous pattern of health-related behaviours between CSs and individuals with NC diagnosis.

The higher prevalence of smoking among the participants with LC is in accordance with the established causal relationship between tobacco exposure and several cancer topographies (Gandini *et al.*, 2008). There were no differences regarding smoking between CSs and participants with NC diagnosis, as in previous studies (Bellizzi *et al.*, 2005; Grimmett *et al.*, 2009). However, nearly 20% of the CSs were current smokers, showing an ample scope for benefiting from smoking cessation, which is especially important among CSs, with a higher baseline risk of tobacco-related conditions than the general population, namely second primary cancers (Khuri *et al.*, 2001; Somerville, 2003) and cardiovascular events (Demark-Wahnefried *et al.*, 2005; Oeffinger and McCabe, 2006).

The prevalence of alcohol consumption was similar across the three groups, confirming findings from previous reports (Bellizzi *et al.*, 2005), despite the amount of daily consumption being higher in participants with LC. The latter is in accordance with the known relation between alcohol drinking and cancer, namely upper aerodigestive tract and liver (Pelucchi *et al.*, 2008). Although a direct comparison is difficult due to differences in definitions and cutoffs across studies, there is still an ample scope for public health interventions, as for smoking, since almost

Table 2 Cancer topography and time for diagnosis or since diagnosis in relation to baseline evaluation, by sex, in cancer survivors and participants with latent cancer

	Men				Women			
	Participants with latent cancer		Cancer survivors		Participants with latent cancer		Cancer survivors	
Topography	*n* (%)	Time from baseline (months)[a,b]	*n* (%)	Time to baseline (months)[a,b]	*n* (%)	Time from baseline (months)[a,b]	*n* (%)	Time to baseline (months)[a,b]
Bladder	6 (8.7)	34.3 (15.5–76.3)	7 (22.0)	100.3 (41.9–117.4)	–	–	–	–
Breast	–	–	–	–	24 (34.3)	58.7 (28.8–82.6)	9 (42.8)	82.2 (29.9–107.1)
Colon and rectum	11 (15.9)	64.3 (41.0–107.6)	6 (18.6)	45.7 (30.5–76.9)	11 (15.7)	32.2 (17.0–54.2)	1 (4.8)	75.8
Female reproductive system[c]	–	–	–	–	8 (11.4)	29.1 (9.7–64.3)	10 (47.6)	49.1 (32.1–93.9)
Lung	8 (11.6)	68.5 (49.2–83.8)	–	–	3 (4.3)	20.9 (5.0–66.3)	–	–
Prostate	16 (23.2)	95.5 (62.0–111.2)	9 (28.1)	11.9 (5.1–24.4)	–	–	–	–
Stomach	7 (10.1)	86.3 (71.0–101.0)	4 (12.5)	81.2 (13.3–144.3)	2 (2.9)	14.0 (8.7–19.3)	–	–
Other	21 (30.4)	58.6 (40.8–96.3)	6 (18.8)	7.8 (4.4–13.2)	22 (31.4)	59.8 (30.6–94.5)	1 (4.8)	8.7
All cancers	69 (100.0)	72.3 (47.0–100.9)	32 (100.0)	27.4 (9.4–88.1)	70 (100.0)	52.2 (20.8–75.2)	21 (100.0)	55.7 (29.9–93.9)

[a]Median (25th percentile–75th percentile).
[b]Does not include data on date of diagnosis from 14 participants, in which cancer diagnosis information was obtained only from death certificates. In these cases, date of diagnosis was computed by subtracting an estimate of survival (based on the median survival for each topography of the other cancer cases in the sample) to the date of death.
[c]Includes cervical, corpus uterus, ovarian and vulvar cancers.

Table 3 Health-related behaviors and anthropometric measures in cancer survivors and participants with no cancer diagnosis at baseline evaluation (according to their status regarding cancer diagnosis at the end of follow-up)

	Participants with no cancer diagnosis at baseline assessment								
	Participants with no cancer (*N*=2261)		Participants with latent cancer (*N*=139)		Cancer survivors (*N*=53)				
	n (%)	Adjusted prevalence (95% CI)[a]	*n* (%)	Adjusted prevalence (95% CI)[a]	*n* (%)	Adjusted prevalence (95% CI)[a]	P^d	P^e	P^f
Smoking									
Current smoker	543 (24.6)	19.2 (17.4–21.2)	34 (25.4)	31.7 (23.5–41.1)	8 (15.7)	22.5 (11.8–38.8)	0.015	0.893	0.245
Former smoker	433 (19.2)	16.2 (14.6–18.0)	35 (25.2)	19.6 (13.8–27.0)	18 (34.0)	26.6 (16.3–40.2)	0.913	0.407	0.663
Tobacco consumption (cigarettes/day)[b,c]		4.0 (3.6–4.4)		7.0 (5.4–8.6)		4.1 (1.6–6.7)	0.005	0.401	0.116
Alcohol consumption									
Current drinker	1628 (73.8)	75.9 (73.9–77.7)	107 (79.9)	81.9 (74.3–87.5)	42 (82.4)	84.1 (71.3–91.8)	0.468	0.632	0.884
Current drinker (≥ 1/2 drinks/day)[g]	857 (41.6)	40.5 (38.2–42.9)	70 (53.9)	43.9 (34.9–53.3)	27 (54.0)	41.0 (27.1–56.3)	0.962	0.490	0.376
Former drinker	165 (7.3)	5.9 (5.0–7.1)	10 (7.2)	4.4 (2.3–8.2)	4 (7.6)	4.3 (1.6–11.3)	0.422	0.613	0.975
Amount of alcohol consumed (g/day)[b,c]		17.0 (16.0–18.0)		25.5 (21.4–29.6)		20.9 (14.3–27.6)	0.022	0.466	0.207
Dietary intake									
Fruit and vegetables (servings/day)[b]		4.4 (4.3–4.5)		3.8 (3.4–4.2)		4.2 (3.6–4.8)	0.008	0.730	0.265
Fruit and vegetables (≥ 5 servings/day)[h]	752 (34.2)	34.0 (32.0–36.0)	33 (25.2)	25.5 (18.7–33.8)	14 (27.5)	27.5 (16.9–41.3)	0.069	0.464	0.835
Fibre (g/day)[b]		23.4 (23.0–23.7)		22.1 (20.7–23.5)		24.9 (22.6–27.2)	0.062	0.259	0.064
Vitamin C (μg/day)[b]		131.8 (129.1–134.4)		120.4 (109.5–131.3)		131.9 (114.4–149.4)	0.091	0.662	0.269
Total energy intake (kcal/day)[b]		2228.1 (2203.8–2252.5)		2283.5 (2183.1–2383.8)		2356.4 (2195.9–2156.9)	0.844	0.908	0.863
Physical activity									
Sports practice	764 (34.6)	34.0 (32.0–36.0)	45 (33.3)	33.4 (25.8–42.0)	26 (51.0)	49.9 (36.3–63.6)	0.737	0.039	0.112
Total physical activity (METS·hours/day)[b]		1.55 (1.53–1.56)		1.51 (1.46–1.56)		1.53 (1.45–1.61)	0.097	0.496	0.638
Health behaviour score (points)		1.74 (1.71–1.78)		1.52 (1.37–1.67)		1.63 (1.39–1.87)	0.005	0.385	0.447
Health behaviour score (>2 points)	459 (21.0)	18.7 (17.0–20.5)	15 (11.5)	11.8 (7.2–18.8)	7 (14.0)	16.8 (8.1–31.5)	0.059	0.762	0.387
Anthropometrics									
Overweight or Obesity	1385 (62.3)	64.2 (62.1–66.3)	95 (70.9)	64.6 (55.4–72.9)	28 (54.9)	44.8 (31.3–59.1)	0.973	0.007	0.038
BMI[b]		26.9 (26.7–27.1)		26.8 (26.0–27.6)		25.4 (24.2–26.6)	0.923	0.035	0.119

95% CI, 95% confidence interval; BMI, body mass index; METS, metabolic energy equivalent task units.

[a]Results are presented as prevalences adjusted simultaneously for age, education and sex and respective 95% confidence intervals, except if otherwise specified.

[b]Results are presented as means adjusted simultaneously for age, education and sex and respective 95% confidence intervals.

[c]These results only apply to current smoker and drinker participants.

[d]Participants with no cancer versus participants with latent cancer, adjusted for age, education and sex.

[e]Participants with no cancer versus cancer survivors, adjusted for age, education and sex.

[f]Participants with latent cancer versus cancer survivors, adjusted for age, education and sex.

[g]According to the recommendations of the American Heart Association of a maximum daily intake of one standard drink for women and two for men (Lichtenstein *et al.*, 2006).

[h]According to the recommendations of the World Cancer Research Fund on 'Food, Nutrition, Physical activity and the Prevention of Cancer' of at least five servings of fruit/vegetables per day (World Cancer Research Fund, 2007).

40% of the survivors drink more than expected from the guidelines of American Heart Association (Lichtenstein *et al.*, 2006).

Participants with LC had a lower consumption of fruit and vegetables and dietary fibre, as expected from the relation between these exposures and cancer risk (Gallus *et al.*, 2004; Lunet *et al.*, 2007). Moreover, in accordance with two population-based CSs studies (Coups and Ostroff, 2005; Eakin *et al.*, 2007), we found similar dietary behaviours between CSs and participants with NC diagnosis, regarding fruits and vegetables, fibre, vitamin C and daily total energy intake. Nevertheless, approximately 75% of the CSs eat fewer than five servings of fruit and vegetables per day.

Our results showed a lower level of total physical activity among participants with LC, near statistical significance, in accordance with the association between sedentary behaviour and cancer, namely colon, endometrium and postmenopausal cancers (Vainio *et al.*, 2002; World Cancer Research Fund, 2007). We also found a higher prevalence of sports practice in the CSs group, but previous studies yielded conflicting findings (Coups and Ostroff, 2005; Bellizzi *et al.*, 2005; Eakin *et al.*, 2007; Grimmett *et al.*, 2009), which may be explained by differences in the moment of evaluation (regarding time since diagnosis and treatment status) and in the validity of physical activity assessment across studies. Several reports confirmed an increasing proportion of CSs meeting the physical activity recommendations as the number of years since diagnosis increased, which could be explained by a progressively decreased disability motivated by the psychological impairment of cancer diagnosis and the side effects of cancer treatment (Bellizzi *et al.*, 2005; Courneya *et al.*, 2007). Nevertheless, in our study, when CSs were grouped by time since diagnosis, the higher adjusted prevalence of sports practice was observed both in CSs for less than median time from diagnosis to baseline (60.9, 95% CI: 41.0–77.7) and for a longer period (38.7, 95% CI: 21.9–59.8).

Overweight/obesity is a modifiable risk factor for cancer and other chronic conditions and is a surrogate of health-related behaviours such as physical exercise and diet. In this study, CSs had a lower BMI than the remaining participants whereas previous studies reported either similar (Bellizzi *et al.*, 2005) or higher BMI levels (Eakin *et al.*, 2007) in CSs. The short time since diagnosis, for some of the participants in our investigation, could contribute to explain our findings, as the proximity to treatment may determine a decrease in the patient weight. However, the prevalence of overweight/obesity was lower both in the participants evaluated a longer (49.2, 95% CI: 30.1–68.5) or a shorter (40.3, 95% CI: 23.0–60.5) time after the diagnosis.

Although these results are ultimately locale-specific, our sample has an expected cancer topography distribution, since we have the most frequent topographies in the LC group (Ries *et al.*, 2007; Berrino *et al.*, 2009) and the topographies with greater survival in the CSs group (Ries *et al.*, 2007; Berrino *et al.*, 2009), which favours a good external validity. The group of NC participants may include a small number of participants with LC that could not be identified in the cancer registry because some of the cancers diagnosed more recently may have not been registered up to 2009, reflecting the dynamic nature of cancer registration and its increasing completeness with time. This, however, is not likely to have influenced our conclusions since the misclassification of participants with LC as NC is expected to have affected only a small number of participants.

As in previous studies on this subject (Coups and Ostroff, 2005; Bellizzi *et al.*, 2005; Eakin *et al.*, 2007; Grimmett *et al.*, 2009), the cross-sectional design precludes the establishment of a temporal relation between cancer diagnosis and change of behaviours. In fact, among the CSs with healthier lifestyles it is not possible to distinguish between those that quitted smoking, increased their fruit and vegetable consumption or started to practise a sport after having a cancer diagnosed, from those that survived longer because they had the latter exposures for a longer time before, since the prognosis is expectedly worse in cancer patients with unhealthy behaviours (Rock and Demark-Wahnefried, 2002; Holmes *et al.*, 2005; Meyerhardt *et al.*, 2006a, 2006b). Although we may not discard the hypothesis that our findings reflect mostly a survival effect rather than a real shift in behaviours after the cancer diagnosis, the observation of important departures from healthier lifestyles among the CSs is not compromised by the cross-sectional study design.

An additional limitation is the small sample size of the CSs group, which that precludes the achievement of robust findings from stratified analyses, namely by cancer topography.

Underestimation of smoking and alcohol consumption and overestimation of physical activity and fruit and vegetable intake are more likely to have occurred among CSs (Rock and Demark-Wahnefried, 2002; Holmes *et al.*, 2005; Meyerhardt *et al.*, 2006a, 2006b), but the magnitude of the differences between CSs and LC participants can hardly be explained by such a bias.

Despite the limitations described above, our study adds to previous reports the comparison of CSs with a healthier subset of the general population, in terms of cancer risk. Further progress in the understanding of health related behaviours of CSs requires large cohort studies powered sufficiently to allow stratification by follow-up duration and type of cancer.

In conclusion, this study shows that the distribution of the exposures to each of the most important risk factors

for cancer among CSs tends to be similar to that observed in the subgroup of the general population with healthier behaviour, despite a still high prevalence of risk factors for chronic diseases, and a joint exposure to a large number of risk factors, demanding health promotion interventions in this specific population.

References

Bellizzi KM, Rowland JH, Jeffery DD, McNeel T (2005). Health behaviors of cancer survivors: examining opportunities for cancer control intervention. *J Clin Oncol* **23**:8884–8893.

Berrino F, Verdecchia A, Lutz JM, Lombardo C, Micheli A, Capocaccia R, *et al.* (2009). Comparative cancer survival information in Europe. *Eur J Cancer* **45**:901–908.

Blair SN, Haskell WL, Ho P, Paffenbarger Jr. RS, Vranizan KM, Farquhar JW, *et al.* (1985). Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. *Am J Epidemiol* **122**: 794–804.

Coups EJ, Ostroff JS (2005). A population-based estimate of the prevalence of behavioral risk factors among adult cancer survivors and noncancer controls. *Prev Med* **40**:702–711.

Courneya KS, Karvinen KH, Vallance JK (2007). *Exercise motivation and behaviour change. Handbook of cancer survivorship*. New York: Springer Publications. pp. 113–132.

Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, *et al.* (2006.) *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000. National Cancer Institute, NIH Publ. No. 05-5302.* Bethesda, MD: National Cancer Institute.

Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM (2005). Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol* **23**:5814–5830.

Do KA, Johnson MM, Doherty DA, Lee JJ, Wu XF, Donget Q, *et al.* (2003). Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control* **14**:131–138.

Eakin EG, Youlden DR, Baade PD, Lawler SP, Reeves MM, Heyworth JS, *et al.* (2007). Health behaviors of cancer survivors: data from an Australian population-based survey. *Cancer Causes Control* **18**:881–894.

Ferreira F, Graca M (1985). *Composition Table of Portuguese Food*. Lisbon: National Institute of Health Dr. Ricardo Jorge.

Gallus S, Bosetti C, La Vecchia C (2004). Mediterranean diet and cancer risk. *Eur J Cancer Prev* **13**:447–452.

Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuveet AB, *et al.* (2008). Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* **122**: 155–164.

Grimmett C, Wardle J, Steptoe A (2009). Health behaviours in older cancer survivors in the English longitudinal study of ageing. *Eur J Cancer* **45**:2180–2186.

Hebert JR, Hurley TG, Ma Y (1998). The effect of dietary exposures on recurrence and mortality in early stage breast cancer. *Breast Cancer Res Treat* **51**:17–28.

Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA (2005). Physical activity and survival after breast cancer diagnosis. *JAMA* **293**:2479–2486.

Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N, *et al.* (2008). Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med* **5**:e12.

Khuri FR, Kim ES, Lee JJ, Winn RJ, Benner SE, Lippman SM, *et al.* (2001). The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. *Cancer Epidemiol Biomarkers Prev* **10**:823–829.

Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, *et al.* (2006). Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* **114**:82–96.

Lopes C, Aro A, Azevedo A, Ramos E, Barros H (2007). Intake and adipose tissue composition of fatty acids and risk of myocardial infarction in a male Portuguese community sample. *J Am Diet Assoc* **107**:276–286.

Lopes C (2000). Reproducibility and validation of a food frequency questionnaire. PhD Thesis, University of Porto Medical School, pp. 79–115.

Lucas R, Rocha O, Bastos J, L. Costa L, Barros H, Lunet N (2009). Pharmacological management of osteoporosis and concomitant calcium supplementation in a Portuguese urban population: the EpiPorto study (2005–2007). *Clin Exp Rheumatol* **27**:47–53.

Lunet N, Valbuena C, Carneiro F, Lopes C, Barros H (2006). Antioxidant vitamins and risk of gastric cancer: a case-control study in Portugal. *Nutr Cancer* **55**:71–77.

Lunet N, Valbuena C, Vieira AL, Lopes C, David L, Carneiro F, *et al.* (2007). Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. *Eur J Cancer Prev* **16**:312–327.

Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, *et al.* (2006a). Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* **24**:3527–3534.

Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, *et al.* (2006b). Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* **24**:3535–3541.

National Institutes of Health (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – the evidence report. *Obes Res* **6** (**Suppl 2**):51S–209S

National Research Council (1989). *Recommended dietary allowances. 10th ed.* Washington, DC: National Academy Press.

Oeffinger KC, McCabe MS (2006). Models for delivering survivorship care. *J Clin Oncol* **24**:5117–5124.

Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C (2008). Alcohol and tobacco use, and cancer risk for upper aerodigestive tract and liver. *Eur J Cancer Prev* **17**:340–344.

RORENO (1988). *Registo Oncologico Regional do Norte*. In IPO-Porto, Edition.

Ramos E, Lopes C, Barros H (2004). Investigating the effect of nonparticipation using a population-based case-control study on myocardial infarction. *Ann Epidemiol* **14**:437–441.

Ries L, Young J, Keel G, Eisner M, Lin Y, Horner MJ, *et al.* (2007). *SEER Survival monograph: cancer survival among adults: US SEER program, 1988–2001, patient and tumor characteristics*. Bethesda, MD: National Cancer Institute, SEER Program; NIH Pub; No. 07–6215.

Rock CL, Demark-Wahnefried W (2002). Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. *J Clin Oncol* **20**: 3302–3316.

Rosso S, De Angelis R, Ciccolallo L, Carrani E, Soerjomataram I, Grande E, *et al.* (2009). Multiple tumours in survival estimates. *Eur J Cancer* **45**:1080–1094.

Sanchez L, Lana A, Hidalgo A, Rodriguez JM, Del Valle Mdel O, Cueto A, *et al.* (2008). Risk factors for second primary tumours in breast cancer survivors. *Eur J Cancer Prev* **17**:406–413.

Somerville HM (2003). Second malignant neoplasms following treatment for primary cancer. *Aust Fam Physician* **32**:25–31.

Stewart B, Kleihues P (2003). *World cancer report*. Lyon: International Agency for Research on Cancer. pp. 11–21.

Travis LB (2006). The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev* **15**:2020–2026.

Vainio H, Kaaks R, Bianchini F (2002). Weight control and physical activity in cancer prevention: international evaluation of the evidence. *Eur J Cancer Prev* **11** (**Suppl 2**):S94–100.

World Cancer Research Fund (2007). *Food, nutrition, physical activity, and the prevention of cancer: a global perspective*. Washington DC: AICR, Edition American Institute for Cancer Research.

World Health Organization (WHO) (1998). *Guidelines for controlling and monitoring the tobacco epidemic*. Geneva: World Health Organization.

PAPER III

Incidence of second primary cancers in North Portugal – a population-based study

Submitted

Incidence of second primary cancers in North Portugal – a population-based study

Luís Pacheco-Figueiredo[1,2,3], Luís Antunes[4], Maria José Bento[4], Nuno Lunet[1,2]

[1] Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal;
[2] EPIUnit – Institute of Public Health – University of Porto (ISPUP), Porto, Portugal
[3] School of Health Sciences, University of Minho, Braga, Portugal;
[4] North Region Cancer Registry (RORENO) – Portuguese Oncology Institute, Porto, Portugal.

Acknowledgements

Luís Pacheco-Figueiredo received a grant from the Fundação para a Ciência e a Tecnologia (SFRH/SINTD/60124/2009)

Abstract

Purpose:

Longitudinal studies are needed to characterize the burden of second primary malignancies among cancer survivors. Therefore, we quantified the incidence rate and cumulative incidence of second primary cancers (SPC) and standardized incidence ratios (SIR) in a population-based cohort of subjects diagnosed with a first primary cancer (FPC).

Methods:

We evaluated a cohort of cancer patients from the Portuguese North Region Cancer Registry (RORENO), with the first diagnosis in 2000-2003 (n=39451), to estimate the incidence rate and cumulative incidence of SPC and standardized incidence ratios (SIR), for different periods of follow-up, up to five years; SPC were defined according to the International Association of Cancer Registries and the International Agency for Research on Cancer guidelines.

Results:

The incidence rate of SPC was more than 5-fold higher in the first two months of follow-up than in the period between two months and five years (metachronous SPC), across which the incidence rates were relatively stable. Cancer survivors had an overall higher incidence rate of cancer than the general population (SIR=1.31; 95% CI: 1.25-1.38), although that difference faded when only metachronous SPC were considered (SIR=1.02; 95% CI: 0.96-1.08). Cancer incidence rates were higher among female lung FPC survivors and lower in prostate FPC cancer survivors than in the general population. The 5-year cumulative risk of developing a metachronous SPC was 3.0%, and reached nearly 5.0% among patients with FPC associated with lower risk of death.

Conclusions:

Cancer survivors had higher incident rates of cancer that the general population, especially due to diagnoses in the first months following the FPC. Nevertheless, after this period SPC remain frequent events among cancer survivors.

Implications for Cancer Survivors

SPC constitute an important dimension of the burden of cancer survivorship, and this needs to be taken into account when defining strategies for surveillance, prevention and counseling.

Key Words: Neoplasms, Second Primary; Population-based cancer registry; Incidence; Mortality.

Introduction

The increasing number of incident cases of cancer [1] and the improvements in survival [2] have been contributing for a growing population of subjects with a previous diagnosis of cancer. It was estimated that in 2012 there were more than 32 million cancer survivors worldwide [3]; these subjects have an increased risk of several adverse health events and use of health resources [4], including the recurrence of the first primary cancer (FPC), cardiovascular diseases or second primary cancers (SPC) [5].

The occurrence of SPC is mostly related to genetic characteristics, persistence of deleterious environmental exposures and late effects of FPC treatment [6]. Recognizing frequent FPC-SPC pairs can also be a useful starting point for investigating possible shared etiologies and mechanisms of carcinogenesis. Quantifying and characterizing the risk of second malignancies can have important implications for surveillance, prevention and counseling.

SPC represented 16.0 % of all incident cancer cases in USA (2003) [5], 6.3% in Europe (1995-1999) [7] and 3.8% in North Portugal (2000-2003) [8]. These differences in the frequency of SPC reflect the heterogeneous distribution of cancer incidence and survival across settings, as well as the distinct sensitivity of population-based cancer registries with different operating times for detecting SPC in cross-sectional analyses [7]. A longitudinal assessment is expected to contribute for more accurate estimates, and a better understanding of the burden of SPC, by providing more clinically relevant measures of incidence.

Therefore, we followed during five years a population-based cohort of cancer survivors to estimate incidence rates of SPC and corresponding standardized incidence ratios (SIR), which reflect the dynamics of SPC diagnosis and their relation with the expected cancer incidence in the general population. Cumulative incidences of SPC were computed to quantify the absolute risk of cancer survivors being diagnosed with another primary cancer.

Methods

Study population and design

We conducted a cohort analysis based on the North Region Cancer Registry (RORENO). This population-based cancer registry (RORENO) was set up in 1988 and covers the whole northern region of Portugal, corresponding to approximately 3.3 million inhabitants, which is nearly one-third of the Portuguese population.

All cases of cancer, other than skin non-melanoma, registered in the period 2000-2003, were followed for five years, until the diagnosis of a new primary cancer or until death, whichever occurred first; the vital status of the cancer patients was assessed through the National Health System database.

Tumor topography and morphology were classified according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) categories, and then recoded to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

Definition of multiple primary cancers (MPC)

To define MPC we followed the guidelines proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) [9]. Briefly, these criteria consider primary cancers those that originally developed in an organ or tissue, not being an extension, a recurrence or a metastasis. Different morphologies (even with a same topography) or dissimilar topographies should be regarded as MPC, regardless of the time between the diagnoses, unless they correspond to systemic cancers, which are considered the same cancer.

Whenever more than two primary cancers were observed in the same patient, only the second primary cancer (SPC) was considered; third and subsequent primary cancers were disregarded for the present analysis.

We classified the SPC as synchronous when diagnosed within two months of the corresponding FPC [10].

Statistical analysis

Person-years at risk (PYAR) among people diagnosed with a FPC was calculated as the time from the diagnosis of the FPC until five years of follow-up, date of death or date of diagnosis of a SPC, whichever came first.

The incidence rate of SPC was computed for different periods ("0m to < 2m" – from the diagnosis until less than two months of follow-up; "≥2m to < 12m" – from two months until less than 12 months of follow-up; "≥12 to ≤60m" – from 12 to 60 months of follow-up) since the diagnosis of the FPC, by dividing the incident cases of SPC by the PYAR within each time interval. Incidence rates were estimated also for women and men, and for the most frequent types of FPC.

Standardised incidence ratios (SIRs) and corresponding 95% confidence intervals (95% CI), derived from the Poisson distribution, were computed to evaluate age-adjusted ratios of cancer incidence rates between cancer survivors and the general population. The SIRs were calculated dividing the observed number of SPC by the expected number of cancer cases in the same period of time, if the cancer incidence rates in the general population had been observed among cancer survivors. The latter were estimated multiplying the PYAR among cancer survivors by the sex- and age group-specific cancer incidence rates observed in the general population of North Portugal in 2006 [11].

We computed the cumulative incidences of metachronous SPC and all cause of death for up to five years, stratified by sex and the most frequent types of FPC. Cumulative incidences were calculated dividing the observed number of cases of SPC or deaths until each period of analysis (2, 6, 12, 24, 36, 48 and 60 months of follow-up) by the total number of survivors in the beginning of the study.

All analyses were conducted using STATA®, version 9.2 (StataCorp LP, College Station, Texas, USA).

Results

Among the 39451 patients with a FPC in 2000-2003, a total of 1589 SPC were observed in the first five years after the diagnosis of the FPC (120473 PYAR), from which 417 (26.2%) were diagnosed within the first two months after the FPC (synchronous tumors), 281 (17.7%) between more than two months and less than one year, and 891 (56.1%) between one and five years.

A total of 61.0% of the SPC were observed among men and 56.6% in subjects aged 65 or more years. Regarding the distribution according to the most common groups of SPC, in relation with the observed for FPC diagnosed in 2000-2003, during the 5-year follow-up there was a lower proportion of SPC of the female breast (6.8% vs. 12.4%), prostate (8.1% vs. 11.9%) and stomach (9.2% vs. 11.1%), and a higher proportion of cancer of the colon and rectum (13.3% vs. 10.0% and 7.9% vs. 5.7%, respectively), lung (10.7% vs. 7.9%) and bladder (6.2% vs. 5.0%) (Table 1).

Incidence rate of SPC and SIR

Overall, the incidence rate of SPC was more than 5-fold higher in the first two months of follow-up than in the period between two months and five years, across which the incidence rates were relatively stable. However, the differences between the 0m to <2m and the ≥2m to ≤60m periods were greater among the individuals with stomach, colon, rectum and lung FPC than among those with breast, prostate or bladder FPC (figure 1).

The incidence rates observed among cancer survivors was more than 30% higher than the expected (SIR=1.31; 95% CI: 1.25-1.38), especially among women (SIR women=1.73; 95% CI: 1.60-1.88 vs. SIR men=1.13; 95% CI: 1.06-1.21). This higher number of observed cases was mainly identified during the first two months of follow-up (synchronous SPC), and when this period was excluded from the analyzes the SIR were much lower (SIR=1.02, 95% CI: 0.96-1.08; SIR women=1.28, 95% CI: 1.17-1.41; SIR men=0.91, 95% CI: 0.85-0.98).

During the first two months of follow-up the SIR were higher, both among women (SIR=10.22; 95% CI: 8.8-11.8) and men (SIR=4.86; 95% CI: 4.3-5.5); the results were similar for the most frequent topographies of FPC (figures 2 and 3).

The incidence rate among female survivors was higher than in the general population across the ≥2m to <12m (SIR=1.37; 95% CI: 1.13-1.67) and the ≥12m to ≤60m (SIR=1.26; 95% CI: 1.13-1.40) follow-up intervals (figure 2). For men, the incidence rates were similar to those observed in the general population in the same periods (≥2m to <12m, SIR=0.91, 95% CI: 0.78-1.06; ≥12m to ≤60m, SIR=0.91, 95% CI: 0.84-0.99) (figure 3).

Among women, the SIR was lower in the ≥2m to <12m period for those with a breast FPC (SIR=0.36; 95% CI: 0.17-0.76). Those with a lung FPC were more likely to develop a SPC during the ≥12m to ≤60 period after the diagnosis of the FPC (SIR=3.00; 95% CI: 1.47-6.11). Among men, prostate cancer survivors showed a lower incidence rate of cancer than the general population in the ≥2m to <12m (SIR=0.52; 95% CI: 0.37-0.74) and ≥12m to ≤60m (SIR=0.67; 95% CI: 0.58-0.78) follow-up intervals. After the first two months of follow-up, there were no statistically significant differences in the cancer incidence rate between the general population and the cancer survivors with other FPC (figures 2 and 3).

Cumulative incidence of SPC and death

The 5-year cumulative incidence of SPC was 3.0% (women: 2.5%; men: 3.4%) and the risk of death in the same period was 46.1% (women: 38.8%; men: 52.1%) (figure 4 and appendix 1).

Women with FPC of the colon or bladder had the highest 5-year risk of developing a SPC, 4.0% and 3.6%, respectively, along with a 5-year cumulative risk of death among the lowest (colon: 46.2%; bladder: 37.8%). Those with lung and stomach FPC had some of the lowest 5-year risk of developing a SPC, 2.5% and 1.7%, respectively, and the highest 5-year risk of death (lung: 83.2%; stomach: 62.0%). Although the female breast cancer survivors had the lowest 5-year risk of death (19.4%), the 5-year risk of developing a SPC was also among the lowest (2.2%) (figure 5 and appendix 1).

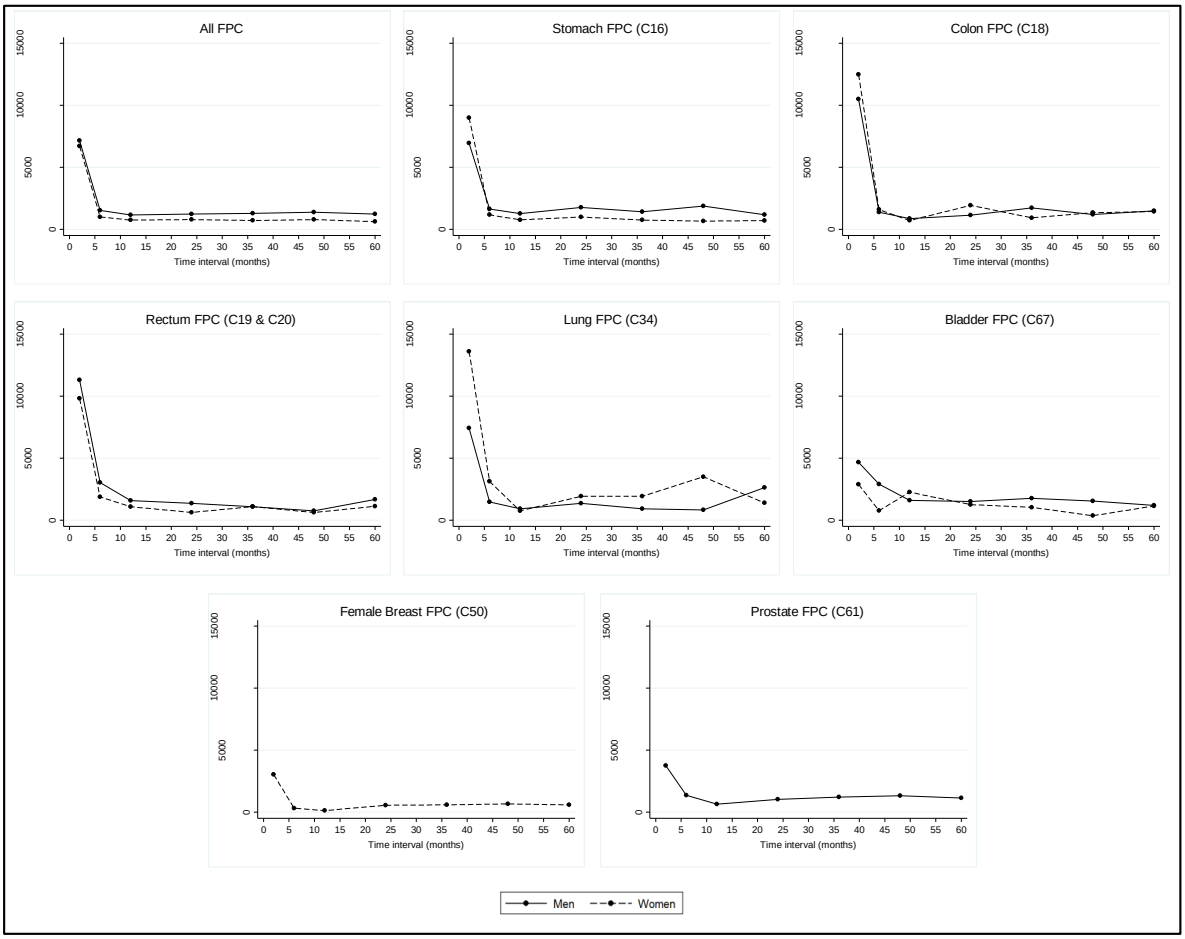
Men with prostate and bladder FPC had the highest 5-year cumulative incidence of SPC, 5.5% and 4.5%, respectively, and were among those with the lowest 5-year risk of death (prostate: 25.0%; bladder: 35.2%). Subjects with a lung or a stomach FPC had the lowest 5-year risk of a SPC, 1.2%

and 2.7%, respectively, and were among those with highest 5-year risk of death (lung: 87.8%; stomach: 67.3%) (figure 5).

Table 1 – Characteristics of the study cohort.

Total	**First primary cancer (FPC)**		**Second primary cancer (SPC)**	
	N	%	N	%
Sex				
Males	21694	55.0	970	61.0
Females	17757	45.0	619	39.0
Age at first diagnosis				
0-14	307	0.8	4	0.3
15-49 years	7356	18.6	213	13.4
50-64 years	11539	29.2	472	29.7
65 years and over	20249	51.3	900	56.6
Follow-up interval				
0 - < 2 months	n.a.		417	26.2
≥ 2 - < 12 months	n.a.		281	17.7
≥ 12 - < 60 months	n.a.		891	56.1
Topography				
Stomach (C16)	4382	11.1	146	9.2
Colon (C18)	3955	10.0	211	13.3
Rectum (C19 & C20)	2240	5.7	125	7.9
Lung (C34)	3136	7.9	170	10.7
Bladder (C67)	1977	5.0	99	6.2
Female Breast (C50)	4894	12.4	108	6.8
Prostate (C61)	4696	11.9	128	8.1
Other	14171	35.9	602	37.9

Figure 1 – Trends in the incidence rates of second primary cancers (SPC) since the diagnosis of the corresponding first primary cancers (FPC).



Incidence rates were estimated and represented for the following intervals: "0 - < 2 months"; "≥ 2 - < 6 months"; "≥ 6 - < 12 months"; "≥ 12 - < 24 months"; " ≥ 24 - < 36 months"; " ≥ 36 - < 48 months"; " ≥ 48 - < 60 months"

Figure 2 – Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) for the diagnosis of a second primary cancer, according to the first primary cancer and follow-up time since its diagnosis, among women.

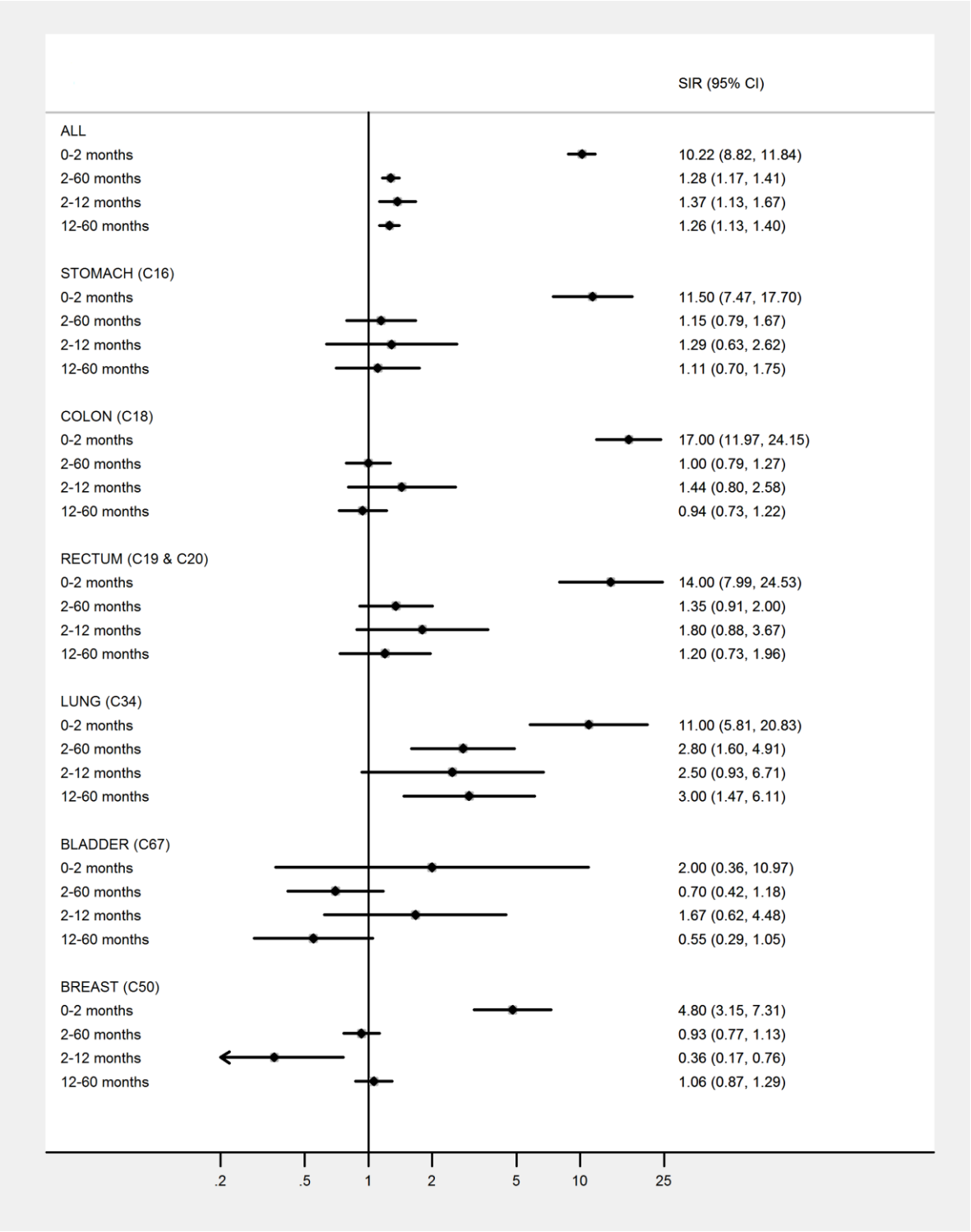


Figure 3 – Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) for the diagnosis of a second primary cancer, according to the first primary cancer and follow-up time since its diagnosis, among men.

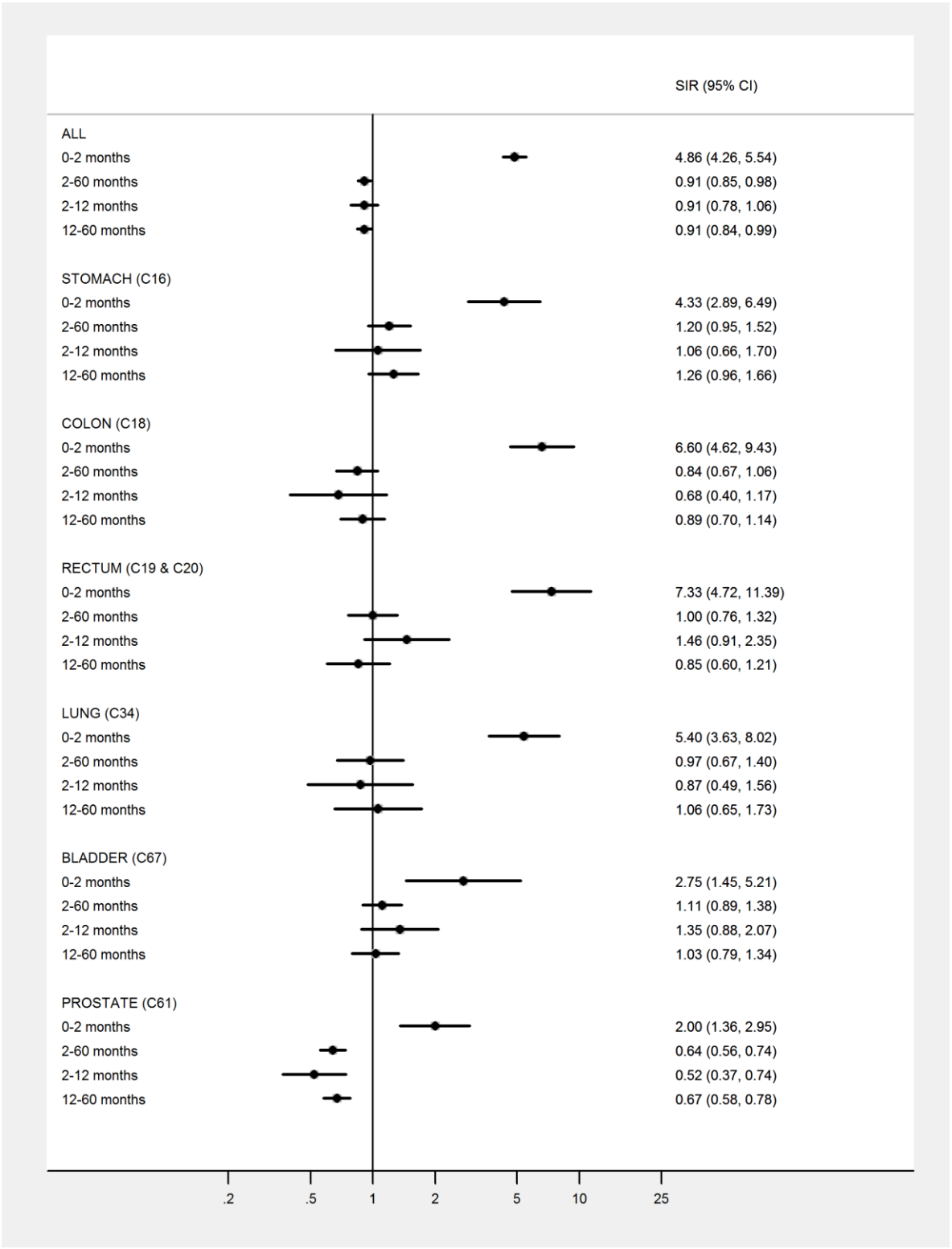
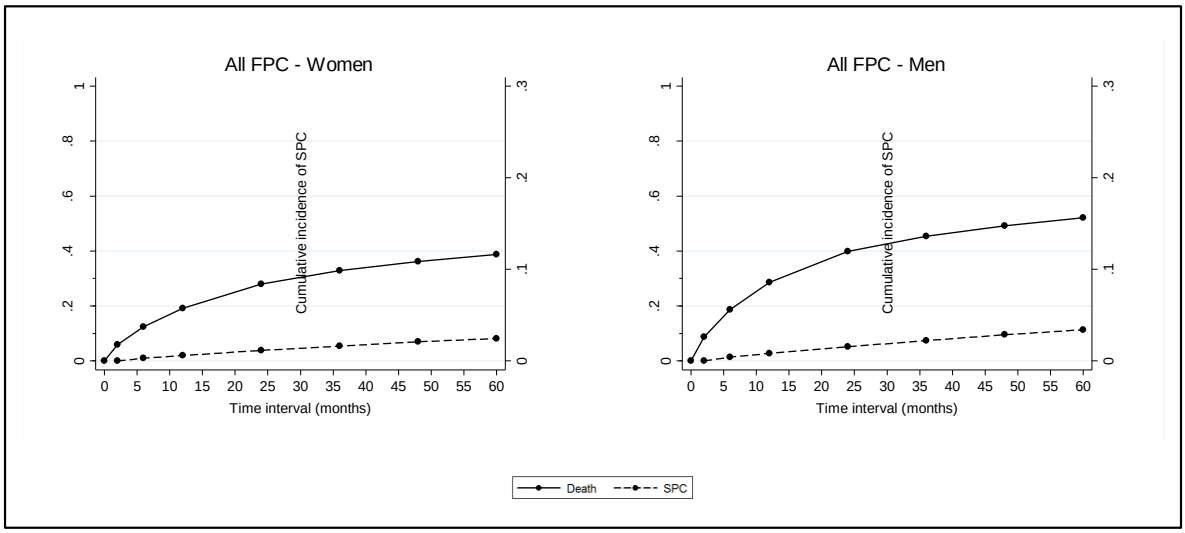
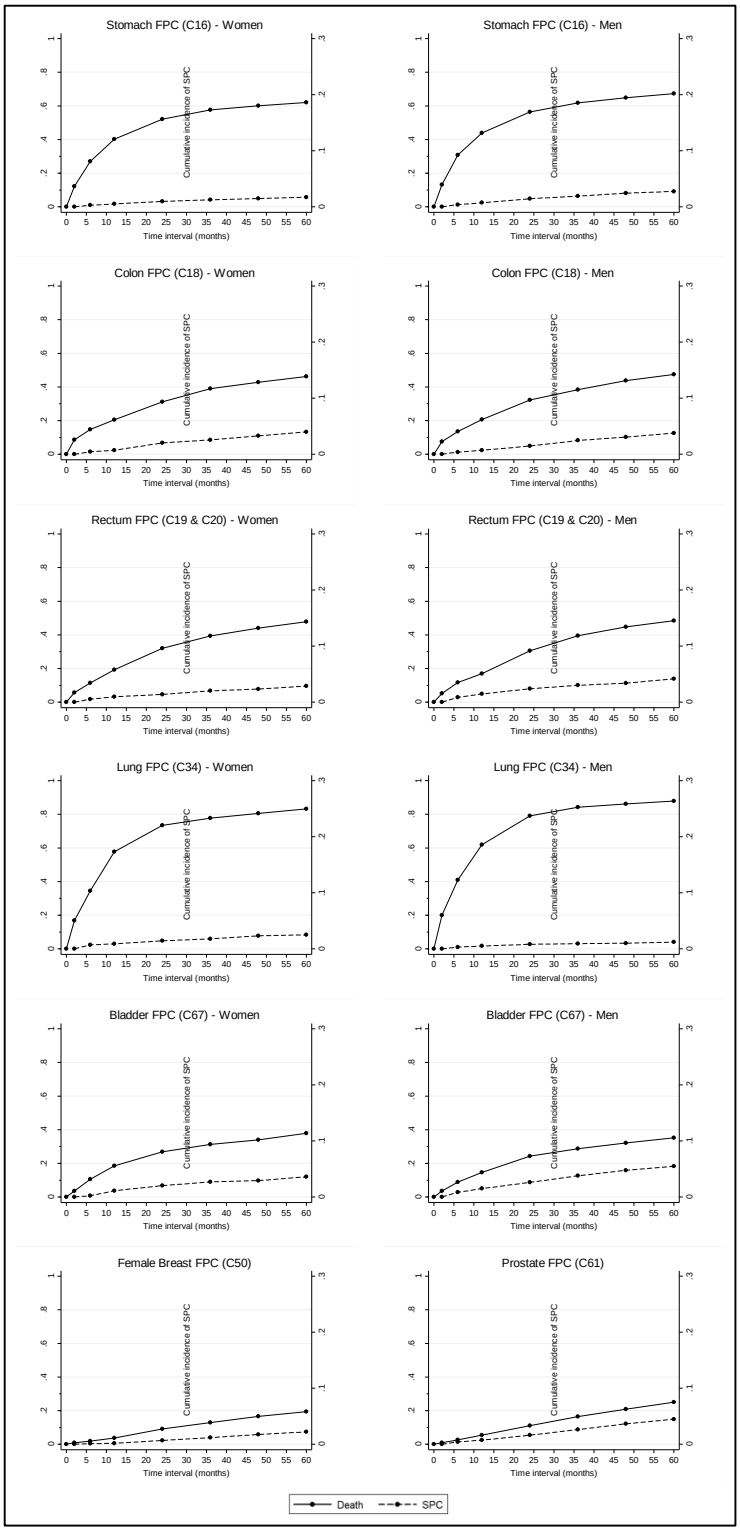


Figure 4 – Cumulative risk of death and incidence of second primary cancers (SPC), among women and men.



Cumulative risks of death were estimated and represented for the following intervals: "0 - < 2 months"; "≥ 2 - < 6 months"; "≥ 6 - < 12 months"; "≥ 12 - < 24 months"; " ≥ 24 - < 36 months"; " ≥ 36 - < 48 months"; " ≥ 48 - < 60 months";
Cumulative incidences of SPC were estimated and represented for the following intervals: "≥ 2 - < 6 months"; "≥ 6 - < 12 months"; "≥ 12 - < 24 months"; " ≥ 24 - < 36 months"; " ≥ 36 - < 48 months"; " ≥ 48 - < 60 months".

Figure 5 – Cumulative risk of death and incidence of second primary cancers (SPC), for the most frequent topographies of the first primary cancers, among women and men.



Cumulative risks of death were estimated and represented for the following intervals: "0 - < 2 months"; "≥ 2 - < 6 months"; "≥ 6 - < 12 months"; "≥ 12 - < 24 months"; " ≥ 24 - < 36 months"; " ≥ 36 - < 48 months"; " ≥ 48 - < 60 months";

Cumulative incidences of SPC were estimated and represented for the following intervals: "≥ 2 - < 6 months"; "≥ 6 - < 12 months"; "≥ 12 - < 24 months"; " ≥ 24 - < 36 months"; " ≥ 36 - < 48 months"; " ≥ 48 - < 60 months".

Discussion

Cancer survivors had an overall higher incidence rate of cancer than the general population of North Portugal, although that difference fades when only metachronous SPC are considered. The 5-year cumulative risk of developing a SPC was 3.0%, and reached nearly 5.0% among patients with FPC associated with lower risk of death.

The incidence rates of cancer were approximately 30% higher among cancer survivors, but similar to the observed in the general population when only the metachronous SPC were considered. The latter result is in agreement with a previous Finish study (SIR=0.99; 95% CI: 0.95-1.03) [12], whereas higher incidence rates of metachronous SPC were observed in Australia (SIR=1.27; 95% CI: 1.25-1.29) [13], France (SIR=1.36; 95% CI: 1.35-1.38) [14], Japan (SIR=1.21; 95% CI: 1.19-1.23) [15] and USA (SIR=1.14; 95% CI: 1.14-1.15) [5], and lower rates were reported in Danish (SIR=0.91; 95% CI: 0.89-0.93) [16], UK (SIR=0.77; 95% CI: 0.75-0.79) [17] and Italian (SIR=0.93; 95% CI: 0.90-0.96) [18] studies. The heterogeneity of these results may reflect different patterns of cancer risk across populations and periods analysed, as well as the use of distinct definitions of SPC and synchronous tumours (intervals ranging from two months up to one year after the diagnosis of the FPC) and differences in the length of follow-up.

Including synchronous SPC in the analyses allowed the comparison of incidence rates since the diagnosis of the FPC, which is seldom presented in other population-based studies [18], and the assessment of the effect of diagnosis anticipation in the incidence rates throughout the follow-up. In our study, more than one quarter of the SPC were synchronous tumors, reflecting the strong influence of common diagnostic and staging procedures performed during the clinical management of the FPC [19, 20] which contributed to an increased number of SPC diagnoses that otherwise would had not been identified soon after the diagnosis of the FPC. Since the FPC topographies with the highest incidence rates of SPC in the first two months corresponded to the lowest incident rates in the remaining 58 months of analysis, excluding the synchronous SPC might have contributed to an underestimation of the incidence rates after the first two months. This tendency for anticipation of the diagnosis of a SPC had already been identified in previous studies, where 20–30% of all SPC diagnosed in the first five years were identified within two months of the incidence date of the FPC [16, 18]. This phenomenon is analogous to the expected trend of the

incidence rate after a screening test, with a strong increase at the beginning (synchronous FPC), when prevalent cases are identified through anticipation of cancer diagnosis, followed by a decrease due to the lack of diagnosis of cancers already identified; afterwards a smooth slope of further increase until the usual incidence levels are reached again [21]. One example that illustrates the impact of excluding a high number of synchronous tumors in the quantification of metachronous SIR, was observed in the UK study [17], which reported lower SIR due to considering one of the largest synchronous periods (12 months).

Several reports had documented that cancer survivors with a more recent diagnosis had a higher SIR of SPC than those diagnosed in earlier years [13, 15]. Although the reasons for those differences are not yet completely understood, cancer screening has been increasing during the past decades [22] and is more frequent among cancer survivors than the general population [23], which may result in higher SPC incidence rates in more recent years.

Prostate cancer survivors had lower incidence rate of cancer than the general population, when analysing the whole follow-up period, in accordance to what was observed in other settings [5, 13, 18]. A possible explanation for those findings is the high proportion of prostate cancers diagnosed by screening, which is more likely among individuals with higher educational and socio-economic status, and consequently with a healthier profile than the general population [24, 25].

Several studies have documented higher metachronous cancer incidence rates among female breast cancer survivors than in general population [5, 13-15], essentially due to tighter medical surveillance [20], a strong link between hormonal-related cancers [26] and a genetic predisposition (such as BRCA1 and BRCA2 syndromes) [27, 28]. However, in our study the rates in female breast cancer survivors were similar to the observed in general population; a plausible explanation for this discrepancy is the high proportion (22%) of synchronous SPC that we observed in breast cancer survivors, reflecting the anticipation of cancer diagnoses. When considering both synchronous and metachronous SPC, the observed SIR was 1.09 (95% CI: 0.91-1.29), which is closer to the observed in other studies [5]. Additionally, since a high proportion of female breast cancers are diagnosed by screening and women adhering to screening tend to be more educated than the general population [29], we may hypothesize that a large proportion of these female cancer survivors had

a healthier behaviour than the general population and, consequently, a lower incidence rate of a SPC.

Women with a lung FPC had a higher cancer incidence rate than the general population, when considering the entire follow-up period, although among men there were no significant differences. A lower competing risk of death among women than in men with lung cancer [30] may contribute to the differences observed. However, since in Portugal women are at an earlier stage of the tobacco epidemic than men [31, 32], this may reflect mostly a more pronounced contrast between women with lung cancer and those from the general population regarding the exposure to risk factors such as smoking.

To our knowledge, this was the first study to estimate the 5-year cumulative risk of developing a subsequent cancer among cancer survivors in Portugal. The 5-year cumulative incidence estimates were lower than those from the SEER, which ranged between 2.8% and 8.9%, respectively for lung and bladder FPC [5]. However, our results show that in North Portugal, as in other settings, SPC should be regarded as a problem commonly encountered in routine medical practice rather than a rare and unusual event to be described in case reports. Moreover, data on the cumulative incidences of SPC provides local clinicians with a benchmark to estimate the probability of cancer survivors developing another cancer within five years.

Despite the strengths of using data from a population-based cancer registry, constituting an important piece of information for understanding the burden of SPC in North Portugal, some limitations need to be discussed. We only presented the overall SIR of SPC across the most frequent FPC, due to the low number of SPC in strata of less frequent FPC, precluding the identification of frequent FPC-SPC pairs, which are a useful starting point for investigating possible shared etiologies and mechanisms of carcinogenesis; this may be improved in future studies with larger samples. Survival is already high for several cancers, and a longer follow-up is needed for a more comprehensive understanding of the burden of SPC among cancer survivors. The completeness of registration of SPC may be higher than for FPC because cancer survivors have contacted with the cancer registry sources when the FPC was identified, which could contribute to an overestimation of SIR; however, the completeness of the registry is high [33], and this is not expected to have a major impact in the SIR estimates. On the other hand, in patients already being

followed a new primary cancer may be confused with recurrence, remaining unregistered; this is more likely to have occurred, depending on the procedures implemented in each source of data for the registry, contributing to an underestimation of the number of SPC.

In conclusion, cancer survivors had higher incident rates of cancer that the general population, especially due to diagnoses in the first months following the FPC. Nevertheless, after this period SPC remain frequent events among cancer survivors, and constitute an important dimension of the burden of cancer survivorship. This needs to be taken into account when defining strategies for surveillance, prevention and counseling.

References

1. Araujo, F., et al., *Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980-2010).* Eur J Prev Cardiol, 2013.
2. De Angelis, R., et al., *Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study.* Lancet Oncol, 2014. **15**(1): p. 23-34.
3. Ferlay, J., et al., *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide*, 2013, Lyon, France: International Agency for Research on Cancer.
4. Pacheco-Figueiredo, L. and N. Lunet, *Health status, use of healthcare, and socio-economic implications of cancer survivorship in Portugal: results from the Fourth National Health Survey.* J Cancer Surviv, 2014.
5. Curtis, R., et al., *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000.* National Cancer Institute, NIH Publ., 2006. **No. 05-5302.**
6. Travis, L.B., *The epidemiology of second primary cancers.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(11): p. 2020-6.
7. Rosso, S., et al., *Multiple tumours in survival estimates.* Eur J Cancer, 2009. **45**(6): p. 1080-94.
8. Pacheco-Figueiredo, L., et al., *Evaluation of the frequency of and survival from second primary cancers in North Portugal: a population-based study.* Eur J Cancer Prev, 2013. **22**(6): p. 599-606.
9. *International rules for multiple primary cancers (ICD-0 third edition).* Eur J Cancer Prev, 2005. **14**(4): p. 307-8.
10. Howe, H.L., *A review of the definition for multiple primary cancers in the United States*2003: Springfield: North American Association of Central Cancer Registries.
11. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2006.
12. Teppo, L., E. Pukkala, and E. Saxen, *Multiple cancer--an epidemiologic exercise in Finland.* J Natl Cancer Inst, 1985. **75**(2): p. 207-17.
13. Youlden, D.R. and P.D. Baade, *The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study.* BMC Cancer, 2011. **11**: p. 83.
14. Jegu, J., et al., *The effect of patient characteristics on second primary cancer risk in France.* BMC Cancer, 2014. **14**: p. 94.
15. Tabuchi, T., et al., *Incidence of metachronous second primary cancers in Osaka, Japan: update of analyses using population-based cancer registry data.* Cancer Sci, 2012. **103**(6): p. 1111-20.
16. Storm, H.H., et al., *Multiple primary cancers in Denmark 1943-80; influence of possible underreporting and suggested risk factors.* Yale J Biol Med, 1986. **59**(5): p. 547-59.
17. Coleman, M.P., *Multiple primary malignant neoplasms in England and Wales, 1971-1981.* Yale J Biol Med, 1986. **59**(5): p. 517-31.
18. Crocetti, E., E. Buiatti, and P. Falini, *Multiple primary cancer incidence in Italy.* Eur J Cancer, 2001. **37**(18): p. 2449-56.
19. Liu, L., et al., *Prevalence of multiple malignancies in the Netherlands in 2007.* Int J Cancer, 2011. **128**(7): p. 1659-67.
20. Nielsen, S.F., B.G. Nordestgaard, and S.E. Bojesen, *Associations between first and second primary cancers: a population-based study.* CMAJ, 2012. **184**(1): p. E57-69.
21. Morrison, A., *Screening in Chronic Disease.*1985: New York, Oxford University Press.
22. *Cancer Trends Progress Report - 2011/2012 Update.* National Cancer Institute, NIH Publ., 2012.
23. Corkum, M., et al., *Screening for new primary cancers in cancer survivors compared to non-cancer controls: a systematic review and meta-analysis.* J Cancer Surviv, 2013. **7**(3): p. 455-63.
24. Rundle, A., et al., *A prospective study of socioeconomic status, prostate cancer screening and incidence among men at high risk for prostate cancer.* Cancer Causes Control, 2013. **24**(2): p. 297-303.

25. Morgan, R.M., et al., *Socioeconomic variation and prostate specific antigen testing in the community: a United Kingdom based population study*. J Urol, 2013. **190**(4): p. 1207-12.
26. Henderson, B.E. and H.S. Feigelson, *Hormonal carcinogenesis.* Carcinogenesis, 2000. **21**(3): p. 427-33.
27. Thompson, D. and D.F. Easton, *Cancer Incidence in BRCA1 mutation carriers.* J Natl Cancer Inst, 2002. **94**(18): p. 1358-65.
28. Mavaddat, N., et al., *Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE.* J Natl Cancer Inst, 2013. **105**(11): p. 812-22.
29. Dourado, F., H. Carreira, and N. Lunet, *Mammography use for breast cancer screening in Portugal: results from the 2005/2006 National Health Survey.* Eur J Public Health, 2013. **23**(3): p. 386-92.
30. Shafer, D. and K. Albain, *Lung cancer outcomes in women.* Semin Oncol, 2009. **36**(6): p. 532-41.
31. Alves, L., J. Bastos, and N. Lunet, *Trends in lung cancer mortality in Portugal (1955-2005).* Rev Port Pneumol, 2009. **15**(4): p. 575-87.
32. Carreira, H., et al., *Trends in the prevalence of smoking in Portugal: a systematic review.* BMC Public Health, 2012. **12**: p. 958.
33. Castro, C., et al., *Assessing the completeness of cancer registration using suboptimal death certificate information.* Eur J Cancer Prev, 2012. **21**(5): p. 478-9.

PAPER IV

Frequency and survival of second primary cancers in North Portugal – a population-based assessment

Eur J Cancer Prev 2013 Nov; 22(6):599-606

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

Luís Pacheco-Figueiredo[a,b,d], Luís Antunes[c], Maria José Bento[c] and Nuno Lunet[a,b]

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.

European Journal of Cancer Prevention 2013, 22:599–606

Keywords: epidemiology, neoplasms, population-based cancer registry, second primary cancer

[a]Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, [b]Institute of Public Health, University of Porto (ISPUP), [c]North Region Cancer Registry (RORENO), Portuguese Oncology Institute and [d]Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal

Correspondence to Nuno Lunet, MPH, PhD, Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
Tel: +351 225513652; fax: +351 225513653; e-mail: nlunet@med.up.pt

Received 22 October 2012 Accepted 12 January 2013

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,

DOI: 10.1097/CEJ.0b013e32835f3bbc

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 (RORENO) 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 EUROCARE (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.

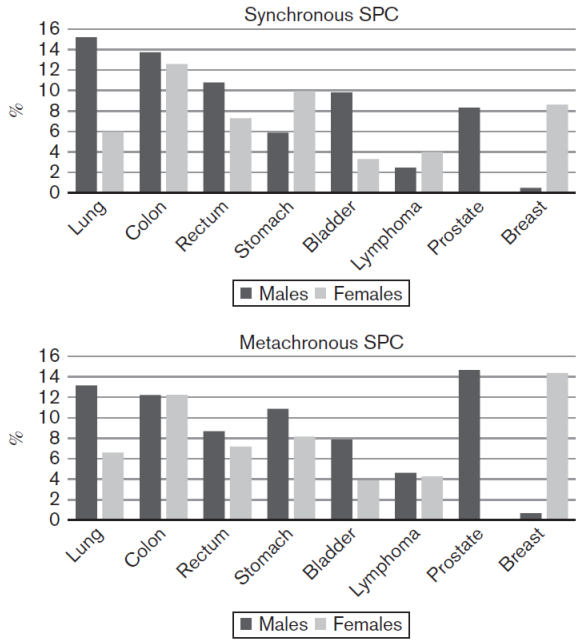
The median age at diagnosis of the 1607 SPCs was 68.9 years, 58.6% ($n = 942$) were men, and the median time between the diagnoses of the FPC and SPC was 21.7 months. The five most frequent SPC topographies were colon ($n = 200$; 12.5%), lung ($n = 171$; 10.7%), stomach ($n = 149$; 9.3%), rectum ($n = 134$; 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 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).

Fig. 1



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

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

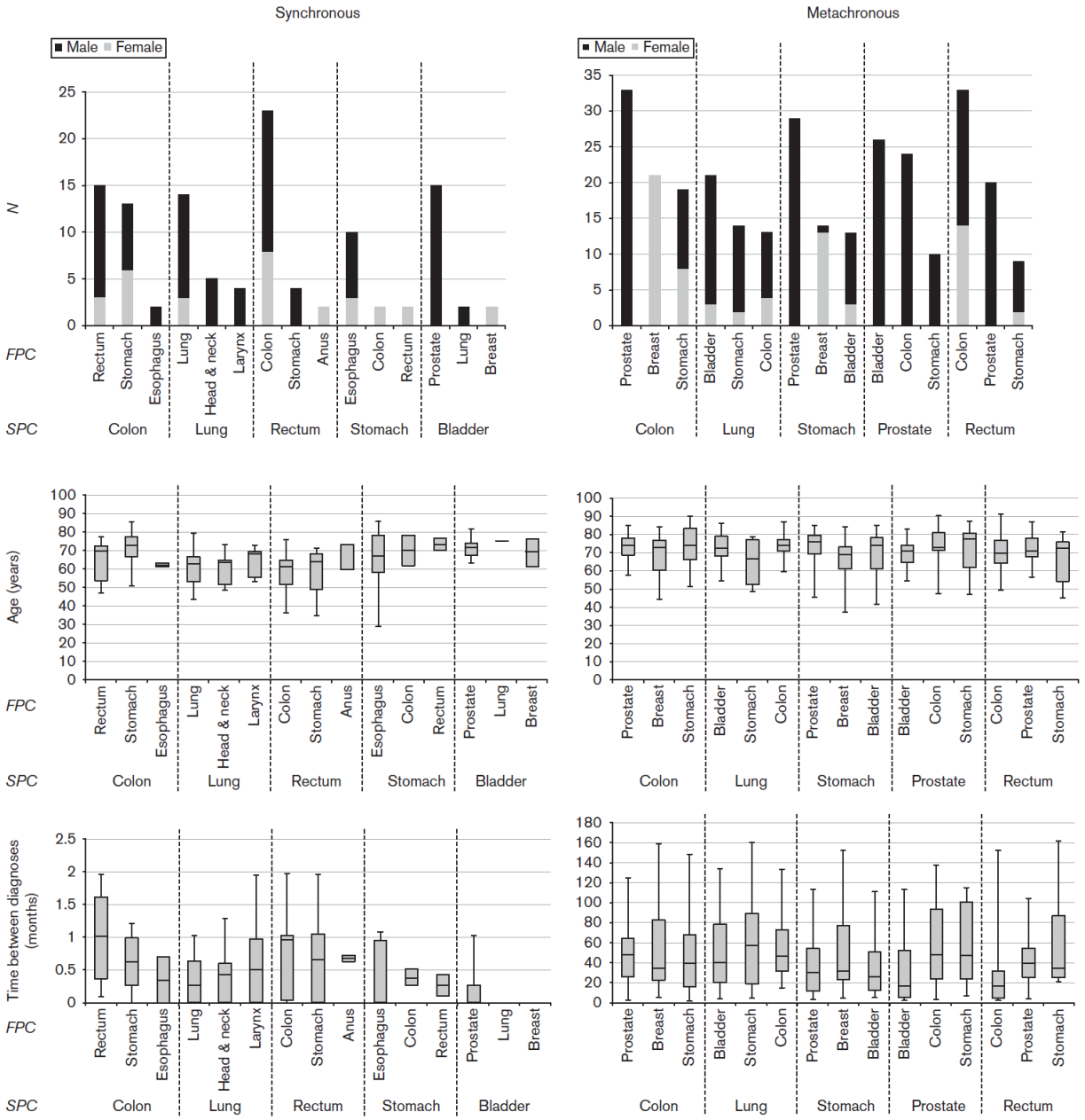
The 5-year survival of all SPCs was 46.1% [95% confidence interval (CI): 43.7–48.6]; it was 47.4% (44.6–50.1) for the metachronous SPCs and 41.7% (36.5–46.8) for the synchronous SPCs. The 5-year survival was lower among the synchronous SPCs for colon (36.2 vs. 50.3%) and prostate (29.4 vs. 71.0%) cancers;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

[a]Only the 10 most frequent topography/morphology groups were listed individually.
[b]Colon – ICD10: C18, lung: C34, rectum: C20, stomach: C16, bladder: C67, prostate: C61, head and neck: C0.0–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.
[a]Only the five most frequent topography/morphology groups were listed individually.
[b]FPC 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 (Youlden 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).

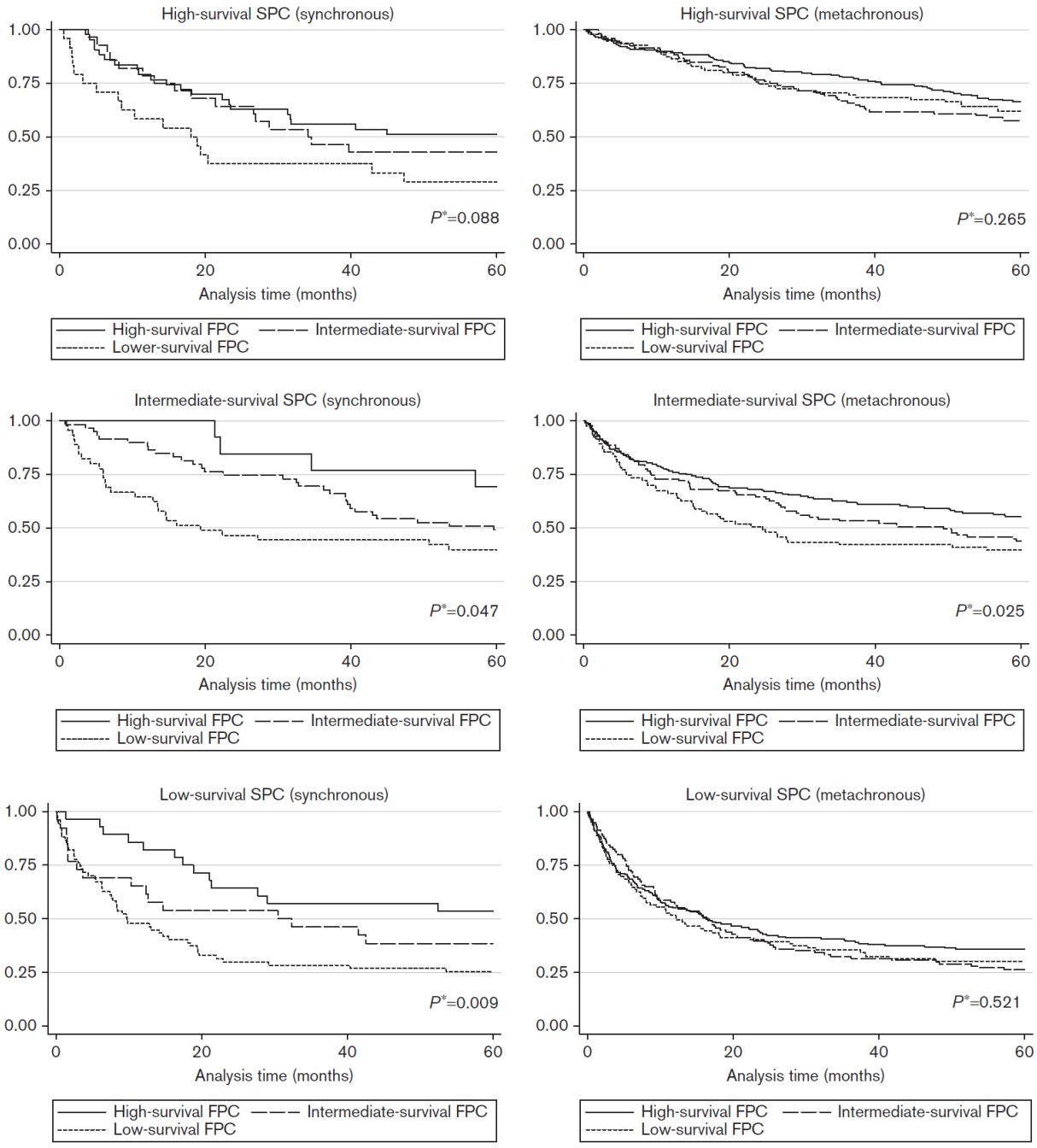
The difference in the frequency of SPCs observed across the cancer registries also depends on the overall and cancer-specific incidence and survival in each setting. In North Portugal, the age-standardized (World reference population) incidence of cancer (249.0/100 000) [Registo Oncologico Regional do 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 EUROCARE 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, 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 (Youlden 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)

[a]Proportion of each topography among all multiple primary tumors.
[b]Number of identified multiple primary tumors and its proportion among the incident cancer cases.
[c]Second 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.

Acknowledgements

L.F. received a grant from the Fundação para a Ciência e a Tecnologia (SFRH/SINTD/60124/2009).

Conflicts of interest

There are no conflicts of interest.

References

Allender S, Scarborough P, Peto V, Rayner M (2008). *European cardiovascular disease statistics*. Oxford: British Heart Foundation.

Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estéve J, *et al.* (1995). *Survival of cancer patients in Europe. The EUROCARE Study.* **Vol. 132**: Lyon: International Agency for Research on Cancer: IARC Scientific Publications.

Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, *et al.* (2008). Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* **9**:730–756.

Curtis R, Freedman DM, Ron E, Ries LA, Hacker DG, Edwards BK, *et al.* (2006). *New malignancies among cancer survivors: SEER cancer registries, 1973–2000. No. 05-5302.* Bethesda, MD: National Cancer Institute, NIH Publishers.

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). *GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 102010.* Lyon, France: International Agency for Research on Cancer.

Francisci S, Capocaccia R, Grande E, Santaquilani M, Simonetti A, Allemani C, *et al.* (2009). The cure of cancer: a European perspective. *Eur J Cancer* **45**:1067–1079.

Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P (2008). Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* **122**:155–164.

Heinavaara S, Hakulinen T (2002). Parametric mixture model for analysing relative survival of patients with multiple cancers. *J Cancer Epidemiol Prev* **7**:147–153.

Heinavaara S, Teppo L, Hakulinen T (2002). Cancer-specific survival of patients with multiple cancers: an application to patients with multiple breast cancers. *Stat Med* **21**:3183–3195.

Heron DE, Komarnicky LT, Hyslop T, Schwartz GF, Mansfield CM (2000). Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. *Cancer* **88**:2739–2750.

Holmberg L, Adami HO, Ekbom A, Bergstrom R, Sandstrom A, Lindgren A (1988). Prognosis in bilateral breast cancer. Effects of time interval between first and second primary tumours. *Br J Cancer* **58**:191–194.

International Agency for Cancer Research (IARC). Cancer Incidence in Five Continents (1999). Available at: *http://ci5.iarc.fr/CI5plus/ci5plus.htm* [Accessed 30 December 2012].

Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, *et al.* (1995). *SEER Cancer Statistics Review 1973–1992: tables and graphs.* Bethesda: NIH Publishers. pp. 96–2789.

Liu L, de Vries E, Louwman M, Aben K, Janssen-Heijnen M, Brink M, *et al.* (2011). Prevalence of multiple malignancies in the Netherlands in 2007. *Int J Cancer* **128**:1659–1667.

Liu YY, Chen YM, Yen SH, Tsai CM, Perng RP (2002). Multiple primary malignancies involving lung cancer-clinical characteristics and prognosis. *Lung Cancer* **35**:189–194.

Lunet N (2011). Helicobacter pylori infection in a region with high risk of gastric cancer. *Arq Med* **25**:213–216.

Lunet N, Pina F, Barros H (2004). Regional trends in Portuguese gastric cancer mortality (1984–1999). *Eur J Cancer Prev* **13**:271–275.

Neugut AI, Meadows AT, Robinson E (1999). *Multiple primary cancers. Introduction*. Philadelphia, PA: Lippincott Williams and Wilkins. pp. 1–12.

Nielsen SF, Nordestgaard BG, Bojesen SE (2012). Associations between first and second primary cancers: a population-based study. *CMAJ* **184**:E57–E69.

Pereira M, Peleteiro B, Capewell S, Bennett K, Azevedo A, Lunet N (2012). Changing patterns of cardiovascular diseases and cancer mortality in Portugal, 1980–2010. *BMC Public Health* **12**:1126.

Ries L, Harkins D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, *et al.* (2006). *SEER Cancer Statistics Review, 1975–2003. November 2005 SEER data submission, posted to the SEER web site 2006.* Bethesda, MD: National Cancer Institute.

RORENO. [North Region Cancer Registry 2007] Portuguese Oncology Institute of Porto, ed. Porto, 2011.

Rosso S, Angelis R, Ciccolallo L, Carrani E, Soerjomataram I, Grande E, *et al.* (2009a). Multiple tumours in survival estimates. *Eur J Cancer* **45**:1080–1094.

Rosso S, Ricceri F, Terracini L, Zanetti R (2009b). Methodological issues in estimating survival in patients with multiple primary cancers: an application to women with breast cancer as a first tumour. *Emerg Themes Epidemiol* **6**:2.

Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R (2009). EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* **45**:931–991.

Stewart B, Kleihues P (2003). *World cancer report.* Lyon: International Agency for Research on Cancer.

Travis LB (2002). Therapy-associated solid tumors. *Acta Oncol* **41**:323–333.

Travis LB (2006). The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev* **15**:2020–2026.

Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, *et al.* (2006). Cancer survivorship – genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst* **98**:15–25.

Youlden DR, Baade PD (2011). The relative risk of second primary cancers in Queensland Australia: a retrospective cohort study. *BMC Cancer* **11**:83.

Working Group Report (2005). International rules for multiple primary cancers (ICD-0 third edition). *Eur J Cancer Prev* **14**:307–308.

General discussion

7. General discussion

The present thesis provides an assessment of different dimensions of the burden of cancer survivorship in Portugal. We evaluated the health-status, the utilization of healthcare resources and the socio-economic condition among CS, concurrently with their exposure to risk factors for chronic diseases. Additionally, we assessed the dynamics of SPC incidence within the increasing number of survivors and the weight of secondary tumors among the incident cancer cases. Since each specific topic was addressed in the individual discussion of the four articles, along this general discussion we intend to integrate our main findings and to further discuss their public-health implications.

Measuring the frequency of cancer survivors in Portugal is an important step through the assessment of the burden associated with cancer survivorship, since the public health relevance of the results obtained from the evaluation of the other outcomes is dependent of the dimension of the problem within the population. Although there are data from the GLOBOCAN estimating the 5-year cancer prevalence [6], the latter underestimates the real number of cancer survivors, because it does not consider those with more than five years of follow-up, which are progressively more frequent due to higher survival rates. In Portugal, according to our results from the Fourth National Health Survey (2005-2006), there were approximately 220 000 cancer survivors, corresponding to 2.2% of the entire population. Eight years later, this frequency is expected to be higher due to the increasing trends observed for cancer incidence (age-standardized incidence rate raised from 198.0 per 100 000 in 2001 to 225.5 per 100 000 in 2007) and the better survival rates among the most frequent topographies [5-year age-standardized survival rates (1995-1999 to 2005-2009): lung (10.4% to 12.8%), colon (48.8% to 60.3%), breast (74.9% to 83.4%) and prostate (81.3% to 89.4%)] [80].

As the number of cancer survivors is estimated to continue rising, the concerns about their health-status, socio-economic situation and health-related behaviors become increasingly meaningful. Our results from the national survey showed that cancer survivors reported a worse perceived health-status and higher levels of short-term incapacity. We expect those individuals to have a poorer quality of life and had suffered changes in their employment status, as observed in other settings [11, 81-83]. A recent meta-analysis demonstrated that the unemployment rate among

cancer survivors is approximately 37% higher than the general population [75], which helps to elucidate the lower levels of family income after the cancer diagnosis that we found in our study. These results, together with the reported higher levels of health-related expenditures, may explain the long-term financial difficulties that we observed in our survey. Therefore, policy makers should consider setting up effective supportive programs to help the most socially disadvantaged cancer survivors, with the perspective of minimizing the financial difficulties and their negative impact in the quality of life and in the disease survival [72], namely through multidisciplinary interventions to enhance return-to-work rates [84].

Another important domain associated with cancer survivorship is the higher risk of comorbidities and new primary cancers development in comparison with the general population, which can result from the persistence of unhealthy lifestyle behaviors, or the maintenance of their effects, among other factors [13]. Therefore, locale-specific data characterizing modifiable health-related behaviors within cancer survivors and comparing them with the general population is useful to support health promotion activities in particular settings. The second study of this thesis, using data from an adult cohort representative of a city (Porto) in North Portugal, showed that the distribution of exposures to each of the most important risk factors for cancer and other chronic diseases among cancer survivors, tended to be similar to the observed in the subgroup of the general population with lower risk of cancer. Nevertheless, a high prevalence of risk factors for chronic diseases and a joint exposure to a large number of risk factors was observed within cancer survivors, showing that there is still an ample scope for these populations benefiting from lifestyle changes, which must be encouraged by clinicians and considered pertinent by public-health stake holders.

The need to establish health promotion interventions in order to minimize the incidence of SPC among cancer survivors becomes increasingly meaningful, as this fearsome event is turning dramatically more frequent [55]. In the third and fourth studies of this thesis, we assessed the frequency of SPC in North Portugal, concurrently with a description of the overall survival among the individuals with more than one tumor, as other important domains of the cancer survivorship.

The results showed that cancer survivors had an approximately 30% higher incidence rate of cancer than the general population, although that difference faded when only metachronous SPC

were considered. The incidence rate of SPC was more than 5-fold higher in the first two months of follow-up than in the period between two months and five years, reflecting the strong influence of common diagnostic and staging procedures, as suggested by the high frequency of gastro-intestinal and genito-urinary synchronous FPC-SPC pairs documented in the fourth study. Moreover, 3% of the patients with a FPC had a metachronous SPC diagnosed within five years, and the probability of having a SPC was nearly 5% among patients with a FPC with expectedly lower risk of death.

At a clinical level, these results highlight SPC as a problem increasingly encountered in routine medical practice rather than a rare and unusual event to be described in case reports. Additionally, they show there is a meaningful scope of benefit from encouraging the change of deleterious lifestyle behaviors among cancer survivors, in accordance with some results from the fourth study, which showed a high proportion of patients with lung SPC that had had previous bladder, head & neck or larynx cancers, illustrating the essential role of smoking as a main risk factor for both the FPC and the SPC. Besides cancer prevention, early diagnosis should also be a matter of concern among clinicians, by means of creating effective surveillance protocols, which might be based on data regarding the most frequent FPC-SPC pairs.

Finally, the survival analyzes within the fourth study had also provided clinically relevant results, as they demonstrated that the contribution of the FPC for the overall survival of SPC patients tends to decrease as the time between the diagnoses increases.

According to our fourth study, between 2002 and 2003, the proportion of SPC among the incident cancer cases registered in North Portugal was 4.0%, which was presumably underestimated due to the short operating time of the cancer registry [14]. Nowadays, it is expected that the real weight of the SPC among the new cancer cases diagnosed in North Portugal would be higher, owing to rising cancer incidence rates and survival improvement [80], in accordance with the proportions observed in other settings [18.0% in USA (2007) [55] and 6.3% in Europe (1995-1999) [14]]. The increasing number of SPC within the whole burden of cancer survivorship, highlight the public-health relevance of this topic, because these individuals affected by more than one primary cancer are associated with an even higher risk of poorer physical and mental status [85], configuring a distinct subgroup among cancer survivors, to whom should be devoted increased attention.

Besides the rising number of SPC, other problems related to cancer survivors contribute to the increasing economic burden of this disease in almost every country [86]. In 2006, approximately 565 million euros were spent for cancer treatment in Portugal, representing 3.9% of the national budget with healthcare [79]. Nevertheless, these estimates did not consider the higher levels of healthcare consumption, apart from cancer treatment, as we documented in the first study of this thesis. In accordance with data from other settings [87], our results showed that cancer survivors had a higher frequency of medical consultations, medication consumption and blood pressure and cholesterol assessments, although more pronounced during the first stages of the disease; therefore the overall weight in health budget due to cancer survivorship is expected to be even higher. Moreover, data from other settings [78] projected an increase of more than 30% with the cost of cancer during the next decade, not only due to population changes, but also to a rise in the price of cancer treatment programs. This scenario poses demanding challenges for the policy makers in the following years, concerning the planning and allocation of resources, especially during a context of economic and financial crisis in Europe.

The results of this thesis highlight several challenges associated with survivorship, regarding not only economic issues, but also the health-status and quality of life of cancer survivors and their families. Primary care is well placed to address some of those challenges, as part of a comprehensive cancer care model that values many other important aspects of follow-up beyond the detection of recurrence, which has been classically considered the standard of care [88]. Primary-care physicians are well trained to deliver those different levels of survivorship care, because they are used to work with the physical, psychological, and social aspects of medicine, and are experts at delivering longitudinal chronic disease management [88]. Evidence suggests that comorbidities, prevention and screening are already well managed by the primary-care physicians in cancer patients and they can also give better support to their families [89, 90]. However, studies with patients have indicated they would welcome greater acknowledgement from their primary-care physicians regarding their diagnosis and treatments and a more integrated support with the hospital care [91].

The “survivorship care plans” (SCP’s), an individualized treatment summary and plan for ongoing care, was proposed as a valuable tool to aid in the management of these concerns, since it

contributes to a better coordination between health practitioners and ease their communication [13]. Many cancer treatment guidelines followed in different settings, suggest or recommend that every cancer patient must be provided with an SCP at the completion of their treatment [92]. However, although cancer survivors and their primary-care physicians were receptive to the concept of SCPs [93-95], the enthusiasm has been tempered by the realization that their implementation is resource-intensive [96-98] and the emerging evidence have only showed a few measurable benefits, such as higher levels of satisfaction among the survivors [92]. Thus, the long-term effect of SCPs on psychosocial, oncological and resource outcomes should continue to be thoroughly evaluated, as it is unlikely that a unique model will suit all survivors, cancer centers or tumor types. Research addressing these variables in a consistent manner is awaited.

Conclusions

8. Conclusions

The main conclusions of this thesis are:

- In the middle of the last decade (2005-2006) the estimated number of cancer survivors was already high in Portugal (approximately 220 000), with worse health-status, higher level of incapacity, more financial difficulties, and greater usage of healthcare services than the general population. The cancer incidence and survival trends point for an increase of this burden during the next decades;

- The distribution of the exposures to each of the most important risk factors for cancer and other chronic diseases among cancer survivors, tended to be similar to the observed in a subgroup of the general population with lower risk of cancer, despite there was still a high prevalence of risk factors for chronic diseases, demanding health promotion interventions in this specific population;

- Cancer survivors had higher incident rates of cancer that the general population, especially due to diagnoses in the first months following the FPC. Nevertheless, after this period SPC diagnoses remained frequent events among cancer survivors, and constitute an important dimension of the burden of cancer survivorship. This needs to be taken into account when defining strategies for surveillance, prevention and counseling;

- There was a considerable proportion of SPC (3.8%) in newly diagnosed cancer cases of North Portugal, in accordance with European estimates from cancer registries with similar operating time. The most common cancers in the general population were also frequent metachronous SPC, while the most frequent FPC were those with highest incidence and survival. The contribution of the FPC to the observed survival of SPC patients tended to decrease as the time between the diagnoses increases.

References

9. References

1. *World Population Prospects: The 2008 Revision.*, U.N.P. Division, Editor 2007, New York: United Nations.
2. Edwards, B.K., et al., *Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden.* Cancer, 2002. **94**(10): p. 2766-92.
3. Araujo, F., et al., *Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980-2010).* Eur J Prev Cardiol, 2013.
4. Allender S, S.P., Rayner M, Leal J, Luengo-Fernandez R, Gray A, *European cardiovascular disease statistics.* British Heart Foundation, 2008.
5. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.* Eur J Cancer, 2013. **49**(6): p. 1374-403.
6. Ferlay, J., et al., *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide*, 2013, Lyon, France: International Agency for Research on Cancer.
7. Bray, F., et al., *Global cancer transitions according to the Human Development Index (2008-2030): a population-based study.* Lancet Oncol, 2012. **13**(8): p. 790-801.
8. CDC and C.f.D.C.a. Prevention, *Surveillance of Demographic Characteristics and Health Behaviours Among Adult Cancer Survivors - Behavioral Risk Factor Surveillance System, United States, 2009*. Vol. 61. 2012: MMWR. 1-23.
9. Shi, Q., et al., *Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors.* Cancer, 2011. **117**(12): p. 2779-90.
10. Curtis, R., et al., *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000.* National Cancer Institute, NIH Publ., 2006. **No. 05-5302.**
11. Mols, F., et al., *Socio-economic implications of cancer survivorship: results from the PROFILES registry.* Eur J Cancer, 2012. **48**(13): p. 2037-42.
12. Meropol, N.J. and K.A. Schulman, *Cost of cancer care: issues and implications.* J Clin Oncol, 2007. **25**(2): p. 180-6.
13. Hewitt, M., et al., *From Cancer Patient to Cancer Survivor: Lost in Transition*2006: Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council. 536.
14. Rosso, S., et al., *Multiple tumours in survival estimates.* Eur J Cancer, 2009. **45**(6): p. 1080-94.
15. Travis, L.B., et al., *Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors.* Nat Rev Clin Oncol, 2013. **10**(5): p. 289-301.
16. Travis, L.B., *The epidemiology of second primary cancers.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(11): p. 2020-6.
17. Khuri, F.R., et al., *The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(8): p. 823-9.
18. Meyerhardt, J.A., et al., *Physical activity and survival after colorectal cancer diagnosis.* J Clin Oncol, 2006. **24**(22): p. 3527-34.
19. Holmes, M.D., et al., *Physical activity and survival after breast cancer diagnosis.* JAMA, 2005. **293**(20): p. 2479-86.
20. Do, K.A., et al., *Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States).* Cancer Causes Control, 2003. **14**(2): p. 131-8.
21. World Cancer Research Fund, ed. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* Washington DC: AICR2007, American Institute for Cancer Research.
22. *Global Status Report on Non-Communicable Diseases 2010.*, WHO.
23. Forman, D., et al. *Cancer Incidence in Five Continents, Vol. X*. 2013. **Vol. X**.

24. Omran, A.R., *The epidemiologic transition: a theory of the epidemiology of population change. 1971.* Milbank Q, 2005. **83**(4): p. 731-57.
25. Parkin, D.M., F.I. Bray, and S.S. Devesa, *Cancer burden in the year 2000. The global picture.* Eur J Cancer, 2001. **37 Suppl 8**: p. S4-66.
26. *Registo Oncologico Nacional.* Instituto Português de Oncologia de Francisco Gentil, 2007.
27. *Registo Oncologico Nacional.* Instituto Português de Oncologia de Francisco Gentil, 2006.
28. *Registo Oncologico Nacional.* Instituto Português de Oncologia de Francisco Gentil, 2001.
29. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2003.
30. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2007.
31. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2006.
32. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2004.
33. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2002.
34. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2005.
35. RORENO, *Registo Oncologico Regional do Norte.* IPO - Porto, 2001.
36. Coleman, M.P., et al., *Cancer survival in five continents: a worldwide population-based study (CONCORD).* Lancet Oncol, 2008. **9**(8): p. 730-56.
37. De Angelis, R., et al., *Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study.* Lancet Oncol, 2014. **15**(1): p. 23-34.
38. von Karsa, L., et al., *Cancer screening in the European Union - Report on the implementation of the Council Recommendation on cancer screening*, E. Commission, Editor 2008: Luxembourg.
39. Kapiteijn, E., H. Putter, and C.J. van de Velde, *Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands.* Br J Surg, 2002. **89**(9): p. 1142-9.
40. Junor, E.J., D.J. Hole, and C.R. Gillis, *Management of ovarian cancer: referral to a multidisciplinary team matters.* Br J Cancer, 1994. **70**(2): p. 363-70.
41. Weitz, J., et al., *Impact of volume and specialization for cancer surgery.* Dig Surg, 2004. **21**(4): p. 253-61.
42. *National Cancer Institute. SEER Cancer Survival Statistics 1975–2010*. [cited 2014 09-10-2014]; Available from: http:// seer.cancer.gov/csr/1975_2007/.
43. RORENO, *Sobrevivência Global, Doentes diagnosticados em 2005-06 – Região Norte.* Registo Oncológico Regional do Norte, 2013. **Instituto Português de Oncologia do Porto, ed. Porto, 2013.** .
44. Mullan, F., *Seasons of survival: reflections of a physician with cancer.* N Engl J Med, 1985. **313**(4): p. 270-3.
45. Soerjomataram, I., et al., *Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions.* Lancet, 2012. **380**(9856): p. 1840-50.
46. Holmes, H.M., et al., *Chronic conditions and health status in older cancer survivors.* Eur J Intern Med, 2014. **25**(4): p. 374-8.
47. Carver, J.R., et al., *American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects.* J Clin Oncol, 2007. **25**(25): p. 3991-4008.
48. Ganz, P.A., et al., *Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study.* J Natl Cancer Inst, 2002. **94**(1): p. 39-49.
49. Massie, M.J., *Prevalence of depression in patients with cancer.* J Natl Cancer Inst Monogr, 2004(32): p. 57-71.
50. *National Cancer Institute. SEER Cancer Statistics Review, 1975–2007*. 2010; Available from: http:// seer.cancer.gov/csr/1975_2007/.
51. Krueger, H., D. McLean, and D. Williams, *The Prevention of Second Primary Cancers*. Progress in Experimental Tumor Research. Vol. 40. 2008: Karger.

52. *International rules for multiple primary cancers (ICD-0 third edition).* Eur J Cancer Prev, 2005. **14**(4): p. 307-8.
53. Weir, H.K., C.J. Johnson, and T.D. Thompson, *The effect of multiple primary rules on population-based cancer survival.* Cancer Causes Control, 2013. **24**(6): p. 1231-42.
54. Howe, H.L., *A review of the definition for multiple primary cancers in the United States*2003: Springfield: North American Association of Central Cancer Registries.
55. Mariotto, A.B., et al., *Multiple cancer prevalence: a growing challenge in long-term survivorship.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(3): p. 566-71.
56. Garber, J.E. and K. Offit, *Hereditary cancer predisposition syndromes.* J Clin Oncol, 2005. **23**(2): p. 276-92.
57. Travis, L.B., et al., *Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations.* J Natl Cancer Inst, 2006. **98**(1): p. 15-25.
58. Metcalfe, K., et al., *Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers.* J Clin Oncol, 2004. **22**(12): p. 2328-35.
59. Thompson, D. and D.F. Easton, *Cancer Incidence in BRCA1 mutation carriers.* J Natl Cancer Inst, 2002. **94**(18): p. 1358-65.
60. Thompson, D. and D. Easton, *Variation in cancer risks, by mutation position, in BRCA2 mutation carriers.* Am J Hum Genet, 2001. **68**(2): p. 410-9.
61. Kirchhoff, T., et al., *BRCA mutations and risk of prostate cancer in Ashkenazi Jews.* Clin Cancer Res, 2004. **10**(9): p. 2918-21.
62. Shinagare, A.B., et al., *Hereditary cancer syndromes: a radiologist's perspective.* AJR Am J Roentgenol, 2011. **197**(6): p. W1001-7.
63. Lynch, H.T. and A. de la Chapelle, *Hereditary colorectal cancer.* N Engl J Med, 2003. **348**(10): p. 919-32.
64. Anand, P., et al., *Cancer is a preventable disease that requires major lifestyle changes.* Pharm Res, 2008. **25**(9): p. 2097-116.
65. World Health Organization (WHO), ed. *Guidelines for Controlling and Monitoring the Tobacco Epidemic*. WHO Tobacco or Health Programme1997.
66. IARC. *Infections - Infections and Cancer Epidemiology Group*. 15-10-2014].
67. de Martel, C., et al., *Global burden of cancers attributable to infections in 2008: a review and synthetic analysis.* Lancet Oncol, 2012. **13**(6): p. 607-15.
68. Berrington de Gonzalez, A., et al., *Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries.* Lancet Oncol, 2011. **12**(4): p. 353-60.
69. Sill, H., et al., *Therapy-related myeloid neoplasms: pathobiology and clinical characteristics.* Br J Pharmacol, 2011. **162**(4): p. 792-805.
70. Davies, C., et al., *Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials.* Lancet, 2011. **378**(9793): p. 771-84.
71. Meropol, N.J., et al., *American Society of Clinical Oncology guidance statement: the cost of cancer care.* J Clin Oncol, 2009. **27**(23): p. 3868-74.
72. Sullivan, R., et al., *Delivering affordable cancer care in high-income countries.* Lancet Oncol, 2011. **12**(10): p. 933-80.
73. Ward, E., et al., *Association of insurance with cancer care utilization and outcomes.* CA Cancer J Clin, 2008. **58**(1): p. 9-31.
74. Weinfurt, K.P., *Value of high-cost cancer care: a behavioral science perspective.* J Clin Oncol, 2007. **25**(2): p. 223-7.
75. de Boer, A.G., et al., *Cancer survivors and unemployment: a meta-analysis and meta-regression.* JAMA, 2009. **301**(7): p. 753-62.

76. de Boer, A.G., et al., *Work ability and return-to-work in cancer patients.* Br J Cancer, 2008. **98**(8): p. 1342-7.
77. Roelen, C.A., et al., *Sickness absence and full return to work after cancer: 2-year follow-up of register data for different cancer sites.* Psychooncology, 2011. **20**(9): p. 1001-6.
78. Mariotto, A.B., et al., *Projections of the cost of cancer care in the United States: 2010-2020.* J Natl Cancer Inst, 2011. **103**(2): p. 117-28.
79. Araujo, A., et al., *[Cost of cancer care in Portugal].* Acta Med Port, 2009. **22**(5): p. 525-36.
80. Allemani, C., et al., *Global surveillance of cancer survival 1995-2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2).* Lancet, 2014.
81. Torp, S., et al., *Change in employment status of 5-year cancer survivors.* Eur J Public Health, 2013. **23**(1): p. 116-22.
82. Yu, M., et al., *Employment experience of cancer survivors 2 years post-diagnosis in the Study of Cancer Survivors-I.* J Cancer Surviv, 2012. **6**(2): p. 210-8.
83. Mols, F., J.W. Coebergh, and L.V. van de Poll-Franse, *Health-related quality of life and health care utilisation among older long-term cancer survivors: a population-based study.* Eur J Cancer, 2007. **43**(15): p. 2211-21.
84. de Boer, A.G., et al., *Interventions to enhance return-to-work for cancer patients.* Cochrane Database Syst Rev, 2011(2): p. CD007569.
85. Andrykowski, M.A., *Physical and mental health status of survivors of multiple cancer diagnoses: findings from the National Health Interview Survey.* Cancer, 2012. **118**(14): p. 3645-53.
86. Guy, G.P., Jr., et al., *Economic burden of cancer survivorship among adults in the United States.* J Clin Oncol, 2013. **31**(30): p. 3749-57.
87. Robin Yabroff, K., et al., *Access to preventive health care for cancer survivors.* Am J Prev Med, 2013. **45**(3): p. 304-12.
88. Watson, E.K., et al., *Cancer survivorship: the impact on primary care.* Br J Gen Pract, 2011. **61**(592): p. e763-5.
89. Khan, N.F., et al., *Cancer screening and preventative care among long-term cancer survivors in the United Kingdom.* Br J Cancer, 2010. **102**(7): p. 1085-90.
90. Khan, N.F., D. Mant, and P.W. Rose, *Quality of care for chronic diseases in a British cohort of long-term cancer survivors.* Ann Fam Med, 2010. **8**(5): p. 418-24.
91. Adams, E., et al., *Views of cancer care reviews in primary care: a qualitative study.* Br J Gen Pract, 2011. **61**(585): p. 173-82.
92. Brennan, M.E., et al., *Survivorship care plans in cancer: a systematic review of care plan outcomes.* Br J Cancer, 2014. **111**(10): p. 1899-908.
93. Brennan, M.E., et al., *Survivorship care after breast cancer treatment--experiences and preferences of Australian women.* Breast, 2011. **20**(3): p. 271-7.
94. Hewitt, M.E., et al., *Perspectives on post-treatment cancer care: qualitative research with survivors, nurses, and physicians.* J Clin Oncol, 2007. **25**(16): p. 2270-3.
95. Kantsiper, M., et al., *Transitioning to breast cancer survivorship: perspectives of patients, cancer specialists, and primary care providers.* J Gen Intern Med, 2009. **24 Suppl 2**: p. S459-66.
96. Brothers, B.M., et al., *Do survivorship care plans impact patients' evaluations of care? A randomized evaluation with gynecologic oncology patients.* Gynecol Oncol, 2013. **129**(3): p. 554-8.
97. Spain, P.D., et al., *Response to a treatment summary and care plan among adult survivors of pediatric and young adult cancer.* J Oncol Pract, 2012. **8**(3): p. 196-202.
98. Jefford, M., et al., *Development and pilot testing of a nurse-led posttreatment support package for bowel cancer survivors.* Cancer Nurs, 2011. **34**(3): p. E1-10.