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The PanCareSurFup Consortium: research and guidelines to improve lives for survivors of childhood cancer

by

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Abstract

Background

Second malignant neoplasms and cardiotoxicity are among the most serious and frequent adverse health outcomes experienced by childhood and adolescent cancer survivors (CCS) and contribute significantly to their increased risk of premature mortality. Due to differences in health care systems, language and culture across the continent, Europe has had limited success in establishing multi-country collaborations needed to assemble the numbers of survivors required to clarify the health issues arising after successful cancer treatment. PanCareSurFup is the first pan-European project to evaluate some of the serious long-term health risks faced by survivors.

Methods

The PanCareSurFup (PCSF) consortium pooled data from 13 data providers and involved 17 European countries to evaluate subsequent primary malignancies, cardiac disease and late mortality in survivors diagnosed between ages 0 and 20. Additionally, PCSF integrated radiation dosimetry to sites of second malignancies and to the heart, developed evidence-based guidelines for long-term care and for transition services, and disseminated results to survivors and the public.

Results

A single dataset comprising 115,596 incident cases of cancer diagnosed from 1940-2011 was created, including 83,333 five-year survivors. This forms the basis for cohort analyses of subsequent malignancies, cardiac disease and late mortality and case-control studies of subsequent malignancies and cardiac disease in five-year survivors.

Conclusions

PCSF delivered specific estimates of risk and comprehensive guidelines to help survivors and care-givers. The expected benefit is to provide every European childhood and adolescent cancer survivor with improved access to care and better long-term health. This paper sets out the overall rationale, methods and preliminary results of PanCareSurFup.

Introduction

Survival after childhood cancer continues to improve, and currently 80% of children diagnosed in developed countries survive for at least 5 years [1]. As estimated 300,000 EU citizens are alive and cured from childhood cancer [2], and their numbers will increase with advancing therapies. However, the toxicities of cancer treatments mean that many survivors face serious and life-threatening late effects that increase their risk of premature mortality and that add to the resources required from healthcare systems [3]. Several different strategies for the delivery of long-term follow-up care exist, with considerable variability in their delivery [4]. This raises important questions relating to the long-term risks that survivors face, the health care systems in place to anticipate and treat their late complications, and the long-term costs and potential savings to governments of their care.

Effective implementation of evidence-based clinical practice guidelines can lead to significant improvements in healthcare delivery, with potential to improve health outcomes and reduce healthcare costs by facilitating rational allocation of resources [5]. Some European countries do not have access to long-term follow-up (LTFU) guidelines, and others have been developed independently of each other, resulting in some discordant recommendations.

There are particular concerns relating to treatment for cancer diagnosed during childhood or adolescence. Organs are not yet fully developed, and may be more susceptible to damage from treatment. Possible genetic factors related to the occurrence of the first cancer could bring susceptibility to a second cancer. The smaller anatomic volume of children makes the scatter doses of radiotherapy more likely to affect healthy organs. Organ damage occurring early in life is likely to lead to significant organ dysfunction because of the additive effects of treatment toxicities coupled with the normal ageing process, and the longer follow-up time during which impairments can develop.

PanCareSurFup (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies, www.pancaresurfup.eu; 2011 – 2017) is a pan-European project funded by the EU to study some of the most serious late effects of cancer during childhood and to develop and promote guidelines for care and prevention. It originated in the PanCare network (www.pancare.eu) [6]. PanCareSurFup (PCSF) studies some of the most serious late effects -- cardiac disease and second malignancies – that can be life-threatening [7]. The third topic in PCSF is late mortality, defined as death occurring after five years from diagnosis. As childhood cancer is rare, and late effects rarer still, many of the previous European studies on late effects have enrolled relatively small numbers of survivors. PanCareSurFup has assembled the largest number of survivors to date, with the goal of providing

accurate estimates of risk for specific late effects, new guidelines and wide dissemination. The success of the consortium in merging detailed treatment information with radiation dosimetry, outcomes residing in cancer registries (second malignancies) and specially-collected clinical (cardiac) outcomes on a large scale, will set the standard for these studies. Furthermore, expanded studies into other late effects, e.g. PanCareLIFE (www.pancarelife.eu), can now be undertaken with confidence. PanCareLIFE is PanCare's second EU-funded consortium; it focusses on fertility, ototoxicity and quality of life and incorporates genetic and clinical studies (Byrne et al, 2018, submitted).

The PanCareSurFup (PCSF) consortium consisted of 8 Work Packages (WPs; Figure 1; Table 1). Following the establishment of a retrospectively-ascertained pan-European cohort of survivors of childhood cancer (WP1) with which to conduct cohort studies of second malignancies (WP4), cardiac disease (WP3) and late mortality (WP5), nested case-control studies within the cohort of second malignancies and cardiac disease were carried out. Individual patient radiation dosimetry (WP2) was calculated and detailed treatment information was collected for survivors included in the nested case-control studies only. Clinical follow-up guidelines (WP6) were designed for health care professionals, survivors and their families, including issues related to transition from paediatric to adult care. PanCareSurFup disseminated information (WP7) about the study to the general public, health professionals and survivor/parent groups. Management expertise to run the consortium resided within WP8.

The tasks and objectives of PCSF were as follows: To meet the needs for sufficient sample size and detailed information on cardiac disease, second malignancies, and late mortality, a dataset that was supra-national in scope, yet extensive in its information on individual patients, was necessary. Collecting and harmonizing these data was the first task of PanCareSurFup; these methods are described by Grabow et al [8]. A second task ran in parallel, namely a survey of European cancer registries to determine the availability and quantity of data on long-term survivors. The goal of radiation dosimetry was to establish the dose and location of radiotherapy for cases and controls enrolled in studies of cardiac disease and second malignancies [9]. The objectives of the cardiac study were to determine the incidence and absolute risk for symptomatic cardiac events in European survivors, and the treatment-related risk factors as well as confirming earlier identified risk factors and identifying new risk factors. PanCareSurFup's pooled studies allowed us to assess risks for further new primary cancers, particularly among survivors aged over 40 years. The initial focus was on cohort studies of second bone cancers and second soft tissue sarcomas, followed by nested case-control studies of both; a second focus is digestive and genitourinary carcinomas as second cancers because these are common cancers related to aging in the general population. The objectives of the

late mortality study within PCSF are to ascertain, validate (to the degree possible), and describe mortality occurring after 5-year survival, and the associated factors and to assess the comparability and quality of causes of death recorded in different countries. These data, and the scientific literature, are being incorporated into guidelines that aim to provide equal access to long-term follow-up care across Europe. The guidelines cover clinical practice, organization of long-term follow-up and transition care practices. This paper summarises the overall methods and provides some descriptive results from the PanCareSurFup consortium.

Methods

Pilot Feasibility Study

As a prelude to the PCSF consortium the PanCare network in 2008 carried out a survey of European countries to determine which cancer registries and institutions could contribute data to a new pan-European consortium [6]. Results indicated that current structures could provide retrospective data on approximately 80,000 childhood and adolescent cancer survivors, including data on second and subsequent cancer data, but limited treatment data; some registries could collect extensive treatment data and cardiac events with extra resources. This information was the basis for a successful application to the European Union's Seventh Framework Programme (FP7) and the PanCareSurFup project commenced in 2011 (Table 2).

PCSF data came from population-based cancer registries (Denmark, Finland, Iceland, Norway, Sweden, Slovenia, Switzerland, Great Britain, Hungary, the Netherlands), a single follow-up study (France) and a hospital-based study, and a multi-institutional hospital-based registry study (OTR-AIEOP, Italy). Discussions during the first year (2011-12) culminated in an agreed PCSF Study Protocol; all participants who were handling data obtained ethics approvals from their relevant authorities.

Quality Control Measures

The Study Protocol established a common variable list for the PCSF dataset, described the process and security arrangements for data collection and transmission, outlined the cohort and case-control methods and lists of eligible conditions and their codes [8]. The Study Protocol was intended to ensure that all data providers followed the same procedures. To provide practical advice and training to data providers in the cohort and case-control studies, including collection of satisfactory radiotherapy and chemotherapy information and secure data transfer, a one-day training meeting for data providers was held in 2012. As a result, the Study Protocol was extended by lengthy written documents to help data providers understand the acceptable types of cardiac disease and their validation, questionnaires for survivors, definitions of second malignancies, eligibility criteria for cases and controls, coding rules, lists of drugs and data collection forms.

Data Collection & Harmonization

The tasks included establishing a privacy policy, methods for data protection and software design and implementation, validation of PCSF data, transfer and encryption, an audit trail, and security. Each data provider uploaded their own data in their chosen format, into a secure on-line container. As the data was received a series of specified plausibility checks was conducted. Ultimately each

dataset was merged into the large PCSF single dataset required for all cohort studies. The datasets required for cohort studies were sent securely to Work Package Leaders for analysis [8]. For the case-control studies, the basic PCSF cohort file was transferred to partner University of Birmingham (UBHAM), where cases were identified and controls selected. UBHAM requested from the data providers details of treatment variables and cardiac data. All the case-control data was stored in UBHAM.

Survey of cancer registries and clinical studies

A second task ran in parallel with the formation of the PCSF cohort. This was to survey all 178 population-based European cancer registries to determine the availability and quantity of data on long-term childhood cancer survivors. Special emphasis was placed on collection of vital status, cause of death, and cardiac events. Also surveyed were 48 chairs of clinical trial studies and 1,700 members of SIOPE (the European branch of the International Society of Paediatric Oncology). The objective was to construct a <u>virtual</u> pan-European database of late effects to enable future access to retrospective and prospective data collection.

Based on these efforts, WP1 created three databases, one each for cancer registry and clinical data and the third for the PCSF cohort data. WP1 will produce an online tool to enable data entry and to search for late effects.

Cardiac disease

Eight data providers (France, Hungary, Italy (2 cohorts), the Netherlands, Slovenia, Switzerland and the United Kingdom) could identify and validate symptomatic cardiac events. Data for five cardiac events -- symptomatic heart failure, ischemia, pericarditis, valvular disease and arrhythmia -- were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). A method of validating CTCAE grades 3 and 4 was developed and published [10]. Strategies used to identify cardiac events included record linkage to population/hospital or regional based databases, and patient- and general practitioner-based questionnaires. Additional information to validate the cardiac events came from questionnaires and telephone queries, hospital records and records from general practitioners.

R2, Q3: INFORMATION ABOUT COMPLETENESS OF DATA ASCERTAINMENT, AND REMOVAL OF DUPLICATES, PLEASE

R2, Q4: INFORMATION ABOUT THE PERCENTAGE OF DATA FROM RECORD LINKAGE AND CLINICAL SOURCES, INCLUDING QUESTIONNAIRES.

The nested case-control study provided more precise estimates of risk, incorporating extensive treatment information and radiation dosimetry. Cases were survivors with symptomatic (CTCAE Grade 3-5) cardiac disease. Controls were drawn for comparison from the remainder of the cohort who did not develop cardiac disease.

For the radiation dosimetry studies, the anthropomorphic phantom was selected that most closely matched the survivor (both cases and controls) at the time of radiation treatment. The radiation therapy charts sent by data providers were interpreted using a locally-developed software programme which is an extension of a Treatment Planning System (TPS), Isogray®. This reproduced the radiotherapy received by the survivor. For each survivor, a whole-body dose distribution estimation was performed. The radiation dosimetry estimates were incorporated into case-control analyses to determine estimates of risk [11]. For PCSF the radiation dosimetrists built phantoms for inclusion in the Treatment Planning Systems; all the organs of each phantom were contoured (delineated), incorporating a range of variants for gender, age and corpulence combinations. The anthropometric phantoms identified 11 structures within the heart. The radiation dosimetry team in Paris reported on the impact of the organ-size variability on dose distribution within and outside the irradiation field [12]; developed mathematical models of radiation fluency outside of photon and electron beams from accelerators used in external radiation therapy, and validated the prediction of the models [13,14]. Because the radiotherapy dose remains the greatest source of error in estimating dose-response relationships, the dosimetrists provided recommendations for estimating these uncertainties [15].

Second malignant neoplasms

For studies of second malignancies in five-year survivors (diagnosed before age 20) PanCareSurFup pooled individual patient data from both population-based cancer registries and major treatment centres for which there was complete ascertainment of further new primary cancers. Data was contributed by 13 institutions in 12 European countries -- Denmark, Finland, France, Hungary, Iceland, Italy, the Netherlands, Norway, Slovenia, Sweden, Switzerland and the United Kingdom. To classify the first primary malignancy (FPN) data were coded according to the third revision of the International Classification of Disease Oncology (ICD-O-3) [16] and classified according to the

International Classification of Childhood Cancer (ICCC) [17]. The Check and Conversion Program of the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries [18] was used as needed. While benign brain tumours were included, some conditions, such as Langerhans cell histiocytosis, were excluded [19].

R2, Q3: INFORMATION ABOUT COMPLETENESS OF DATA ASCERTAINMENT,

Text from Fidler bone paper: The ascertainment method for SPNs varied by country (Supplementary Table 1, available online), but the following sources were utilized: population-based cancer registries, late effect clinics, questionnaires, medical records and hospital data, national mortality records, and health insurance registries. Validation of all SPNs was undertaken principally using pathology reports, although occasionally other definitive diagnostic reports were used.

 AND REMOVAL OF DUPLICATES,

R2, Q4: INFORMATION ABOUT THE PERCENTAGE OF DATA FROM RECORD LINKAGE AND CLINICAL SOURCES, INCLUDING QUESTIONNAIRES.

R2, Q5: HOW WERE SURVIVORS' ADDRESSES OBTAINED AND WHAT METHODS WERE USED TO FIND SURVIVORS LOST TO FOLLOW-UP? HOW ARE PRIVACY ISSUES HANDLED?

R2, Q7: NUMBER OF ORIGINAL CANCER TREATMENT RECORDS OBTAINED

Text from Fidler bone paper: Validation of all SPNs was undertaken principally using pathology reports, although occasionally other definitive diagnostic reports were used. To be included, SPNs had to be histologically different from the FPN and have a malignant behavior code

R2, Q9: FOR HOW MANY IS DETAILED CLINICAL DATA AVAILABLE?

Each case was matched to one control.

For each case and control an attempt was made to locate the original cancer treatment records by each institution. For survivors treated with radiotherapy the data providers made extensive searches to obtain copies of the simulation files and radiation charts [9]. The cumulative radiation dose to the site of the second tumour development for each case, and to the identical location within the matched control was individually estimated. All the information sent by data providers was used: histology/pathology reports, surgical/operative reports, reports of scans, treatment charts and/or treatment diagrams in the medical records to delineate the SPN contours.

General population rates were obtained from IARC's *Cancer Incidence in Five Continents Time Trends* [20]. Each country's population rates were used when this information was not available [19].

Late mortality

Late mortality data was contributed by population-based registries (Italy-population-based, Denmark, Finland, Iceland, Sweden, and Slovenia), from registries of 5-year survivors of childhood cancer (France, Hungary, the Netherlands, Switzerland and the UK) and from the Italian Off-Therapy Register. Only simple treatment data was available. Due to the wide time span of observation data providers classified causes of death according to different versions of ICD. The underlying cause of death and up to nine contributing causes were captured, when available. Validation of the causes of death was done on a sample using death certificates, hospital records and autopsy reports. Background death rates were obtained from *mortality.org*.

R2, Q3: INFORMATION ABOUT COMPLETENESS OF DATA ASCERTAINMENT, AND REMOVAL OF DUPLICATES, PLEASE

R2, Q4: INFORMATION ABOUT THE PERCENTAGE OF DATA FROM RECORD LINKAGE AND CLINICAL SOURCES, INCLUDING QUESTIONNAIRES.

R2, Q5: HOW WERE SURVIVORS' ADDRESSES OBTAINED AND WHAT METHODS WERE USED TO FIND SURVIVORS LOST TO FOLLOW-UP? HOW ARE PRIVACY ISSUES HANDLED?

R2, Q7: NUMBER OF ORIGINAL CANCER TREATMENT RECORDS OBTAINED

Guidelines, long-term follow-up & transition

As a first step an online questionnaire survey identified current long-term follow-up practice, and particularly the use of guidelines, in Europe. The aim was to aid in the development, dissemination and implementation of the new pan-European guidelines to be developed by PanCareSurFup. Responses were received from 31 countries (overall response rate 70%) including 24 of 26 EU countries contacted (92%) [21]. A collaboration was established with the International Guideline Harmonisation Group for late effects of childhood cancer (IGHG; www.ighg.org) to work together on late effects surveillance Separately, PCSF is developing surveillance guidelines for those late effects not yet addressed in the IGHG collaboration.

Results

The overall PCSF cohort consisted of 115,596 individuals, of whom 83,333 were 5-year survivors whose follow-up started at 5 years from diagnosis of a first malignancy. The balance were incident cases with follow-up since diagnosis, who either died before the 5-year mark, or were diagnosed less than 5 years before the closure of the PCSF study. The five-year survivor cohort formed the basis for the studies of cardiac disease, second malignancies and late mortality. The numbers included in each study varied with the relevant eligibility criteria.

Results from the questionnaire concerning the availability and quantity of data for long-term follow-up in Europe (WP1) were based on a 46% response rate from the population-based registries. Only 14% of responders had data on any late effect other than late death and subsequent malignancy. Of the responders 75% would require some dedicated funding for collection of these data, amounting to an estimated €38 million as an initial investment with €1.2 million annual running costs. From among the clinical recipients of the questionnaire, 35 surveys were completed from 20 European countries and Israel. Their databases held between 27 and 30,000 survivors (mean 3,350) each. Twelve data providers sent a total of 2,481 radiation therapy records of survivors who had been treated with radiotherapy for inclusion in the cardiac case-control studies.

After application of eligibility criteria, the PanCareSurFup cardiac cohort consisted of 59,915 5-year childhood cancer survivors whose first malignancies were diagnosed between 1940 and 2009 and classified according to ICCC-3 [17]. For studies of second and subsequent malignancies PCSF included 69,460 eligible five-year survivors, among whom 4,228 further new primary cancers developed. Results from the PCSF cohort studies of second malignancies of bone and soft tissue sarcoma show that, overall, survivors of a first cancer are 21.7 times more likely than the general population to be diagnosed with a subsequent bone cancer; survivors of certain first malignancies (retinoblastoma, bone sarcoma and soft tissue sarcoma) were most at risk of a bone cancer. However, the risk is small, with an overall absolute excess risk (AER) of 1.99; Figure 2) [19]. Soft tissue sarcomas developed most often among survivors whose first cancer was either retinoblastoma or Wilms tumour. The overall AER (absolute excess risk) for soft tissue sarcomas as SMNs was 2.5 (Table 3) [22].

For analysis of late mortality, the 5-year survivor cohort included 79,441 survivors. By the end of follow-up, 9,247 had died. The leading cause of death was the primary cancer, followed by a second cancer. Cancer and non-cancer deaths fell steeply with every decade of diagnosis up to the present.

However, late mortality exceeded the mortality expected throughout the whole observation period (Figure 3) [23].

The guidelines survey showed that their use varies considerably between and within countries. Guidelines in use include recommendations regarding physical LAEs (late adverse effects) for which surveillance should be performed (n=22, 96%), the specific groups of survivors at risk of the specified LAEs, and also the frequency at which surveillance of these LEAs should be carried out (both n=23, 100%). The survey highlighted the absence of recommendations in existing guidelines for many aspects of LTFU and revealed widespread recognition of the need for pan-European LTFU guidelines that include aspects of service delivery as well as the actual content of LTFU care [21].

A handbook from the guidelines group outlines the methodology involved in production of guidelines for surveillance of late effects [24]. In collaboration with IGHG five guidelines have been published so far, concerning surveillance for breast cancer, cardiomyopathy, premature ovarian insufficiency, male gonadotoxicity and thyroid cancer [25,26,27,5,28]. In addition to new guidelines for second CNS tumours, pituitary dysfunction, metabolic syndrome, vasculopathy, and others PCSF is working on guidelines for care delivery, the first of which concerns transition from paediatric to adult care [29].

The dissemination work package held two major conferences. The first, in 2011, in Dublin, Ireland, was the first Irish conference on survivorship. The conference succeeded in its aims of creating networks of survivors and parents: CanCare4Living (CC4L), the Irish association for survivors and families (www.cancare4living.ie) was one outcome. A second conference in Brussels in May 2016 targeted policy-makers, survivors and families and researchers (http://www.pancaresurfup.eu/pancaresurfup/pancaresurfup-is-hosting-a-european-conference/). Other dissemination activities included two bicycle races for survivors in Italy and a cruise event in Genoa; all were accompanied by workshops about long-term survival. WP7 also disseminated a series of brochures about PCSF in a number of European languages (http://boyneresearch.ie/brochures.html).

The Publication Committee maintains a list of publications and presentations, and has set in place a policy to ensure the highest publication quality. At the final PCSF meeting (Erice, October 2016), the General Assembly agreed that the Publication Committee would continue into the future and enlarge itself to become a Sustainability Committee. Furthermore, it was agreed that requests from outside investigators for use of the PCSF data would be welcome after 5 years has elapsed from the end of the study.

Communication is the key to keeping a large multi-national consortium working together; this was the work of the management group in WP8. Their tasks included creation of the periodic reports

and transmission of deliverables to the EU, as well as the request for the extension, progress monitoring of data delivery, and web site management. The PCSF consortium met twice yearly in person, in conjunction with PanCare meetings (http://www.pancare.eu/en/meetings/). Meetings were from 1 to 1 ½ days long. The data collection Work Packages met every two weeks over several years to discuss progress and solve problems. To support and guide the project included an Ethical and Scientific Advisory Board. WP8 handled the timely reporting of deliverables to the EU and the request for the extension.

Discussion

This paper has outlined the design and some results of the PanCareSurFup consortium. The design of PCSF addresses the long-standing problem of studies that include large numbers of cancer survivors with little clinical information versus studies that have detailed clinical data but on a relatively small number of survivors. By assembling the largest number of survivors to date, with detailed treatment data on cases and controls (this is the text referred to by R2, Q9), PCSF's design overcomes this problem. PCSF offers opportunities to evaluate time trends and dose-response effects and to assess outcomes of treatments on specific small subsets of survivors.

PanCareSurFup has demonstrated the feasibility of conducting a complex data-retrieval exercise across Europe. Cardiac disease is an outcome not routinely collected by cancer registries; yet PCSF has shown that it is possible to collect these complex data in a standardized fashion, and on a large cohort. PCSF has created sophisticated models of radiation exposure to healthy organs that were being used to develop more accurate estimates than would be possible without radiation dosimetry. The clinical data linked to detailed treatment information lead to more accurate estimates of risk, and to the emergence of new associations. Incorporation of this new information will contribute to development of more effective guidelines for prevention of both second malignancies and cardiac disease.

Results of the PCSF study should influence future treatment of childhood cancer in the direction of maintaining continuing improvements in survival, while becoming even less toxic. At the same time, follow up of the childhood cancer survivors must be improved to further reduce late deaths, especially those due to secondary neoplasms.

The PCSF Consortium has already had the very positive effects of raising standards for clinical long-term follow-up, and has spurred the establishment of clinical databases by partners for future use. Another result of this collaboration is the production of the Survivor Passport, now adopted by a number of European governments https://www.siope.eu/activities/joint-projects/survivorship-passport/). It also provides a structure on which to build future studies of new agents with currently unknown outcomes. The coverage of PCSF within Europe approximates a population-based study, since the majority of the data was derived from national cancer registries, thus reducing selection bias and allowing application of to a general population.

The results of the guideline survey highlighted the need for pan-European guidelines to inform clinicians, survivors / families and healthcare systems about how LTFU care should be delivered and what it should include. They have also provided an important baseline to inform subsequent dissemination and implementation of the guidelines across Europe. Significant gaps in knowledge of

late effects were identified and targeted for future research. Now based in PanCare this work will continue with the aim to establish European standards surveillance and counselling for late effects. Wide adoption of these guidelines will help reduce inequalities in access to care across Europe and within countries.

PCSF has many practical benefits for survivors and their health care professionals including providing information for counselling, educating and empowering survivors; development of clinical follow-up guidelines; assistance in preparing survivorship care plans, and providing educational material for health-care professionals. In addition, the information from PCSF will help with evaluating risks as well as benefits of proposals for future treatment protocols; with advising national health authorities in relation to groups at sufficiently high risk to consider recall for counselling, screening or other interventions; with identifying low-risk groups for whom self-management may be more appropriate; and providing risk stratification evidence to national health authorities to inform decisions regarding intensity of clinical follow-up.

The PCSF Consortium was limited to a small number of serious outcomes, while studying these in detail. Future studies (e.g., PanCareLIFE; www.pancarelife.eu) will be required to extend these methods to other outcomes. Potential biases may exist, for instance, extensive treatment data and radiation dosimetry is only available for survivors enrolled within the case-control studies of second malignancies and cardiac disease. Thus, results of the cohort analyses are limited to the available data in the cancer registries.

The information gathered for the PCSF cohort is a valuable resource which will help in future approaches to assemble large consortia using the existing PanCare network.

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FIGURES

FIGURE 1.

Flow chart showing the relationship between the components of PanCareSurFup.
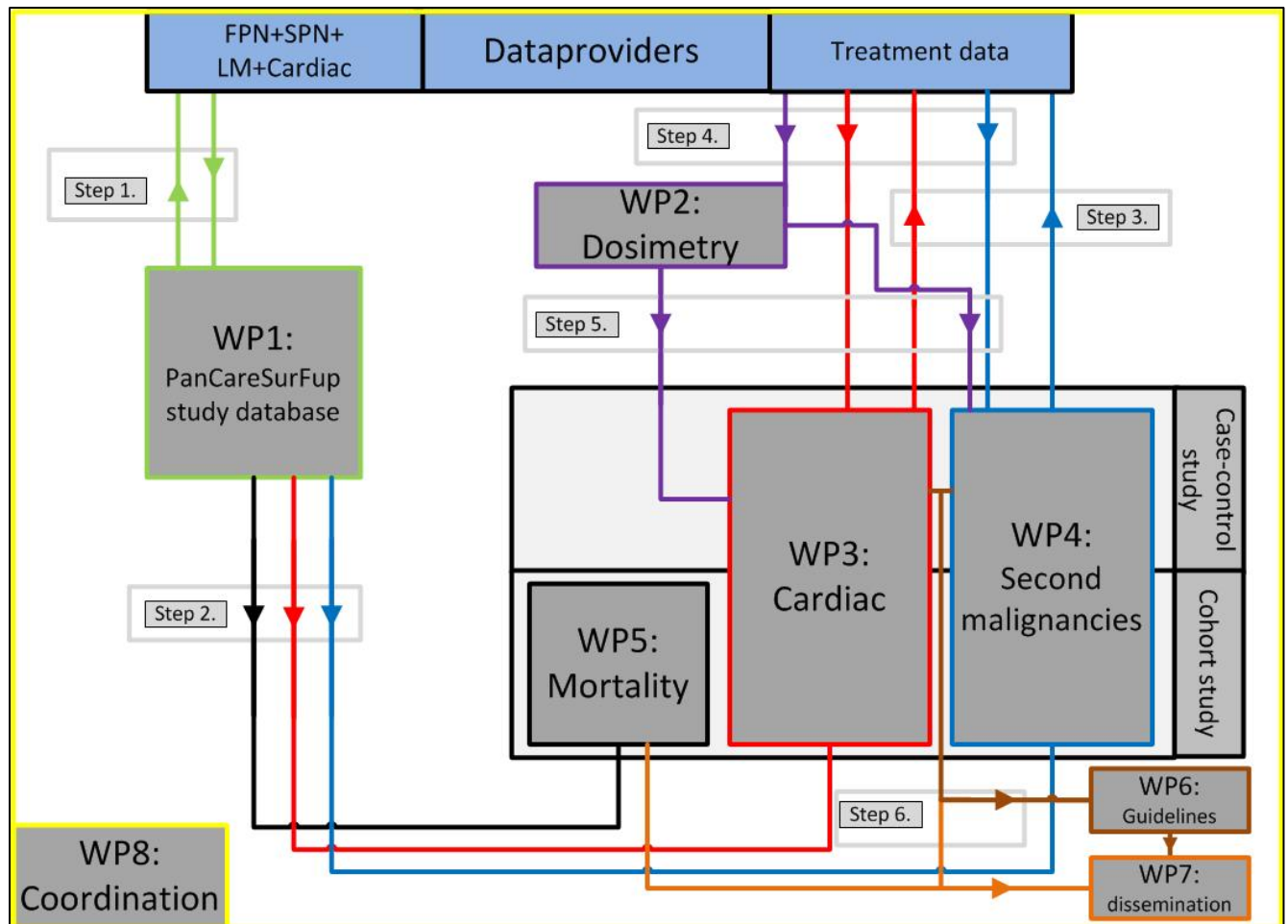
Figure 1. Legend. FPN=First primary neoplasm; SPN=Second primary neoplasms; WP=Work Package. Step1=Setup of PCSF database and data collection systems at UMC-Mainz; Step 2=WP1 sends out call for data; Step 3 ; Step 4 ; Step 5 ; Step 6=Results are used to assemble guidelines (WP6) and for dissemination (WP7)

Figure 2. Cumulative probability curves for bone subsequent primary neoplasms (SPNs). Data from the PanCareSurFup consortium. From Fidler et al, 2017, with permission.

Cumulative Incidence of a Bone SPN

Figure 3. Rates (%) of death among five-year survivors and background in the European

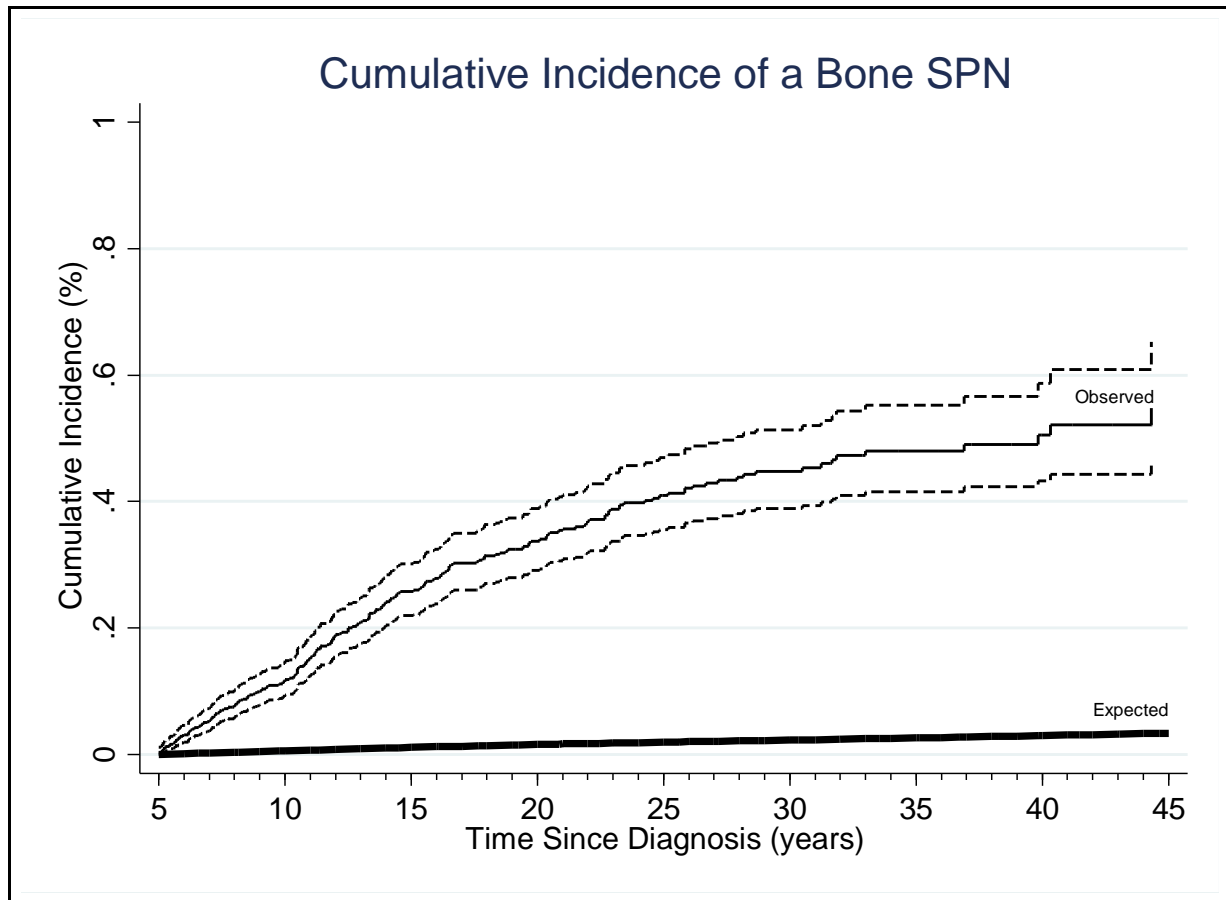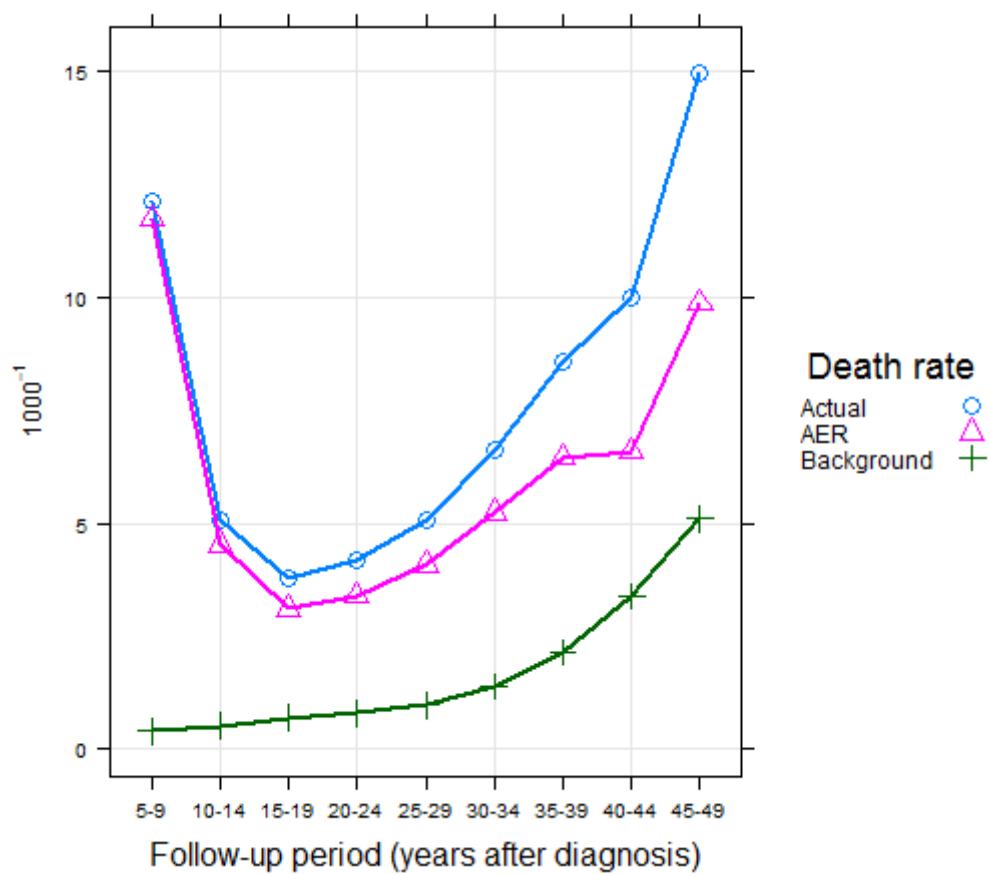PanCareSurFup late mortality cohort (AER=absolute excess risk)

TABLES

TABLE 1. List of Work Packages in PanCareSurFup

WP no.	Name of WP	WP Leader	Institution
1.	Data collection & harmonization	Desiree Grabow	UMC-Mainz, Germany
2	Radiation dosimetry	Florent de Vathaire	Institut Gustave Roussy, Paris, France
3.	Cardiac disease	Leontien Kremer	AMC, Amsterdam, Netherlands
4.	Second malignant neoplasms	Mike Hawkins	University of Birmingham. UK
5.	Late mortality	Stanislaw Garwicz	Lund University, Sweden
6	Guidelines, long-term follow-up & transition	Roderick Skinner	University of Newcastle, UK
7	Dissemination & training	Momcilo Jankovic	MBBM, Monza, Italy
8	Management & coordination	Lars Hjorth	Lund University, Sweden

TABLE 2. PanCareSurFup Partnering Institutions & Additional Data Providers

Name of partnering institution	Country	Data provider (Yes/No)	Name of lead person
Lunds Universitet (ULUND)	Sweden	Yes	Lars Hjorth (Coordinator)
University of Newcastle-upon-Tyne (UNEW)	UK	No	Roderick Skinner
Istituto Giannina Gaslini (IGG)	Italy	Yes*	Riccardo Haupt
Universität der Johannes Gutenberg-Universität Mainz (UMC-Mainz)	Germany	No	Desiree Grabow
Boyne Research Institute(BOYNE)	Ireland	No	Julianne Byrne
St. Anna Children's Hospital (STANNA)	Austria	No	Eva Frey
Academisch Medisch Centrum bij de Universiteit van Amsterdam (AMC)	Netherlands	Yes	Leontien Kremer
Semmelweis University (USEM)	Hungary	Yes	Edit Bardi
Universita degli Studi di Torino (UNITO)	Italy	Yes	Carlotta Sacerdote
Great Ormond Street Hospital (GOSH)	UK	No	Gill Levitt
Universität Bern (UBERN)	Switzerland	Yes	Claudia Kuehni
Institut Gustave Roussy (IGR)	France	Yes	Florent de Vathaire
The University of Birmingham (UBHAM)	UK	Yes	Mike Hawkins
Fondazione Monza e Brianza per il Bambino e la sua Mamma (MBBM)	Italy	Yes*	Momcilo Jankovic
SIOP Europe (SIOPE)	Belgium	No	Samira Essiaf
Centre International de Recherche sur le Cancer (IARC)	France	No	Eva Steliarova-Foucher
Additional data providers			
Institute of Oncology, Ljubljana	Slovenia	Yes	Lorna Zadravec Zaletel
Kræftens Bekæmpelse (Danish Cancer Society Research Center, Copenhagen)	Denmark	Yes	Jeannette Falck Winther
Norwegian Cancer Registry, Oslo	Norway	Yes	Finn Wesenberg
Finnish Cancer Registry, Turku University, Turku	Finland	Yes	Päivi-Maria Lähteenmäki
Iceland Cancer Registry	Iceland	Yes	Thorgerdur Gudmundsdottir

*Provided data as part of the Italian hospital-based AIRTUM group.

Table 3: Standardized incidence ratios (SIRs) and absolute excess risks (AERs) of developing a subsequent primary soft tissue sarcoma (STS) in 69,460 5-year survivors of childhood cancer in the European PanCareSurFup SPN cohort, by histological type of STS

STS Diagnosis	O/E	SIR (95%CI)	AER (95%CI)
All STS	301*/19.2	15.7 (14.0 to 17.6)	2.5 (2.2 to 2.8)
Malignant Peripheral Nerve Sheath Tumor	45/1.1	40.6 (29.6 to 54.3)	0.4 (0.3 to 0.5)
Leiomyosarcoma	80/2.7	29.9 (23.7 to 37.2)	0.7 (0.5 to 0.8)
Fibromatous Neoplasms	55/4.5	12.3 (9.3 to 16.0)	0.4 (0.3 to 0.6)
Malignant Fibrous Histiocytoma	25/0.9	28.3 (18.3 to 41.7)	0.2 (0.1 to 0.3)
Fibrosarcoma	27/1.1	25.1 (16.5 to 36.5)	0.2 (0.1 to 0.3)
Dermatofibroma	3/2.5	1.2 (0.2 to 3.5)	0.0 (-0.0 to 0.0)
Rhabdomyosarcoma	22/1.6	13.4 (8.4 to 20.4)	0.2 (0.1 to 0.3)
Liposarcoma	19/1.8	10.5 (6.3 to 16.4)	0.2 (0.1 to 0.2)
Synovial Sarcoma	9/1.3	6.8 (3.1 to 12.9)	0.1 (0.0 to 0.1)
Other Specified Sarcoma	4/0.6	6.3 (1.7 to 16.2)	0.0 (-0.0 to 0.1)
Blood Vessel Tumor	12/2.5	4.8 (2.5 to 8.3)	0.1 (0.0 to 0.1)
Clear Cell Sarcoma	0/0.1	—	—
Alveolar Soft Part Sarcoma	0/0.1	—	—
Unspecified Sarcoma	55/2.6	20.9 (15.8 to 27.3)	0.5 (0.3 to 0.6)

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardized incidence ratio, AER- absolute excess risk per 10,000 person-years, 95%CI- 95% confidence interval.

— Results not reliable due to small (or zero) number of STS events

* Among 299 individuals. 1 individual had unspecified sarcoma and fibrosarcoma; 1 individual had 2 separate rhabdomyosarcomas.

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