



PanCare Childhood and Adolescent Cancer
Survivor Care and Follow-up Studies

PanCareSurFup

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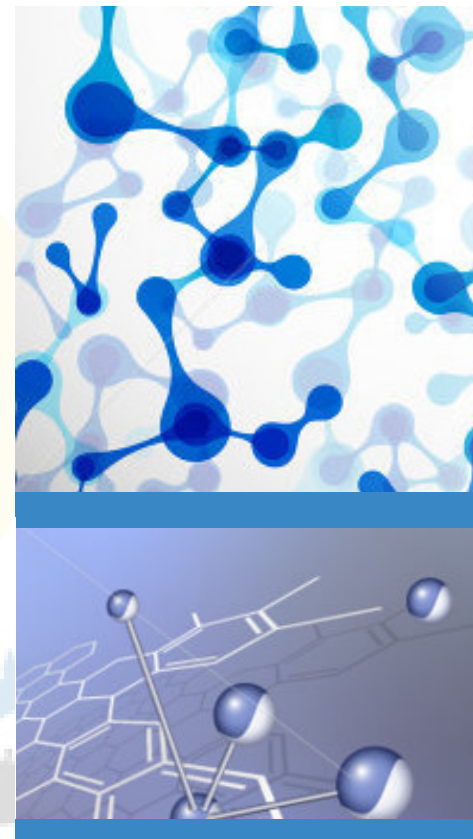
PanCareSurFup Bulletin, Issue nr. 2

PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies

We are delighted to present to you the second Bulletin of PanCareSurFup, the first project aiming to provide every childhood cancer survivor in Europe with better access to care and better long-term health, by carrying out pan-European studies into the complications of long-term survival.

In this issue we are interviewing Professor Mike Hawkins, Director of the Centre for Childhood Cancer Survivors Studies at the University of Birmingham, UK. His centre leads the largest ever population-based investigation of adverse health and social outcomes among survivors of childhood cancer. Since 2010, Mike and his team run the Teenage and Young Adult Cancer Survivor Study, currently carrying out research on 170,000 individuals aged 15 to 39 years, diagnosed with cancer and surviving at least 5 years from diagnosis. Mike is an adviser in several key national groups (the UK Cancer Research Institute, Cancer Intelligence Network and Cancer Survivorship Initiative), and he has published over 100 papers in scientific and clinical journals, mostly relating to the long-term health and social consequences of being treated for cancer.

Within PanCareSurFup, not only Mike leads Work Package 4 on 'Subsequent primary neoplasms: cohort and nested case-control studies', but he also contributes to several other project's work packages. Mike's team scientifically assesses the risks of all types of subsequent primary neoplasm, including sarcomas and carcinomas, by analysing the survivors' cohorts established by WP1, storing biological material for future DNA studies, and by determining (through nested case-control studies) the radiotherapy and chemotherapy-related aspects associated with the increased risk for sarcomas and carcinomas.



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Latest developments in PanCareSurFup

Work Package 2: Radiation dosimetry

Work Package 2 has finished creating and validating a new radiation therapy reconstruction software. This software may be considered as an extension of a treatment-planning system, which allows estimating the whole body radiation dose, to include an automatic repositioning of most of the organs and to have an estimate of radiation dose volume histogram for each organ. This new software will not be used in epidemiology, but in clinical research. WP2 also made investigations on the consequences of organs' volume variability depending on radiation dose estimation. A publication will be also submitted in the next days. All is ready for performing the best possible radiation dose estimations for the cardiac and secondary cancer case control study. We are waiting to receive the records of a maximum of patients as soon as possible

Work Package 4: Subsequent primary neoplasms: cohort and nested case-control studies

There are two aspects which distinguish PanCareSurFup from previous attempts to address questions relating to subsequent primary neoplasms. Firstly, the large number of survivors available, almost 80,000 survivors, provides much more statistical power to address the research questions of interest. In particular, investigating the effects of particular chemotherapeutic drugs and potential interactions between aspects of treatment is likely to be considerably enhanced as compared with single country approaches. Furthermore, to satisfactorily address the impact of genotypes certainly requires the pan-European numbers. Secondly, because of the history of population-based cancer registration (going back to the 1940's in the Nordic countries and the 1960's in the UK) we have the largest group of truly long-term survivors ever assembled. So the opportunities to answer questions relating to survivors as they enter those decades of life when members of the general population develop problems such as cancer, circulatory, lung and kidney problems is unrivalled.

Work Package 5: Late mortality

Work Package 5 is investigating death occurring more than 5 years after the childhood cancer diagnosis. It is called "late mortality", but in reality this mortality is precocious and excessive compared to the corresponding age groups in the background population. We are establishing a pan-European cohort of 5 year survivors for which all deaths can be ascertained and for which an official cause of death is available. The primary goal is to analyse total and cause-specific mortality and to relate absolute and excess risks of death to gender, type of childhood cancer, age at diagnosis, period of cancer diagnosis and, in a subset of patients, type of treatment. The secondary goals are to validate the official causes of death in a sample of patients and to clarify, in those countries where mortality data are not readily available, the reasons for the lack of information.

Work Package 6: Guidelines, long-term follow-up and transition

PanCareSurFup WP6 is developing clinical practice guidelines for the prevention, early detection and treatment of late side effects of childhood and adolescent cancer. These will include guidelines for the follow up of survivors, as well as for the organisation of long term follow-up care including transition to age appropriate care for survivors of adult age, and for promotion of a healthy lifestyle.

Work Package 7: Dissemination and Training

At present, waiting for the results that will come up from the intense activity of the other Work Packages (especially WP6 and its "Guidelines" for follow up of long term survivors and their transition to adulthood, with the involvement of adult specialists and family doctors), we successfully promoted a few media events ([Dublin conference](#); [the two editions of the Race of Brave Bikers](#) in Marostica, Italy; the upcoming [MSC Cruise Gala dinner](#) in Genova, Italy). On these occasions, we had chance to inform media of the existence and intense activity of [Pancare](#) and [PanCareSurFup](#). The links with other important networks like [ENCCA](#) and [SIOPE](#) gave us more visibility and the possibility of some joint initiatives. A survivors' group also belonging to [ICCCPO](#) was created, and many connections were established through social networks like Facebook and Twitter. We are working hard to be ready and achieve our ultimate goal by the end of the project.

Work Package 8: Management and Coordination

All partners met for the [PanCareSurFup](#) General Assembly in Amsterdam last 2-3 October. It was a very good meeting, with important and constructive feedback from the [PanCareSurFup](#) Ethical and Scientific Advisory Board. The Work Package leaders are following up on the topics covered. [PanCareSurFup](#) has two new associated EU-funded projects that have spun off the work of [PanCare](#), [PanCareSurFup](#) and [ENCCA](#): [EXPO-r-NeT](#), a pilot network of cooperation between oncology centres to implement European standards of care for children with cancer and [PanCareLIFE](#), a 5-year research project covering the topics of fertility and ototoxicity. All partners are also currently preparing the 2nd report for the European Commission. The next [PanCareSurFup](#) General Assembly will take place on 14-15 May in Wroclaw, Poland.

PanCareSurFup Partners

The project's dissemination team interviews Prof. Mike Hawkins from the Centre for Childhood Cancer Survivors Studies (UK) and leader of Work Package 4.

Can you describe how you got involved in PanCareSurFup?

I have been contributing evidence towards an understanding of the risks and causes of late adverse health and social outcomes occurring after treatment for childhood cancer for almost my entire career. I was originally appointed to initiate population-based investigations of causes of late mortality and the risks and causes of subsequent primary neoplasms after childhood cancer diagnosed throughout Britain, based with the National Registry of Childhood Tumours at the University of Oxford. In 1998 I initiated the [British Childhood Cancer Survivor Study](#) and, more recently, the Teenage and Young Adult Cancer Survivor Study. My research team is therefore monitoring the long-term health of all those diagnosed with cancer before the age of 40 years in Britain. Internationally, I have had long standing research collaboration with Dr. Florent de Vathaire in Paris and, subsequently, I was invited to join the [Early and Late Toxicity Education Committee](#) of the International BFM Study Group by Drs Riccardo Haupt and Momcilo Jankovic and Professor Jorn Beck. With Florent and Riccardo, among others, we obtained funding for a FP6-grant GENE-RAD-RISK (an international collaborative study of the joint influences of radiation and genotype on breast cancer risk). I was a founding member of PanCare, so it was natural that I should be closely involved in developing PanCareSurFup.

What do we know, and what do we not know about secondary malignancies in childhood cancer survivors?

We know the types of subsequent primary neoplasms which develop in the initial two to three decades after treatment for childhood cancer. Broadly an excess risk of subsequent primary leukaemia is observed in the first decade following treatment; known specific types of chemotherapy are particularly associated with highest excess risks, and there is clear evidence of a dose-response. An excess risk of subsequent primary solid cancer tends to appear after a decade from treatment (sometimes several decades as with meningiomas), and higher cumulative dose of exposure to radiotherapy is the principal element of anti-cancer treatment which is related to larger excess risks, although for some cell types there is evidence of cell kill at the highest exposures.

A critically important outstanding question relates to the risk of subsequent primary neoplasms as survivors, in large numbers, enter those decades of life when the common cancers of mature adulthood (including breast, prostate, bowel and lung cancer) begin their inexorable increase in risk in the general population. We know that subsequent primary neoplasms are the cause of death responsible to the greatest proportion of premature mortality among survivors (see paper).

Because the risk of cancer of some sites is relatively high in the general population, only a small excess multiplicative risk would give rise to a large number of additional cancers being observed among survivors as we illustrated in a recent paper.

Tell us what is the aim of the case-control studies planned for the pan-European database, and how can this improve the quality-of-life of survivors?

For the reasons just given we shall be concentrating on digestive and genitourinary cancers as subsequent primary cancers, to determine the extent to which previous cumulative exposure to specific types of chemotherapy and previous cumulative exposure to radiotherapy are related to the excess risks already observed for these cancers in cohort studies. We are also collecting a sample of DNA to provide the opportunity to determine whether specific genotypes experience particularly strong dose-response relationships. We shall also be investigating the occurrence of bone cancer and soft tissue sarcomas in a similar way, because of the relatively high risk of occurrence of these cancers among survivors of childhood cancer.

The way in which the evidence gained should improve the quality-of-life of survivors is broadly three-fold. Firstly, such evidence should be made available to survivors as well as health professionals. For survivors, such knowledge should empower them to be aware of potential risks and to seek medical advice should anything potentially untoward be experienced. Secondly, such evidence provides a basis for rationally planning long-



'Relay For Life' is an event that took place in the city of Worcester on 4th September 2010, with people walking around a sports track for 24 hours. The event was an opportunity for survivors of cancer (and others) to raise money for Cancer Research UK, the largest charity funding cancer research in the UK.

term clinical follow-up of existing survivors so that those most at risk receive greatest attention in terms of clinical follow-up and interventions aimed at identifying problems as early as possible, or possibly preventing them. Thirdly, in the planning of future treatment protocols, evidence of long term risks as well as cure of original disease may be taken into account.

What is unique about PanCareSurFup's risk assessment for secondary malignancies?

There are two aspects which distinguish PanCareSurFup from previous attempts to address questions relating to subsequent primary neoplasms. Firstly, the large number of survivors available, almost 80,000 survivors, provides much more statistical power to address the research questions of interest. In particular, investigating the effects of particular chemotherapeutic drugs and potential interactions between aspects of treatment is likely to be considerably enhanced as compared with single country approaches. Furthermore, to satisfactorily address the impact of genotypes certainly requires the pan-European numbers. Secondly, because of the history of population-based cancer registration (going back to the 1940's in the Nordic countries and the 1960's in the UK) we have the largest group of truly long-term survivors ever assembled. So the opportunities to answer questions relating to survivors as they enter those decades of life when members of the general population develop problems such as cancer, circulatory, lung and kidney problems is unrivalled.

Your institution takes the lead of Work Package 4 'Subsequent primary neoplasms: cohort and nested case-control studies', but you are also part of other Work Packages of the project. How is your work scheduled and how do you manage to deal with such a wide range of tasks?

Both within my own research team and across PanCareSurFup there is a great team spirit and so the work is shared. On my own team I have an excellent Deputy Work Package Leader, Dr Raoul Reulen; Dr Clare Frobisher also provides excellent post-doctoral support; an excellent IT Manager, David Winter; excellent administration support, Julie Kelly; and four very supportive PhD students, Chloe Bright, Miranda Fidler, Joyeeta Guha and Jeff Wong. Across PanCareSurFup regular (mostly weekly) data collection, teleconferences are very well attended. In addition, the leaders of Work Packages 1 (Peter Kaatsch), 2 (Florent de Vathaire), 3 (Leontien Kremer), 4 (myself) and 5 (Stanislaw Garwicz) have a teleconference every month with Julie Byrne and Lars Hjorth. The ethos of PanCareSurFup has always been 'can do' and friendly. It has proved a delightful collaboration.

Are there good synergies with the other Work Packages, and how do you see them continuing beyond the life of this EU project?

The network of collaboration established under PanCareSurFup has developed an excellent 'esprit de corps', characterised by professionalism and friendliness. As to the future, there is already a sister EU-funded project, PanCareLIFE, and a new consortium, ExPO-r-Net (European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment), is being taken forward as a three-year project by DG SANCO.

What have been the main challenges to date?

Scale and complexity!

Describe your typical working day.

My days vary quite a lot, but I hope that, by the end of each of them, my research team is a little nearer delivering on the various goals we have both nationally and internationally.

What do you love most about your job?

Scientific enquiry towards the goal of making life better for those who survive cancer. As a scientist, it is very rewarding to have an idea, obtain funding to undertake the necessary research and ultimately produce new evidence relevant to the lives of survivors of cancer. As I have become more senior, it gives me increasing pleasure to 'bring-on' younger investigators with a view to passing on the tools for enquiry to the next generation.



Prof. Hawkins with some of his collaborators at a recent event on survivorship

Describe one of your proudest moments/an achievement you are particularly proud of.

Presenting results to an audience that comprises survivors of cancer. Of course, providing evidence which is likely to change clinical practice in a way that is likely to save lives is very rewarding, but to get the immediate feedback and approval from a group of cancer survivors really does touch my heart. Thankfully there are good news stories to tell as well as bad.

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