PhD Studentship - **Investigation of risks of conditions managed in primary care among survivors of childhood, teenage and young adult cancer**

Summary

It has been shown that long-term survivors of cancer diagnosed when young are at risk of dying from causes other than cancer, for example heart disease, and investigation has indicated that this is related to the treatment that they received. Survivors of cancer diagnosed when children, teenagers and young adults will likely live for many decades, and therefore it is of utmost importance to understand the long-term risks, and identify groups at the highest risk of developing certain adverse conditions. Quantification of such risks will help clinicians to focus care, policy makers to improve evidence-based clinical guidelines and care plans and patients to understand what they might expect. Once cancer survivors have been discharged, they are typically managed in the community by GPs, and may be diagnosed with certain conditions that can be managed completely without the need for a hospital visit. Therefore, it is of vital importance to understand this aspect of a patient's healthcare, and it is something that has been previously unavailable at a national level for cancer survivors.

PHE has now entered a partnership with NHS Business Services Authority to receive England-wide prescribing information for all individuals in England, therefore filling the gap outlined above. This proposal therefore outlines a programme of work to measure the long-term risk of developing certain health conditions among 5-year survivors of cancer, as determined by a patient's prescriptions.

Description of Project

Background to cancer population of interest

Survivors of cancer diagnosed in teenagers and young adults are internationally recognised as an understudied population. They have sometimes fallen into a gap in medical expertise between the childhood and adult cancer survivor populations. Teenage and young adult cancers are distinct in terms of tumour distribution, hormonal factors, tumour biology, potential reluctance to engage with clinicians, socio-economic and lifestyle factors [1]. Those individuals who survive can expect to live for many decades, giving time for late effects to develop. Thus, there is a need for specialised research of the teenage and young adult (TYA) cancer population, particularly with a focus on late effects. The Department of Health, the National Institute for Health and Clinical Excellence and the National Cancer Research Institute have all identified a need for accurate information concerning the risk of adverse health outcomes among survivors of cancer diagnosed in teenage and young adulthood.

As with the TYA cancer population, childhood cancer survivors can expect to live for many decades. Therefore research is needed which focuses on quantifying the excess risk of adverse health outcomes which survivors experience. This will provide an evidence base for risk stratification and planning interventions. Quality of life is of vital importance for these survivors.

Increasing survival [2] is resulting in an increasing population of childhood, teenage and young adult (CTYA) cancer survivors. As of 31st December 2013, there were 97,300 males and 145,600 females alive in England who were diagnosed with cancer between birth and aged 39 years from 1948 onwards [3].

Observational cohort studies are vital to understand a patient's experience in a 'real-world' setting. The University of Birmingham has established two national observational cohort studies, to investigate the late outcomes among the CTYA cancer population: the British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS). These cohorts have provided good evidence for excess mortality, morbidity and hospitalisations among survivors of both childhood, and teenage and young adult cancers. For decades following their cancer diagnosis, cancer survivors are at substantial excess risk of death particularly from secondary primary neoplasms [4-6]. Deaths due to circulatory disease have been shown to account for the greatest percentage of excess deaths among mature childhood cancer survivors [4]. The type of circulatory disease varies substantially depending on cancer type and its treatment, and the risk is particularly high among those patients

who received chest irradiation or anthracyclines, which are known to be cardiotoxic [7]. An excess risk of cardiovascular disease has also been investigated and demonstrated among survivors of TYA cancer [8], and an increased risk of hospitalisation for cerebrovascular events has clearly been demonstrated [9]. Survivors also experience significantly higher levels of mental health dysfunction [6] and survivors experience excess use of both primary and secondary care [10]. This illustrates the breadth of adverse health outcomes which develop in excess, and the increased burden on the health service that needs to be understood to be managed effectively for both the patient and the system.

Adverse health events, however, are not solely defined by death or inpatient hospitalisations. A substantial proportion of adverse health outcomes are managed in primary care. This was demonstrated among the questionnaire respondents of the BCCSS, where 16.5% of the 10,000 long-term survivors of childhood cancer had spoken to a doctor in the last two weeks, which was significantly higher than expected from the general population (odds ratio = 1.2 (95% CI 1.1 – 1.3)) [10]. Thus, despite the good evidence on adverse outcomes such as mortality and hospitalisations, there is, to our knowledge, no evidence of community managed health problems. Until the partnership with NHSBSA, there has been little opportunity to ascertain primary care information at the population level across England. This is a unique opportunity to investigate the extent of prescribed medication for individuals, which would be useful to improve evidence-based clinical follow-up guidelines for these patients through risk stratification and plan appropriate interventions.

Hypothesis

Long-term survivors of childhood, teenage and young adult cancers will experience more adverse health outcomes (as identified by their prescribing patterns), which are managed in the community, as compared to their demographically matched peers and this is likely to vary in relation to type of cancer, its treatment, age and calendar year of treatment and years from treatment.

Objectives

1) Identify adverse health outcomes of interest including circulatory, pulmonary, renal, hepatic and endocrine diseases and mental health problems (for example depression, anxiety or serious mental health conditions like psychosis), and develop a methodology to measure these using prescribing patterns in consultation with clinical colleagues. This could be a particular combination of drugs dispensed within a certain time frame; it could use the indication for the medication; or could be a progression of drugs prescribed. Consideration will be needed for established risk factors for a major adverse event, for example hypertension medication and the link to cardiovascular events. Circulatory disease will be important because it accounts for the greatest number of non-neoplastic causes of death, similarly respiratory disease, and mental health outcomes, as defined by the presence of anti-depressants.
2) Develop a methodology to quantify the extent of community healthcare use among cancer survivors, as determined by their prescribing history
3) Assess the excess prescribing among 5-year cancer survivors as compared to the general population. This will be achieved through investigation of observed and expected risks from specific adverse health outcomes.
4) Identify subgroups of patients (defined in terms of type of cancer, age at treatment, calendar year of diagnosis, period of follow-up, attained age and sex) at a substantially increased risk of specific adverse health outcomes, as defined by Objective 1.
5) Investigate cumulative risk for the adverse health outcomes of interest by attained age of the survivor.
6) Scope a subset analysis to correlate the cardiovascular outcomes as defined by prescribing activity to those that resulted in a hospitalisation, as recorded in the Hospital Episode Statistics Admitted Patient Care dataset, in the preceding years.

The over-arching objective is that the findings from this work can provide an evidence base for risk stratification, development of evidence-based clinical follow-up guidelines and planning interventions to reduce excess risks. All of this is currently unavailable.

One of the specific objectives of the BCCSS is "to investigate the risk of cardiac, pulmonary, renal, hepatic, intestinal and other major organ toxicity in relation to types of childhood cancer and its treatment". This objective extends to the TYACSS, which aims to "investigate the observed and expected risks of … specific types of non-cancer morbidity (including cardiovascular, pulmonary, urological, hepatic and endocrine conditions)". Thus the specific objectives for this PhD studentship very closely align to the overall objectives of the two studies.

Clinical and policy implications

To our knowledge this will be the largest study to investigate the community managed adverse healthcare outcomes among CTYA cancer survivors. The implications of this work are therefore broad, and will undoubtedly provide the most reliable, unbiased and comprehensive evidence base available for:

a) counselling, educating and empowering survivors;
b) drafting, reviewing and updating clinical guidelines so that intensity of follow-up relates to risks of adverse health outcomes;
c) preparing "survivorship care plans" as appropriate following completion of treatment and prior to discharge;
d) educating health care professionals;
e) evaluating alternative proposals for future treatment protocols from a risk as well as a benefit perspective;
f) assessing potential recalls to clinic for screening tests and other interventions among those subgroups of survivors at a substantially increased risk;
g) provide a basis for more detailed epidemiological and clinical studies of subgroups at substantially increased risk to determine causative factors.

Milestones

The key milestones for this PhD studentship are:

1) Transfer viva at the end of year 1
2) Confirmation of status process at the end of year 2
3) Dissemination of findings and engagement with clinicians, as outlined in the section below
4) Dissemination of findings to clinicians, through either Professional Meetings organised by the Children's Cancer and Leukaemia Group (CCLG) or the Teenagers and Young Adults with Cancer (TYAC) conference
5) Presentation of findings at an international conference, targeting ESLCCC or the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer
6) Publication of findings in a peer-review publication(s)

Methodology

The focus of this project is on the long-term prescribing patterns of cancer survivors; therefore each individual will enter risk at the latest of the date of achievement of 5-year survival from cancer diagnosis or the date of start of follow-up with respect to prescriptions and contribute person-years until the exit date. The exit date will be defined as the date associated with that first event of the following: date of prescription, date of death, or end of current follow-up with respect to prescriptions.

Excess prescriptions will be calculated using standard cohort techniques as defined by Breslow and Day [11]. Population-based expected prescription rates will be calculated as the number of prescriptions divided by the mid-year population estimate of England in the specific strata. Strata will be defined on age (5-year groups), sex and calendar year (1-year groups). Observed prescribing patterns will be calculated using prescriptions data for cancer patients, formatted into a time-at-risk survival format. Both multiplicative and absolute excess risks will be calculated. Standardised Prescription Ratios (SPRs) estimate the proportion increase in the prescribing rate for a particular outcome compared with rates in the general population, and Absolute Excess Risks (AERs) estimate the absolute excess prescribing rate compared with the general population. SPRs will be calculated as O/E and AERs per 10,000 person-years at risk as [(O – E) / pyrs]*10000, where O and E are the observed and expected numbers of prescriptions, respectively, and 'pyrs' is the total person years at risk.

To examine the variation in risk across patient characteristics, for example sex, type of cancer and age at cancer diagnosis, and to therefore evaluate the simultaneous effect of these factors, multivariable Poisson regression models will be utilised.

Cumulative risks by attained age at prescription will be estimated using Cox regression. Age-specific rates are assumed constant across calendar years of diagnosis, and therefore different treatment cohorts.

Internal analyses will be possible, where the risk of specific adverse health outcomes will be compared over the period at risk using Poisson regression. This will identify particular subgroups at greatest risk of the adverse health outcome.

References

1	Adolescent and Young Adult Oncology Progress Review Group (2006). Closing the gap: Research and care imperatives for adolescents and young adults with cancer
2	Office for National Statistics. Dataset: Childhood cancer survival in England. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/childhoodcancersurvivalinengland Accessed 19/09/2017
3	Macmillan-NCRAS partnership. Updated UK Complete Cancer Prevalence for 2013 Workbook for UK nations and UK combined. http://www.ncin.org.uk/view?rid=3415 Accessed: 19/09/2017
4	Fidler MM, Reulen R, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study BMJ 2016; 354 :i4351
5	Wong KF, Reulen RC, Winter DL, et al. Risk of Adverse Health and Social Outcomes Up to 50 Years After Wilms Tumor: The British Childhood Cancer Survivor Study. Journal of Clinical Oncology 2016 34:15, 1772-1779
6	Fidler MM, Ziff OJ, Wang S, et al. Aspects of mental health dysfunction among survivors of childhood cancer. British Journal of Cancer. 2015;113(7):1121-1132.
7	Fidler MM, Reulen RC, Henson K, et al. Population-based long-term cardiac-specific mortality among 34,489 five-year survivors of childhood cancer in Great Britain. Circulation. 2017;135(10):951-963.
8	Henson KE, Reulen RC, Winter DL, et al. Cardiac Mortality Among 200 000 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age: The Teenage and Young Adult Cancer Survivor Study. Circulation. 2016 Nov 15;134(20):1519-1531. Epub 2016 Nov 7.
9	Bright CJ, Hawkins MM, Guha J, et al. Risk of Cerebrovascular Events in 178 962 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age: The TYACSS (Teenage and Young Adult Cancer Survivor Study). Circulation. 2017 Mar 28;135(13):1194-1210.
10	Rebholz CE, Reulen RC, Toogood AA, et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol. 2011 Nov 1;29(31):4181-8. doi: 10.1200/JCO.2011.36.5619. Epub 2011 Sep 26.
11	Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC scientific publications. 1987; 82: 1-406.