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review

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Late effects in survivors of teenage and young adult cancer: does age matter?

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Background: Late effects (LEs) after cancer treatment are increasing. After childhood cancer, substantial risks include physical, psychological and social LE and vary with age. Teenagers and young adults (TYA) present with particular cancers; their risk of LE may relate to cancer site, treatment or their age itself. The LEs after TYA-onset cancers are described in relation to age at diagnosis of primary tumour.

Patients and methods: Data were extracted from Medline English language articles, 1999–2009. Keywords were late effect/s, late toxicity and survivor and the frequent TYA cancer sites. Only those articles that reported the relation between LEs risks with age at diagnosis were included.

Results: The majority of known LEs are described after TYA cancer. No study primarily aimed to relate TYA age to LEs. Many studies did not report LE by age. TYA-specific risks are seen in cardiac toxicity, second malignancies, pulmonary complications and psychosocial difficulties when compared with older or younger cancer survivors.

Conclusions: TYA age brings specific LE risks after cancer. Prospective population-based collection of LE data after TYA cancer will inform the development of appropriate services to effectively manage LE.

Key words: adolescents, cancer, late effects, morbidity, teenager, young adult

introduction

Cancer survival is increasingly prevalent, with ~1.6 million long-term cancer survivors in the UK. Consequently, survivorship issues have moved from the margin to mainstream of the health agenda [1]. Those living beyond cancer are at increased risk of physical, psychological and social sequelae of their diagnosis and its treatment. To address these issues, the National Cancer Survivor Initiative was launched in England in September 2008 [1].

Late effects (LEs) are well described in survivors of childhood cancer as a result of comprehensive population-based studies, such as the British Childhood Cancer Survivor Study (BCCSS) and the Childhood Cancer Survivor Study (CCSS) in North America. Over 60% of long-term survivors experience at least one morbidity, and 30% have a significant health impairment [2, 3]. For each cancer group, survivors who received their diagnosis and treatment at an older age within childhood (whole population 0–21 years) are more likely to report chronic health problems [2]. After childhood cancer, the risks of neurological, gonadal and some other LE correlate with age at diagnosis and treatment [4].

Teenagers and young adults (TYA) often fall between paediatric and adult oncology practice, a 'lost tribe'. The likelihood of developing a malignancy between ages 16 and 29 years is approximately double that for the risk under the age of 16 years [5]. The profile of cancers in TYA is also distinct from adults or children [6]. This cohort, like children, can expect to live for many decades if cured from their malignancy. TYA may experience a spectrum of LE simply because of their pattern of disease and the necessary treatments or may have a distinct pattern of LE because of their age.

The National Institute for Clinical Health and Excellence 'Improving outcomes guidance for children and young people with cancer' mandates LE services for TYA. However, there is limited description of LE after cancer diagnosed in TYA to inform the design of this service [7]. A systematic review of the literature was undertaken to describe published evidence of LE of common cancers in TYA and to examine the research question 'is the risk of particular LE correlated with age at cancer onset, when TYA are compared with survivors of younger-onset or older-onset cancer?'

patients and methods

A Medline and PubMed search was carried out of the English language literature published between 1999 and 2009 using the keywords late effect/s, late toxicity and survivor in conjunction with the tumour types most frequent among TYA: leukaemia and lymphomas, CNS tumours, sarcomas, germ cell tumours, malignant melanoma and selected carcinomas (thyroid, cervical, breast) [5]. The search was restricted by date to best reflect current

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practice. Bibliographies of review articles and studies were used to identify additional relevant material. Articles were excluded if the follow-up after cancer was <5 years, the defined age range of the study population did not report including any patients aged 16–30 years and the researchers did not report an age effect. Although all studies were examined that reported examining LE risk by age, this report includes only those who report a statistically significant risk comparing TYA to patients of other ages at diagnosis, whether a raw or age-adjusted comparison of LE rates. Univariate and multivariate analyses of association are described, as reported in the original articles, to make the nature of any associations clear.

results

Results of the literature search are summarised in Figure 1. The initial literature search using the keywords outlined in the methods returned 3142 articles. Two thousand six hundred and fifty-six of these were rejected following review of the abstract as not relevant. The remaining 486 were examined by our inclusion and exclusion criteria, resulting in 51 relevant articles that describe an age effect (summarised in Table 1). We present data describing the reported LE after common TYA malignancies where age at diagnosis was identified as a risk factor.

leukaemia and lymphoma

Haematological malignancy accounts for up to a third of cancers affecting TYA [5]. The published studies reporting LE among survivors of leukaemia and lymphoma are numerous and varied, reflecting their high incidence among our population of interest and high cure rates. These LEs of childhood leukaemia and lymphoma have been reviewed elsewhere [59, 60].

second malignant neoplasms. There is an extensive body of evidence describing second malignancies among survivors of haematological malignancies, particularly Hodgkin's lymphoma. Evidence to support age at diagnosis as a risk factor for a subsequent primary cancer is conflicting, to an extent related to the increasing background cancer rate with increasing age. Many studies reflect that due to increasing background risk of cancer with increasing age, relative risk (RR) tends to decrease with increasing age, while measurements of absolute risk [such as absolute excess risk (AER)] and cumulative incidence tend to increase. While many large studies examine for trend, such as 'young age' at diagnosis as an independent risk factor for leukaemia survivors ($P < 0.01$, for trend, age at diagnosis grouped as 0–4, 5–9, 10–14 and ≥15 years), others seek to determine specific risk for particular age groups [8]. Comprehensive review of MacArthur across multiple tumour sites reports a standardised incidence ratio (SIR) for second malignant neoplasm (SMN) of 6.3 and 4.6 in leukaemia and lymphoma patients, respectively, and patients diagnosed <10 years had apparently higher risk than older patients (SIR 10.6 versus 4.0) [53]. However, the AER for each age group is similar (1.7) that, the authors suggest, reflects the higher background cancer rate with increasing age in the general population. However, this pattern does not always hold true for all SMNs. In the case of subsequent breast cancers, both

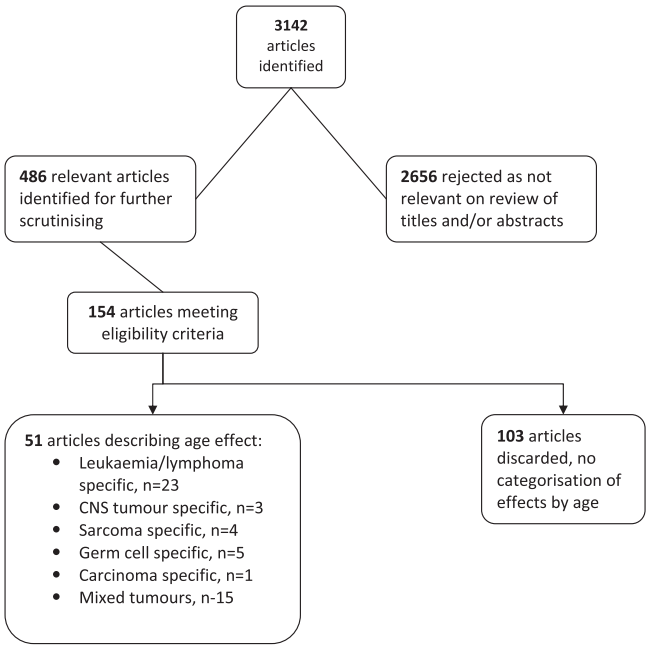

Figure 1. Results of initial search and numbers of included articles. CNS, central nervous system.

relative and absolute risks appear to decrease with increasing age at diagnosis of lymphoma [9]. It is now widely accepted that young women who received mediastinal radiotherapy for HD are at significantly increased risk for breast cancer and screening guidelines have been introduced that specifically address this [61].

Although survivors of haematological cancer are certainly at increased risk of subsequent primary cancers, most of the data reporting an age effect do so in a cohort of mixed diagnoses, where identifying age at diagnosis of a specific neoplasm as an independent risk factor is either not possible or attempted [54, 62–64]. No study reports TYA survivors of leukaemia and lymphoma to be at increased risk compared with those diagnosed in childhood.

fertility. Childhood haematological cancer and its treatment has a significant impact on subsequent fertility; age at diagnosis of malignancy has been reported to be of significance. Ovarian failure is more common among those diagnosed at age 13–20 years compared with those at age <12 years [18]. Conversely, males treated at a younger age, <9 years, have reduced fertility compared with sibling controls following chemoradiotherapy (RR = 0.26, $P = 0.03$) for fatherhood aged 18–21 years, while those treated at older ages have non-significantly different fertility [22]. However, age has no significant effect for parenthood after age 21 years and whether their findings reflect biochemical disturbance or lifestyle choice is unconfirmed.

cardiovascular/pulmonary effects. In general, diagnosis of haematological cancer before adolescence confers greater risk for cardiovascular disorders than in older adulthood, while for pulmonary disease (lung fibrosis and pleurisy), age >15 years compared with younger groups is associated with the greatest risk [23–29]. Higher relative rates of cardiovascular disease in

Table 1. Studies that report an age effect for development of specific late effects by site of primary malignancy

Reference	Population size	Effect examined	Age effect findings
Haematological malignancies			
Neglia et al. [8]*	13 581	SMNs	Young age at diagnosis associated with increased risk for SMN
van Leeuwen et al. [9]	1253	SMNs	≤20 years at diagnosis, RR = 12.7; 21–30 years, RR = 6.9; 31–39 years RR = 4.9
Munker et al. [10]	1120	SMNs	Risk of breast cancer after radiotherapy: <30 years at diagnosis, RR = 5.4, ≥30 years RR = 1.9
Ng et al. [11]	1319	SMNs	<20 years at diagnosis, RR = 10.7, AER = 71.0; 20–50 years, RR = 4.9, AER = 88.5; >50 years, RR = 2.4, AER = 211
Foss Abrahamsen et al. [12]	1024	SMNs	≤40 years at diagnosis, SIR = 6.2, AER = 10.0; 41–50 years, SIR = 3.7, AER = 209; 51–60 years, SIR = 2.5, AER = 265; >60 years, SIR = 2.1, AER = 372. For breast cancer, both SIR and AER were significantly higher if diagnosed <25 years
Cellai et al. [13]	1524	SMNs	<28 years at diagnosis, RR = 1; 28–44 years, RR = 2.1; >44 years, RR = 6.2
Hodgson et al. [14]	18 862	SMNs	RR and AER decreased with age at diagnosis ($P < 0.001$)
Andersson et al. [15]	4623	SMNs	<40 years at diagnosis, SIR = 4.3; ≥40 years, SIR = 2.14
Schonfeld et al. [16]	35 511	AML	<35 years, EAR = 4.2–7; ≥35 years, 6.4–9.9 depending on year of diagnosis
De Bruin et al. [17]	1122	Breast cancer	≤20 years, SIR = 17.6, AER = 79; 21–30 years, SIR = 7.0, AER = 62; 31–40 years, SIR = 3.2, AER = 42; >41–50 years, SIR = 1.4, AER = 11
Basu et al. [18]	398	Breast cancer	Significantly higher risk age >12versus ≤12 years ($P = 0.033$)
Wahner-Roedler et al. [19]	653	Breast cancer	<30 years at diagnosis, SMR = 8.5; ≥30 years, SMR = 1.2
De Bruin et al. [20]	2567	Malignant mesothelioma	≤30 years at diagnosis, SIR = 66.8; 31–50 years, SIR = 15.0
Chemaitilly et al. [21]*	3390	Ovarian failure	13–20 years at diagnosis, OR for ovarian failure = 1.8 compared with younger age groups
Byrne et al. [22]	213	Fertility	Diagnosis <9 years is less likely to father a child compared with sibling controls
Mulrooney et al. [23]*	14 358	Cardiotoxicity	CHF: 0–4 years at diagnosis, HR = 3.9; 5–9 years, HR = 2.3. Valvular dysfunction: 0–4 years, HR = 2.7; 5–9 years, HR = 2.5; 10–14 years, HR = −1.5
Swerdlow et al. [24]	7033	Cardiotoxicity	RR of death from MI decreases with increasing age at first treatment. AER increases with older age at first treatment except for those aged >65 years
Reinders et al. [25]	258	Cardiotoxicity	Increasing age at radiation associated with increased risk of developing IHD in multivariate analysis ($P < 0.001$)
Aleman et al. [26]	1474	Cardiotoxicity	SIR for angina and congestive heart failure significantly increased if <20 years at diagnosis: angina SIR = 11.6; CHF 18.2 compared with older age
Andersson et al. [27]	6946	Cardiotoxicity	SIR for coronary artery disease: <40 years at diagnosis = 2.94; >40 years. SIR = 1.61. SIR for CHF: <40 years at diagnosis = 10.1; >40 years at diagnosis, SIR = 1.32
Mertens et al. [28]*	12 390	Pulmonary complications	Lung fibrosis: age at diagnosis >15 years compared with <5 years, RR = 1.9. Pleurisy: age at diagnosis >15 years compared with <5 years, RR = 2.4
De Bruin et al. [29]	2201	Cerebrovascular	Trend for increased SIR with younger age at first treatment of stroke ($P = 0.004$) and TIA ($P = 0.01$)
Garmey et al. [30]	1451	Obesity and BMI	In females, chemotherapy and CrRT >10 Gy at <10 years at diagnosis: increased BMI compared with siblings 0.44 U/year. In females, chemotherapy and CrRT >10 Gy 10–20 years at diagnosis: increased BMI compared with siblings 0.35 U/year ($P = 0.01$). In males, CrRT >10 Gy <10 years at diagnosis had an increased BMI compared with siblings

Table 1. (*Continued*)

Reference	Population size	Effect examined	Age effect findings
Razzouk et al. [31]	422	Obesity	Younger children at diagnosis had a greater likelihood of becoming overweight or obese as compared with older age at diagnosis
Meacham et al. [32]*	7195	BMI	Females with lymphoma: age of diagnosis 5–9 years, increased OR of being underweight compared with 15–20 years at diagnosis (OR = 2.5, $P = 0.02$). Males with lymphoma: risk of being underweight: <4 years at diagnosis, OR = 12.4; 5–9 years, OR = 5.6 compared with 15–20 years at diagnosis
Kadan-Lottick et al. [33]*	9261	Osteonecrosis	Among ALL survivors rate of osteonecrosis: <10 years diagnosis rate = 0.2% ($P = 0.02$), >16 years at diagnosis rate = 2.8% ($P0 = .039$). Older age at diagnosis of cancer higher RR of osteonecrosis
Kaste et al. [34]	57	BMD	<3.5 years at diagnosis of ALL had a significant increase in BMD (younger age protective, older age at risk of loss of BMD)
Sklar et al. [35]	1791	Thyroid dysfunction	RR for hypothyroidism by age at diagnosis: >15 years, RR = 1.5, $P = 0.0001$ as independent risk factor
Thompson et al. [36]*	60	Relationships	Older age of diagnosis had fewer relationships compared with controls ($P = 0.02$)
Glover et al. [37]	555	Mood	Rate of mood disturbance according to age at diagnosis: <12 years, 29.5%; >12 years, 15.7% ($P < 0.001$)
Lown et al. [38]*	10 398	Alcohol consumption	Diagnosis during late adolescence (15–21 years) protective (OR = 0.7) compared with peers
Zebrack et al. [39]*	303	Worries and image	Those diagnosed at older age had a more positive life outlook compared with younger age at diagnosis
Mitby et al. [40]*	12 430	Education	Need for special education classes according to age at diagnosis: 0–5 years, 35.9%; 6–10 years, 26.2%; 11–15 years, 13.3%; 16–20 years, 9.5% (compared with siblings)
Pang et al. [41]*	10 399	Employment	Increased risk for never being employed if age at diagnosis ≤3 years compared with those diagnosed >3 years (OR = 1.4)
CNS tumours			
Gourney et al. [42]	921	Final height and BMI	Females diagnosed <9 years who received radiotherapy at elevated risk of obesity. Adult short stature associated with younger age at diagnosis
Packer et al. [43]	1607	Neurologic sequelae	Those diagnosed ≤4 years old at greater risk for seizure disorder compared with older children
Fouladi et al. [44]	524	CNS injury	≤5 years at time of radiotherapy associated with increased risk of lacunar infarct
Koch et al. [45]*	2384	Education	Significantly increasing trend in attaining youth education with increasing age at diagnosis
Sarcomas			
Ji et al. [46]	6672	SMNs	SIR for SMN = 2.06 ≤20 years at diagnosis, 1.41 >20 years at diagnosis
Cohen et al. [47]	1499	SMNs	O/E ratio for development of SMN: <10 years at diagnosis = 9.1, ≥10 years = 5.2
Kaste [48]*	99	BMD	Risk of BMD deficit increased significantly with younger age at diagnosis ($P = 0.044$)
Felder-Puig et al. [49]	60	Quality of life	Diagnosis during adolescence (14–19 years) associated with more problems than those diagnosed during childhood or adulthood
Nagarajan et al. [50]	694	Social factors	Amputees >12 years at diagnosis less likely to graduate from high school (OR = 0.6), college (OR = 0.8) or ever have a job (OR = 0.2)
Germ-cell tumours			
Travis et al. [51]	40 576	SMNs	RR and EAR for SMN decreased with increasing age at diagnosis

Table 1. (*Continued*)

Reference	Population size	Effect examined	Age effect findings
Wanderas et al. [52]	2201	SMNs	SMN rate <30 years at diagnosis 7.8%, ≥30 years at diagnosis 2.1%
MacArthur et al. [53]*	2322	SMNs	<10 years at diagnosis, SIR for development of SMN = 10.6, ≥10 years at diagnosis = 4.0
Hammal et al. [54]*	4072	SMNs	<15 years at diagnosis, SIR for development of SMN = 9.4, ≥15 years at diagnosis = 3.1
Van den Belt-Dusebout et al. [55]	2339	Cardiovascular disease	3.7-fold increase MI following mediastinal radiotherapy; 1.9-fold increase MI following PVB chemotherapy. Younger age at diagnosis associated with increased risk
Fossa et al. [56]	38 907	Mortality	<10 years at diagnosis, RR for cardiac mortality = 0, ≥10 years at diagnosis = 9.6
Fossa et al. [57]	85	Renal function	Age at treatment associated with long-term impairment (continuous variable)
Melanoma and selected carcinomas			
Brown et al. [58]	2158	SMNs	Excess of non-thyroid second cancers, greatest in people aged 25–40 years at diagnosis compared with other ages

Many studies report across multiple tumour sites but have been included in the table under the section in which they appear in the text (*indicates those reporting across multiple tumour sites).

AER, absolute excess risk; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BMD, bone mineral density; BMI, body mass index; CHF, congestive heart failure; CNS, central nervous system; CrRT, cranial radiotherapy; EAR, excess absolute risk; HR, hazard ratio; IHD, ischaemic heart disease; MI, myocardial infarction; O/E, observed/expected ratio; OR, odds ratio; PVB, cisplatin, vinblastine, bleomycin; RR, relative risk; SIR, standardised incidence ratio; SMN, second malignant neoplasms; SMR, standardised mortality ratio; TIA, transient ischaemic attack.

those treated at a younger age are postulated to result from: (i) a combination of low background incidence and (ii) immature cardiovascular tissue that may be more vulnerable to radiotherapy and chemotherapy.

endocrine and metabolic effects. Acute lymphoblastic leukaemia survivors are at increased risk of becoming overweight or obese if diagnosed at younger age (<10 or <6 years) compared with older patients [30, 31]. However, female survivors of lymphoma aged 5–9 years at diagnosis have increased risk of being underweight as an adult compared with those aged 15–20 years[odds ratio (OR) = 2.5] [32]. Similarly, among males, young age at diagnosis was also associated with low body mass index (BMI).

Cancer treatment-induced bone loss can cause significant morbidity to survivors. Among leukaemia survivors, older age at diagnosis increases risk for bone mineral density loss in addition to greater risk for avascular necrosis [33, 34]. Treatment before the age of 15 years is associated with increased risk (RR = 1.5, $P = 0.0001$) for hypothyroidism [35].

psychosocial effects. It has been reported that older age at diagnosis is associated with difficulty forming new relationships; however, it is possible that this reflects less time to adjust between treatment and entering such relationships or increased stability in an existing relationship [36]. Otherwise, older age at diagnosis appears to be protective against effects including alcohol misuse, mood disturbance, outlook on life, educational achievement and employment status [37–41].

central nervous system tumours

second malignant neoplasms. Development of SMNs, particularly subsequent central nervous system (CNS) tumours such as gliomas and meningiomas, is an established LE among childhood survivors, with reported fourfold increase in their development compared with the general population [65]. However, no literature was available to comment on TYA age effect.

endocrine and metabolic effects. Final height and BMI was investigated in 921 brain cancer survivors reporting young age at diagnosis as one of the strongest risk factors for adult short stature (≤9 versus 10–20 years) [42]. Additionally, among female patients only, younger age at diagnosis was associated with increased risk for obesity ($P < 0.001$ for trend). Both height and weight were self-reported in this study, which may be a limitation. Further to this, seizure disorder and CNS injury are more likely among the youngest patients (<5 years) [43, 44].

While multiple endocrinopathies such as hypothalamic and thyroid disorders are described among childhood survivors, no literature was available to comment on a TYA age effect.

psychosocial effects. Survivors of childhood CNS tumours, including TYA, have reduced chance of attaining higher education compared with sex- and age-matched controls. However, their chances of success increase with increasing age at diagnosis, so there may be a protective effect of TYA age compared with younger children [45].

sarcomas

second malignancies. Soft tissue sarcoma survivors are at increased risk for subsequent malignant neoplasms [46, 47].

Those treated at younger ages are at increased risk. Firstly, Ji et al. [46] describe those diagnosed ≤20 years at increased risk (SIR for SMN = 2.06, >20 years SIR for SMN = 1.41). Cohen et al. [47] support this reporting those diagnosed <10 years observed/expected ratio (O/E) = 9.1, ≥10 years O/E ratio = 5.2.

endocrine and metabolic effects. Kaste et al. [48] examined bone mineral density after sarcoma treatment in patients up to 21 years of age. They observed a relative protective effect for TYA compared with younger children, with the odds of low bone mineral density reducing by 16% per increasing year of age at diagnosis.

psychosocial effects. Looking at age effects in quality of life within and across cancer sites, a significant effect on social well-being was found among adolescents treated for bone cancer [49]. Those who became unwell age at 14–19 years reported more problems with social well-being (specifically family relationships and the ability to mix with others) than those diagnosed during childhood or adulthood.

When compared with sibling controls, bone tumour patients aged >12 years at diagnosis who underwent an amputation are reported as being significantly less likely to graduate from high school (OR = 0.6, $P = 0.047$) and college (OR = 0.8, $P = 0.037$) and ever have a job (OR = 0.2, $P = 0.003$) [50]. Similarly, they are reported as less likely to have health insurance than their siblings (OR = 0.7) [50].

germ-cell tumours

second malignant neoplasms. Among over 40 000 testicular cancer survivors, ∼15 000 of whom were <30 years at time of diagnosis [51], the O/E ratio for development of a second cancer was 1.41 correlated with radiotherapy, chemotherapy and combinations. The second cancers that patients were at the highest risk of developing were gastric, pancreatic and tumours of connective tissue. Specific and significant increases in excess relative risk (ERR) and excess absolute risk were seen in patients who were younger at diagnosis. Those diagnosed at age 20 years had a nearly threefold increase in ERR for second solid cancers compared with those diagnosed at age 40 years. Among testicular cancer survivors, diagnosis at age <30 years also appears to be a significant risk factor for developing a second germ-cell tumour, with a 36-fold increase in RR [52]. Compared with those diagnosed during childhood, TYA are at slightly greater excess risk of second cancer, although this must be balanced by their higher precancer population risk [53, 54].

cardiovascular and pulmonary effects. Among 2339 testicular cancer survivors, followed up for a median of 18 years, a moderately increased risk for premature myocardial infarction (MI) was observed [55]. Within this cohort, cardiac impairment is a particular risk for TYA compared with older adults. Being <30 years at diagnosis was associated with an increased SIR for MI (SIR = 1.37). Mortality from all circulatory diseases is also reported as significantly elevated in men diagnosed at age <35 years [56].

renal effects. Renal impairment is reported among testicular cancer survivors with a lower glomerular filtration rate after >850 mg/m^2 of cisplatin and after chemotherapy plus abdominal radiotherapy. Renal damage often remains subclinical, so would require routine assessment to detect it [57]. Fosså et al. [57] reported young age to be associated with reduced risk of renal impairment in patients who received radiotherapy for a germ-cell tumour. Long-term renal impairment was independently predicted by increasing age (β 0.09 in logistic regression).

melanoma and selected carcinomas

No studies examined for the effect of age at diagnosis on LEs in melanoma survivors. Among breast cancer (and to a lesser extent cervical cancer) survivors, there is a growing body of evidence reporting LEs >5 years of follow-up. However, the median age of patients at diagnosis in these studies is 50–60 years. Using their median age to describe any age effect (e.g. <50 versus ≥50 years) is not informative for TYA.

The only carcinoma we found reporting age effect was among a thyroid population. Among 30 000 thyroid cancer survivors, followed up over a maximum of 30 years and with an age range of 4–100 years, Brown et al. [58] observed a slight excess of non-thyroid second cancers, greatest in people aged 25–40 years at diagnosis compared with other ages.

discussion

We present the first comprehensive review of the published literature specifically describing the spectrum of LE of the diagnosis and treatment of cancer in TYA patients.

After cancer in childhood, comprehensive programmes such as the BCCSS and the CCSS prospectively collect data regarding LE of treatment. Many, but not all, findings from these childhood long-term studies will be seen in long-term survivors of adult cancer [66]. Participants in these studies were up to 16 and 21 years old at diagnosis, respectively. However, we identified no published prospective data that primarily focus upon TYA.

Clinicians managing patients with haematological cancer have been the forerunners of such work; there are almost twice as many leukaemia/lymphoma specific studies as for all other tumours. By collating information from studies that investigated tumour sites that effect TYA and limiting our search to studies that included TYA, we have described the long-term adverse effects. However, without TYA focussed studies, large areas remain unreported or unexamined. Moreover, our review is limited by the varying comparison groups and methods for describing risk. Uniformity in prospectively collected data would greatly strengthen the growing body of evidence.

It has been reported that young age at treatment is a risk factor for some LE among cancers common in middle age, such as breast cancer [67, 68]. Many, but not all, papers accounted for population risk in determining whether excess LE risk was observed in different age groups. It is not possible to account for age attained in making such a comparison between age groups, while simultaneously ensuring similar durations of follow-up to ensure comparable ascertainment of LE. Most papers reported results in terms of comparable duration of follow-up.

We have described many areas where being TYA at diagnosis may confer altered risk for a specific LE. Younger age at diagnosis is a risk factor for developing cardiovascular disease, second malignancies and death from non-cancer causes among testicular cancer and Hodgkin's disease survivors particularly. TYA diagnosed with primary bone cancer may have greater problems with psychosocial adjustment and social well-being. We believe that if this area was examined further, more detailed studies will reveal further data.

The provision of comprehensive care to young people after cancer places an obligation upon health services to establish LE services for TYA patients. Such services are currently in under development with primary and secondary care within the UK National Cancer Survivor Initiative. Their correct design, reflecting personalised assessment of need and information provision, may avoid haphazard management and the expensive consequences of untreated effects including cardiovascular and psychosocial morbidity.

Accurately characterising individuals at high risk who would benefit from a tailored screening programme is crucial. Factors to be considered would include age at diagnosis, primary tumour site or other patient characteristics including comorbidities. Identifying underlying genetic or molecular factors that might identify these patients at higher risk for late sequelae would radically alter approaches to survivorship but data are sparse. Development of new technology, bioinformatics and biomarkers alongside clinical trial cooperative groups may be a future direction [69]. The UK National Cancer Research Institute TYA study group proposes to investigate the long-term morbidity specifically of cancer treatment in TYA through developing a research database. Such an approach can establish the risks of LE comprehensively, identify those at risk and inform the design and timing of surveillance programmes in a cost-effective manner.

conclusions

There is much published literature about LE after cancer that includes a TYA population, but age is commonly not examined or described. Where it is examined, frequently age impacts upon the risk of LE. To obtain a true picture of the LE of cancer treatment in TYA, prospective systematic LE data collection is required if personalised, risk-stratified long-term follow-up care is to be provided with efficacious use of health service resources.

disclosure

The authors declare no conflict of interest.

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