Self-reported endocrine late effects in adults treated for brain tumours, Hodgkin and non-Hodgkin lymphoma: a registry based study in Northern Germany

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Abstract

Objective: Due to the increasing success and survival rates in the primary treatment of malignancies derived from the CNS as well as the hematopoietic system, endocrine late effects of cancer and its therapy are of growing importance. Despite evaluation of these late effects in patients treated for cancer in childhood, the impact on adults remains largely unclear.

Methods: 1035 adult patients primarily diagnosed with a CNS malignancy, a Hodgkin (HL) or non-Hodgkin lymphoma (NHL) between 1998 and 2008 were recruited via the regional epidemiological cancer registry covering ~2.8 million inhabitants in the federal state of Schleswig-Holstein, Northern Germany. The prevalence of endocrine disorders and current psychosocial impairment was assessed employing several questionnaires (SF-36v1, WHO-5).

Results: Fully completed questionnaires of 558 patients were available for subsequent analysis showing markedly reduced overall performance and psychological status when compared to German reference data. Thyroid disorders were reported in 16.3% of patients with 10.4% suffering from hypo- and 5.9% from hyperthyroidism. Overall, 17.6% stated to be affected by diabetes mellitus with an increased rate of 21.1% among NHL patients and 11.5% of participants were affected by osteoporosis.

Conclusion: Compared to German population based studies on the prevalence of diabetes mellitus, osteoporosis and thyroid disorders the frequency of all these endocrine problems was significantly increased in CNS, HL, and NHL cancer survivors. These data confirm that not only children and adolescents but also adult cancer patients are at risk for therapy associated endocrine late effects.

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Introduction

With increasingly successful therapeutic strategies for a wide spectrum of malignancies a continuously growing number of long-term cancer survivors have been

recognized to suffer from late effects of either the cancer itself or treatment sequelae (1, 2, 3). Large register based studies from the UK and USA which focussed on the

long-term effects in children suggested that a large number of these cancer survivors are particularly affected by late effects on the endocrine system. From these childhood data, it can be expected that overall between two and three million patients in Germany suffer from at least one chronic condition following cancer therapy (4, 5, 6). However, there are only a few systematic studies on late effects in adult cancer patients so far although the latter constitute the vast majority of long-term cancer survivors (7, 8, 9, 10).

Follow-up by oncologists is conventionally performed within a time frame of 5 years after the initial diagnosis of a malignant disease in accordance with tumour-specific guidelines. A patient who remains cancer-free thereafter is considered to be cured and the frequency of routine work-up is drastically reduced (11, 12). Subsequent examinations aim at detecting signs of relapse or progression of the malignant disorder but not on the identification of therapy-related effects. International studies including a systematic clinical follow-up on extended cohorts revealed that the risk of relapse decreases with an increasing time interval to the initial diagnosis; in contrast, the incidence particularly of endocrine late effects remains significantly elevated for many years even in the absence of any signs of relapse from the initial malignant disease. These data are almost exclusively derived from paediatric cancer survivors with a prevalence of at least one chronic disease in up to 70% of cases 30 years after initial diagnosis and about 50% related to an endocrine disorder (13, 14). These effects are frequently associated with unspecific symptoms such as fatigue and impaired capability of physical performance. Their clinical significance as well as the need for a specific diagnostic investigation is comprehensively outlined in several guidelines including the recently published German guideline on 'Endocrine aftercare following oncological diseases in childhood and adolescence' (<http://www.awmf.org/leitlinien/detail/ll/025-030.html>) as well as the Scottish guideline on 'Long term follow up of survivors of childhood cancer' (<http://www.sign.ac.uk/pdf/sign132.pdf>). Currently, however, it is still unclear to what extent these observations can be adopted for the oncological follow-up of late effects after treatment for a malignant disorder in patients who were adults at initial diagnosis. Currently, no systematic data on the prevalence of endocrine sequelae of cancer therapy in adults are available.

As data from children and adolescents suggested that the highest frequency of endocrine late effects are observed in patients with Hodgkin (HL) or non-Hodgkin lymphoma (NHL) and CNS tumours (CNS-T) we restricted our analysis to these patients (15, 16, 17, 18, 19).

In the present study we thus assessed the prevalence and distribution of endocrine late effects in adult long-term cancer survivors. This analysis should explore the frequency of late effects in this cohort which will help to generate programs for a structured follow-up program aimed at the early detection of late effects in this continuously growing population.

Subjects and methods

Potential study participants for our study on endocrine late effects in cancer survivors were identified by the dataset of the epidemiologic cancer registry of the federal state of Schleswig-Holstein, Germany. We restricted our analysis to patients with CNS-T (CNS-T, defined as ICD-10 C71), HL (HL defined as ICD-10 C81) or NHL (NHL defined as ICD-10 C82, C83, C84 or C85) diagnosed and initially treated between 1998 and 2008. All patients consented to be contacted for research purposes at the time of notification to the registry.

We contacted 1033 participants 5–15 years after diagnosis of CNS-T (8.8%, $n=91$), HL (22.6%, $n=233$) or NHL (68.6%, $n=709$; of these 222 patients with C82, 385 with C83, 34 with C84 and 68 with C85) (Supplementary Table S1, see section on supplementary data given at the end of this article) and asked to complete a set of questionnaires including items about demographic data, selected symptoms of endocrine diseases as well as self-reported physical and cognitive impairment. The paper-based questionnaire contained the following validated and reliable questionnaires: the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v1) (20, 21) and the WHO-5 questionnaire about well-being (22). The remaining questions were tested with ten persons for their comprehensibility.

The health-related quality of life (HRQOL) was determined by using the SF-36v1 (20, 21) and depressive symptoms by using the WHO-5 questionnaire about well-being (22). The scales of the SF-36v1 are scored from 0 to 100, with higher scores representing a better HRQOL. Clinicopathological data were provided by the registry.

Statistical analyses

Qualitative data was described with relative and absolute frequencies and quantitative data with arithmetic mean and s.d.

According to the manual raw data from the SF-36v1 was summarized into the physical (PCS) and the mental component scale (MCS). Those scores were transformed into norm-based scores, using normative data for the

German population (20, 21). The WHO-5 (including five questions) was analyzed using the sum score, with a maximum of five points per question (22). A score below 13 indicates poor wellbeing and is an indication for testing for depression under ICD-10 (<http://www.gp-training.net/protocol/psychiatry/who/whodep.htm>). A sum score of 19–25 represents very good well-being while a score of less than seven points indicates a clinically relevant depression. Correlation between the categorized WHO-5 sum scores and the PCS and MCS was tested with Spearman correlation.

For comparing the prevalence of selected endocrine diseases the age-adjusted prevalence rates of the general population were calculated on the basis of current epidemiological studies from Germany (23, 24, 25, 26).

Because of the slight difference between the entity groups prevalences are reported separately by sex. Data were analysed using SPSS version 20.

Ethical approval

The study protocol was approved by the ethical review board of the University of Luebeck.

Results

Study participants

Of the 1033 patients contacted, 557 (response rate 53.9%) responded with completed questionnaire and informed consent to participate in the study; 12 (1.2%) completed questionnaires were sent back but no informed consent was given. Furthermore, 62 (6.0%) persons actively refused participation, meaning that these patients responded to the questionnaire but stated at the beginning of the survey that they did not want to participate in the study. 237 (22.9%) persons did not respond and 94 (9.1%) persons moved to an unknown address. 72 (6.9%) persons were already deceased.

There were no notable differences between responding and eligible non-responding persons (excluding deceased persons and those who moved to unknown address). The non-responders received radiotherapy (52.4% vs 60.8%), immunotherapy (9.0% vs 14.2%) and bone marrow transplantation (1.3% vs 3.9%) less often. Men responded more often (51.4% vs 56.3%) as compared to women (48.6% vs 43.7%). All these trends did not reach statistical significance. Furthermore, age at diagnosis (53.3 ± 16.5 years vs 52.7 ± 14.6 years) and mean follow up time (8.9 ± 2.9 years vs 9.2 ± 3.0 years) did not differ between the two groups.

The overall population consisted of 313 (56.2%) men and 244 women, of whom 42 patients had a CNS-T (7.5%), 117 patients were diagnosed with HL (21.0%) and 398 patients with NHL (71.5%; of these 139 patients with C82, 218 with C83, 5 with C84 and 36 with C85). The mean age at diagnosis was 52.7 ± 14.6 years. The NHL-participants (mean age = 56.7 ± 12.5 years) were about 10–15 years older at diagnosis than participants with CNS-T or HL. The time since diagnosis was on average 9.6 ± 3.0 years. The mean BMI was 27.2 ± 5.79 kg/m². Altogether 48.1% ($n=268$) of participants underwent surgery, 76.1% ($n=424$) received chemotherapy and 60.9% ($n=339$) received radiotherapy (Table 1). 14.2% ($n=79$) of participants reported a recurrence and only 1.1% ($n=6$) metastases.

Secondary diseases and medication

On average about 17.2% of participants were treated with any kind of thyroid medication ($n=96$) (Table 2). The most frequently reported cause for hormone replacement was hypothyroidism (in total: 10.4%, $n=58$; CNS-T 9.5%, $n=4$; HL 18.3%, $n=22$; NHL 8.0%; $n=32$) (Fig. 1). Hyperthyroidism was reported by 5.9% of all study participants ($n=33$; CNS-T 11.9%, $n=5$; HL 4.3%, $n=5$; NHL 5.8%, $n=23$), and 9.2% reported thyroid nodules ($n=51$; CNS-T 9.5%; $n=4$; HL 6.8%; $n=8$; NHL 9.8%; $n=39$). Goiter was reported by 3.9% of participants ($n=22$; CNS-T 9.3%, $n=4$; HL 3.4%, $n=4$; NHL 3.5%, $n=14$).

Overt diabetes mellitus was reported by 17.6% ($n=98$) of participants. This was particularly frequent in the subgroup of patients with NHL (CNS-T 7.1%, $n=3$; HL 9.4%, $n=11$; NHL 21.1%, $n=84$; Fig. 1). Fitting to these data 13.5% of participants reported to receive antidiabetic medication (in total $n=75$; CNS-T 2.4%, $n=1$; HL 6.8%, $n=8$; NHL 16.6%, $n=66$; Table 2).

The self-reported prevalence of hyperlipidemia was 28.9% ($n=161$; CNS-T 23.3%, $n=10$; HL 23.3%, $n=27$; NHL 32.4%, $n=124$). Osteoporosis was reported by 11.5% ($n=64$) of participants (NHL 13.3%, $n=53$; HL 5.1%, $n=6$; CNS-T 11.6%, $n=5$) and 50.3% ($n=280$) reported symptoms indicative for muscle- and joint-disorders.

Currently, ongoing replacement therapy with recombinant growth hormone (GH) was reported by 0.4% ($n=2$; NHL 0.3%, $n=1$; HL 0.9%, $n=1$), while 1.1% ($n=6$) reported previous treatment with GH at some point since diagnosis (NHL 0.8%, $n=3$; HL 2.5%, $n=3$).

Finally, erectile dysfunction was reported by 41.1% of male participants ($n=128$; CNS-T 35.0%, $n=7$; HL 28.2%, $n=20$; NHL 46.3%, $n=101$; Fig. 2). Of the participating women, 29% reported that menopause occurred abruptly

Table 1 Characteristics of the study participants (absolute and (relative)) frequencies.

	All <i>n</i> = 557	NHL <i>n</i> = 398	HL <i>n</i> = 117	CNS-T <i>n</i> = 42
Age at diagnosis (years) ^a				
Mean ± s.d.	52.7 ± 14.6	56.7 ± 12.5	42.4 ± 15.5	43.7 ± 13.0
Age at survey (years)				
Mean ± s.d.	62.3 ± 14.5	66.2 ± 12.4	52.4 ± 15.5	53.1 ± 12.8
BMI (kg/m ²)				
Mean ± s.d.	27.2 ± 5.2	27.2 ± 5.1	27.3 ± 5.7	26.6 ± 4.7
Sex				
Female	244 (43.8)	176 (44.2)	46 (39.3)	22 (52.4)
Male	313 (56.2)	222 (55.8)	71 (60.7)	20 (47.6)
Occupational status				
Education/studies/reeducation	7 (1.3)	4 (1.0)	3 (2.6)	0 (0.0)
Unemployed	4 (0.7)	2 (0.5)	1 (0.9)	1 (2.4)
Not-working ^b	358 (64.3)	284 (71.4)	44 (37.6)	30 (71.4)
Parttime	34 (6.1)	22 (5.5)	12 (10.3)	0 (0.0)
Fulltime	117 (21.0)	57 (14.3)	51 (43.6)	9 (21.4)
Other	19 (3.4)	16 (4.0)	3 (2.6)	0 (0.0)
Missing	18 (3.2)	13 (3.3)	3 (2.6)	2 (4.8)
Marital status				
Married or civil union	358 (64.3)	268 (67.3)	68 (58.1)	22 (52.4)
Married, but living apart	10 (1.8)	6 (1.5)	0 (0.0)	4 (9.5)
Single	61 (11.0)	27 (6.8)	26 (22.2)	8 (19.0)
Widowed	58 (10.4)	50 (12.6)	7 (6.0)	1 (2.4)
Divorced	51 (9.2)	34 (8.5)	11 (9.4)	6 (14.3)
Missing	19 (3.3)	13 (3.3)	5 (4.3)	1 (2.4)
Surgery ^a				
Yes	268 (48.1)	171 (43.0)	57 (48.7)	40 (95.2)
No	201 (36.1)	161 (40.5)	39 (33.3)	1 (2.4)
Missing	88 (15.8)	66 (16.6)	21 (17.9)	1 (2.4)
Radiotherapy ^a				
Yes	339 (60.9)	209 (52.5)	91 (77.8)	39 (92.9)
No	127 (22.8)	112 (28.1)	14 (12.0)	1 (2.4)
Missing	91 (16.3)	77 (19.3)	12 (10.3)	2 (4.8)
Chemotherapy ^a				
Yes	424 (76.1)	292 (73.4)	111 (94.9)	21 (50.0)
No	95 (17.1)	77 (19.3)	3 (2.6)	15 (35.7)
Missing	38 (6.8)	29 (7.3)	3 (2.6)	6 (14.3)
Endocrine therapy ^a				
Yes	7 (1.3)	6 (1.5)	0 (0.0)	1 (2.4)
No	332 (59.6)	236 (59.3)	65 (55.6)	31 (73.8)
Missing	218 (39.1)	156 (39.2)	52 (44.4)	10 (23.8)
Immunotherapy ^a				
Yes	79 (14.2)	77 (19.3)	2 (1.7)	0 (0.0)
No	244 (43.8)	163 (41.0)	50 (42.7)	31 (73.8)
Missing	234 (42.0)	158 (39.7)	65 (55.6)	11 (26.2)
Bone marrow transplantation ^a				
Yes	22 (3.9)	22 (5.5)	0 (0.0)	0 (0.0)
No	276 (49.6)	194 (48.7)	51 (43.6)	31 (73.8)
Missing	259 (46.5)	182 (45.7)	66 (56.4)	11 (26.2)

^aRegister data.

^bRetirement, disability annuity, housework, illness/unable to work.

after their cancer treatment (*n* = 70; CNS-T 12.9%, *n* = 9; HL 20%, *n* = 14; NHL 67.1%, *n* = 47). The mean age of these women was 45.5 ± 8.7 years (CNS-T 41.7 ± 8.5 years, HL 41.1 ± 7.9 years, NHL 47.5 ± 8.4 years). Altogether 20% (*n* = 14) of the affected women were under or at the age of 40 years.

HRQOL and well-being

Altogether 54.6% (*n* = 304) of the participants reported increased lack of energy, tiredness and inefficiency. These symptoms occurred more frequently in the CNS-T group than in all other groups (CNS-T 73.8%, *n* = 31; HL 44.4%, *n* = 52; NHL 55.5%, *n* = 221).

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Table 2 Reports of current medication of the study participants (absolute and (relative)) frequencies.

	All <i>n</i> =557	NHL <i>n</i> =398	HL <i>n</i> =117	CNS-T <i>n</i> =42
Antihypertensive drugs				
Yes	254 (45.6)	200 (50.3)	43 (36.8)	11 (26.2)
No	300 (53.9)	196 (49.2)	74 (63.2)	30 (71.4)
Missing	3 (0.5)	2 (0.8)	0	1 (2.3)
Antidiabetics				
Yes	75 (13.5)	66 (16.6)	8 (6.8)	1 (2.4)
No	480 (86.2)	330 (82.9)	109 (93.2)	41 (97.6)
Missing	2 (0.4)	2 (0.5)	0	0
Thyroid medications				
Yes	96 (17.2)	56 (14.1)	33 (28.2)	7 (16.7)
No	460 (82.6)	341 (85.7)	84 (71.8)	35 (83.3)
Missing	1 (0.2)	1 (0.3)	0	0
Antidepressants				
Yes	60 (10.8)	46 (11.6)	8 (6.8)	6 (14.3)
No	495 (88.9)	350 (87.9)	109 (93.2)	36 (85.7)
Missing	2 (0.4)	2 (0.5)	0	0
Male sexual hormones ^a	<i>n</i> =313	<i>n</i> =222	<i>n</i> =71	<i>n</i> =21
Yes	3 (1.0)	2 (0.9)	1 (1.4)	0
No	306 (97.8)	216 (97.3)	70 (98.6)	20 (100.0)
Missing	4 (1.3)	4 (1.8)	0	0
Growth hormones				
Yes	2 (0.4)	1 (0.3)	1 (0.9)	0 (0.0)
No	551 (98.9)	393 (98.7)	116 (99.1)	42 (100.0)
Missing	4 (0.7)	4 (1.0)	0	0

^aMen only.

According to the results of the WHO-5 questionnaire clinically relevant depression was observed in 11.7% (*n*=65) of participants (CNS-T 28.6%, *n*=12; HL 11.1%, *n*=13; NHL 10.1%, *n*=40; Fig. 3). In addition, the results of the SF-36v1 questionnaire showed overall good mental (MCS; 46.3±13.7) and physical quality of life (PCS; 44.6±11.6). WHO-5 sum scores correlated highly with PCS (*r*s=0.378, *P*<0.001) and MCS scores (*r*s=0.707, *P*<0.001). Accordingly, SF-36v1 scores were lowest for those with a clinical relevant depression according to the WHO-5 criteria (WHO-5 score <7; PCS 24.9±12.5, MCS 36.5±11.0) (Fig. 3).

Contact to physician

In the last 12 months before the survey, almost all participants (98.9%, *n*=545) had contact to a physician and most frequently to a general practitioner (87.3%, *n*=477). Concerning other medical specialisations, NHL-participants most frequently visited an ophthalmologist (52.6%, *n*=204), HL-participants an oncologist (38.8%, *n*=45) and the CNS-T-participants a neurologist (68.3%, *n*=28).

Discussion

Late effects of cancer treatment are an increasingly recognized problem. It has been described predominantly in patients suffering from cancer during childhood and adolescence whereas hardly any data are available for the huge majority of patients treated for cancer in adulthood (7, 8, 9, 10). This study is the first population-based survey focussing on self-reported potential endocrine late effects in adult cancer survivors. When comparing results from this registry based study to currently available epidemiological data on the frequency of endocrine disorders in Germany (23, 24, 25, 26), an increased prevalence of these diseases in adult long-term cancer survivors is obvious and similar to that observed in patients diagnosed with cancer during childhood and adolescence (13, 17).

To the best of our knowledge this is the first report revealing an enhanced incidence of disorders such as osteoporosis (11.5% vs 7.6% in the general population) and diabetes mellitus (17.6% vs 13.8%) in a German cohort of adults followed after cancer treatment. We compared our data to recently published, age-adjusted normative data derived from large population based

Figure 1

Prevalence (percent with 95% CI) of selected diseases in the study population and the general population (23, 24, 25).

Inclusion criteria (osteoporosis): patients ≥ 50 years (male: $n=211$, female $n=159$).

studies from Germany as no data set of an age and sex matched cohort for a case control study was available (24, 25) (Fig. 1). These observations fit to previously published studies from UK where the evaluation of a General Practitioner database revealed a comparably increased risk of osteoporosis and diabetes, particularly in patients with non-Hodgkin disease. Interestingly, despite our expectations that children and adolescents would be more prone to develop late effects, especially of the bone, the frequencies of adult late effects observed in this study appear to be largely similar (5, 27, 28, 29, 30, 31, 32, 33). There are a number of potential underlying mechanisms, which due to the nature of the study must

remain speculative. They include the frequent therapeutic use of corticosteroids in the context of chemotherapy, a transient or persistent hypogonadism or radiation therapy of the abdomen and/or the skeletal system (34).

Functional deficiencies of the thyroid gland also occur at an elevated frequency (17.2% vs 11.6%) when comparing our data with German age-adjusted population-based studies (26). The incidence of replacement therapy in the context of hypothyroidism was elevated more than twofold (10.4% vs 4.8%). Comparably, a substantial impact of long-term cancer survivorship following cancer treatment was identified for the overall less common hyperthyroidism, the causes of which were

Figure 2

Prevalence (percent with 95% CI) of erectile dysfunction in the male study population and the general population (39).

not assessable in the current self-disclosure based study (23). Numerous past studies were able to profoundly establish irradiation of the head and neck region as an independent and dose dependent risk factor for the development of a functionally relevant thyroid disorder (35). We could not demonstrate an increased frequency of new benign and/or malignant thyroid nodules in our cohort of cancer survivors. As ultrasound of the thyroid is typically used in the standard evaluation of patients treated with thyroid medication in Germany this finding argues against an important role of cancer treatment in the formation of new thyroid nodules. The results contradict the findings in children and adolescents where the nodular changes due to irradiation are increased (36, 37). Potential causes for this apparent discrepancy remain speculative. They include an elevated sensitivity towards irradiation in the thyroid gland at a younger age and changes in the overall dose of irradiation. The latter appears to be relevant as the impact on the risk of developing a thyroid carcinoma is reversed at a cumulative irradiation dose of >20 Gy due to the continuous destruction of the organ itself. These data were however not retrieved for this study. Moreover, the length of clinical follow-up needs to be considered in this context as the majority of irradiation induced thyroid malignancies arise >10 years after local radiotherapy. It appears possible that the median time of clinical follow-up was too short in our current study and therefore no significantly elevated incidence of secondary malignancies was observed in any location as exemplarily depicted for thyroid neoplasia (14, 38).

Almost half of all male participants in our study reported on reduced libido and/or erectile dysfunction. This resembles a significant increase of the specific relative risk when compared to the general population (Fig. 2) (39). These observations are most likely secondary effects caused by a therapy-associated decrease in gonadal

functionality (40, 41, 42, 43). As untreated male hypogonadism (frequently observed following cranial irradiation) is a major risk factor for the development of premature osteoporosis, this may be one explanation for the high prevalence of this disorder in male long-term cancer survivors.

As the average age within the study group at diagnosis was 52.7 years, only a minor fraction developed acute or premature ovarian failure as frequently described after childhood cancer treatment (44). Due to this composition of our study group a systematic analysis of potential deficiencies in female sex hormones and their functional implications was not performed. It would however be interesting to assess this topic in further studies.

Numerous studies found a lack in GH (GH-deficiency) to be a dose dependent adverse effect of an irradiation of the neurocranium (18, 19, 45, 46). Surprisingly, only 1.1% of participants in our current study received a GH replacement therapy. None of these had been treated for tumours of the CNS, which are frequently treated by local radiation therapy and may subsequently develop GH deficiency. Adult-onset GH-deficiency (e.g. following cancer treatment) may lead to rather unspecific clinical manifestations including chronic fatigue-like symptoms, constipation, dry skin and weight increase. Interestingly, a substantial subset of our patients reported such symptoms with no apparent concurring clinical cause. It is therefore tempting to speculate that the number of diagnosed patients and the real number of long-term cancer survivors suffering from GH-deficiency may substantially differ due to a lack of clinical awareness (47) and that at least a proportion of symptoms categorized as 'chronic fatigue syndrome', may result from undiagnosed secondary endocrine disorders (48, 49).

Figure 3

Results for the SF-36 mental component scale (mean with s.d.) separated by WHO-5 categories (< 13 points indicating poor well-being) and tumour entity.

This may have a major impact on the care of patients as the specific needs of long-term cancer survivors concerning these endocrine problems may not be sufficiently met in the transition from primary oncological care to routine GP follow-up (15, 50, 51). Moreover, complex endocrinological disorders such as pituitary deficiency require specialized endocrinological evaluation not generally included in the previous mentioned settings which may result in these diseases remaining underdiagnosed despite annual medical contact in the vast majority of patients.

When we compared the depression scores of our patients with the data from healthy cohorts in Germany, norm-based PCS and MCS scores of the overall population were close to 50, whereas 27% of the study population showed MCS scores <40 and 12% had WHO-5 scores indicative of a clinically manifest depression. These observations confirm the results of several previously published international studies and support the need for regular psychological/psychiatric evaluation of cancer patients and cancer survivors (13, 52, 53, 54).

There are some limitations to our study. The size of the study group is limited and we restricted our analysis to three cancer entities. Moreover, our observations are derived from questionnaire-based voluntary self-disclosures and not the actual medical records, which may distort our information on concurrent diseases and introduce inaccuracy regarding medical treatment. However, other health-care studies have shown that patients can provide valid (55) and reliable (56, 57, 58) information about their treatment and diseases. Furthermore, the epidemiological cancer registry only collected data concerning first line therapy following initial diagnosis. It is therefore possible that some patients received additional treatment at relapse. At the time of the survey, none of the patients were receiving oncological therapy. The aim of this study was to assess the frequency of late effects after cancer therapy, defined as any disease occurring after therapy with a possible causal link to the specific treatment. As from our current data, a connection between a specific treatment and a particular late effect could not be derived. This matter remains an important subject for future studies. Additionally, we were forced to rely on historic data derived from independent population-based studies as an age-adjusted cohort was not available for comparative studies.

In summary, we were able to show that long-term cancer survivors with cancer treatment in adulthood are at a significantly elevated risk of developing endocrine and/or metabolic disorders such as hypo- or hyperthyroidism, osteoporosis as well as diabetes mellitus

as has been reported for children and adolescents. Based on the incidence of NHL in Germany of ~15/100 000 citizens per year and the combined disease related mortality, there are expected to be over 7000 patients every year newly considered long term NHL survivors (<http://www.lymphome.de/InfoLymphome/NonHodgkinLymphome/HaeufUrsache.jsp>; http://www.tumorregister-muenchen.de/facts/surv/surv_C8285G.pdf). Even with regard to this rare entity, there are almost four times as many adult patients potentially suffering from late effects following NHL therapy than the overall annual incidence of cancer in childhood in Germany (<http://www.kinderkrebsregister.de/>) supporting the relevance of potential endocrine late effects in patients treated primarily in adulthood.

Routine oncological follow-up for most entities terminates 5 years after initial diagnosis when no signs of persistence or recurrence have emerged. Thereafter, most patients are referred to their GP for subsequent clinical follow-up. Our findings clearly show that a substantial subset of adult long-term cancer survivors can be expected to develop therapy-related late endocrine disorders, which due to their degree of complexity, will require interdisciplinary attention as it is already implemented following childhood cancer (59).

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0174>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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