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Original Article

Patient-Reported Outcomes of Accelerated Aging: A Novel Approach to Investigate Second Cancer Risk in Adolescent and Young Adult (18–39 Years) Cancer Survivors

Daniël J. van der Meer[1,2,‡], Susan Zevenbergen[1,2,‡], Carla Vlooswijk[3], Rhodé M. Bijlsma[4], Suzanne E.J. Kaal[5], Jan Martijn Kerst[1], Jacqueline M. Tromp[6], Monique E.M.M. Bos[7], Tom van der Hulle[8], Roy I. Lalisang[9], Janine Nuver[10], Mathilde C.M. Kouwenhoven[11,12], Winette T.A. van der Graaf[1,7], Olga Husson[*,1,2,13]

[1]Department of Medical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, North Holland, The Netherlands
[2]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, North Holland, The Netherlands
[3]Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, Utrecht, The Netherlands
[4]Department of Medical Oncology, University Medical Center, Utrecht, Utrecht, The Netherlands
[5]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Gelderland, The Netherlands
[6]Department of Medical Oncology, Amsterdam University Medical Centers, Amsterdam, North Holland, The Netherlands
[7]Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, South Holland, The Netherlands
[8]Department of Medical Oncology, Leiden University Medical Center, Leiden, South Holland, The Netherlands
[9]Department of Internal Medicine, Division of Medical Oncology, GROW-School of Oncology and Reproduction, Maastricht UMC+ Comprehensive Cancer Center, Maastricht, Limburg, The Netherlands
[10]Department of Medical Oncology, University Medical Center Groningen, Groningen, The Netherlands
[11]Department of Neurology, Amsterdam University Medical Centers, Amsterdam, North Holland, The Netherlands
[12]Cancer Center Amsterdam, Cancer treatment and quality of life, Amsterdam, North Holland, The Netherlands
[13]Department of Surgical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, South Holland, The Netherlands

[*]Corresponding author: Olga Husson, Department of Surgical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Tel: +31 10 704 0704; Email: o.husson@erasmusmc.nl
[‡]These authors shared first authorship.

Abstract

Background: Adolescent and young adult cancer survivors (AYAs, aged 18-39 years at first diagnosis) have a higher second cancer risk. Accelerated aging is hypothesized as underlying mechanism and has been described clinically by 6 indicators; fatigue, low quality of sleep, low mood, lack of motivation, subjective memory complaints, and poor exercise tolerance. Using patient-reported outcomes, we aimed to identify clusters of accelerated aging among AYA cancer survivors and to investigate their association with second cancer development.

Patients and Methods: Patient, tumor, and treatment data were obtained from the Netherlands Cancer Registry. Patient-reported clinical indicators and second cancer data were obtained from the SURVivors (5-20 years) of cancer in AYAs (SURVAYA) questionnaire study between 1999 and 2015. Latent class and multivariable logistic regression analyses were performed.

Results: In total, $n = 3734$ AYA survivors with known second cancer status ($n = 278$ [7.4%] second cancers) were included. Four latent clusters were identified and named based on their clinical indicator features; (1) high accelerated aging (31.3%), (2) intermediate accelerated aging without poor exercise tolerance (15.1%), (3) intermediate accelerated aging without lack of motivation (27.4%), and (4) low accelerated aging (26.2%). AYAs in the high accelerated aging cluster were more likely to have second cancer (odds ratio: 1.6; 95% CI, 1.1-2.3) compared to the low accelerated aging cluster.

Conclusion: AYAs with a higher burden of accelerated aging were more likely to develop a second cancer. Validation of the clinical indicators and how to best capture them is needed to improve (early) detection of AYAs at high risk of developing second cancer.

Key words: adolescents and young adults; cancer survivors; patient-reported outcomes; second cancer; accelerated aging; oncology.

Implications for Practice

If proven valid, the use of reliable patient-reported clinical indicators that can accurately capture the cellular changes underlying accelerated aging could provide a simple and noninvasive way to measure the accelerated aging burden among cancer survivors. This information may enable the detection of early signs of accelerated aging during follow-up, which can then benefit the quality of life of cancer survivors by providing important direction to the development of targeted interventions. Findings of this first explorative study are promising, but more research is needed before the clinical indicators should be adopted in clinical practice.

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Introduction

In the Netherlands, adolescents and young adults (AYAs) are defined as those aged 18 to 39 years at the time of their first cancer diagnosis.[1] Nevertheless, the age group that defines AYAs varies between countries and can be adjusted depending on the research question.[2] AYAs form a distinct population that is diagnosed with a unique spectrum of different cancer types, including those typically seen at pediatric (eg, leukemia, neuroblastoma), older adult age (eg, colorectal carcinoma, breast carcinoma) and some with the highest incidence at AYA age (eg, testicular cancer, thyroid carcinoma).[3] There is also evidence that AYA cancers are biologically different compared to malignancies developed at an older age.[4] In addition to their disease, AYAs are also confronted with age-specific challenges, such as living on their own, studying and having the desire to start a family.[5]

The number of AYAs diagnosed with cancer is increasing worldwide.[6-9] Simultaneously, the 5-year relative survival among AYAs is above 85%, resulting in a growing population of young cancer survivors at increased risk of developing survivorship related medical issues, including a 1.2 to 2-fold higher second cancer risk compared to the general population in high-income countries.[9-17] Cancer survivors in general also have an increased risk of developing chronic health diseases, suggesting an early onset of aging.[18-20] Although aging is a complex biological process that is difficult to study, there is growing evidence that cancer and treatments that cure or control cancer are associated with a higher risk of accelerated aging by speeding up the accumulation of cellular damage.[18,20] This process of accelerated aging within an individual is defined as having a higher biological age than the chronological age.[20] The underlying cellular changes responsible for accelerated aging are described in the concept of hallmarks of aging and include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.[21] To increase knowledge, Cesari et al[22] proposed 6 clinical indicators that describe accelerated aging and can be measured in a noninvasive way. These indicators are the clinical expression of the hallmarks of aging and include fatigue, low quality of sleep, low mood, lack of motivation, subjective memory complaints, and poor exercise tolerance.

Despite the fact that aging is one of the major risk factors for cancer[18,23] and that survival rates of AYAs have improved, there is still little knowledge on how cancer (treatment) affects the aging process within AYAs. Accelerated aging processes have been associated with increased second primary cancer risk,[20] but these findings are mostly based on childhood cancer survivors and do not extrapolate well to the AYA population.[18,20,24]

To increase knowledge about the impact of accelerated aging on second primary cancer development in AYAs, research should be conducted on this topic. This explorative study aims to perform latent class analysis to first investigate whether clusters of accelerated aging can be identified and, secondly, to investigate the association between possible accelerated aging clusters and second primary cancer development among AYA cancer survivors in the Netherlands.

Patients and Methods

Data Source and Study Population

Patient-reported outcome data were obtained from the population-based questionnaire study among SURVivors of cancer in AYAs (SURVAYA), which contains Health-related Quality of Life (HRQoL) data that were retrospectively collected to examine the psychosocial and medical health outcomes of 5 to 20-year first primary AYA cancer survivors in the Netherlands. Survivors of cancer at AYA age were identified from the Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and contains complete records of all newly diagnosed malignancies with national coverage since 1989. Identified survivors were invited to participate in the SURVAYA study by their (former) medical specialist. Willing participants were asked to complete a survey (online or paper) with questions based on the European Organization for Research and Treatment for Cancer (EORTC) survivorship core questionnaire (QLQ-SURV100) between May 2019 and June 2021.[25] More detailed recruitment information about the SURVAYA study is provided elsewhere.[1] The SURVAYA database is already linked to the NCR, which was further used to obtain objective data on patient, tumor and treatment characteristics, including age at first cancer diagnosis, and follow-up time since first cancer diagnosis. Data were included of all 5 to 20-year AYA cancer survivors that were aged 18 to 39 years at the time of their first cancer diagnosis between 1999 and 2015 and participated in the SURVAYA study. Nonmalignant tumors and cases with an unknown or missing second primary cancer status were excluded.

Measures

Second Primary Cancer

Self-reported second primary cancer information was included as the health outcome of interest and was obtained from the SURVAYA database, where it was questioned as "Have you been diagnosed with cancer again at any time after your first cancer diagnosis?". On a 4-point scale, participants could fill-in what applied the most from the following outcomes: "No", "Yes, recurrence of original cancer diagnosis or metastasis of original cancer diagnosis", "Yes, a different kind of cancer, namely", and "I don't know". Outcomes were dichotomized to second tumor (yes/no), where the new "Yes" category included the "Yes, a different kind of cancer, namely" outcome only. All other outcomes were included in the "No" category, except for the outcome "I don't know", which was excluded (n = 18, 0.5%).

Indicators of Accelerated Aging

To identify latent clusters based on different response patterns of the 6 clinical indicators of accelerated aging, we identified related QLQ-SURV100 questions within the SURVAYA database. The full list of questions, which were identified per clinical indicator, is provided in Supplementary Table S1. For most questions, participants were asked to indicate symptoms on a 4-point scale what applied most to them during the past week. Symptoms of exercise tolerance were assessed in general. Questions were all coded with the 4 options "Never", "Sometimes", "Often" and "A lot". We dichotomized the above 4-point scale into "Yes" ("Sometimes", "Often", and "A lot") and "No" ("Never"). For each clinical indicator, a

singular question that best described the definition proposed by Cesari et al[22] was selected for inclusion in the main analysis based on expert opinion only, as no literature was available for further guidance. For this reason, a sensitivity analysis was also performed to investigate the robustness of our initial findings by using a different set of clinical indicator related questions (Supplementary Table S1).

Covariates

Sociodemographic and clinical factors that were associated with accelerated aging or (second) cancer development were identified based on the literature and included as covariates. Sociodemographic factors that were identified, included sex, age at first cancer diagnosis and patient-reported sedentary behavior, smoking, alcohol, and drugs use. Clinical factors included active follow-up status, time since diagnosis, family history of cancer and first primary cancer chemotherapy, radiotherapy, and hormone therapy.[12,23,26-35]

Statistical Analysis

Latent class analysis was conducted with Latent GOLD version 6.0 (Statistical Innovations Inc., Belmont, MA, USA) to identify clusters of AYAs based on their response patterns of the clinical indicators of accelerated aging. The core assumption underlying the latent class methodology is that clusters exist and that across cases they demonstrate patterns of observed scores.[36] The latent class analysis was performed, using the following 3 steps.

Step 1: Selecting a Latent Class Model

We first identified the best fit latent class model (aim 1). A one-class model was fitted, and classes were added until a best-fit model was identified. Models were all fitted with the default maximum likelihood estimator. Model selection was based on multiple fit statistics, including the Bayesian Information Criterion (BIC) and Akaike information criterion (AIC), with lower IC values indicating a better model fit.[37] Considering the more strict penalization for model complexity, the BIC outcome was decisive in selecting the final model when different models were indicated by the various criterion.[37]

Step 2: Classification of Individuals

Diagnostic criteria were also taken into consideration, including entropy which indicates the accuracy that the model defines clusters based on the posterior probabilities.[36] Values can vary from 0 to 1, with values closer to 1 indicating better class membership assignment. An entropy cutoff of 0.8 was used to define acceptable assignment of class membership. Bivariate residuals were assessed to test the local independency assumption, with values below 3 indicating no violation.[38]

Step 3: Investigating Relation with External Variables

To investigate the association between the accelerated aging clusters and second primary cancer (aim 2), covariate-adjusted multivariable binary logistic regression analysis was performed with SPSS Statistics, version 27, IBM SPSS, Chicago, IL, USA. Odds ratios (ORs) and 95% confidence intervals (CIs) were assessed to see whether the latent clusters of accelerated aging were independently associated with second cancer development. *P*-values < .05 indicated statistical significance.

Results

Study Population

In total, $n = 4010$ AYAs were extracted from the SURVAYA study. From this selection, we included $n = 3734$ patients with available second primary cancer status. Characteristics of AYA cancer survivors are presented in Table 1 and Supplementary Table S2. Mean age at first cancer diagnosis was 31.6 years (standard deviation [SD] = 5.9). The majority was female (61.1%). The most common first primary cancer types included breast cancer (23.7%), germ cell tumors (17.6%), and lymphoid hematological malignancies (14.8%). From the included patients, $n = 278$ (7.4%) reported a second primary cancer (69.1% females and 30.9% males).

Clustering Based on the Indicators of Accelerated Aging

Latent class analysis identified multiple accelerated aging clusters based on the set of questions that was selected to define the clinical indicators. The best-fit 4-cluster model was selected based on the BIC, AIC, and AIC3, which all agreed. At 0.6, the bivariate residuals were far below 3, indicating that the local independency assumption was satisfied. Entropy of the selected model was below the 0.8 cutoff at 0.6, indicating poor posterior class membership assignment (Supplementary Table S3). Most AYAs within the 4-cluster model belonged to cluster 1 (31.3%), which scored high (probabilities > .7) on most clinical indicators of accelerated aging and was, therefore, named the "high accelerated aging" cluster because of these characteristics (Fig. 1). The least amount of AYAs belonged to cluster 2 (15.1%), which scored intermediate (probabilities between 0.4 and 0.8) on most clinical indicators, except for poor exercise tolerance (probability 0.03). Therefore, this cluster was named "intermediate accelerated aging without poor exercise tolerance". Cluster 3 included 27.4% of the AYA population where they scored intermediate on most clinical indicators, except for lack of motivation (probability 0.03). This cluster was, therefore, named "intermediate without lack of motivation". Cluster 4 contained 26.2% of the AYA population, who scored low on all clinical indicators (probabilities ≤ 0.3) of accelerated aging and was named the "low accelerated aging" cluster for this reason (Fig. 1). Baseline characteristics of the different clusters are presented in Supplementary Table S4. Relatively speaking, most females (70.1%), smokers (48.4%), and alcohol drinkers (82.0%) were included in the high accelerated aging cluster. Subjects in this cluster were also most often still under active follow-up (66.4%) and most often reported having a second primary cancer (9.8%) compared to the other clusters.

Association Between Accelerated Aging Clusters and Second Primary Cancer

Outcomes of the multivariable binary logistic regression analysis are presented in Table 1. ORs indicated that AYAs in the high accelerate aging cluster had a 1.6-times (95% CI, 1.1-2.3, $P < .01$) higher odds of having second cancer compared with those in the low accelerated aging cluster after adjusting for sociodemographic and clinical factors. No significant effects were found for the intermediate clusters.

Sensitivity Analysis

Using a different set of questions, a best-fit 4-cluster model with similar clinical indicator patterns to the main analysis

Table 1. Population characteristics and binary logistic regression odds ratios and 95% confidence intervals of the identified clusters of accelerated aging and their association with developing a second primary cancer among adolescent and young adult (AYA) cancer survivors aged 18-39 years at the time of first primary cancer diagnosis in the Netherlands between 1999 and 2015.

Characteristics[a]	Total population *n*= (%)	Second primary cancer[d] *n*= (%)	No second cancer, *n*= (%)	OR (95% CI)	*P*-value
Clusters of accelerated aging[b]					
Cluster 1: High accelerated aging	1156 (31.3)	113 (40.9)	1043 (30.5)	1.6 (1.1-2.3)	**.007**
Cluster 2: Intermediate accelerated aging without poor exercise tolerance	558 (15.1)	33 (12.0)	525 (15.4)	1.1 (0.7-1.7)	.745
Cluster 3: Intermediate accelerated aging without lack of motivation	1012 (27.4)	75 (27.2)	937 (27.4)	1.2 (0.8-1.7)	.360
Cluster 4: Low accelerated aging	968 (26.2)	55 (19.9)	913 (26.7)	REF	REF
Missing[a]	40	2	38		
Sex					
Male	1452 (38.9)	86 (30.9)	1366 (39.5)	1.3 (0.9-1.7)	.133
Female	2282 (61.1)	192 (69.1)	2090 (60.5)		
Age at first diagnosis (years)					
18-24	577 (15.5)	27 (9.7)	550 (15.9)	1.0 (1.0-1.1)	**.003**
25-34	1645 (44.1)	112 (40.3)	1533 (44.4)		
35-39	1512 (40.5)	139 (50.0)	1373 (39.7)		
Under active follow-up					
Yes	2131 (57.1)	187 (67.5)	1944 (56.3)	0.5 (0.4-0.6)	**<.001**
No	1598 (42.8)	90 (32.5)	1508 (43.7)		
Missing[a]	5	1	4		
Time since first diagnosis (years)					
5-9	1268 (34.0)	61 (21.9)	1207 (34.9)	1.1 (1.1-1.2)	**<.001**
10-14	1308 (35.0)	73 (26.3)	1235 (35.7)		
15-20	1158 (31.0)	144 (51.8)	1014 (29.3)		
Smoking					
Yes	1617 (43.4)	137 (49.3)	1480 (42.9)	1.1 (0.9-1.5)	.412
No	2113 (56.7)	141 (50.7)	1972 (57.1)		
Missing[a]	4	0	4		
Alcohol					
Yes	3146 (84.3)	229 (82.4)	2917 (84.5)	0.9 (0.7-1.3)	.724
No	586 (15.7)	49 (17.6)	537 (15.6)		
Missing[a]	2	0	2		
Drugs					
Yes	928 (24.9)	70 (25.2)	858 (24.9)	1.2 (0.9-1.7)	.185
No	2803 (75.1)	208 (74.8)	2595 (75.2)		
Missing[a]	3	0	3		
Sedentary behavior (hours/week)					
Median (IQR)	13 (10-18)	14 (10-17)	13 (10-18)	1.0 (1.0-1.0)	.399
Missing[a]	56	3	53		
Family history of cancer					
Yes	2533 (67.9)	198 (71.2)	2335 (67.6)	1.0 (0.8-1.2)	.644
No	910 (24.4)	61 (21.9)	849 (24.6)		
I don't know	288 (7.7)	252 (6.8)	269 (7.8)		
Missing[a]	3	0	3		
Radiotherapy[c]					
Yes	1779 (47.7)	141 (51.1)	1638 (47.4)	0.9 (0.7-1.2)	.624
No	1951 (52.3)	135 (48.9)	1816 (52.6)		
Missing[a]	4	2	2		
Chemotherapy[c]					
Yes	2117 (56.8)	157 (56.9)	1960 (56.8)	1.0 (0.7-1.3)	.882
No	1613 (43.2)	119 (43.1)	1494 (43.3)		

Table 1. Continued

Characteristics[a]	Total population *n*= (%)	Second primary cancer[d] *n*= (%)	No second cancer, *n*= (%)	OR (95% CI)	*P*-value
Missing[a]	4	2	2		
Hormone therapy[c]					
Yes	457 (12.3)	40 (14.5)	417 (12.1)	0.9 (0.6-1.3)	.490
No	3273 (87.8)	236 (85.5)	3037 (87.9)		
Missing[a]	4	2	2		
Total	3734 (100.0)	278 (100.0)	3456 (100.0)		

Odds ratios were adjusted for sex, age at first cancer diagnosis, active follow-up status, time since first cancer diagnosis, smoking, alcohol, drugs, sedentary behavior, family history of cancer, radiotherapy, chemotherapy, hormone therapy. Significant *P*-values are in bold.
[a]Missing groups were not included in the percentage calculations of the characteristics. Percentages may not total to 100% due to rounding.
[b]Clusters were identified with latent class analysis, using questions related to clinical indicators of accelerated aging from the population-based questionnaire study among SURVivors of cancer in AYAs (SURVAYA). In total, *n* = 40 cases with missing values on the clinical indicator of accelerated aging were excluded by the latent Gold software.
[c]Treatment received at any time during the treatment process, irrespective of duration or completion.
[d]Second primary cancer was self-reported. Missing cases and "I don't know" were excluded from further analysis.
Abbreviations: CI: confidence interval; OR: Odds ratio; IQR: interquartile range.

was identified and significant higher odds of second cancer were now also observed for AYAs belonging to both intermediate accelerated aging clusters compared with those in the low accelerated aging cluster (Supplementary Fig. S1 and Supplementary Tables S5-S7).

Discussion

This explorative study identified 4 different accelerated aging clusters, including a "high accelerated aging", "intermediate accelerated aging without poor exercise tolerance", "intermediate accelerated aging without lack of motivation", and a "low accelerated aging" cluster. AYAs belonging to the high accelerated aging cluster had a higher odds of having second primary cancer compared to the low accelerated aging cluster. This was also the case for both intermediate accelerated aging clusters in the sensitivity analysis when using a different set of clinical indicator questions.

Clustering Based on the Indicators of Accelerated Aging

To our knowledge, this is the first study to investigate the impact of clinically defined accelerated aging on second cancer development in AYA cancer survivors by using patient-reported outcomes and the clinical indicators of accelerated aging that were proposed by Cesari and colleagues to cluster subjects.[22] Clustering of subjects based on patient-reported symptoms of fatigue, depression, and low quality of sleep among cancer survivors has been done by other studies that reported a positive correlation and co-occurrence between these symptoms.[39,40] It is well-described in the literature that fatigue is a highly prevalent symptom throughout the survivorship continuum.[41] This is consistent with our findings, which show that fatigue was prevalent across 3 of the 4 accelerated aging clusters that were identified. Although survivors in the intermediate accelerated aging without poor exercise tolerance cluster seemingly maintained an excellent physical functioning in exercise tolerance, they still had a high probability of experiencing fatigue. Previous findings have shown that survivors have a declined physical function after cancer treatment, but that improvement over time is possible.[42] This could explain the good exercise tolerance within the intermediate accelerated aging without poor exercise tolerance cluster, but not the other intermediate cluster. Despite poor exercise tolerance, survivors belonging to the other intermediate cluster experienced almost no lack of motivation and low mood, indicating low symptoms of depression.[43,44] Altogether, these findings illustrate the complexities and differences in (emotional) issues that can arise in young cancer survivors.

Association Between Accelerated Aging Clusters and Second Primary Cancer

Studies investigating risk factors of second cancer among AYA cancer survivors are scarce and often limited to the more well-known factors, such as smoking, alcohol intake, and previous cancer treatment.[12,28,30,32-35] Studying these well-known risk factors can be difficult considering that accurate treatment dose/exposure data are often unavailable, specifically in population-based cancer registries. Exploring novel factors, like accelerated aging, that could further explain second cancer development and help improve disease prevention and the quality of life in cancer survivors may be crucial.[20,23,45] Accelerated aging processes, like cellular senescence (ie, irreversible arrest of cell proliferation) and DNA damage, have been associated with increased second primary cancer risk by an accumulating body of evidence.[20,46-48] Many commonly used cancer treatments (eg, chemotherapy, radiotherapy, CDK4/6 inhibitors, epigenetic modulators, and immunotherapy) induce cell senescence to preclude cancer cells from proliferating.[20,46] These treatments often also cause complex proinflammatory responses known as a senescence-associated secretory phenotype (SASP), which can lead to accelerated aging and tumorigenesis in cancer survivors by promoting cell proliferation, migration, invasiveness, angiogenesis, and epithelial-mesenchymal transition of cancer cells.[20,46-48] Evidence also suggest that DNA damage (ie, DNA double-strand breaks) accelerates aging[20,49,50] and DNA damage from alkylating agents has been associated with increased leukemia risk[20,51] but can likewise result from radiotherapy and cytotoxic drug therapies.[52] Pranikoff et al further described that young adult cancer survivors experience more frailty and decreased muscle mass, which indicates accelerated aging and was associated with an increased risk of

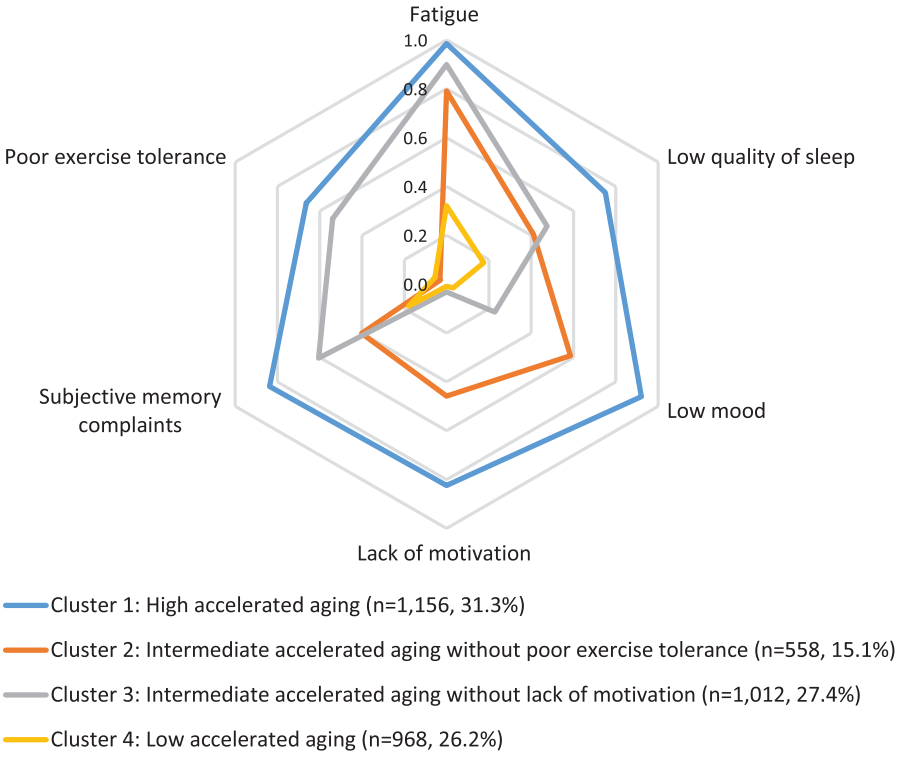

Figure 1. Latent patterns of the 6 clinical indicators of accelerated aging based on the estimated best-fit 4 cluster-model among adolescent and young adult (AYA) cancer survivors aged 18-39 years at the time of first primary cancer diagnosis in the Netherlands between 1999 and 2015. The x-axis lists the names of the clinical indicators, and the y-axis provides the average probability of class membership for each of the indicators. High scores indicate an increased probability of the indicator.

adverse health outcomes, including fatigue and worse overall physical health.[53]

Future Perspective

Findings of this first exploration support the hypothesis that cancer survivors with a higher accelerated aging burden are more likely to develop a second cancer. Nevertheless, outcome inconsistencies for the intermediate accelerated aging clusters between our main and sensitivity analysis indicate that the set of questions selected to represent the clinical indicators can affect the observed relation between the clusters of accelerated aging and second cancer development. As such, more research into the representativeness and the formal definition of the clinical indicators of accelerated aging should be conducted before incorporating this knowledge in clinical practice. The QLQ-SURV100 is a relatively new tool in patient-reported outcome studies, therefore, clinically relevant cutoff scores indicating problems (eg, for high accelerated aging burden) are lacking. Recent work by Lidington and colleagues, identified cutoff scores for 9 scales of the EORTC QLQ-C30 that indicate the need for supportive needs among AYAs.[54] The use of validated questionnaires specifically developed to measure the clinical indicators may also enable researchers to better capture symptoms related to a high accelerated aging burden among cancer survivors. For example, the self-reported 20-item Multidimensional Fatigue Inventory (MFI) scale,[55] specifically designed to evaluate fatigue, may be such a questionnaire and might be used to explore accelerated aging in future research. Reliable patient-reported outcome measurements of the accelerated aging indicators may optimize causal research into the effect of accelerated aging on survivorship-related (adverse) health outcomes (eg, second cancer), which may enable the detection of early signs of accelerated aging during follow up. Such valuable information may benefit the psychosocial and medical-related quality of life of cancer survivors by providing important direction to the development of targeted interventions that mitigate the underlying clinical processes.

Limitations

This study has several limitations. First, the SURVAYA data were not collected for the purpose of this study and, therefore, the questionnaire may not contain the optimal set of questions to capture the clinical indicators of accelerated aging. The current definition of the clinical indicators by Cesari et al also leaves room for interpretation. Our findings that a high burden of accelerated aging increases the odds of second cancer should, therefore, be interpreted with caution, specifically because of the outcome inconsistencies observed when including a different set of questions to define the clinical indicators in our main and sensitivity analysis. As such, research on how to best define the clinical indicators of accelerated aging and the best way to capture this information is needed to increase reliable knowledge and uptake of accelerated aging in AYA

cancer research. This might also improve entropy, which in this study was below the 0.8 cutoff that is typically stated to indicate acceptable assignment of class membership. Second, some malignancies may have been incorrectly classified as second primary cancer, since it was self-reported. This is likely considering that 7.4% of our study population reported having a second primary cancer, which is relatively high compared to other studies, leading to a possible overestimation of the amount of second primary cancers in this study.[10,12,13,16] Unfortunately, we were unable to ascertain second cancer status with objective data from the Netherland cancer registry. Data about time since second cancer diagnosis was also not available. As such, the possibility exists that the second cancer diagnosis and treatment may have caused the accelerated aging symptoms (inverse association). This is highly likely considering that the retrospective SURVAYA questions reflected the experience of patients within the last week for most clinical indicators. Finally, it must be noted that there likely is a healthy survivorship bias considering the inclusion of 5 to 20-year survivors. Also, healthy individuals are more likely to have participated in the SURVAYA study, causing a possible underestimation of the accelerated aging and second primary cancer burden. Findings may also not be translatable to the entire AYA survivors population considering that certain demographic groups were overrepresented within the SURVAYA database (mostly highly educated White women).[1]

Conclusion

In conclusion, findings of this first explorative study demonstrate that AYA cancer survivors can be divided into 4 clusters of accelerated aging based on the proposed clinical indicators and that AYAs with a higher burden of accelerated aging have higher odds to develop second primary cancer compared to those with a low burden of accelerated aging. Nevertheless, outcomes should be interpreted cautiously, as the data used in this study were collected for a different purpose. Likewise, further research into the representativeness of the clinical indicators of accelerated aging and the best way to capture them is needed before this information should be incorporated in clinical practice to aid earlier detection of AYAs that have a higher risk of second cancer development.

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Conflict of Interest

Mathilde C.M. Kouwenhoven reported expert testimony for SAG Neurology EMA (no fee), advisory scientific committee (no fee) for Centre for Human Drug Research, Leiden. Winette T.A. van der Graaf reported advisory role with PTC Therapeutics and Springworks (to the institute) and research grant from Lilly (to the institute). The other authors indicated no financial relationships.

Author Contributions

Conception/design: D.J.v.d.M., S.Z., W.T.A.v.d.G., O.H. Provision of study material or patients: C.V., R.M.B., S.E.J.K., J.M.K., J.M.T., M.E.M.M.B., T.v.d.H., R.I.L., J.N., M.C.M.K. Collection and/or assembly of data: C.V., O.H. Data analysis and interpretation: D.J.v.d.M., S.Z. Manuscript writing: D.J.v.d.M., S.Z., O.H. Final approval of manuscript: All authors.

Data Availability

Population-based cancer registry data used in this study can be requested from the Netherlands Cancer Registry (request number: K22.274). Patient-reported outcome data from the SURVAYA questionnaire study can be obtained upon reasonable request from Dr. Olga Husson, principal investigator at the Netherlands Cancer Institute (o.husson.nki.nl).

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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