Association of cancer with functional decline at old age- a longitudinal study in Danish twins

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Title: Association of cancer with functional decline at old age- a longitudinal study in Danish twins

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Abstract

Introduction: There is evidence that older adults with cancer have a higher risk of functional decline than cancer-free older adults. However, few studies are longitudinal, and none are twin studies. Thus, we aimed to investigate the relationship between cancer and functional decline in older adult (aged 70+ years) twins.

Materials and Methods: Cancer cases in Longitudinal Study of Aging Danish Twins were identified through the Danish cancer registry. Functional status was assessed using Hand Grip strength (HGS) (6 years follow-up), and self-reported questions on mobility (10 years follow-up) and cutoffs were defined to assess functional decline. Cox regression models were performed for all the individual twins. In addition, we extended the analysis to discordant twin pairs (twin pairs with one having cancer and the other being cancer-free), to control to a certain extend for (unmeasured) shared confounders (genetic and environmental factors).

Results: The analysis based on individual twins showed that individual twins with cancer are at increased hazard of worsening HGS (HR = 1.37, 95% CI: 1.04,1.80) than cancer-frees. Among the discordant twin pairs, twins with cancer had a higher hazard of worsening HGS (HR = 3.50, 95% CI: 1.15,10.63) than cancer-free cotwins. In contrast, there was no evidence of a difference between hazard of experiencing mobility decline for cancers compared to cancer-frees, in both individual twins and discordant twin pairs analyses.

Discussion: Cancer was associated with HGS functional decline in old individual twins and discordant pairs. Our results strengthen the importance of comprehensive geriatric assessment in older adults with cancer, as well as the importance of routine assessment of functional status. Promoting physical activity through exercise training programs could enable to prevent functional decline in older adults with cancer.

Keywords: older adults, cancer, functional decline, hand grip strength, mobility, twins

Introduction

Functional status is a broad topic that encompasses a wide variety of abilities needed to accomplish daily tasks and meet fundamental needs [1-3]. The risk of functional decline increases with age and studies have shown that many factors, including cancer, are associated with functional decline [4-6]. As the population ages, the number of cancers increases, and older adults are particularly prone to a decline in functional status that might be due to cancer and or its treatment [3, 7]. According to a recent review, functional decline in patients with cancer is multifactorial with shared risk factors such as social factors, comorbidities, tumor- and treatment-related factors [3]. In addition, functional decline in older adults with cancer seems to be accelerated [3]. Identifying whether older patients with cancer have a higher risk of functional decline than cancer-free older adults make a profound contribution in promoting healthy aging as well as preventing and managing if it is diagnosed early.

Older individuals with cancer have faster functional decline than those cancer-free suggesting that cancer and/or its treatment might change the aging trajectory [8]. Cancer patients who received surgery, chemotherapy, or radiation were more likely to experience a decline in functional status, especially in the first year after diagnosis compared to those without cancer [9]. The functional status of most cancer patients declines in the first year after diagnosis, but among long-term cancer survivors, functional status seems to return to pre-cancer levels. The rate of decline may differ depending on the type of cancer and may be influenced by comorbidities [9]. Among the studies looking at cancer as a risk factor for functional decline, most have focused on self-reported functional status, such as basic activities of daily living whereas few has been conducted using [9, 10] objective measurements of physical performance such as hand grip strength [8]. Additionally, considering cancer status and functional status longitudinally can provide more insights into its trajectories [3].

Twin studies are advantageous as a paired twin design can pave the way to understanding the familial effects on functional decline. Twins are representative of their background populations, beneficial for matching, and important in identifying the influence of genetic and environmental factors [11]. Notably, the discordant twin pair design in which one twin is diagnosed with cancer and the other is not is a powerful approach for

controlling familial confounding [12]. The match of a case twin with a cancer-free cotwin allows to control for certain unmeasured shared confounding factors (genetic and environmental). Matching within monozygotic (MZ) pairs control to some extend for genetic and early childhood environmental factors, while matching within dizygotic (DZ) pairs control partially the childhood environmental factors.

Although there is substantial evidence linking cancer and functional decline, few studies have been longitudinal, [3, 6, 9, 13] and none of these are twin studies. Therefore, the aim of our study was to investigate the relationship between cancer and functional decline using both direct observations and self-reported functional status measurements in older adult Danish twins. Matched design has some drawbacks in being vulnerable to unobserved non-shared confounders. Hence, an unmatched analysis including individual twins (singletons and pairs) which treats twins as singletons was performed in addition to the matched analysis (including discordant pairs), which takes the familial effects into account.

Materials and Methods

Study Population

Longitudinal Study of Aging Danish Twins (LSADT) is a longitudinal cohort study that started in 1995 in Denmark from a survey on twins as a national Danish health register [14]. A detailed description and an overview of inclusion waves, participation numbers and follow-ups of LSADT has previously been reported [15]. Briefly, members of like-sex twin pairs born in Denmark prior to 1920 were included in 1995 and followed up every two years until 2005. New participants were also included in 1997, 1999, and 2001 and subsequently followed at two-year intervals. The LSADT cohort includes 4,731 individual twins who completed the baseline assessment, either through in-person interview or by proxy. Because twins were selected without regard to their co-twin's mortality, many of the participating twins did not have a surviving co-twin who participated in the survey. As a result, many of the participants in LSADT are ‘singleton twins’ [16]. At the inclusion and follow-ups, information was collected on sociodemographic characteristics, medical history and diseases, medication, neurocognitive testing, physical functioning, and psychological well-being. Information on survival status was retrieved from the Danish Central Person Register, which is continuously

updated [17]. Our study included individual twins and discordant pairs for cancer from the LSADT cohort with at least one measurement on functional status.

Cancer cases diagnosed from January 1, 1944, to January 20, 2005, in the LSADT participants were identified through the Danish Cancer Registry, which has recorded all new malignant tumors in the Danish population since 1943 [18]. All Danish residents have been assigned a unique personal identification number enabling to identify them in all national Danish registries. As some LSADT participants were diagnosed with more than one cancer in the period: i) the primary cancer was chosen if it occurred during the LSADT follow-up, ii) the following cancer in the LSADT follow-up was chosen if an individual was diagnosed with cancer at least 10 years before inclusion in the LSADT. Basal cell carcinoma and non-melanoma skin cancers were excluded.

Outcomes

In LSADT, functional status was assessed every two years by direct and self-reported measurements; the direct measurement included hand grip strength (HGS) (6 years follow-up, from wave 1999 to 2005), whereas the self-reported measurement included mobility (10 years follow-up, from wave 1995 to 2005). An overview of the participation number and duration of follow-up for each population of functional status measurements are shown in **Supplementary Figures S1-S2**.

The HGS is an estimate of upper limb strength and correlates with strength in other muscle groups, so it has been used to estimate overall strength [19]. It was measured in kilogram by a hand-held dynamometer, using a maximum of three measurements taken with the strongest hand i.e., If one hand does not have three attempts, the remaining 1 or 2 measurements were counted. It was set to be missing if all the three attempts were not made at least on one hand, or if there was a difference of 20 kg or more between two measures on one hand [19]. Weak HGS was defined as a HGS < 26kg for men and < 16kg for women [8, 20].

Mobility was assessed using the Activities of Daily Living (ADL) Strength [21]. The ADL strength scale is a composite measure of mobility disability that measures the ability to perform activities in a given environment. It contains 11 items measuring basic activities related to the ability to do indoor (e.g. walking up and down the stairs, engaging in any kind of hard exercise) and outdoor (e.g. taking an outdoors walk, running without resting) activities. Before computing the scale score, items were transformed to a 1 to 4 scale, where 1 = could

do without fatigue, 2 = could do with fatigue, 3 = could do with difficulty or an aid, and 4 = could not do. Hence, the scale score is an average of the 11 items, with higher scores indicating lower levels of strength. If an item was missing, the mean for that item was substituted. If more than one item was missing, the scale was coded as missing [21]. As no cutoff is available to define mobility decline using this scale, we inspected the Receiver-operated characteristics (ROC) curves to determine best cutoff points for mobility decline, using the HGS as a reference. Cut-off points for maximizing the sensitivity and specificity were determined using the Youden Index [22]. The ROC analysis for determining ADL strength decline cutoff based on the Youden index resulted in cutoff = 1.9, with sensitivity = 69% and specificity = 73%. Hence, an ADL strength score > 1.9 was defined as low mobility.

Thus, in the present study, functional decline was defined as the occurrence of weak HGS and/or low mobility through LSADT follow-up.

Covariates

Sociodemographic and health-related variables from LSADT inclusion which were previously reported as associated with functional decline were considered as covariates [4, 10, 23]. Considered sociodemographic factors were sex, marital status (married, divorced, widowed), and education (primary, secondary, post-secondary). Education was coded according to the International Standard Classification of Education (ISCED). Regarding health-related factors, we considered smoking status (never, former, current), BMI (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m2), self-rated health (good, fair, poor), depression (yes, no), cognitive impairment (yes, no), and Charlson's comorbidity index (CCI). Depression score was computed as the sum of the affect and somatic scores, as previously described [24]. Cognitive impairment was evaluated using the mini-mental state examination (MMSE) and a threshold of 24 [25], with MMSE score inferior to 24 considered as cognitive impairment. CCI, a weighted index that represents the prevalence of 19 chronic diseases over a predetermined period, was calculated according to an updated version ICD-10 diagnostic coding from Danish National Patient Registry, with higher scores indicating increased morbidity [26, 27].

Statistical Analyses

To study functional decline over time in the above functional status measurements, we performed functional data analysis [28]. With discrete data, the ability to look at changes over time is limited as analysis involve looking mostly at follow-ups (time points) which describes little information in between. We obtained fitted curves for each individual over a time period by the observed period. This is done through basis splines that are piecewise polynomials constrained to join smoothly at time points. This provided interpolated values of the functional measurements for the outcomes in the study.

We analyzed the two functional measurement outcomes, HGS and mobility, as 1) time-to-event which is the age at occurrence of decline (weak HGS or low mobility) and 2) continuous variables.

For the time-to-event as outcomes, we estimated the non-parametric cumulative incidence of functional decline by cancer status for all the individual twins (singletons and pairs), using the Aalen-Johansen estimator, taking censoring, left truncation (delayed entry), and competing risk of death into account [29]. The cumulative incidence defines as the risk of event before time *t*. We estimated the lifetime risk for functional decline as risk of functional decline before age 85. Next, Cox regression was used with cancer as a time-varying covariate, age as the underlying time scale, to estimate the association between the occurrence of functional decline, adjusting for within pair dependence in the models. All associations were adjusted for the sociodemographic and health-related characteristics at the inclusion (sex, self-rated health, marital status, depression, CCI, education, BMI, smoking and, cognitive impairment). We extended the analysis for studying association among the twin pairs to control to a certain extend for (unmeasured) shared confounders by comparing discordant pairs for cancer. We used the stratified Cox regression model where the baseline hazard functions are pair specific. The proportional hazard assumption was evaluated based on Scaled Schoenfeld residuals. Hazard ratios (HRs) and 95% confidence intervals (CIs) from the regression models were reported.

For the two functional measurements, HGS and mobility as continuous variables, we looked whether there was any evidence of a significant difference in functional measurements between cancer twin and cancer-free co-twins at 6, 12, 18, and 24 months after cancer diagnosis, using the within-between mixed model regression, controlling for the unmeasured shared confounders within and between twins [30]. Model validation was done to investigate the normality of residuals and random effects. An alpha error of 0.05 was accepted. All the statistical analyses were carried out using the statistical software R version 4.1.1.

The study was conducted under approval by the Danish Scientific Ethics Committees and in agreement with the Helsinki II declaration. All participants in the surveys have given written informed consents.

Results

From 4,731 individual twins in LSADT, 2,886 individuals had at least one HGS measurement and 4,713 individuals at least one mobility measurement (**Supplementary Table S1**). Of these, 3,951 were cancer-free at follow-up and 780 had a diagnosis of cancer (569 were diagnosed before inclusion in LSADT (prevalent), and 211 from inclusion to last follow-up visit in LSADT (incident)). The most common types of cancer in LSADT were breast, bladder, prostate, colon, and lung cancers. Sociodemographic and health-related descriptive characteristics of the LSADT population for HGS and mobility at inclusion are shown in **Supplementary Table S2**. In both HGS and mobility population outcomes, more than 50% of the population sample was female, had a median age of 75.1 [IQR: 71.8, 81.9], was married, and had at least a secondary education. At inclusion, median of HGS was 24 [IQR: 19, 32] for individuals with cancer and 25 [IQR: 20, 35] for those without cancer. Median of mobility was 1.7 [IQR: 1.4, 2.8] for individuals with cancer and 1.6 [IQR: 1.3, 2.4] for cancer-frees.

At inclusion, median of HGS for cancer twins was 25 [IQR: 20, 33] and for cancer-free cotwins was 25 [IQR: 20, 35]. Median of mobility for cancer twins was 1.6 [IQR: 1.4, 2.5] and for cancer-free cotwins was 1.6 [IQR: 1.3, 2.3] (**Supplementary Table S3**).

Results based on individuals

The cumulative incidence of functional decline for two populations by age stratifying by cancer status (cancer, cancer-free) and sex (male, female) appear in **Figures 1 and S3**. The lifetime risk for weak HGS in individuals with cancer and without cancer was estimated approximately 40% and 30% respectively. In addition, the lifetime risk for low mobility in individuals with cancer and without cancer was estimated approximately 60% and 50% respectively (**Figure 1**). Moreover, from cumulative curves stratified by cancer status and sex, men with no cancer appeared to have a lower risk of developing weak HGS and mobility when compared to both men with cancer and women with and without cancer (**Figure S3 A)**. Both men and women with cancer had a higher risk of low mobility, but women were worse than men (**Figure S3 B**).

From the adjusted Cox regression, hazard of developing weak HGS for individuals with cancer was 37% higher than that of cancer-frees (HR: 1.37, 95% CI: 1.04,1.80). There was no evidence of a difference between hazard of experiencing low mobility for cancer individuals compared to cancer-frees after adjustment (HR: 1.15, 95% CI: 0.96,1.38) (**Table 1**).

Results based on discordant pairs

The cumulative incidence of functional decline for discordant pairs (including 138 pairs with HGS and 278 pairs with mobility measurements) showed a higher risk of worsening in functional capacity of cancer twin for HGS and mobility compared to cancer-free cotwin (**Figure 2).** The lifetime risk for weak HGS in twin with cancer and cotwin without cancer was estimated approximately 40% and 18% respectively. In addition, the lifetime risk for low mobility in twin with cancer and cotwin without cancer was estimated approximately 65% and 58% respectively. From the stratified Cox regression, the hazard of developing weak HGS for twin cancer was 3.5 times that of cancer-free cotwin (HR: 3.50, 95% CI: 1.15,10.63). There was no evidence of a statistically significant difference between hazard of experiencing low mobility for cancer twins compared to cancer-free cotwins (HR: 1.71, 95% CI: 0.94,3.10) (**Table 2**).

As a sensitivity analysis we looked at the analysis of MZ and DZ discordant twins separately. Results can be found in **Supplementary Table S4**.

Furthermore, we assessed whether there is any evidence of significant difference in HGS and mobility measurements between twin with incident cancer and cancer-free co-twin longitudinally at 6, 12, 18 and 24 months after cancer diagnosis. After controlling for within and between shared confounders in the model, twins with cancer had a 3.59 kg (95% CI: -6.53, -0.65) decrease in HGS compared to cancer-free cotwins. There was no evidence of statistically significant difference of decline in mobility between cancer twin and cancer-free co-twin. However, there was a significant decline in the trajectories of mobility in cancer twins at 18 and 24 months compare to the mobility measurement at cancer diagnosis (**Table 3**).

Discussion

This study, aimed at investigating the relationship between cancer and functional decline in older adult Danish twins. Both in individual twins and discordant twin pairs, older adults with cancer presented higher HGS decline than cancer-free older adults. Similar results were not found regarding mobility decline. To our knowledge, this is the first twin study investigating the relationship between cancer and functional decline in a longitudinal twin cohort.

In our study, older adults with cancer had a higher hazard of weak HGS than cancer-free individuals (for both individual twins and discordant twin pairs, even when considering the incident cancers only), and the association for discordant pairs was stronger than for individual twins. In the sensitivity analysis enabling us to control for certain genetic and environmental factors in MZ and DZ twins, hazard of frailty for MZ and DZ twins with cancer was larger than their cotwins without cancer. These results were similar when analyzing all pairs, however, no evidence of statistical significance was observed in MZ and DZ pairs due to the small number of pairs. Our findings are consistent with previous studies showing that patients with cancer were more likely to have a decline in HGS than those without cancer [8, 31, 32]. Moreover, men seemed to have a lower risk of developing weak HGS when compared to women, in both cancer-free and cancer individuals. While studies reported steeper HGS decline in men than in women [33, 34], partly explain by higher maximum voluntary contraction and greater HGS in men throughout life [35], studies also reported lower prevalence of weak HGS in men [36-38].

The association between cancer and functional decline, here occurrence of weak HGS, is probably multifactorial including cancer and non-cancer related factors. Regarding cancer factors, it is difficult to disentangle whether the decline is due to the disease or its treatments. Indeed, functional decline may be partly attributed to the adverse effects of cancer treatments, which affect the biological process known as “hallmark of aging” [39] related to cancer and functional decline or contribution of genes and environmental factors. Several studies have reported associations between cancer-related treatment and functional decline [3]. These associations were mainly shown for systemic and radiation therapies, while the impact of surgery on functional decline is less clear. As we included cancer and cancer-free older adults in our study, we did not consider

cancer treatments, but further research could address this question by studying determinants of functional decline in older adults with cancer.

Regarding mobility, no evidence of a difference between hazard of cancers and non-cancers in both individuals and discordant twin pairs (including analysis of MZ and DZ discordant pair separately) was observed. However, both men and women with cancer appeared to have a higher non-significant risk of low mobility, and women were worse than men. A recent study reported that mobility limitations increased consistently from age 50 years and women were more likely than men to have a mobility limitation between the ages of 50 and 80 [40]. Differences in functional decline between individuals with and without cancer have been demonstrated in several studies using self-reported assessments [9, 10]. However, comparing our results to previous ones is difficult as functional status was mainly assessed using instrumental activities of daily living (IADL) [41] and ADL [42] in previous studies. Functional limitations can be hierarchized [43] as mobility limitations or low limitations measured by the Rosow–Breslau scale [44], moderate activity limitations measured by Lawton's IADL [41], and severe activity limitations measured by Katz's ADL [42]. The self-reported questionnaire used in the LSADT is a scale close to Rosow–Breslau scale [44], evaluating mobility and low functional limitation. As mobility limitations are not rare in older adults, we cannot dismiss the possibility that a large part of individuals in our cohort already presented with mobility limitations at inclusion, reducing the probability to observe a decline [45]. Indeed, a recent study on participants from 14 countries reported that mobility limitations increased consistently from age 50 years and reported a probability of mobility limitations at age 80 ranging from 40 to 60% [40].

Maintaining functional abilities in daily living is the key determinant for healthy aging, and a key issue for older adults themselves [46-48]. Several studies report that functional impairment is associated with adverse health outcomes, such as hospitalizations, institutionalization, and mortality, but also with increased health costs and poorer quality of life [49-51]. In the way to address declines in functional status, it appears important to identify factors contributing to functional decline in older adults. Although functional decline is part of the aging process and age is a major risk factor, this decline can be accelerated by other factors including age-related diseases (e.g. dementia, stroke, cardiovascular diseases, depression, visual impairment, osteoarthritis, etc.) [52-55]. The present work contributes to improving knowledge about these factors by highlighting the

importance of cancer in functional decline. Our results strengthen the importance of comprehensive geriatric assessment in older adults with cancer. They also support the importance of routine assessment of functional status in this population to detect functional decline early and help preserving functional abilities, e.g. by implementing physical activity interventions [56]. Several studies report a positive association between physical activity and hand grip strength [57-60], as well as between physical activity and activity limitations in older adults [61-63]. Thus, promoting physical activity in older adults could also prevent functional decline and contribute to better quality of life. Physical activity could be included through exercise training in prehabilitation or follow-up programs for older cancer patients. Indeed, some randomized clinical trials showed the benefit of these programs in body strength and physical functioning [64, 65].

The first strength of this study lies on the longitudinal design enabling us to look at the trajectories of functional status changes over several years of follow-ups (6 years for HGS, 10 years for mobility). In addition, the use of twin data provided familial risk and trajectories of functional decline through comparison of cancer twin with cancer-free cotwin. The usage of a matched twin pair design enhanced the validity and efficiency of the analysis controlling for certain (unmeasured) shared confounding factors. This feature makes the design particularly attractive as confounding factors may be dissected empirically beyond what is achievable in other design of study [11]. Importantly, our twin data including both MZ and DZ twins enabled us to control for certain genetic and environmental factors that are shared by both cancer and functional decline. In fact, MZ pairs enable controlling to some extend for genetic and early childhood environmental factors and DZ pairs partially for early childhood environmental factors. Then, our analyses including all individual twins were controlled for many important sociodemographic and health-related factors. Although this study was not set out to establish causality, we were able to make inferences about the temporal relationship between the exposure and the outcomes. Finally, time-to-event analysis was performed with the competing risk of death taken into account as the risk of functional decline in the absence of competing risk of death may result in a risk estimate bias.

Our study also presents some limitations. First, we lacked self-reported measurements related to moderate or severe functional limitation as the ADL [42] and IADL [41], which are probably the most important in older adults. In fact, functional limitation is part of the aging process with low functional limitation coming first and

is not rare in older adults. In addition, moderate or severe limitation has more consequences in daily living. Second, previous studies suggested that functional decline is different regarding cancer types and that for some cancers e.g. for breast cancer, years after cancer diagnosis, functional status is close to cancer-free individuals [9]. However, we were not able to study the varying impact of cancer types due to small samples in a longitudinal aspect. Third, in our study there could be unobserved confounding dropouts due to poor health. This is treated in paper by Frederiksen et al. 2006 using longitudinal measurements of HGS [19], through inverse probability weighting approach to remedy this. In our paper, this also played a role where we focus on the comparison of cancer and cancer-frees. Having these cancer cases unobserved for HGS or mobility would expect the difference larger. Hence, we see our estimates as conservative. Moreover, it is important to note that for both HGS and mobility the percentages of missing values was low.

In summary, our study showed that individual twins and twin pairs with cancer have a higher hazard of developing weak HGS than those without cancer. Future research may investigate whether cancer impact functional decline even before diagnosis, as well as quantifying important determinants of functional decline in older adult twins with cancer by comparing the excess risk of twin cases to that of a cancer-free co-twin. These studies will shed further light on the relationship between functional decline and cancer and determine whether some individuals are more at risk than others. It is important that clinicians who treat older patients with cancer provide a long-term care plan including regular functional status assessments and exercise interventions to mitigate, prevent, and reverse this decline. Our results support the importance of comprehensive geriatric assessment (CGA) to identify impairments in older adults. However, CGA is known to be time-consuming and may be difficult to implement for all older adults in clinical practice. Thus, screening tools as G8 or VES-13 might be used as a tool to assess the functional status of old patients with cancer to accurately capture their susceptibility to accelerated decline.

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Competing interests

The authors declare that they have no conflicts of interest.

Data availability Statement

According to Danish and EU legislations, transfer and sharing of individual-level data require prior approval from the Danish Data Protection Agency and require that data sharing requests are dealt with on a case-by-case basis. However, we welcome any enquiries regarding collaboration and individual requests for data sharing. Requests can be directed to JvBH, jhjelmborg@health.sdu.dk.

Authors contributions

Conceptualization and design, A.M., J.v.B.H., A.G., J.R. and M.E; methodology A.M., J.v.B.H., and A.G.; formal analysis, A.M.; writing original manuscript, A.M.; project administration, A.M. and J.v.B.H.; review and editing, A.M., J.R., M.E., J.J., J.v.B.H., and A.G. All authors have read and agreed to the published version of the manuscript.

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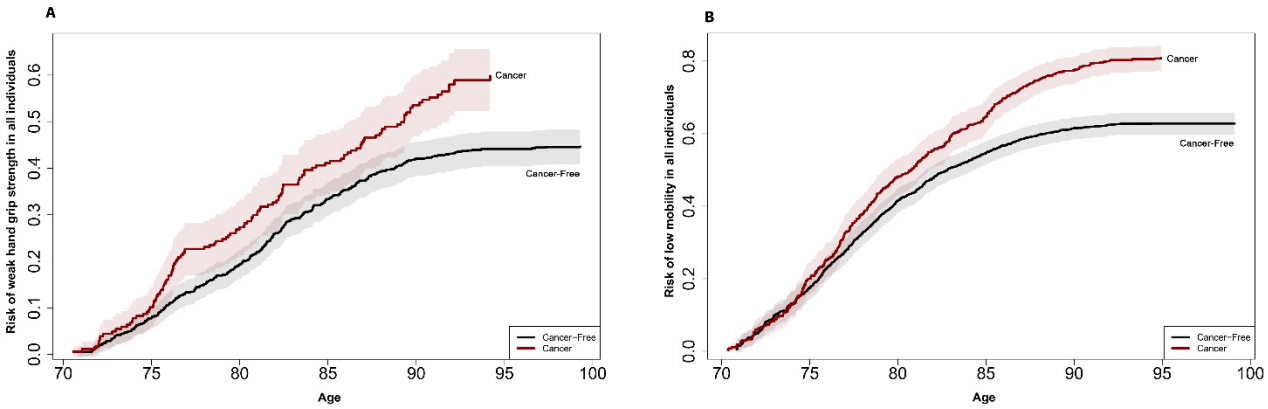

524
525 **Figure 1.** Cumulative incidence and 95% confidence interval for A) HGS, B) mobility for all individual
526 twins by age stratifying by cancer status.

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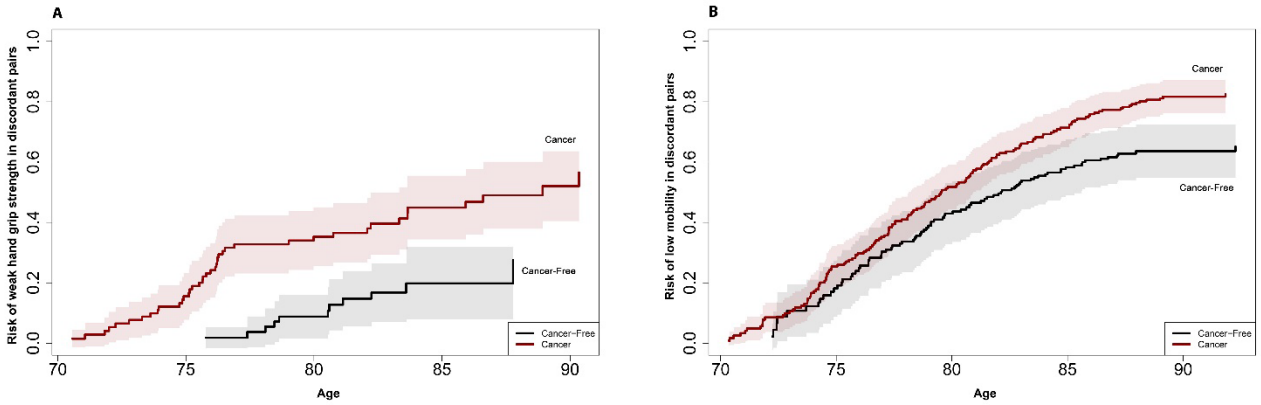

528

529 **Figure 2.** Cumulative incidence and 95% confidence interval A) HGS, B) mobility for discordant twin pairs;
530 cancer twin and cancer-free cotwin.

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Table 1. Association between cancer status and occurrence of functional decline including all individual twins in HGS and mobility populations using Cox regression.

	Unadjusted		Adjusted	
	HR	**95% CI**	**HR**	**95% CI**
HGS	1.23	(1.00,1.51)	1.37	(1.04,1.80)
Mobility	1.25	(1.11,1.42)	1.15	(0.96,1.38)

Abbreviations: 95% CI: 95% confidence interval; HR: Hazard ratio; HGS: Hand Grip Strength.
Adjusted for: sex, self-rated health, marital status, depression, CCI, education, BMI, smoking, and cognitive impairment.

Table 2. Association between cancer status and occurrence of functional decline for discordant twin pairs in HGS and mobility population outcomes using stratified Cox regression.

	HR	**95% CI**
HGS (N = 138 pairs)	3.50	(1.15, 10.63)
Mobility (N = 278 pairs)	1.71	(0.94, 3.10)

Abbreviations: 95% CI: 95% confidence interval; HR: Hazard ratio; HGS: Hand Grip Strength

Table 3. Associations between cancer status and functional measures for HGS and mobility over time at 6, 12, 18, and 24 months after cancer diagnosis in discordant pairs using Within-Between mixed effects models.

		Estimate (coefficient)	**95% CI**
	cancer status	-3.59	(-6.53, -0.65)
	time (6 months)	-0.06	(-0.49, 0.72)
HGS	time (12 months)	-0.04	(-0.47, 0.39)
(N = 25 pairs)	time (18 months)	0.06	(-0.37, 0.49)
	time (24 months)	0.14	(-0.29, 0.57)
	cancer status	0.12	(-0.09, 0.34)
	time (6 months)	0.03	(-0.01,0.08)
Mobility	time (12 months)	0.06	(0.01, 0.10)
(N = 67 pairs)	time (18 months)	0.09	(0.04, 0.13)
	time (24 months)	0.12	(0.07, 0.16)

Abbreviations: 95% CI: 95% confidence interval; HGS: Hand Grip Strength

Supplementary Materials

Association of cancer with functional decline at old age-a longitudinal study in Danish twins

Afsaneh Mohammadnejad, Jesper Ryg, Marianne Ewertz, Juulia Jylhävä, Jacob v. B. Hjelmborg, Angéline Galvin

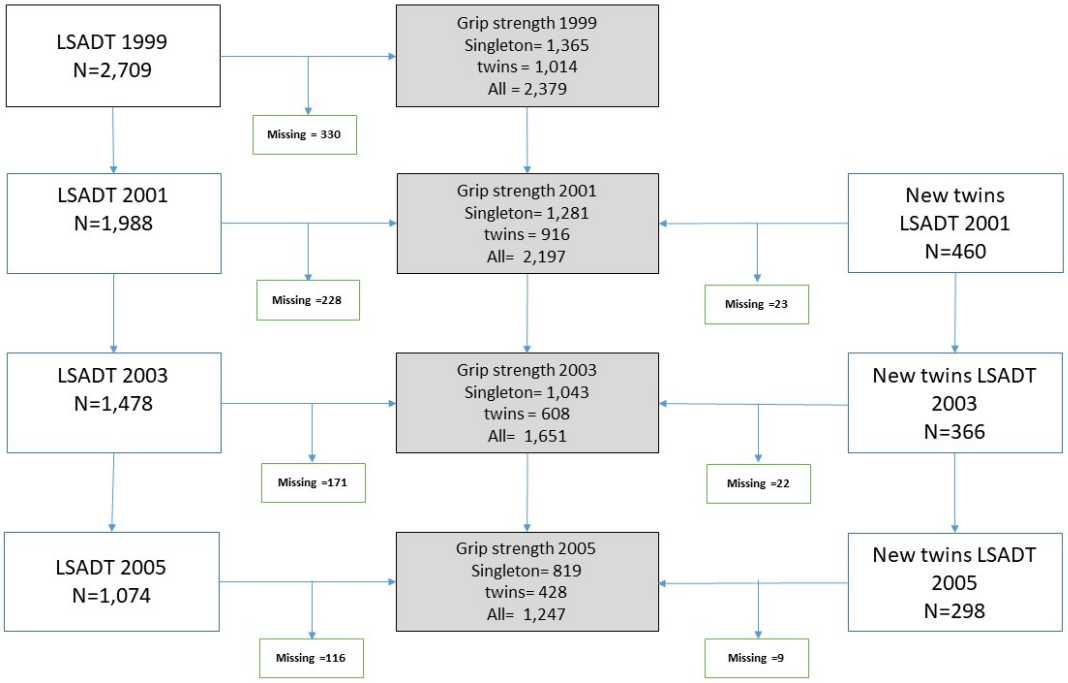


Figure S1. Description of Hand Grip strength measures in the Longitudinal Study of Aging Danish Twins (LSADT). The start of follow-up is 1999 and individuals are follow-up every two years until 2005. New participants were included in 2001, and 2003 and subsequently followed at two-year intervals. Number of missing participants which is due to drop-out, death, invalid measure (if there was a difference of 20 kg or more between two measures on one hand) or no measure is shown.

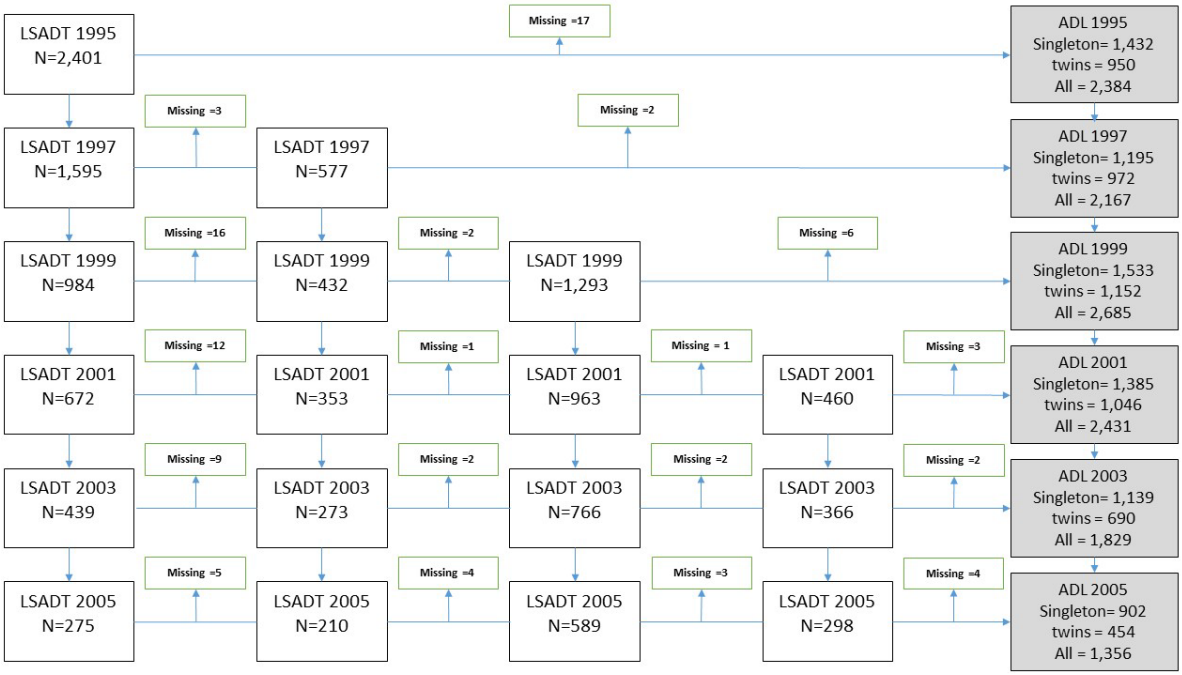
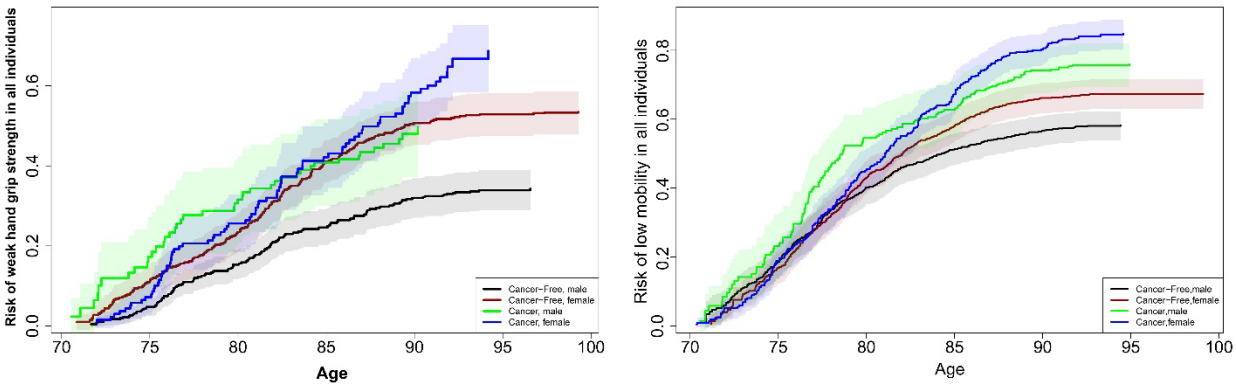


Figure S2. Description of ADL strength (mobility) measures in the Longitudinal Study of Aging Danish Twins (LSADT). The start of follow-up is 1999 and individuals are follow-up every two years until 2005. New participants were included in 1997, 1999, 2001, 2003, and subsequently followed at two-year intervals. Number of missing participants due to drop-out, death or invalid measure is shown.



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573 **Figure S3.** Cumulative incidence and 95% confidence interval for A) HGS, B) mobility for all individual twins by age,
574 stratified by cancer status (cancer, cancer-free) and sex (men, women).

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578 **Table S1.** Description of the number of individuals and twin pairs in HGS and mobility populations
579 from the LSADT* population.

Cohort	HGS*	Mobility
No. of Individuals	2,886	4,713
Cancer	377	659
Cancer-free at follow-up	2,509	4,054
Pairs	658	1,147
Discordant for cancer	138	278
MZ *	56	101
DZ *	80	166
OS*	2	8
UZ*	0	3
Concordance for cancer	11	26
MZ *	5	12
DZ *	6	13
OS*	0	1

580 *LSADT: Longitudinal Study of Aging Danish twins; HGS: Hand Grip Strength; MZ: Monozygotic twins; DZ:
581 Dizygotic twins; OS: Opposite sex DZ twins; UZ: Unknown zygosity twins
582

583 **Table S2.** Sociodemographic and health-related characteristics of the LSADT population for HGS
584 and mobility populations at inclusion by cancer status.

	HGS* population		Mobility population	
Characteristic	**Cancer**	**Cancer-Free at follow-up**	**Cancer**	**Cancer-Free at follow-up**
N	377	2,509	659	4,054
Age (median [IQR])	76.2 [72.2, 81.0]	75.1 [71.8, 79.9]	76.9 [74.1, 81.9]	76.2 [73.2, 81.4]
Female (%)	221 (58.6)	1371 (54.6)	396 (60.1)	2385 (58.8)
Education (%)				
Primary	29 (7.8)	212 (8.6)	69 (10.6)	429 (10.8)
Secondary	257 (69.5)	1805 (72.9)	464 (71.6)	2953 (74.0)
Post-Secondary	84 (22.7)	458 (18.5)	115 (17.7)	606 (15.2)
Self-rated health (%)				
Good	226 (60.1)	1752 (69.9)	364 (58.4)	2660 (69.4)
Fair	120 (31.9)	587 (23.4)	192 (30.8)	843 (22.0)
Poor	30 (8.0)	169 (6.7)	67 (10.8)	330 (8.6)
Marital Status (%)				
Never Married			36 (5.5)	253 (6.2)
Married	195 (51.7)	1448 (57.8)	303 (46.0)	1940 (47.9)
Divorced	35 (9.3)	134 (5.3)	47 (7.1)	223 (5.5)
Widowed	147 (39.0)	923 (36.8)	273 (41.4)	1634 (40.3)
BMI*, kg/m^2 (%)				
Underweight	23 (6.2)	102 (4.1)	41 (6.3)	198 (5.0)
Normal	186 (50.3)	1264 (50.8)	343 (53.1)	2077 (51.9)
Overweight	131 (35.4)	891 (35.8)	210 (32.5)	1361 (34.0)
Obese	30 (8.1)	233 (9.4)	52 (8.0)	363 (9.1)
Smoking (%)				
Never	112 (29.7)	800 (31.9)	220 (33.6)	1399 (34.7)
Former	126 (33.4)	762 (30.4)	206 (31.5)	1215 (30.1)
Current	139 (36.9)	945 (37.7)	229 (35.0)	1421 (35.2)
Cognitive impairment (%)	59 (15.7)	332 (13.3)	124 (20.1)	758 (20.0)
Depression (median[IQR])	20 [18, 25]	20 [18, 23]	21 [18, 25]	20 [18, 24]
CCI*(median [IQR])	2 [2, 4.5]	2 [0, 3]	2 [2, 4]	2 [0, 3]

585 *HGS: Hand Grip strength; BMI: Body Mass Index; CCI: Charlson's comorbidity index
586

587

588 **Table S3.** Sociodemographic and health-related characteristics of discordant twin pairs in the LSADT cohort
589 for HGS and mobility populations at inclusion by cancer status.

	HGS* population		Mobility population	
Characteristic	**Twin Cancer**	**Co-twin Cancer-Free**	**Twin Cancer**	**Co-twin Cancer-Free**
N	138	138	278	278
Age (median [IQR])	74.7 [71.9, 77.7]	74.6 [71.9, 77.9]	76.0 [73.4, 79.4]	76.0 [73.5, 79.4]
Female (%)	86 (62.3)	84 (60.9)	183 (65.8)	181 (65.1)
Education (%)				
Primary	8 (5.9)	8 (6.0)	26 (9.5)	25 (9.2)
Secondary	85 (63.0)	92 (68.7)	186 (68.1)	200 (73.5)
Post-Secondary	42 (31.1)	34 (25.4)	61 (22.3)	47 (17.3)
Self-rated health (%)				
Good	87 (63.0)	97 (70.3)	161 (59.4)	184 (68.9)
Fair	40 (29.0)	32 (23.2)	79 (29.2)	65 (24.3)
Poor	11 (8.0)	9 (6.5)	31 (11.4)	18 (6.7)
Marital Status (%)				
Never Married			14 (5.0)	19 (6.8)
Married	76 (55.1)	72 (52.2)	133 (47.8)	116 (41.7)
Divorced	13 (9.4)	14 (10.1)	23 (8.3)	22 (7.9)
Widowed	49 (35.5)	52 (37.7)	108 (38.8)	121 (43.5)
BMI*, kg/m^2 (%)				
Underweight	9 (6.6)	8 (5.8)	17 (6.2)	17 (6.2)
Normal	76 (55.9)	72 (52.6)	158 (57.7)	148 (53.6)
Overweight	40 (29.4)	48 (35.0)	78 (28.5)	90 (32.6)
Obese	11 (8.1)	9 (6.6)	21 (7.7)	21 (7.6)
Smoking (%)				
Never	42 (30.4)	43 (31.2)	98 (35.4)	93 (33.6)
Former	47 (34.1)	44 (31.9)	89 (32.1)	91 (32.9)
Current	49 (35.5)	51 (37.0)	90 (32.5)	93 (33.6)
Cognitive impairment (%)	17 (12.3)	13 (9.5)	48 (17.8)	48 (18.1)
Depression (median[IQR])	20 [18, 24]	21 [18, 24]	21 [18, 25]	21 [18, 24]
CCI*(median[IQR])	2.5 [2, 5]	2 [0, 4]	2 [2, 4]	2 [0, 3]

590 *HGS: Hand Grip strength; BMI: Body Mass Index; CCI: Charlson's comorbidity index

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Table S4. Association of cancer with functional decline using stratified Cox regression: discordant pair analyses of all pairs, MZ pairs, and DZ pairs.

	All pairs		MZ* pairs		DZ* pairs	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
HGS*	3.50	(1.52, 10.63)	2.50	(0.49, 12.89)	4.50	(0.97, 20.83)
Mobility	1.65	(0.90, 3.01)	1.10	(0.47, 2.59)	2.43	(1.01, 5.86)

* MZ: Monozygotic twins; DZ: Dizygotic twins; HGS: Hand Grip Strength

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