

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

Mohammadnejad, Afsaneh; Ryg, Jesper; Ewertz Kvistgaard, Marianne; Jylhävä, Juulia ;  
Hjelmborg, Jacob; Galvin, Angéline

*Published in:*  
Scandinavian Journal of Public Health

*DOI:*  
10.1177/14034948241240823

*Publication date:*  
2024

*Document version:*  
Accepted manuscript

*Citation for published version (APA):*  
Mohammadnejad, A., Ryg, J., Ewertz Kvistgaard, M., Jylhävä, J., Hjelmborg, J., & Galvin, A. (2024). Association of cancer with functional decline at old age- a longitudinal study in Danish twins. *Scandinavian Journal of Public Health*. <https://doi.org/10.1177/14034948241240823>

Go to publication entry in University of Southern Denmark's Research Portal

**Terms of use**

This work is brought to you by the University of Southern Denmark.  
Unless otherwise specified it has been shared according to the terms for self-archiving.  
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.  
Please direct all enquiries to [puresupport@bib.sdu.dk](mailto:puresupport@bib.sdu.dk)

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

3 **Running title: Functional decline and cancer**

4  
5 Afsaneh Mohammadnejad<sup>1,\*</sup>, Jesper Ryg<sup>2,3,4</sup>, Marianne Ewertz<sup>2,4</sup>, Juulia Jylhävä<sup>5,6</sup>, Jacob v. B. Hjelmberg<sup>1,7</sup>,  
6 Angéline Galvin<sup>1,8</sup>  
7

- 8  
9 1. Epidemiology, Biostatistics and Biodemography, Department of Public Health, University of  
10 Southern Denmark, Denmark  
11 2. Academy of Geriatric Cancer Research (AgeCare), Odense University Hospital, Odense, Denmark  
12 3. Department of Geriatric Medicine, Odense University Hospital, Odense, Denmark  
13 4. Department of Clinical Research, University of Southern Denmark, Odense, Denmark  
14 5. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden  
15 6. Faculty of Social Sciences, Unit of Health Sciences and Gerontology Research Center, University of  
16 Tampere, Tampere, Finland  
17 7. The Danish Twin Registry, University of Southern Denmark, Denmark  
18 8. Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219,  
19 Bordeaux, France

20  
21 Email-Addresses:

22 AM: [amohammadnejad@health.sdu.dk](mailto:amohammadnejad@health.sdu.dk) (ORCID: 0000-0003-4184-7518)

23 JR: [jesper.ryg@rsyd.dk](mailto:jesper.ryg@rsyd.dk) (ORCID: 0000-0002-8641-3062)

24 ME: [mewertz@health.sdu.dk](mailto:mewertz@health.sdu.dk) (ORCID: 0000-0002-5965-969X)

25 JJ: [juulia.jylhava@ki.se](mailto:juulia.jylhava@ki.se) (ORCID: 0000-0003-0250-4491)

26 JvBH: [jhjelmborg@health.sdu.dk](mailto:jhjelmborg@health.sdu.dk) (ORCID: 0000-0001-9630-9149)

27 AG: [agalvin@health.sdu.dk](mailto:agalvin@health.sdu.dk) (ORCID: 0000-0001-9957-5418)  
28  
29  
30

31 \*Corresponding author:

32 Afsaneh Mohammadnejad, PhD,  
33 Epidemiology, Biostatistics and Biodemography,  
34 Department of Public Health, Faculty of Health Science,  
35 University of Southern Denmark,  
36 Campusvej 55, DK-5230, Odense M, Denmark,  
37 e-mail: [amohammadnejad@health.sdu.dk](mailto:amohammadnejad@health.sdu.dk), Tel: +45 65 50 38 25  
38  
39

## Abstract

40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63

**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 extent 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

## 64 **Introduction**

65

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

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

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

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

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

## 102 **Materials and Methods**

### 103 **Study Population**

104

105 Longitudinal Study of Aging Danish Twins (LSADT) is a longitudinal cohort study that started in 1995 in  
106 Denmark from a survey on twins as a national Danish health register [14]. A detailed description and an  
107 overview of inclusion waves, participation numbers and follow-ups of LSADT has previously been reported  
108 [15]. Briefly, members of like-sex twin pairs born in Denmark prior to 1920 were included in 1995 and  
109 followed up every two years until 2005. New participants were also included in 1997, 1999, and 2001 and  
110 subsequently followed at two-year intervals. The LSADT cohort includes 4,731 individual twins who  
111 completed the baseline assessment, either through in-person interview or by proxy. Because twins were  
112 selected without regard to their co-twin's mortality, many of the participating twins did not have a surviving  
113 co-twin who participated in the survey. As a result, many of the participants in LSADT are 'singleton twins'  
114 [16]. At the inclusion and follow-ups, information was collected on sociodemographic characteristics, medical  
115 history and diseases, medication, neurocognitive testing, physical functioning, and psychological well-being.  
116 Information on survival status was retrieved from the Danish Central Person Register, which is continuously

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

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

## 126 **Outcomes**

127

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

133 The HGS is an estimate of upper limb strength and correlates with strength in other muscle groups, so it has  
134 been used to estimate overall strength [19]. It was measured in kilogram by a hand-held dynamometer, using  
135 a maximum of three measurements taken with the strongest hand i.e., If one hand does not have three attempts,  
136 the remaining 1 or 2 measurements were counted. It was set to be missing if all the three attempts were not  
137 made at least on one hand, or if there was a difference of 20 kg or more between two measures on one hand  
138 [19]. Weak HGS was defined as a HGS < 26kg for men and < 16kg for women [8, 20].

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

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

## 155 **Covariates**

156

157 Sociodemographic and health-related variables from LSADT inclusion which were previously reported as  
158 associated with functional decline were considered as covariates [4, 10, 23]. Considered sociodemographic  
159 factors were sex, marital status (married, divorced, widowed), and education (primary, secondary, post-  
160 secondary). Education was coded according to the International Standard Classification of Education (ISCED).  
161 Regarding health-related factors, we considered smoking status (never, former, current), BMI (<18.5, 18.5–  
162 24.9, 25–29.9, and  $\geq 30$  kg/m<sup>2</sup>), self-rated health (good, fair, poor), depression (yes, no), cognitive impairment  
163 (yes, no), and Charlson’s comorbidity index (CCI). Depression score was computed as the sum of the affect  
164 and somatic scores, as previously described [24]. Cognitive impairment was evaluated using the mini-mental  
165 state examination (MMSE) and a threshold of 24 [25], with MMSE score inferior to 24 considered as cognitive  
166 impairment. CCI, a weighted index that represents the prevalence of 19 chronic diseases over a predetermined  
167 period, was calculated according to an updated version ICD-10 diagnostic coding from Danish National Patient  
168 Registry, with higher scores indicating increased morbidity [26, 27].

## 169 **Statistical Analyses**

170

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

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

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

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



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

## 200 Results

201

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

213 At inclusion, median of HGS for cancer twins was 25 [IQR: 20, 33] and for cancer-free cotwins was 25 [IQR:  
214 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:  
215 1.3, 2.3] (**Supplementary Table S3**).

### 216 Results based on individuals

217

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

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

### 230 Results based on discordant pairs

231

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

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

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

250

## 251 Discussion

252

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

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

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

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

280 Regarding mobility, no evidence of a difference between hazard of cancers and non-cancers in both individuals  
281 and discordant twin pairs (including analysis of MZ and DZ discordant pair separately) was observed.  
282 However, both men and women with cancer appeared to have a higher non-significant risk of low mobility,  
283 and women were worse than men. A recent study reported that mobility limitations increased consistently from  
284 age 50 years and women were more likely than men to have a mobility limitation between the ages of 50 and  
285 80 [40]. Differences in functional decline between individuals with and without cancer have been demonstrated  
286 in several studies using self-reported assessments [9, 10]. However, comparing our results to previous ones is  
287 difficult as functional status was mainly assessed using instrumental activities of daily living (IADL) [41] and  
288 ADL [42] in previous studies. Functional limitations can be hierarchized [43] as mobility limitations or low  
289 limitations measured by the Rosow–Breslau scale [44], moderate activity limitations measured by Lawton’s  
290 IADL [41], and severe activity limitations measured by Katz’s ADL [42]. The self-reported questionnaire used  
291 in the LSADT is a scale close to Rosow–Breslau scale [44], evaluating mobility and low functional limitation.  
292 As mobility limitations are not rare in older adults, we cannot dismiss the possibility that a large part of  
293 individuals in our cohort already presented with mobility limitations at inclusion, reducing the probability to  
294 observe a decline [45]. Indeed, a recent study on participants from 14 countries reported that mobility  
295 limitations increased consistently from age 50 years and reported a probability of mobility limitations at age  
296 80 ranging from 40 to 60% [40].

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

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

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

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

332 is not rare in older adults. In addition, moderate or severe limitation has more consequences in daily living.  
333 Second, previous studies suggested that functional decline is different regarding cancer types and that for some  
334 cancers e.g. for breast cancer, years after cancer diagnosis, functional status is close to cancer-free individuals  
335 [9]. However, we were not able to study the varying impact of cancer types due to small samples in a  
336 longitudinal aspect. Third, in our study there could be unobserved confounding dropouts due to poor health.  
337 This is treated in paper by Frederiksen et al. 2006 using longitudinal measurements of HGS [19], through  
338 inverse probability weighting approach to remedy this. In our paper, this also played a role where we focus on  
339 the comparison of cancer and cancer-frees. Having these cancer cases unobserved for HGS or mobility would  
340 expect the difference larger. Hence, we see our estimates as conservative. Moreover, it is important to note  
341 that for both HGS and mobility the percentages of missing values was low.

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

354

355 **Financial support**

356

357 This work was supported by The Academy of Geriatric Cancer Research (AgeCare), grant number 71778,

358 Odense University Hospital, Denmark.

359

360 **Competing interests**

361

362 The authors declare that they have no conflicts of interest.

363

364 **Data availability Statement**

365

366 According to Danish and EU legislations, transfer and sharing of individual-level data require prior approval

367 from the Danish Data Protection Agency and require that data sharing requests are dealt with on a case-by-

368 case basis. However, we welcome any enquiries regarding collaboration and individual requests for data

369 sharing. Requests can be directed to JvBH, [jhjelmberg@health.sdu.dk](mailto:jhjelmberg@health.sdu.dk).

370

371 **Authors contributions**

372

373 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.;

374 formal analysis, A.M.; writing original manuscript, A.M.; project administration, A.M. and J.v.B.H.; review

375 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

376 of the manuscript.

377

## 378 References

379

- 380 1. Leidy, N.K., *Functional status and the forward progress of merry-go-rounds: toward a coherent*  
381 *analytical framework*. Nurs Res, 1994. **43**(4): p. 196-202.
- 382 2. Meert, G., et al., *Functional status in older patients with cancer and a frailty risk profile: A*  
383 *multicenter observational study*. J Geriatr Oncol, 2022. **13**(8): p. 1162-1171.
- 384 3. Muhandirame, J., et al., *Functional Decline in the Cancer Patient: A Review*. Cancers (Basel), 2022.  
385 **14**(6).
- 386 4. Stuck, A.E., et al., *Risk factors for functional status decline in community-living elderly people: a*  
387 *systematic literature review*. Soc Sci Med, 1999. **48**(4): p. 445-69.
- 388 5. Galvin, A., et al., *Determinants of functional decline in older adults experiencing cancer (the*  
389 *INCAPAC study)*. J Geriatr Oncol, 2019. **10**(6): p. 913-920.
- 390 6. Dunlop, D.D., et al., *Incidence of functional limitation in older adults: the impact of gender, race,*  
391 *and chronic conditions*. Arch Phys Med Rehabil, 2002. **83**(7): p. 964-71.
- 392 7. Muhandirame, J., et al., *The acceleration of ageing in older patients with cancer*. J Geriatr Oncol,  
393 2021. **12**(3): p. 343-351.
- 394 8. Siddique, A., E.M. Simonsick, and L. Gallicchio, *Functional decline among older cancer survivors in*  
395 *the Baltimore longitudinal study of aging*. Journal of the American Geriatrics Society, 2021. **69**(11):  
396 p. 3124-3133.
- 397 9. Petrick, J.L., et al., *Functional status declines among cancer survivors: trajectory and contributing*  
398 *factors*. J Geriatr Oncol, 2014. **5**(4): p. 359-67.
- 399 10. van Abbema, D., et al., *Functional status decline in older patients with breast and colorectal cancer*  
400 *after cancer treatment: A prospective cohort study*. J Geriatr Oncol, 2017. **8**(3): p. 176-184.
- 401 11. Hjelmborg, J.B., et al., *The heritability of prostate cancer in the Nordic Twin Study of Cancer*. Cancer  
402 Epidemiol Biomarkers Prev, 2014. **23**(11): p. 2303-10.
- 403 12. Skytthe, A., et al., *Cancer Incidence and Mortality in 260,000 Nordic Twins With 30,000 Prospective*  
404 *Cancers*. Twin Res Hum Genet, 2019. **22**(2): p. 99-107.
- 405 13. Sehl, M., et al., *Decline in physical functioning in first 2 years after breast cancer diagnosis predicts*  
406 *10-year survival in older women*. J Cancer Surviv, 2013. **7**(1): p. 20-31.
- 407 14. Pedersen, D.A., et al., *The Danish Twin Registry: An Updated Overview*. Twin Res Hum Genet, 2019.  
408 **22**(6): p. 499-507.
- 409 15. McGue, M. and K. Christensen, *Social activity and healthy aging: a study of aging Danish twins*.  
410 Twin Res Hum Genet, 2007. **10**(2): p. 255-65.
- 411 16. Christensen, K., et al., *A Danish population-based twin study on general health in the elderly*. J Aging  
412 Health, 1999. **11**(1): p. 49-64.
- 413 17. Pedersen, C.B., et al., *The Danish Civil Registration System. A cohort of eight million persons*. Dan  
414 Med Bull, 2006. **53**(4): p. 441-9.
- 415 18. Gjerstorff, M.L., *The Danish Cancer Registry*. Scand J Public Health, 2011. **39**(7 Suppl): p. 42-5.
- 416 19. Frederiksen, H., et al., *Age trajectories of grip strength: cross-sectional and longitudinal data among*  
417 *8,342 Danes aged 46 to 102*. Ann Epidemiol, 2006. **16**(7): p. 554-62.
- 418 20. Alley, D.E., et al., *Grip strength cutpoints for the identification of clinically relevant weakness*. J  
419 Gerontol A Biol Sci Med Sci, 2014. **69**(5): p. 559-66.
- 420 21. Christensen, K., et al., *Genetic and environmental influences on functional abilities in Danish twins*  
421 *aged 75 years and older*. J Gerontol A Biol Sci Med Sci, 2000. **55**(8): p. M446-52.
- 422 22. Fluss, R., D. Faraggi, and B. Reiser, *Estimation of the Youden Index and its associated cutoff point*.  
423 Biom J, 2005. **47**(4): p. 458-72.
- 424 23. van der Vorst, A., et al., *Limitations in Activities of Daily Living in Community-Dwelling People Aged*  
425 *75 and Over: A Systematic Literature Review of Risk and Protective Factors*. PLoS One, 2016. **11**(10):  
426 p. e0165127.

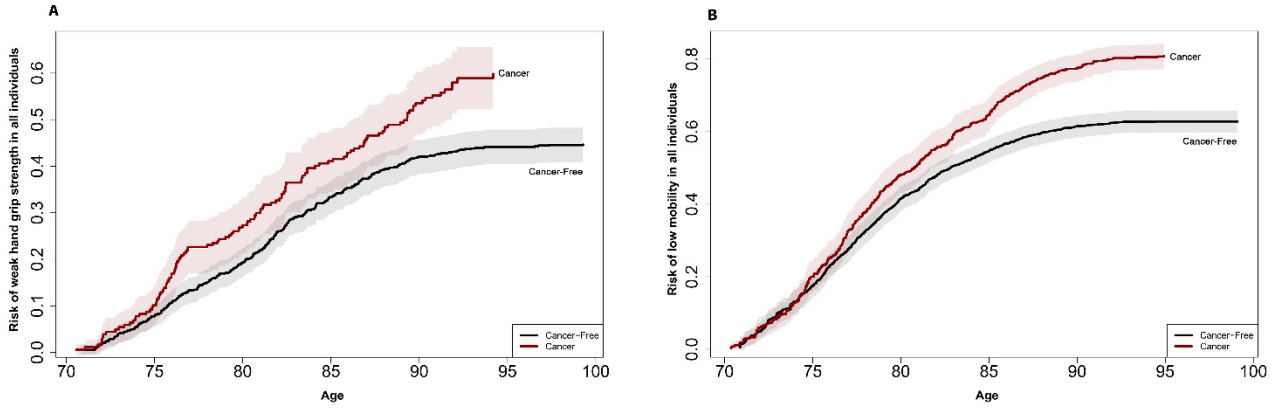


- 427 24. McGue, M. and K. Christensen, *Genetic and environmental contributions to depression*  
428 *symptomatology: evidence from Danish twins 75 years of age and older*. J Abnorm Psychol, 1997.  
429 **106**(3): p. 439-48.
- 430 25. Folstein, M.F., S.E. Folstein, and P.R. McHugh, "Mini-mental state". *A practical method for grading*  
431 *the cognitive state of patients for the clinician*. J Psychiatr Res, 1975. **12**(3): p. 189-98.
- 432 26. Thygesen, S.K., et al., *The predictive value of ICD-10 diagnostic coding used to assess Charlson*  
433 *comorbidity index conditions in the population-based Danish National Registry of Patients*. BMC  
434 Med Res Methodol, 2011. **11**: p. 83.
- 435 27. Ryg, J., et al., *Barthel Index at hospital admission is associated with mortality in geriatric patients: a*  
436 *Danish nationwide population-based cohort study*. Clin Epidemiol, 2018. **10**: p. 1789-1800.
- 437 28. Ramsay, J.O., B.W. Silverman, and SpringerLink, *Functional data analysis*, in *Springer series in*  
438 *statistics*. 2005, Springer
- 439 Springer New York: New York
- 440 New York, NY.
- 441 29. Scheike, T.H., K.K. Holst, and J.B. Hjelmberg, *Estimating heritability for cause specific mortality*  
442 *based on twin studies*. Lifetime Data Anal, 2014. **20**(2): p. 210-33.
- 443 30. Sjölander, A., T. Frisell, and S. Öberg, *Causal Interpretation of Between-Within Models for Twin*  
444 *Research*. 2012. **1**(1): p. 217-237.
- 445 31. Alibhai, S.M., et al., *Impact of androgen-deprivation therapy on physical function and quality of life*  
446 *in men with nonmetastatic prostate cancer*. J Clin Oncol, 2010. **28**(34): p. 5038-45.
- 447 32. Luo, J., et al., *Trajectories of objectively measured physical function among older breast cancer*  
448 *survivors in comparison with cancer-free controls*. Breast Cancer Res Treat, 2022. **193**(2): p. 467-  
449 476.
- 450 33. Suetta, C., et al., *The Copenhagen Sarcopenia Study: lean mass, strength, power, and physical*  
451 *function in a Danish cohort aged 20–93 years*. Journal of cachexia, sarcopenia and muscle, 2019.  
452 **10**(6): p. 1316-1329.
- 453 34. Sternäng, O., et al., *Factors associated with grip strength decline in older adults*. Age and ageing,  
454 2015. **44**(2): p. 269-274.
- 455 35. Wearing, J., et al., *Handgrip strength in old and oldest old Swiss adults—a cross-sectional study*. BMC  
456 geriatrics, 2018. **18**: p. 1-9.
- 457 36. Pratt, J., et al., *Grip strength performance from 9431 participants of the GenoFit study: normative*  
458 *data and associated factors*. Geroscience, 2021. **43**(5): p. 2533-2546.
- 459 37. de Araújo Amaral, C., et al., *Factors associated with low handgrip strength in older people: data of*  
460 *the Study of Chronic Diseases (Edoc-I)*. BMC Public Health, 2020. **20**: p. 1-10.
- 461 38. Huebner, M., F. Lawrence, and L. Lusa, *Sex Differences in Age-Associated Rate of Decline in Grip*  
462 *Strength When Engaging in Vigorous Physical Activity*. Int J Environ Res Public Health, 2022. **19**(17).
- 463 39. López-Otín, C., et al., *The hallmarks of aging*. Cell, 2013. **153**(6): p. 1194-1217.
- 464 40. Bloomberg, M., et al., *Sex differences in functional limitations and the role of socioeconomic factors:*  
465 *a multi-cohort analysis*. Lancet Healthy Longev, 2021. **2**(12): p. e780-e790.
- 466 41. Lawton, M.P. and E.M. Brody, *Assessment of older people: self-maintaining and instrumental*  
467 *activities of daily living*. Gerontologist, 1969. **9**(3): p. 179-86.
- 468 42. Katz, S., *Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of*  
469 *daily living*. J Am Geriatr Soc, 1983. **31**(12): p. 721-7.
- 470 43. Barberger-Gateau, P., et al., *A hierarchical model of domains of disablement in the elderly: a*  
471 *longitudinal approach*. Disabil Rehabil, 2000. **22**(7): p. 308-17.
- 472 44. Rosow, I. and N. Breslau, *A Guttman health scale for the aged*. J Gerontol, 1966. **21**(4): p. 556-9.
- 473 45. Murabito, J.M., et al., *Temporal trends in self-reported functional limitations and physical disability*  
474 *among the community-dwelling elderly population: the Framingham heart study*. Am J Public  
475 Health, 2008. **98**(7): p. 1256-62.

- 476 46. Rudnicka, E., et al., *The World Health Organization (WHO) approach to healthy ageing*. *Maturitas*,  
477 2020. **139**: p. 6-11.
- 478 47. Pate, R., et al., *What Matters Most: A Needs Assessment of Older Adults*. *The American Journal of*  
479 *Geriatric Psychiatry*, 2023. **31**(3, Supplement): p. S93.
- 480 48. Ballmer, T. and B. Gantschnig, *Maintaining autonomy: How older persons with chronic conditions*  
481 *and their significant others interpret, navigate, and overcome everyday difficulties*. *Scandinavian*  
482 *Journal of Occupational Therapy*, 2024. **31**(1): p. 2249959.
- 483 49. Brown, R.T., et al., *Association of Functional Impairment in Middle Age With Hospitalization,*  
484 *Nursing Home Admission, and Death*. *JAMA Internal Medicine*, 2019. **179**(5): p. 668-675.
- 485 50. Greysen, S.R., et al., *Functional Impairment: An Unmeasured Marker of Medicare Costs for*  
486 *Postacute Care of Older Adults*. *J Am Geriatr Soc*, 2017. **65**(9): p. 1996-2002.
- 487 51. Li, H.-W., et al., *Quality of Life among Community-Dwelling Middle-Aged and Older Adults: Function*  
488 *Matters More than Multimorbidity*. *Archives of Gerontology and Geriatrics*, 2021. **95**: p. 104423.
- 489 52. Cipriani, G., et al., *Daily functioning and dementia*. *Dement Neuropsychol*, 2020. **14**(2): p. 93-102.
- 490 53. Keeney, T., et al., *Functional Trajectories of Persons with Cardiovascular Disease in Late Life*. *J Am*  
491 *Geriatr Soc*, 2019. **67**(1): p. 37-42.
- 492 54. Ulrike, D., et al., *The inter-relationship between depressed mood, functional decline and disability*  
493 *over a 10-year observational period within the Longitudinal Urban Cohort Ageing Study (LUCAS)*.  
494 *Journal of Epidemiology and Community Health*, 2021. **75**(5): p. 450.
- 495 55. Verbeek, E., Y.M. Drewes, and J. Gussekloo, *Visual impairment as a predictor for deterioration in*  
496 *functioning: the Leiden 85-plus Study*. *BMC Geriatr*, 2022. **22**(1): p. 397.
- 497 56. Ashikali, E.M., et al., *Intrinsic Capacities, Functional Ability, Physiological Systems, and Caregiver*  
498 *Support: A Targeted Synthesis of Effective Interventions and International Recommendations for*  
499 *Older Adults*. *Int J Environ Res Public Health*, 2023. **20**(5).
- 500 57. Laddu, D.R., et al., *Physical Activity Trajectories and Associated Changes in Physical Performance in*  
501 *Older Men: The MrOS Study*. *J Gerontol A Biol Sci Med Sci*, 2020. **75**(10): p. 1967-1973.
- 502 58. Pan, P.-J., et al., *Physical fitness and its correlation with handgrip strength in active community-*  
503 *dwelling older adults*. *Scientific Reports*, 2022. **12**(1): p. 17227.
- 504 59. Cooper, A., et al., *Bidirectional association between physical activity and muscular strength in older*  
505 *adults: Results from the UK Biobank study*. *Int J Epidemiol*, 2017. **46**(1): p. 141-148.
- 506 60. Bilajac L, J.D., Žuljević H, Glavić MM, Vasiljev V, et al, *The influence of physical Activity on handgrip*  
507 *strength of elderly*. *Arch Gerontol Geriatr Res*, 2019. **4**(1): p. 020-024.
- 508 61. Amaral Gomes, E.S., et al., *The Association of Objectively Measured Physical Activity and Sedentary*  
509 *Behavior with (Instrumental) Activities of Daily Living in Community-Dwelling Older Adults: A*  
510 *Systematic Review*. *Clin Interv Aging*, 2021. **16**: p. 1877-1915.
- 511 62. Osuka, Y., et al., *Association between exercise type and the decline in instrumental activities of daily*  
512 *living in community-dwelling older women: A 4-year prospective study*. *Preventive Medicine*, 2018.  
513 **112**: p. 23-30.
- 514 63. Jin, Y., K. Hreha, and I. Hong, *Physical activity and functional status in older adults: Mediating effect*  
515 *of cognitive function*. *Alzheimer's & Dementia*, 2023. **19**(S8): p. e064406.
- 516 64. Winters-Stone, K.M., et al., *A randomized-controlled trial comparing supervised aerobic training to*  
517 *resistance training followed by unsupervised exercise on physical functioning in older breast cancer*  
518 *survivors*. *J Geriatr Oncol*, 2022. **13**(2): p. 152-160.
- 519 65. Mclsaac, D.I., et al., *Home-based prehabilitation with exercise to improve postoperative recovery for*  
520 *older adults with frailty having cancer surgery: the PREHAB randomised clinical trial*. *British Journal*  
521 *of Anaesthesia*, 2022. **129**(1): p. 41-48.

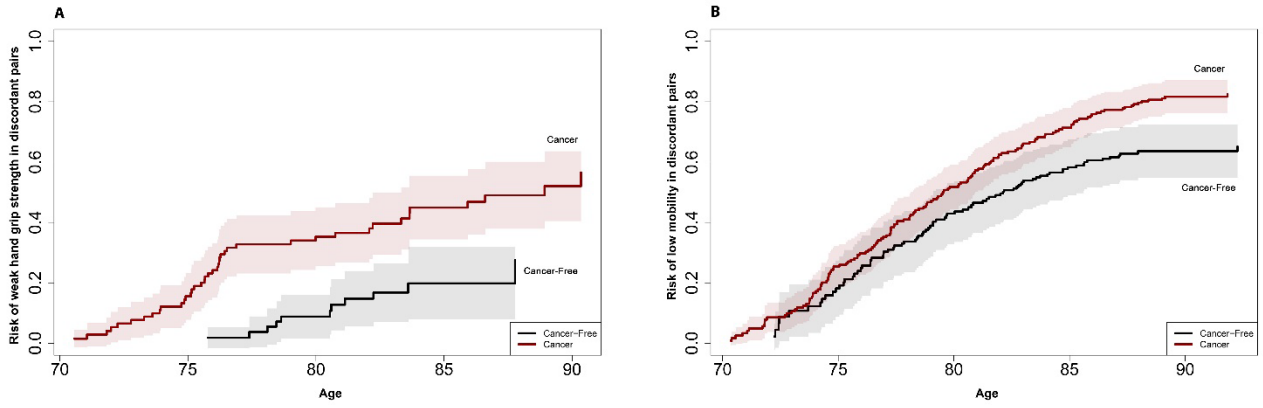
522

523



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.

527



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.

531

532

533

534 **Table 1.** Association between cancer status and occurrence of functional decline including all  
 535 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)

536 Abbreviations: 95% CI: 95% confidence interval; HR: Hazard ratio; HGS: Hand Grip Strength.  
 537 Adjusted for: sex, self-rated health, marital status, depression, CCI, education, BMI, smoking, and cognitive impairment.  
 538

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

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

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

542

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

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

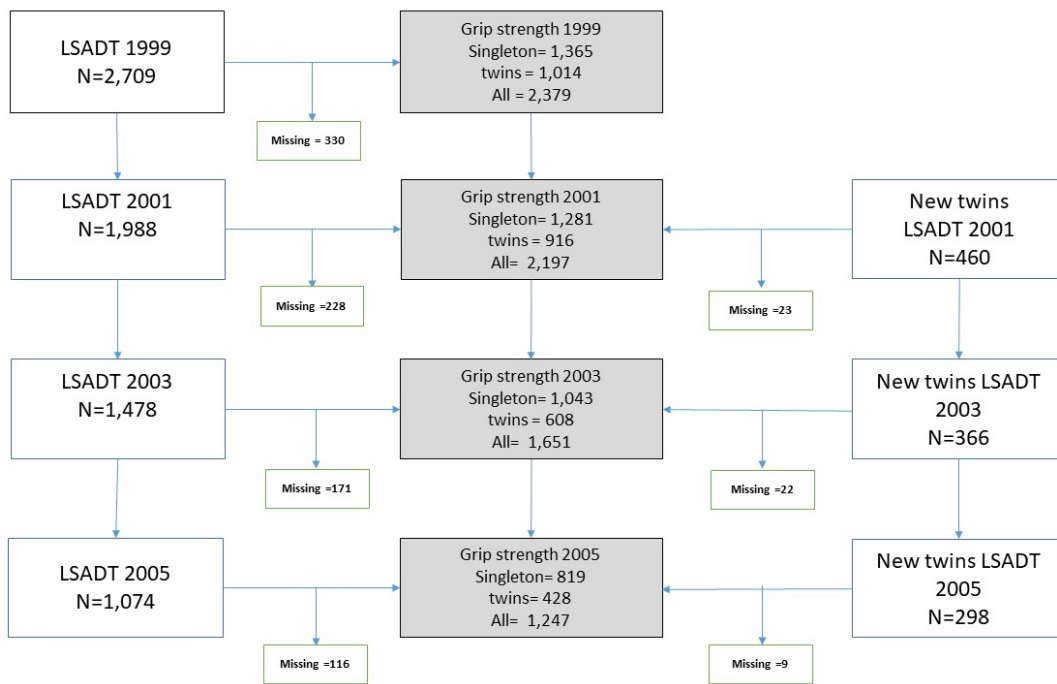
546 Abbreviations: 95% CI: 95% confidence interval; HGS: Hand Grip Strength

547  
548  
549  
550  
551  
552  
553  
554  
555  
556

## Supplementary Materials

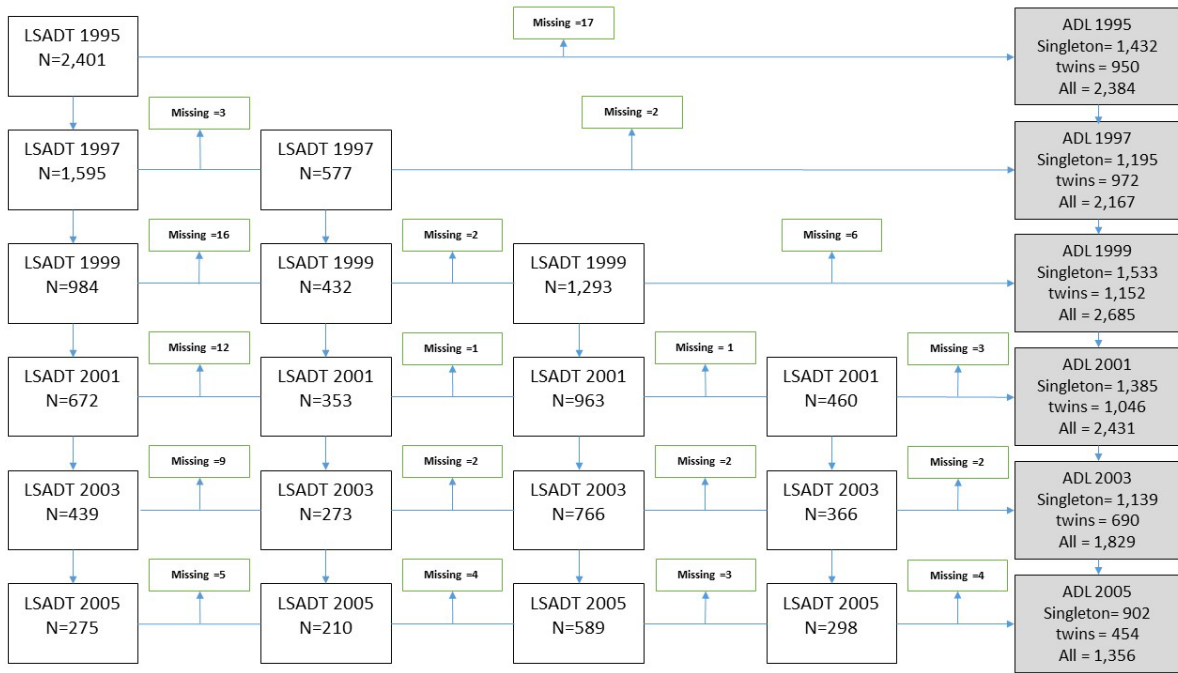
# Association of cancer with functional decline at old age-a longitudinal study in Danish twins

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



557  
558  
559  
560  
561  
562  
563  
564

**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.

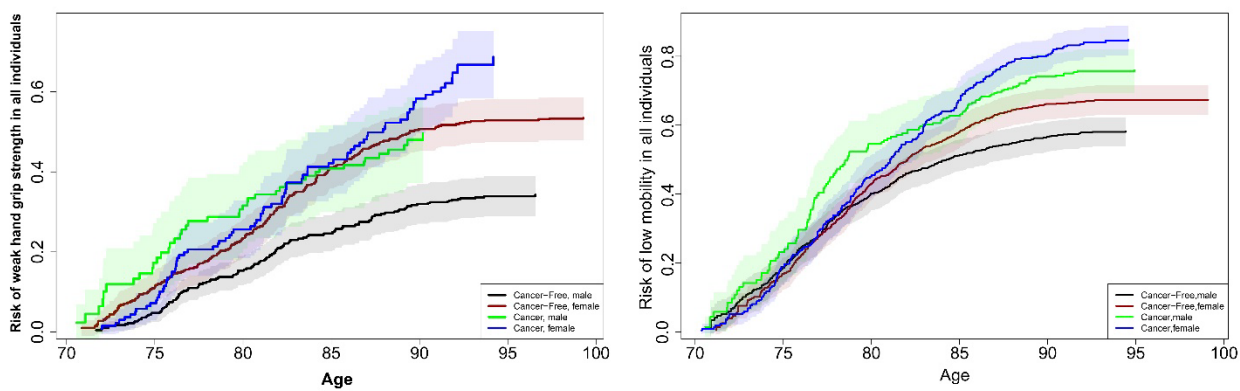


565

566

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

571



572

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).

575

576



577

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

<b>Cohort</b>	<b>HGS*</b>	<b>Mobility</b>
<b>No. of Individuals</b>	2,886	4,713
Cancer	377	659
Cancer-free at follow-up	2,509	4,054
<b>Pairs</b>	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 zygotity 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.

Characteristic	HGS* population		Mobility population	
	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 <sup>2</sup> (%)				
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.

Characteristic	HGS* population		Mobility population	
	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 <sup>2</sup> (%)				
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

591

592

593

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

596

597

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

598

599

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

600

601