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Loneliness and social isolation increase cancer incidence in a cohort of Finnish middle-aged men. A longitudinal study

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ABSTRACT

Globally, cancer is the second leading cause of death. Loneliness has been suggested as a risk factor for cancer mortality. However, connections between loneliness, social isolation, and cancer are poorly understood. In our longitudinal study (mean follow-up: 20.44 years) of 2570 middle-aged men, loneliness, social isolation, and health-related factors were measured at baseline. Cox proportional hazards analysis was used to examine the association between cancer incidence, loneliness, and social isolation. The effect of relationship status on cancer mortality among cancer patients was tested with the Kaplan-Meier method. Loneliness was associated with total cancer incidence after adjustments for tested lifestyle and health-related covariates. Social Isolation was associated with total cancer incidence, except when adjusted for lifestyle, diet, or Human Population Laboratory (HPL) Depression Scale scores. Loneliness was associated with lung cancer incidence, except when adjusted for HPL Depression Scale scores. There was no significant association between social isolation and lung cancer. Neither loneliness nor social isolation were connected with prostate or colorectal cancer. Being single at baseline was associated with worse survival outcomes for cancer patients. Our findings suggest that regardless of the social network size, loneliness among middle-aged men is associated with an increased likelihood of cancer.

1. Introduction

Globally, cancer is the second leading cause of death, and has already become the most common cause of death in high-income countries (Dagenais et al., 2019; World Health Organization Cancer, 2018). While research on the most common cancer risk factors is abundant, knowledge of the effects of psychosocial factors, such as loneliness and social isolation, is scarce. Social isolation refers to the objective lack of social contacts with other people, whereas loneliness is the negative perception of social isolation, i.e. the subjective feeling of being lonely. Loneliness and social isolation are claimed to affect physical health as strongly as some widely known health risks, such as smoking or obesity (Holt-Lunstad et al., 2015), and a link between loneliness and cancer mortality in the general population has recently been reported (Kraav et al., 2020).

Cancer incidence has been associated with psychosocial risk factors such as stress, depression, and low social support (Antoni et al., 2006; Lutgendorf and Sood, 2011). Previous research has demonstrated that especially among men, living alone reduces the survival time after being diagnosed with cutaneous malignant melanoma (Eriksson et al., 2014). Being single makes it more likely that cancer will not be diagnosed at an early stage (Buja et al., 2018). After receiving a cancer diagnosis, social support is important in helping the patient to initiate treatment in accordance with the prescribed treatment protocol. In a British study, patients who lived alone received less combination chemotherapy and secondary surgery, thus suggesting that living alone is an independent risk factor for poor survival in metastatic colorectal cancer (Cavalli-Björkman et al., 2012).

Clinical studies indicate that stress, chronic depression, social support, and other psychological factors might influence cancer onset and

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progression (Antoni et al., 2006), whereas social support appears to be one of the key psychological factors that have shown prognostic value in cancer progression (Nausheen et al., 2010). A Chinese study found that social support may help break the link between loneliness and depression among elderly residents in nursing homes (Zhao et al., 2018). Psychosocial stress alters the endocrine and immune systems by up-regulating the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (Nausheen et al., 2010; Lutgendorf and Sood, 2011) and can alter multiple physiological processes involved in tumor pathogenesis (Antoni et al., 2006). Loneliness may be an important psychosocial factor associated with cancer severity (Nausheen et al., 2010). Nevertheless, present knowledge regarding the linkage between loneliness, social isolation, and cancer is scarce (Leigh-Hunt et al., 2017).

In the current study, we examined a) the association of loneliness and social isolation with cancer incidence and b) the effect of living alone vs living with somebody on survival among cancer patients. Both loneliness and social isolation were used as continuous variables in the sample of middle-aged men (42–61 years) with a very long follow-up time of 20.44 years. In particular, we aimed to 1) examine whether both loneliness and social isolation increase cancer incidence, 2) analyze the effects of loneliness and social isolation on different cancer types, and 3) explore the effects of lifestyle, as well as somatic and psychiatric symptoms, on these associations. A further aim was to 4) investigate the effect of being in a relationship vs being single, widowed or divorced on cancer mortality among those who were diagnosed with cancer during the follow-up period.

2. Methods

2.1. Sample

The total sample consisted of 2682 men who participated in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. The baseline data were collected between 1984 and 1989. All the variables except the cancer incidence data were obtained from the baseline measurements. The baseline data collection, as well as sociodemographic and other background characteristics of the sample, are described in detail elsewhere (Salonen et al., 1992). By using nationally comprehensive register data for cancer, we were able to confirm that there was no loss to follow-up in the sample. The proportion of missing values was 3.8%. The data was observed to be missing completely at random (Little's MCAR test chi-square = 0, p = 1) and were imputed with the expectation-maximization algorithm.

To avoid reverse causality (Liu and Floud, 2017), individuals who had been diagnosed with cancer at baseline (n = 51) or who received a cancer diagnosis within two years after the baseline data collection (n = 63) were excluded from the analysis. The final sample consisted of 2570 men aged 42–61 years at baseline.

All procedures involving the participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The KIHD Study has been approved by the Research Ethics Committee of Kuopio University. All the participants provided written informed consent.

2.2. Variables

2.2.1. Outcome variable: cancer incidence

Cancer incidence and information on cancer sites were ascertained by computer linkage to the National Cancer Registry by using the Finnish personal identification code, which is a unique code given to every resident in Finland. The present article is based on data on cancer diagnoses that occurred before January 2012. The follow-up time ended for each patient either with the first incident cancer or, if cancer did not occur, with the participant's death for other reasons, or with the time when the outcome data were retrieved from the National Cancer Registry. Participants were followed up for a mean of 20.44 years, (SD. 7.06, range 2.02–28.78), and the mean age at cancer diagnosis was 69.96 years (SD. 7.00, range 45.05–85.53).

2.2.2. Measurements of loneliness and social isolation

To estimate loneliness and social isolation, two scales were constructed (Kraav et al., 2020). The Loneliness Scale consisted of 11 items that measured subjective satisfaction with one's social life, feelings of loneliness and the perceived discrepancy between desired and actual social contacts. Higher scores on the loneliness scale indicated higher levels of loneliness, the maximum score being 66 and the minimum score 0. Cronbach's alpha for the Loneliness Scale was 0.73. The Social Isolation Scale consisted of 10 items that measure the objective occurrence of certain social events. The scale utilized multi-categorical questions and questions in which the answer indicated the number of times the event had occurred. Higher scores indicated increased levels of social isolation, the maximum score being 28 and the minimum score 0. Cronbach's alpha for the Social Isolation Scale was 0.67. To test the effect of cohabitation on cancer incidence, we repeated the analyses after removing marital status from the Social Isolation Scale.

2.3. Covariates

2.3.1. Lifestyle variables

Information on smoking status was collected at baseline using a self-administered questionnaire. A subject was defined as a smoker if he had ever smoked (cigarettes, cigars, or a pipe) on a regular basis (Salonen et al., 1992). Alcohol consumption was assessed by using a structured quantity–frequency method involving a drinking behavior questionnaire covering the previous 12 months and was measured in grams per week (Ihanainen et al., 1989). The energy expenditure resulting from conditioning leisure time physical activities was assessed by using a 12-month history modified from the Minnesota Leisure Time Physical Activity Questionnaire. The intensity of physical activity was measured in metabolic units (metabolic equivalent of task, MET, or metabolic equivalent of oxygen uptake), with one MET being equivalent to an energy expenditure of approximately 1 kcal/kg * hour and oxygen consumption being 3.5 ml/kg * minute. Energy expenditure expressed in kcal/week for each activity was estimated by multiplying the metabolic index of the activity (MET * hour/week) by the body weight in kilograms (Lakka et al., 1996).

2.3.2. Depression measures

Depressive symptoms were assessed at baseline with the 18-item Human Population Laboratory (HPL) Depression Scale, which was developed for screening general population samples (Kaplan et al., 1987; Tolmunen et al., 2003, 2004, 2010). It conceptually resembles other brief symptom checklists such as the Center for Epidemiological Studies Depression Scale (CES-D) (Roberts, 1980; Roberts and O'Keefe, 1981). To avoid multicollinearity, we modified the depression scale for the analyses in this article and removed two items concerning loneliness ("I feel lonely or remote from other people" and "Social withdrawal even from people I am close to"). Cronbach's alpha for the HPL Depression Scale was 0.56 (0.46 for the modified scale). We also performed the analyses with the unmodified HPL Depression Scale.

2.3.3. Socioeconomic status measures

A socioeconomic status (SES) score was calculated at baseline including information on occupation, income, housing tenure, and ownership of material goods (Lynch and Kaplan, 1997).

2.3.4. Hs-CRP measures

Blood samples were collected from participants in an overnight fasted state. They had also abstained from smoking for 12 hours and avoided alcohol use for three days. The participants rested in a supine

position for 30 minutes before blood sampling. Copper-free needles and tubes were used for collecting and storing blood.

High-sensitivity C-reactive protein (hs-CRP) was measured with an immunometric assay, the Immulite High Sensitivity CRP Assay (Diagnostic Products Corporation, Los Angeles, California, USA), which has been standardized against the World Health Organization (WHO) International Reference Standard for CRP Immunoassay 85/506. At the level of 3.2 mg/L, the within-run coefficient of variation was 2.8% and the total coefficient of variation was 3.1%.

2.3.5. Metabolic and cardiovascular health variables

Systolic blood pressure was measured using a random-zero mercury sphygmomanometer by taking the mean of six measurements: three in a supine position, one standing, and two sitting (Lakka et al., 2002). Low-density lipoprotein cholesterol (LDL-C) was extracted from fresh serum by a method combining ultracentrifugation and precipitation during the medical examination (Lakka et al., 2002). A history of cardiovascular disease (CVD) was defined as a diagnosis of CVD other than high blood pressure at baseline. An estimate of the average number of hours slept at night was recorded with the following question: "How many hours do you usually sleep at night?" ($\leq$6 h, 6.5 h, 7 h, 7.5 h, 8 h, 8.5 h, 9 h, 9.5 h, $\geq$10 h). In the current analysis, we used the sleep variable reduced into three categories: $\leq$6.5 h, 7–8 h, and $\geq$8.5 h (Luojus et al., 2017). Body mass index (BMI) was recorded as the weight in kilograms divided by the square of the height in meters.

2.3.6. Baltic Sea Diet Score

The healthiness of the diet was evaluated by using a slightly modified Baltic Sea Diet Score (BSDS) (Tertsunen et al., 2020). The BSDS is a measure indicating adherence to the healthy Nordic diet, which consists of foods typically produced in the Nordic countries (Kanerva et al., 2014). Higher scores reflect greater adherence to the Baltic Sea diet in the analysis, and the score was used as a continuous variable.

2.4. Statistical methods

The chi-squared test was used to analyze group differences in the categorical variables, while normally distributed continuous variables were analyzed with the Student's *t*-test, and the Mann–Whitney *U* test was used in the comparisons of other continuous variables.

Cox proportional hazards analysis (method: Enter) was used to examine the association between cancer incidence, loneliness, and social isolation. The variables for adjustments were chosen based on their possible influence on the health status or their connection to loneliness and social relationships. Altogether, nine models were constructed: Model 1 was adjusted for age in years; Model 2 was adjusted for age and SES in adulthood (Fleisch Marcus et al., 2017); Model 3 was adjusted for age and lifestyle variables (alcohol consumption, smoking, and physical activity) (Schwingshackl et al., 2017); Model 4 was adjusted for age and the BSDS score (Mentella et al., 2019); Model 5 was adjusted for age and sleep quantity (McNeil et al., 2019); Model 6 was adjusted for age and HPL Depression Scale scores (Beutel et al., 2019; Sotelo et al., 2014); Model 7 was adjusted for age and hs-CRP (Mantovani et al., 2008); Model 8 was adjusted for age and somatic variables (systolic blood pressure, LDL-C, BMI, and CVD history) (Angel et al., 2019; O'Keeffe et al., 2018; Bagnardi et al., 2015; Stout et al., 2017); and Model 9 was adjusted for all of the above-described variables.

The Kaplan-Meier model was used to calculate the probability of cancer survival among those diagnosed with cancer during the follow-up, depending on whether the participant was in a relationship or single (single or widowed or divorced). The significance of differences between the Kaplan-Maier curves was assessed by using the log-rank test.

The analyses were performed with SPSS Statistics 27 for Mac statistical software (SPSS Inc., Chicago, IL). Two-tailed *p*-values below 0.05 were considered statistically significant.

3. Results

During the follow-up period, 649 participants were diagnosed with cancer (25.3%), including 236 (9.2%) participants diagnosed with prostate cancer, 87 (3.4%) with lung cancer, and 79 (3.1%) with colorectal cancer. Other types of cancer were less frequent and were not analyzed separately. Altogether, 283 participants died due to cancer during the follow-up.

The background characteristics of the men with and without cancer diagnoses can be found in Table 1. The participants with cancer incidence were older than their healthy counterparts, drank more alcohol, and were more often smokers.

In multivariate models, loneliness was associated with total cancer incidence even after adjusting for all covariates (i.e., age, SES, alcohol consumption, smoking, physical activity, BSDS, hours slept at night, HPL depression scale scores, hs-CRP, systolic blood pressure, LDL-C, BMI, and CVD history) (Table 2). Loneliness was associated with lung cancer incidence, except when adjusted for HPL Depression Scale scores (Model 6) or when all covariates were included in the model at the same time (Model 9) (Table 4). There was no association between loneliness and prostate cancer (Table 3) or colorectal cancer (Table 5). Social isolation was associated with total cancer incidence, except when adjusted for lifestyle variables (Model 3), BSDS (Model 4), HPL Depression Scale scores (Model 6), or when all covariates were included in the model at the same time (Model 9). Social isolation was not associated with the incidence of prostate, lung, or colorectal cancer (Tables 2–5). Furthermore, we also performed the analyses with the unmodified HPL Depression Scale and the results were essentially the same (data not shown).

To test the effect of relationship status on cancer incidence, we removed the information related to it from the Social Isolation Scale and repeated all multivariate analyses. The results remained essentially the

Table 1
Background characteristics of the study population according to cancer incidence during the follow-up. Values are medians (interquartile ranges), unless otherwise stated.

	No cancer (n = 1921)	Cancer by 2012 (n = 649)	Test value	p-value
Age, mean (SD)	52.66 (5.3)	53.90 (4.6)	-5.752	<0.001[a]
Smoking, n (%)	570 (29.7)	249 (38.4)	16.890	<0.001[c]
Alcohol g/week	30.00 (5.89-88.33)	35.70 (6.43-105.38)	-1.981	0.048[b]
Physical activity (kcal/d)	85.2 (29.4-189.6)	84.4 (31.9-188.3)	-0.210	0.834[b]
HPL Depression Scale scores	1 (0-2.8)	1 (0-3)	-0.666	0.505[b]
Socioeconomic status, mean (SD)	12.18 (5.1)	12.50 (5.1)	-1.362	0.173[a]
Hs-CRP	1.30 (0.70-2.46)	1.34 (0.75-2.57)	-1.007	0.314[b]
BMI, mean (SD)	26.87 (3.6)	26.87 (3.5)	-0.059	0.953[a]
Systolic blood pressure, mean (SD)	134.42 (16.85)	133.62 (17.63)	1.024	0.306[a]
LDL-C, mean (SD)	4.03 (0.99)	4.08 (1.05)	-1.209	0.227[a]
Self-reported sleep quantity, mean (SD)	2.88 (1.66)	2.89 (1.77)	-0.053	0.985[a]
Baltic Sea Diet scores, mean (SD)	12.88 (3.93)	12.63 (4.07)	1.390	0.165[a]
Loneliness Scale scores	11.8 (8-18)	12 (8-19.5)	-1.289	0.197[b]
Social Isolation Scale scores, mean (SD)	13.18 (4.83)	13.39 (4.93)	-0.918	0.359[a]
Modified Social Isolation Scale* scores, mean (SD)	12.90 (5.06)	13.18 (4.83)	-0.901	0.363[a]

[a] Student's *t*-test;
[b] Mann–Whitney *U* test;
[c] Chi-Squared test
* Relationship status excluded.

Table 2
Cox regression table for loneliness[a], social isolation[a], and total cancer incidence ($n = 649$).

	Loneliness HR[b] (CI 95%)	Social isolation HR[b] (CI 95%)
Model 1.	1.10 (1.03-1.19) $p = 0.009$	1.09 (1.01-1.17) $p = 0.033$
Model 2.	1.10 (1.02-1.19) $p = 0.012$	1.08 (1.00-1.17) $p = 0.046$
Model 3.	1.09 (1.01-1.18) $p = 0.019$	1.07 (0.10-1.16) $p = 0.066$
Model 4.	1.10 (1.02-1.18) $p = 0.012$	1.08 (1.00-1.17) $p = 0.050$
Model 5.	1.10 (1.03-1.19) $p = 0.009$	1.09 (1.01-1.17) $p = 0.033$
Model 6.	1.10 (1.01-1.19) $p = 0.033$	1.08 (1.00-1.17) $p = 0.061$
Model 7.	1.10 (1.03-1.20) $p = 0.008$	1.09 (1.01-1.17) $p = 0.037$
Model 8.	1.10 (1.03-1.19) $p = 0.009$	1.09 (1.01-1.18) $p = 0.029$
Model 9.	1.10 (1.01-1.20) $p = 0.028$	1.07 (0.99-1.16) $p = 0.086$

Model 1: adjusted for age.
Model 2: adjusted for age and adulthood socioeconomic status.
Model 3: adjusted for age and lifestyle variables (alcohol consumption, smoking, and physical activity).
Model 4: adjusted for age and Baltic Sea Diet Score.
Model 5: adjusted for age and hours slept at night.
Model 6: adjusted for age and HPL Depression Scale score.
Model 7: adjusted for age and hs-CRP.
Model 8: adjusted for age and somatic variables (systolic blood pressure, low-density lipoprotein cholesterol, body mass index, and past history of cardiovascular disease).
Model 9: adjusted for all the above-described variables (i.e., age, alcohol consumption, smoking and physical activity, HPL Depression Scale score, socioeconomic status, low-density lipoprotein cholesterol, history of cardiovascular disease, systolic blood pressure, hs-CRP, BDSD, and hours slept at night).
[a] Z-scores of the scales are used.
[b] Hazard ratios (HR) show the increase in the risk of cancer incidence for each 1-SD increase in the scale in question.

Table 3
Hazard ratios for loneliness[a] and social isolation[a] regarding prostate cancer incidence ($N = 236$).

	Loneliness HR[b] (CI 95%)	Social isolation HR[b] (CI 95%)
Model 1.	1.12 (0.99-1.26) $p = 0.080$	1.01 (0.89-1.15) $p = 0.846$
Model 2.	1.13 (1.00-1.29) $p = 0.057$	1.03 (0.90-1.17) $p = 0.671$
Model 3.	1.11 (0.99-1.26) $p = 0.086$	1.02 (0.89-1.15) $p = 0.825$
Model 4.	1.12 (0.99-1.26) $p = 0.079$	1.01 (0.89-1.15) $p = 0.863$
Model 5.	1.12 0.987-1.26) $p = 0.080$	1.01 (0.89-1.15) $p = 0.847$
Model 6.	1.23 (1.07-1.41) $p = 0.003$	1.04 (0.91-1.18) $p = 0.606$
Model 7.	1.16 (0.99-1.26) $p = 0.077$	1.02 (0.89-1.16) $p = 0.807$
Model 8.	1.11 (0.99-1.26) $p = 0.082$	1.01 (0.89-1.15) $p = 0.860$
Model 9.	1.23 (1.07-1.41) $p = 0.003$	1.05 (0.92-1.20) $p = 0.463$

Model 1: adjusted for age.
Model 2: adjusted for age and adulthood socioeconomic status.
Model 3: adjusted for age and lifestyle variables (alcohol consumption, smoking, and physical activity).
Model 4: adjusted for age and Baltic Sea Diet Score (BSDS).
Model 5: adjusted for age and hours slept at night.
Model 6: adjusted for age and HPL Depression Scale score.
Model 7: adjusted for age and hs-CRP.
Model 8: adjusted for age and somatic variables (systolic blood pressure, low-density lipoprotein cholesterol, body mass index, and past history of cardiovascular disease).
Model 9: adjusted for all the above-described variables (i.e., age, alcohol consumption, smoking, physical activity, HPL Depression Scale score, socioeconomic status, low-density lipoprotein cholesterol, history of cardiovascular disease, systolic blood pressure, hs-CRP, BSDS, and hours slept at night)ablef.
[a] Z-scores of the scales are used.
[b] Hazard ratios (HR) show the increase in the risk of cancer incidence for each 1-SD increase in the scale in question.

Table 4
Cox regression table for loneliness[a] and social isolation[a] regarding lung cancer incidence ($N = 87$).

	Loneliness HR[b] (CI 95%)	Social isolation HR[b] (CI 95%)
Model 1.	1.29 (1.06-1.50) $p = 0.006$	1.23 (1.00-1.52) $p = 0.052$
Model 2.	1.26 (1.05-1.51) $p = 0.013$	1.19 (0.96-1.46) $p = 0.109$
Model 3.	1.24 (1.03-1.49) $p = 0.021$	1.16 (0.94-1.43) $p = 0.169$
Model 4.	1.27 (1.05-1.52) $p = 0.012$	1.19 (0.96-1.46) $p = 0.107$
Model 5.	1.28 (1.07-1.54) $p = 0.006$	1.23 (1.00-1.51) $p = 0.053$
Model 6.	1.20 (0.97-1.49) $p = 0.088$	1.18 (0.95-1.45) $p = 0.131$
Model 7.	1.29 (1.08-1.55) $p = 0.005$	1.22 (0.99-1.50) $p = 0.002$
Model 8.	1.27 (1.06-1.51) $p = 0.010$	1.23 (0.99-1.50) $p = 0.068$
Model 9.	1.21 (0.98-1.49) $p = 0.074$	1.11 (0.90-1.37) $p = 0.342$

Model 1: adjusted for age.
Model 2: adjusted for age and adulthood socioeconomic status.
Model 3: adjusted for age and lifestyle variables (alcohol consumption, smoking and physical activity).
Model 4: adjusted for age and Baltic Sea Diet Score (BSDS).
Model 5: adjusted for age and hours slept at night.
Model 6: adjusted for age and HPL Depression Scale Score.
Model 7: adjusted for age and hs-CRP.
Model 8: adjusted for age and somatic variables (systolic blood pressure, low-density lipoprotein cholesterol, body mass index and past history of cardiovascular disease).
Model 9: adjusted for all the above-described variables (i.e., age, alcohol consumption, smoking and physical activity, HPL Depression Scale Score, socioeconomic status, low-density lipoprotein cholesterol, history of cardiovascular disease, systolic blood pressure, and hs-CRP, BSDS and hours slept at night).
[a] Z-scores of the scales are used.
[b] Hazard ratios (HR) show the increase in the risk of cancer incidence for each 1-SD increase in the scale in question.

Table 5
Hazard ratios for loneliness[a] and social isolation[a] regarding colorectal cancer incidence (N = 79).

	Loneliness HR[b] (CI 95%)	Social isolation HR[b] (CI 95%)
Model 1.	0.90 (0.70-1.15) $p = 0.394$	1.04 (0.84-1.30) $p = 0.719$
Model 2.	0.89 (0.69-1.14) $p = 0.359$	1.03 (0.83-1.29) $p = 0.792$
Model 3.	0.89 (0.69-1.14) $p = 0.347$	1.04 (0.83-1.29) $p = 0.760$
Model 4.	0.90 (0.70-1.15) $p = 0.389$	1.04 (0.83-1.30) $p = 0.726$
Model 5.	0.90 (0.70-1.16) $p = 0.419$	1.05 (0.84-1.30) $p = 0.697$
Model 6.	0.88 (0.67-1.16) $p = 0.359$	1.05 (0.84-1.31) $p = 0.702$
Model 7.	0.90 (0.70-1.15) $p = 0.394$	1.04 (0.84-1.30) $p = 0.719$
Model 8.	0.90 (0.70-1.15) $p = 0.384$	1.04 (0.84-1.30) $p = 0.710$
Model 9.	0.86 (0.65-1.14) $p = 0.297$	1.04 (0.82-1.30) $p = 0.765$

Model 1: adjusted for age
Model 2: adjusted for age and adulthood socioeconomic status
Model 3: adjusted for age and lifestyle variables (alcohol consumption, smoking, and physical activity)
Model 4: adjusted for age and Baltic Sea Diet Score (BSDS)
Model 5: adjusted for age and hours slept at night
Model 6: adjusted for age and HPL Depression Scale score
Model 7: adjusted for age and hs-CRP
Model 8: adjusted for age and somatic variables (systolic blood pressure, low-density lipoprotein cholesterol, body mass index, and past history of cardiovascular disease)
Model 9: adjusted for all the above-described variables (i.e., age, alcohol consumption, smoking, physical activity, HPL Depression Scale score, socioeconomic status, low-density lipoprotein cholesterol, history of cardiovascular disease, systolic blood pressure, hs-CRP, BSDS, and hours slept at night)
[a] Z-scores of the scales are used.
[b] Hazard ratios (HR) show the increase in the risk of cancer incidence for each 1-SD increase in the scale in question.

same (Supplementary Table 1).

There was no association between loneliness or social isolation and cancer mortality among those participants who were diagnosed with cancer during the follow-up (Supplementary Table 2). We tested the survival rates of those participants who were diagnosed with cancer during the follow-up to examine whether relationship status alone, irrespective of loneliness or social isolation scales, affected survival after a cancer diagnosis. The average estimated survival time for those cancer patients who were single, divorced, or widowed at baseline was 7851 days (95% CI = 7303.2 to 8398.8) and for those who were married or

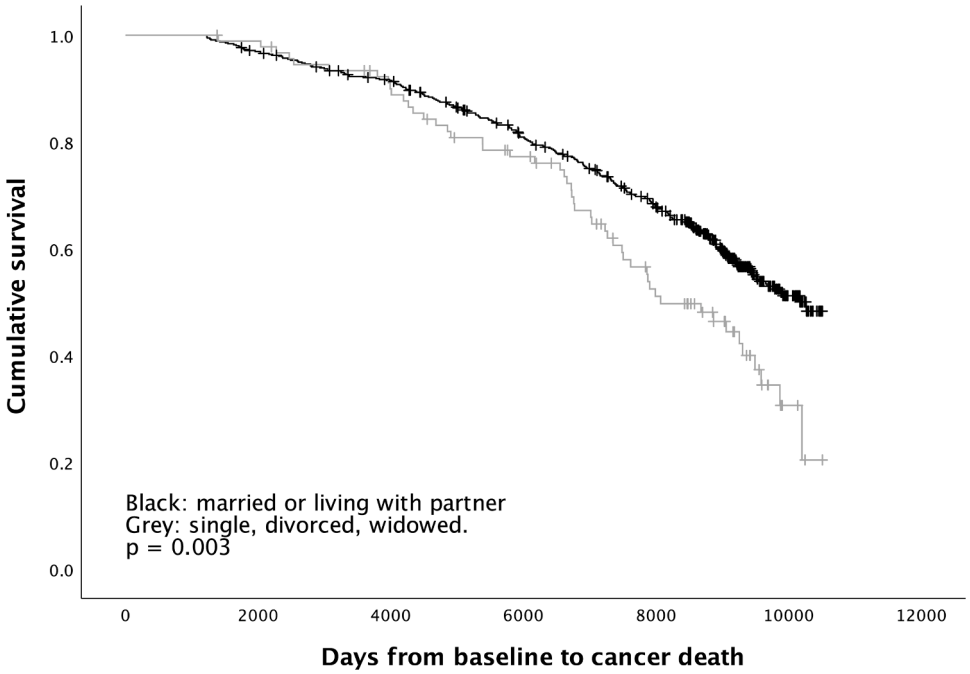

Fig. 1. Kaplan-Meier estimates (survival functions) showing the risk of cancer mortality in cancer patients ($N = 649$) according to their relationship status (living alone, $N = 52$; living with somebody, $N = 525$).

living with a partner it was 8533.4 days (95% CI = 8309.5 to 8757.3) (i.e., 21.5 years vs 23.4 years). The difference in survival according to Kaplan-Meier analysis was statistically significant (Fig. 1).

4. Discussion

4.1. Main findings

We found both loneliness and social isolation to associate with total cancer incidence and loneliness to associate with lung cancer incidence. However, social isolation was not associated with the incidence of lung cancer. Neither loneliness nor social isolation associated with prostate cancer or colorectal cancer. According to Kaplan-Meier analysis, there was a connection between relationship status at baseline and the survival time after receiving a cancer diagnosis.

4.2. Comparison with previous literature

4.2.1. Loneliness, social isolation, and cancer incidence

Our findings concerning the higher risk of cancer incidence in lonely and socially isolated men compared to their non-lonely and socially connected counterparts are in agreement with previous studies. In a Polish study, social isolation, poverty, and low involvement in religious activities associated with lung cancer incidence (Orlewska et al., 2018). Nausheen et al. (2010) discovered that implicitly measured loneliness independently predicted the expression of immunohistochemical vascular endothelial growth factor (VEGF) in tumors of the colon and rectum. In a Japanese cohort study, a lack of social support (including emotional support from family and friends) was connected with a higher risk of both colorectal cancer incidence and mortality in men (Ikeda et al., 2013).

4.2.2. Inflammation

Loneliness has several potential adverse effects on biological stress processes. In an English longitudinal study on ageing, the onset of loneliness in men was associated with an increase in the inflammatory markers CRP, ferritin, and fibrinogen (Vingeliene et al., 2019). According to epidemiological studies, inflammation predisposes individuals to various types of cancer, and underlying infections and inflammatory responses are linked to 15–20% of all deaths from cancer worldwide (Mantovani et al., 2008). Chronic inflammation has been observed to pre-dispose to various types of cancer, so a pro-inflammatory bias may not only result in the depressive symptoms frequently observed in cancer patients, but could also be responsible for the development of the cancer itself in vulnerable populations (Sotelo et al., 2014). However, in our study, the connection between loneliness, social isolation, and total cancer incidence, as well as lung cancer incidence, remained significant despite adjustments for hs-CRP.

4.2.3. Depression

Inflammatory changes related to cancer or its treatment may be connected with the development of depressive symptoms in cancer patients, which go beyond the stress and emotional impact of merely receiving the cancer diagnosis (Sotelo et al., 2014). Loneliness has been recognized as a mediator for the effect that living alone has on depression (Park et al., 2017; Kraav et al., 2020), and it has been suggested to be an independent risk factor for depression (Luanaigh and Lawlor 2008), especially among older people (Beutel et al., 2019). In our study, the adjustments for HPL Depression Scale scores did not greatly alter the associations between loneliness and cancer incidence, except in the case of lung cancer incidence. The connection between social isolation and total cancer incidence became statistically nonsignificant after adjusting the results for HPL Depression Scale scores.

4.2.4. Socioeconomic status

A low SES is considered to predict greater mortality in cancer patients. Social isolation and living in poor neighborhoods are also associated with greater cancer mortality (Fleisch Marcus et al., 2017). Among our participants, the difference in baseline SES between those who received and did not receive a cancer diagnosis was not statistically significant. Furthermore, adjusting the multivariate models for adulthood SES did not essentially change the results. Finland, as a Nordic welfare state, is determined to reduce health inequality and is actively working towards decreasing health-related differences between socio-demographic groups (Rotko et al., 2011). According to a large study that compared 37 countries from the Human Mortality Database,

on average, the lowest inequality and highest life expectancy for men existed in the Nordic welfare states (Popham et al., 2013). This may explain why our results do not confirm previous findings on the effect of a low SES on cancer mortality (Fleisch Marcus et al., 2017).

4.2.5. Lifestyle

Approximately 5–10% of all tumor diseases are caused by genetic predisposition, while the remaining 90–95% can be explained by environmental conditions and lifestyle (Schwingshackl et al., 2017; Anand et al., 2008), particularly by smoking, alcohol use, obesity and an unbalanced diet, and lack of exercise (Mentella et al., 2019; Schwingshackl et al., 2017; Ligibel et al., 2014; Anand et al., 2008).

Obesity has been proposed as a risk factor for prostate cancer (Angel et al., 2019), but the connections between diet, appetite-regulating hormones, BMI, and prostate cancer are still unclear (Cuzick et al., 2014). The Mediterranean diet has been found to have a positive effect on cancer prevention due to the high content of antioxidants and anti-inflammatory nutrients (Mentella et al., 2019). Due to differences in food cultures, the Mediterranean diet may not be easily adopted in other countries, and the Baltic Sea Diet Score (BSDS) is therefore used in Nordic countries to illustrate healthy diet choices (Kanerva et al., 2014). Smoking is the leading cause of lung cancer (O'Keeffe et al., 2018) and an established risk factor for prostate cancer (Cuzick et al., 2014), as well as colorectal cancer occurrence and mortality (Walter et al., 2014). Alcohol consumption increases the risk of cancer in different sites, including the colorectum, and there is also accumulating evidence that alcohol consumption is associated with prostate cancer (Bagnardi et al., 2015). Physical exercise has been connected with cancer prevention in various studies (Ruiz-Casado et al., 2017; Todoric et al., 2016). Furthermore, a recent review suggested that exercise promotes significant improvements in clinical, functional, and, in some populations, survival outcomes (Stout et al., 2017). In our current study, we used lifestyle variables (smoking, alcohol consumption, and physical exercise) as covariates in Cox regression analysis. Adjustments for lifestyle factors did not change the effect of loneliness on total cancer incidence or lung cancer incidence. The connection between social isolation and total cancer incidence was lost after adjusting for lifestyle variables. We adjusted our results for BSDS scores, which did not alter the effect of loneliness on cancer incidence, but it did alter the effect of social isolation on cancer incidence. Furthermore, adjusting the results for variables linked to cardiovascular risk (BMI, LDL cholesterol, past history of CVD, and systolic blood pressure) did not change the effect of loneliness or that of social isolation on cancer incidence.

4.2.6. Relationship status

We tested the effect of relationship status on cancer mortality among cancer patients. Our results reflect previous similar findings reviewed in the meta-analysis by Pinquart and Duberstein (2009). They found that the relative risk of cancer mortality among married respondents was 12% lower than in unmarried persons, while never-married respondents had a significant survival disadvantage compared to divorced or widowed individuals. It has been suggested that living alone has a stronger effect on cancer mortality in men than women (Lai et al., 1999). Men living alone were found to have significantly lower survival rates after a diagnosis of cutaneous malignant melanoma than men living with a partner, partially attributed to a more advanced stage at diagnosis (Eriksson et al., 2014).

4.3. Strengths and limitations

Loneliness and social isolation were only measured during baseline data collection; therefore, we could not consider the changes that occurred in the levels of loneliness or the social network of the participants. Similarly, the relationship status was only measured during baseline data collection. It is possible that for some of the participants, numerous changes occurred in their living arrangements and relationships during the follow-up period, and having information about these changes would have enhanced the discussion of possible explanatory mechanisms. The main strengths of our study are the long follow-up and large variety of covariates, as well as the possibility to use continuous variables to measure loneliness and social isolation. We were also able to reduce the risk of reverse causality by excluding those who received a cancer diagnosis during the first two years after baseline data collection. Our sample was a representative sample of aging Finnish men and the results can be generalized within this group. However, they cannot be generalized to women or other races.

We examined the connection between loneliness, social isolation, and the incidence of different cancer types, and found an association between loneliness, social isolation, and total cancer incidence, as well as an association between loneliness and the incidence of lung cancer. Moreover, we found no association between loneliness and prostate or colorectal cancer, or between social isolation and prostate, lung, or colorectal cancer. We had no variables that would have helped us further investigate hypothetical mechanistic explanations for our observations. Future research with more biological and metabolomic information should address this issue.

5. Conclusion

We found both loneliness and social isolation to associate with total cancer incidence. Furthermore, loneliness was associated with the incidence of lung cancer. However, the mechanisms behind these associations remained unclear and are a topic for further research. Based on current research, we can recommend the development of targeted interventions for middle-aged men who suffer from loneliness, regardless of the size of their social network.

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CRediT authorship contribution statement

Siiri-Liisi Kraav: Formal analysis, Writing – original draft, Visualization. **Soili M. Lehto:** Writing – review & editing. **Jussi Kauhanen:** Writing – review & editing, Supervision. **Sari Hantunen:** Writing – review & editing. **Tommi Tolmunen:** Writing - review & editing, Supervision.

Declaration of Competing Interest

Authors of the manuscript "Loneliness and social isolation increase cancer incidence in a cohort of Finnish middle-aged men. A longitudinal study." have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113868.

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