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ORIGINAL RESEARCH

Associations Between Self-Rated Health and Mortality in the Norwegian Women and Cancer (NOWAC) Study

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Purpose: We investigated the association between self-rated health (SRH) and cancer incidence and SRH and all-cause mortality among Norwegian women.

Population and Methods: We used data from 110,104 women in the Norwegian Women and Cancer (NOWAC) cohort aged 41–70 years at baseline. We used flexible parametric survival analysis with restricted cubic splines to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between SRH and mortality in the entire cohort. We employed the same method in a multistate design to assess associations between baseline SRH and 1) cancer incidence, and 2) all-cause mortality in subgroups of women who did and did not receive a cancer diagnosis during follow-up.

Results: With very good SRH as reference category for all associations and median age at end of follow-up, lower SRH was associated with increased mortality ($HR_{good\ SRH}$ 1.19, 95% CI 1.12–1.26) and $HR_{poor\ SRH}$ 1.81, 95% CI 1.66–1.97). Lower SRH at baseline was associated with cancer incidence ($HR_{good\ SRH}$ 1.14, 95% CI 1.08–1.20 and $HR_{poor\ SRH}$ 1.44, 95% CI: 1.32–1.58). Poor baseline SRH was associated with increased mortality for women who received a cancer diagnosis ($HR_{poor\ SRH}$ 1.20, 95% CI 1.04–1.39), and SRH showed a strong association with increased mortality for women who stayed cancer free ($HR_{good\ SRH}$ 1.59, 95% CI 1.44–1.77 and $HR_{poor\ SRH}$ 3.34, 95% CI 2.91–3.84).

Conclusion: Lower SRH at baseline predicted increased cancer risk and all-cause mortality in middle-aged to older women. Poor SRH at baseline predicted all-cause mortality in women who later received a cancer diagnosis. Both good and poor SRH at baseline predicted all-cause mortality in women who stayed cancer-free, and the association was stronger for these women compared to both the entire cohort and to women who were subsequently diagnosed with cancer.

Keywords: self-rated health, cohort study, multistate, cancer, mortality, women

Introduction

Despite improved diagnostic methods, screening, and treatment for the most prevalent cancer types, the overall burden of cancer is rising worldwide due to increased incidence and life expectancy,[1] making the health and quality of life of cancer survivors a public health issue that requires attention and research. Improved prevention and risk reduction are crucial to further reduce morbidity, mortality, and other cancer-related health challenges faced by these survivors.

Several prospective, population-based studies have shown that self-rated health (SRH) predicts all-cause mortality, independent of other risk factors.[2–4] SRH is a measure commonly used in population-based surveys; participants usually rank it on a four- or five-point scale based on their perceived overall health. The underlying mechanisms by which SRH predicts mortality are not well understood, but SRH correlates well with general health status and may incorporate information that is not easily measured or quantified, such as psychosocial conditions, underlying physical conditions and coping abilities, objective health information, symptoms, and health-related behavior.[5,6] A recent study using data from the UK Biobank study found that cross-matched poor SRH and unfavorable health status derived from patient journals

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were associated with increased mortality risk, with similar effect estimates as those calculated from studies on SRH and mortality.[7] SRH is a straightforward and short question to pose to a patient in a clinical setting. Given its inclusive content, we believe SRH could be used clinically for health assessment, risk assessment, and monitoring of patients undergoing cancer treatment.

The prospective design of the Norwegian Women and Cancer (NOWAC) study and its linkage to the Cancer Registry of Norway and the Norwegian Cause of Death Registry allow researchers to study the ability of pre-diagnostic SRH to predict mortality among women who receive a cancer diagnosis during follow-up. Nabulsi et al found that low pre-diagnostic SRH was associated with a moderate increase in all-cause mortality in a retrospective cohort study of patients with multiple myeloma.[8] To the best of our knowledge, no one have studied the association between pre-diagnostic SRH and all-cause mortality in women who later receive a cancer diagnosis in a healthy cohort. The aims of this study were to investigate the association between SRH and all-cause mortality in the entire NOWAC cohort, as well as the association between pre-diagnostic SRH and 1) incident cancer risk in the entire cohort, and 2) all-cause mortality in subgroups of women who did and did not receive a cancer diagnosis during follow-up.

Materials and Methods

Study Design and Participants

The NOWAC study is a nationally representative, prospective cohort study of Norwegian women that was initiated in 1991. In total, 172,472 randomly sampled women aged 30–70 years received up to four questionnaires between 1991 and 2017. The study has been described in more detail previously.[9] The NOWAC study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants gave written informed consent and completed questionnaires that collected information on sociodemographic factors, lifestyle behaviors, anthropometry, and general health. The study was performed in accordance with the Declaration of Helsinki.

We used baseline measurements to ensure that all measurements were pre-diagnostic for women who received a cancer diagnosis during follow-up. We used baseline data from enrollment questionnaires for women recruited between 1996 and 2007. For women recruited between 1991 and 1992, we used measurements from the first follow-up questionnaire completed in 1998 as baseline, since the enrollment questionnaires used in 1991–1992 lacked information on household income. As 10,596 women were lost to follow-up between 1991 and 1998, we included an initial study sample of 161,876 women aged 41–70 years old. We further excluded participants with less than 1 year of follow-up (n=815), missing information on SRH (n=16,808), prevalent cancer (n=6323), and with incomplete information on selected covariates (n=27,826), leaving 110,104 participants in the final analytical sample (Figure 1).

Assessment of Self-Rated Health, Covariates, Cancer Diagnosis, and Death

Participants were asked to rate their overall health on a four-item scale including “very good”, “good”, “poor”, or “very poor”. In four questionnaires, SRH was divided into self-rated physical health and self-rated mental health rather than one global SRH item.

Participants rated their physical activity level using a 10-level global scale that includes physical exercise, leisure time activity, and work-related activity, where 1 represents the lowest and 10 the highest level of physical activity. They also reported their current weight (kg), height (cm), smoking habits (including smoking status, age at initiation, and average daily numbers of cigarettes smoked at different age intervals), frequency of consumption of specified alcoholic beverages, duration of education, household income, and whether they were living with a spouse or partner.

Data from the NOWAC study was linked to that of the Cancer Registry of Norway, the Norwegian Cause of Death Registry, and the National Population Register, to identify incident cancer diagnoses (classified using the International Classification of Diseases Revision 10, ICD-10),[10] dates of diagnoses, date of death, and date of emigration, respectively, during follow-up, which ended on 31st December 2018.

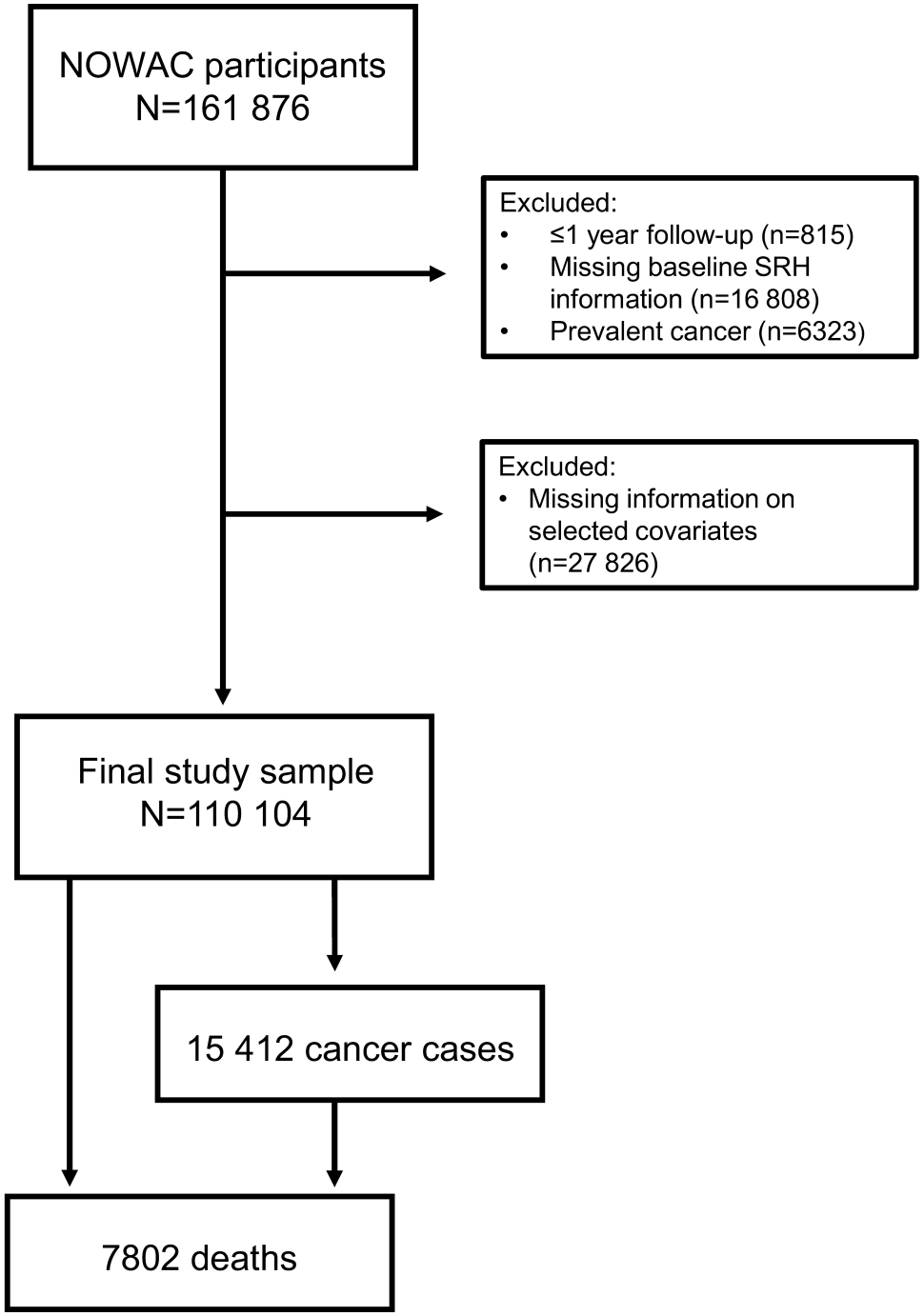

Figure 1 Flow chart of the study sample, the Norwegian Women and Cancer (NOWAC) study.
Abbreviation: SRH, self-rated health.

Statistical Analysis

We made a directed acyclic graph (DAG) using the DAGitty software (available from http://dagitty.net)[11] to identify potential confounders of the association between pre-diagnostic SRH and all-cause mortality. Confounders in the DAG were similar to those we identified from published literature and those we included based on our expert knowledge. We identified age, physical activity level, body mass index (BMI), smoking habits, alcohol consumption, duration of education, household income, and living with a spouse or partner as confounders (Supplementary Figure 1).

SRH was categorized as very good, good, or poor, which combined the responses "poor" and "very poor", as very few participants reported "very poor" SRH. In questionnaires that divided SRH into self-rated physical and mental health, only participants who reported equal categories for both were included and assigned to that SRH category.

Physical activity level was categorized as low (1–4), moderate (5–7), and high (8–10). We calculated BMI from self-reported height and weight and categorized it as underweight (<18.5 kg/m^2), normal weight (18.5<25 kg/m^2), overweight (25<30 kg/m^2), and obese (≥30 kg/m^2). Smoking habit was a combined variable that included smoking status (never, former, and current) and pack years (0–9, 10–19, ≥20). We categorized alcohol consumption in grams of ethanol per day (0, 0.1–4.9, 5–9.9, ≥10); duration of education according to the Norwegian education system (0–9, 10–12, 13–16, and ≥17 years); household income as 0–300,000, 301,000–450,000, 451,000–600,000, and >600,000 Norwegian kroner; and living with a spouse/partner or not as yes or no.

Participants were followed from the date of return of the baseline questionnaire until date of death, emigration, or the end of follow-up (31st December 2018), whichever occurred first. We used participant's age as the underlying time scale as it seems to yield less biased estimates compared to conventional age adjustment in prospective cohort studies where age is a strong predictor of the outcome.[12,13] In the multivariable model, we adjusted for physical activity level, BMI, smoking habits, alcohol consumption, duration of education, household income, and living with a spouse or partner.

To assess the association between baseline SRH and all-cause mortality in the full cohort, we used the stpm2 package for Stata[14] to fit a flexible parametric model using restricted cubic splines with 3 knots modelling the baseline hazard function to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). We ran the model with SRH as a time-dependent covariate with 1 knot for the time-dependent effect. The number of knots was selected using the Akaike information criterion.

Multistate Survival Analysis

We investigated the association between baseline SRH and cancer incidence (ICD-10 codes: C00-97 and D37-48), and the association between baseline SRH and all-cause mortality in women who did and did not receive a cancer diagnosis during follow-up, using multistate survival analysis.

We used the multistate package for Stata[15] to split the dataset into three transitions: baseline to cancer diagnosis (transition 1), baseline to death (transition 2), and cancer diagnosis to death (transition 3), defining three possible states: alive (state 1), diagnosed with cancer (state 2), and dead (state 3). Transition 1 and 2 were mutually exclusive and participants who received a cancer diagnosis during follow-up were censored for transition 2. For transition 1, we fit a flexible parametric model using restricted cubic splines with 3 knots for the baseline hazard function to calculate HRs and 95% CIs. Baseline SRH was modelled with 2 degrees of freedom for the time-dependent effect of SRH on cancer risk. For transitions 2 and 3, we fit flexible parametric models with 2 knots and included baseline SRH with 1 degree of freedom for the time-dependent effect of SRH on mortality risk. For all transitions, we used age as the underlying timescale and adjusted for physical activity level, BMI, smoking status, alcohol consumption, duration of education, household income, and living with a spouse or partner (Figure 2). For transition 3, we also did a sub-analysis with cancer site as a strata variable with strata listed in Supplementary Table 1 to check for bias from differences in prognosis between cancer sites. The results from the stratified sub-analysis are listed in Supplementary Table 2.

All analyses were performed using Stata V.17.0 (StataCorp, College Station, TX).

Results

Study Sample Characteristics

The 110,104 women in the study sample were aged 41–70 years old at baseline. Of these women, 32.1% (35,373 women) reported very good, 61.1% (67,244 women) good, and 6.8% (7487 women) poor baseline SRH. A higher proportion of women with poor baseline SRH reported a low physical activity level, high BMI, current smoking, shorter education, and lower income, compared to women with very good baseline SRH. Women with poor baseline SRH were older and more likely to live alone compared to women with very good baseline SRH (Table 1).

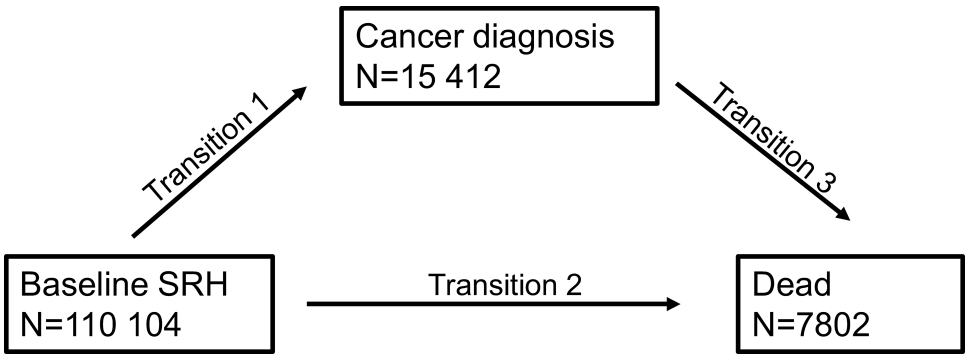

Figure 2 Multistate design illustrating three transitions that were investigated using flexible parametric survival models. We calculated hazard ratios for the association between baseline self-reported health (SRH) and incident cancer diagnosis (transition 1), baseline SRH and death in the subgroup of women who did not receive a cancer diagnosis (transition 2), and baseline SRH and death in the subgroup of women who received a cancer diagnosis during follow-up (transition 3).

Total follow-up time included 1,804,751 person-years, and mean follow-up time was 16.4 years (range: 2–22 years). During follow-up, 15,412 women were diagnosed with cancer and 7802 died. Average time from baseline to cancer diagnosis was 9.7 years (0–22 years). Figure 3 displays Kaplan–Meier survival curves for the age-adjusted baseline hazard function for survival by SRH category.

Self-Rated Health and All-Cause Mortality

Both good and poor baseline SRH were associated with increased all-cause mortality in the full NOWAC cohort (Figure 4). At the median age at the end of follow-up (68 years), HRs for all-cause mortality were 1.19 (95% CI

Table 1 Descriptive Characteristics of the Norwegian Women and Cancer Cohort (N=110,104) at Baseline by Self-Rated Health (SRH) Category

	n	Very Good SRH N=35,373	Good SRH N=67,244	Poor SRH N=7487
		n (%)	n (%)	n (%)
Age (years)	110 104			
41–50	46,372	16,240 (45.91)	27,648 (41.12)	2484 (33.18)
51–60	57,689	16,895 (47.76)	33,647 (50.04)	4174 (55.75)
61–70	9989	2238 (6.33)	5949 (8.85)	829 (11.07)
Physical activity level (1–10)				
Low (1–4)	26,563	4818 (13.62)	17,705 (26.33)	4040 (53.96)
Moderate (5–7)	65,375	21,379 (60.44)	41,058 (61.06)	2938 (39.24)
High (8–10)	18,166	9176 (25.94)	8481 (12.61)	509 (6.80)
Body mass index (kg/m^2)				
Underweight (BMI <18.5)	1446	414 (1.17)	843 (1.25)	189 (2.52)
Normal weight (18.5 < BMI <25)	64,561	24,364 (68.88)	37,020 (55.05)	3177 (42.43)
Overweight (25 < BMI <30)	33,328	8952 (25.31)	21,916 (32.59)	2460 (32.86)
Obese (BMI ≥30)	10,769	1643 (4.64)	7465 (11.10)	1661 (22.19)

(*Continued*)

Table 1 (Continued).

	n	Very Good SRH N=35,373	Good SRH N=67,244	Poor SRH N=7487
		n (%)	n (%)	n (%)
Smoking habits				
Never	38,008	13,930 (39.38)	21,864 (32.51)	2214 (29.57)
Former + 0–9 total pack-years	30,041	10,986 (31.06)	17,474 (25.99)	1581 (21.12)
Former + 10–19 total pack-years	7005	2095 (5.92)	4366 (6.49)	544 (7.27)
Former + ≥20 total pack-years	2846	691 (1.95)	1833 (2.73)	322 (4.30)
Current + 0–9 total pack-years	10,981	3288 (9.30)	7011 (10.43)	682 (9.11)
Current + 10–19 total pack-years	13,519	2994 (8.46)	9392 (13.97)	1133 (15.13)
Current + ≥20 total pack-years	7704	1389 (3.93)	5304 (7.89)	1011 (13.50)
Alcohol consumption (g/day)				
0	22,859	6012 (17.00)	14,467 (21.51)	2300 (31.79)
0.1–4.9	53,193	16,397 (46.35)	33,300 (49.52)	3496 (46.69)
5–9.9	22,469	8581 (24.26)	12,901 (19.19)	987 (13.18)
≥10	11,583	4383 (12.39)	6576 (9.78)	624 (8.33)
Duration of education (years)				
0–9	21,758	4239 (11.98)	15,118 (22.48)	2401 (32.07)
10–12	37,634	11,002 (31.10)	24,013 (35.71)	2619 (34.98)
13–16	32,355	12,261 (34.66)	18,486 (27.49)	1608 (21.48)
≥17	18,357	7871 (22.25)	9627 (14.32)	859 (11.47)
Household income (NOK)				
0–300,000	33,764	7733 (21.86)	22,278 (33.13)	3753 (50.13)
301,000–450,000	30,054	9000 (25.44)	19,116 (28.43)	1938 (25.88)
451,000–600,000	23,381	8277 (23.40)	14,030 (20.86)	1074 (14.34)
>600,000	22,905	10,363 (29.30)	11,820 (17.58)	722 (9.64)
Living with spouse or partner				
Yes	88,115	28,768 (81.33)	53,842 (80.07)	5505 (73.53)
No	21,989	6605 (18.67)	13,402 (19.93)	1982 (26.47)

Abbreviations: SRH, self-rated health; NOK, Norwegian kroner.

1.12–1.26) for good vs very good baseline SRH and 1.81 (95% CI 1.66–1.97) for poor vs very good baseline SRH (Supplementary Table 3). For poor baseline SRH, the HR estimate declined during follow-up.

Self-Rated Health and Cancer Risk, and All Cause-Mortality in Subgroups

Lower baseline SRH was associated with receiving a cancer diagnosis during follow-up (Figure 5A). At the median age at the end of follow-up (62 years), HR for mortality was 1.14 (95% CI 1.08–1.20) for good vs very good baseline SRH and 1.44 (95% CI 1.32–1.58) for poor vs very good baseline SRH (Supplementary Table 3).

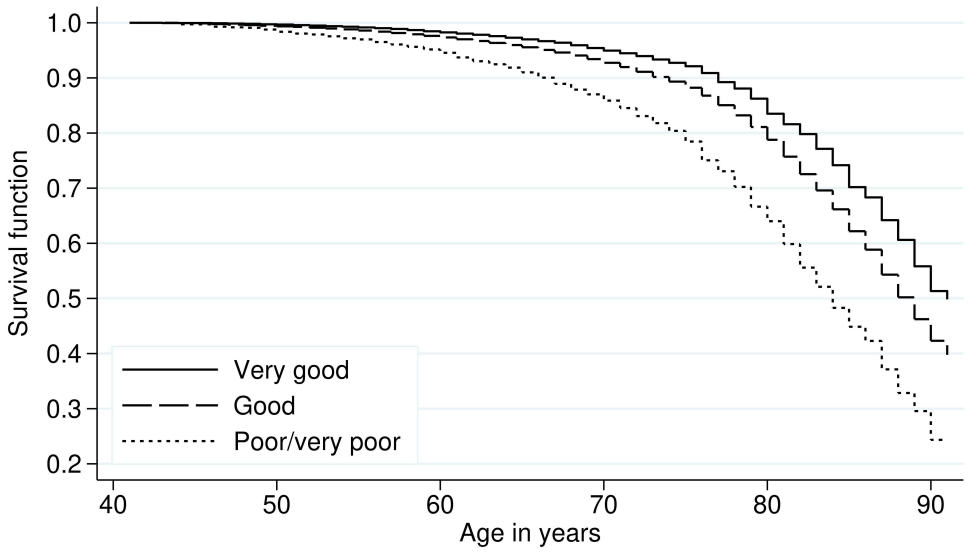

Figure 3 Kaplan-Meier survival curves by self-reported health category for the age-adjusted baseline hazard function in the full cohort of the Norwegian Women and Cancer study (n=110,104).

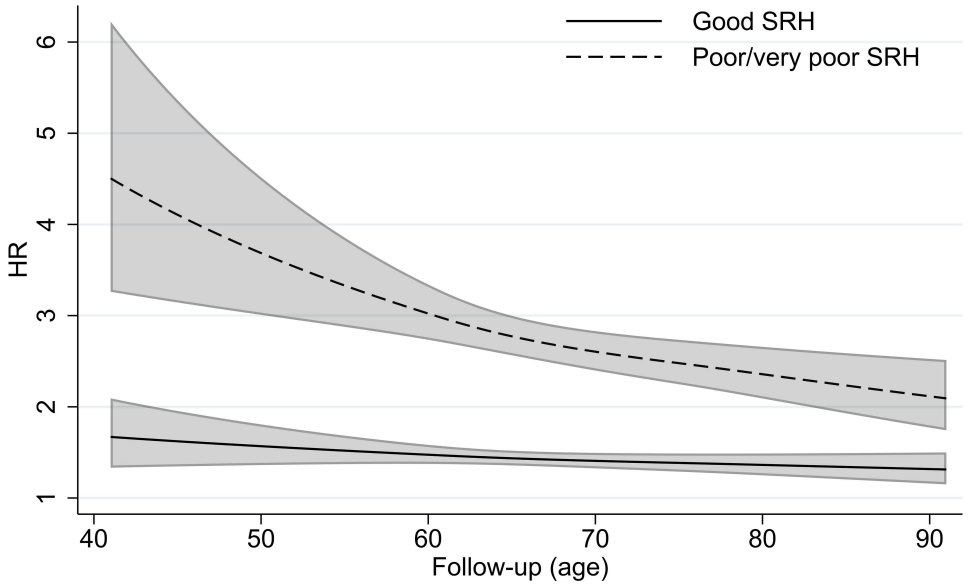

Figure 4 Association (hazard ratios [HRs] with 95% confidence intervals) between baseline self-rated health (SRH) and all-cause mortality in the full cohort of the Norwegian Women and Cancer study (n=110,104), assessed with flexible parametric modelling using restricted cubic splines with 3 knots to baseline SRH and 1 degree of freedom for the time-varying effect of baseline SRH. The model was adjusted for age, physical activity level, body mass index, smoking habits, alcohol consumption, duration of education, household income, and living with a spouse or partner.

Baseline SRH was also associated with mortality in subgroups of women who did and did not receive a cancer diagnosis during follow-up. For women who did not receive a cancer diagnosis, baseline SRH was associated with increased all-cause mortality when poor and good baseline SRH were compared to very good baseline SRH (Figure 5B). HR for mortality at median age at end of follow-up (68 years) was 1.59 (95% CI 1.44–1.77) for good vs very good baseline SRH and 3.34 (95% CI 2.91–3.84) for poor vs very good baseline SRH. Poor baseline SRH was associated with increased mortality after cancer diagnosis (Figure 5C) (HR 1.20, 95% CI 1.04–1.39 at age 68) (Supplementary Table 3).

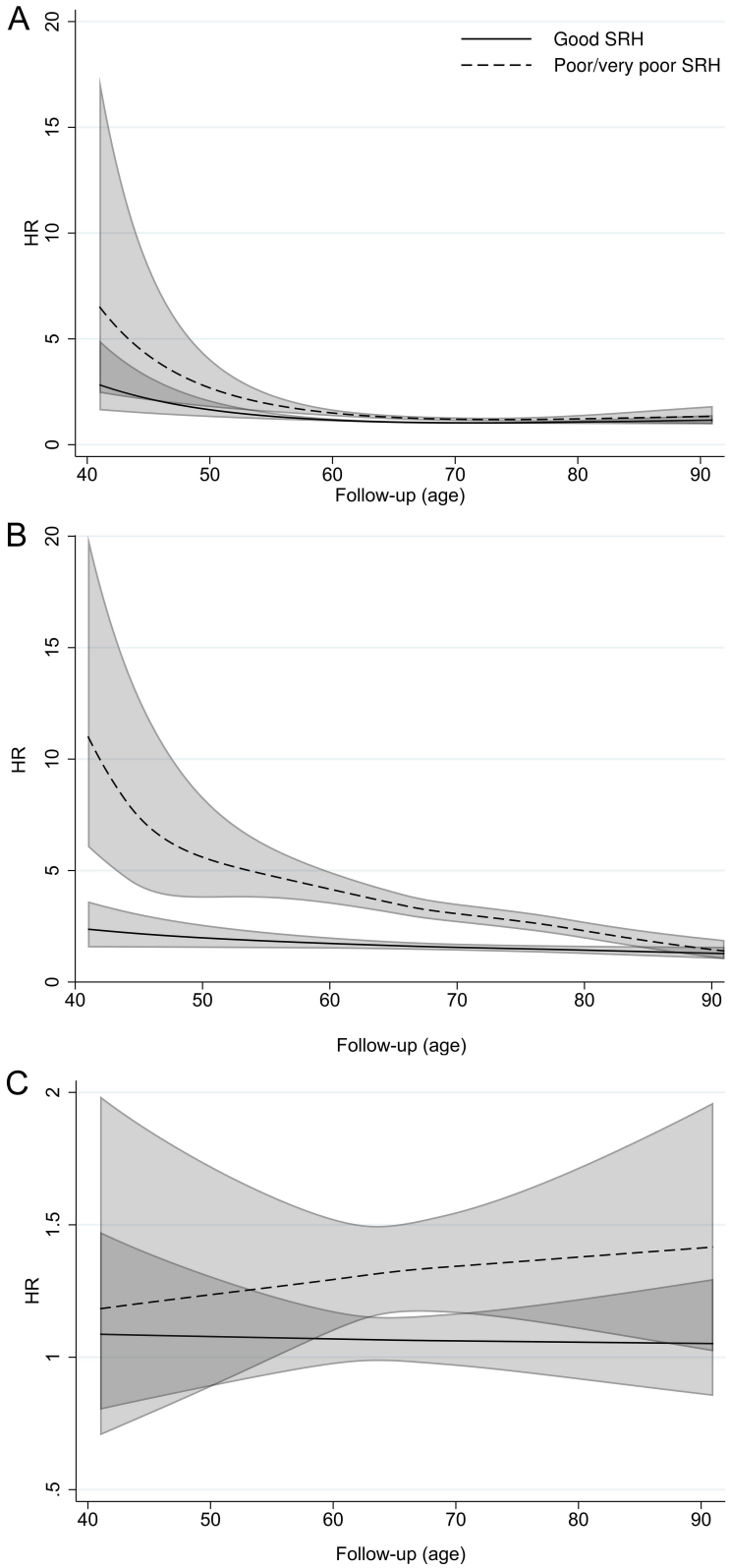

Figure 5 Associations (hazard ratios [HRs] with 95% confidence intervals) between baseline self-rated health (SRH) and cancer incidence in the full cohort of the Norwegian Women and Cancer study (N=110,104) (**A**), all-cause mortality in the subgroup of women who did not receive a cancer diagnosis (**B**), all-cause mortality in the subgroup of women who did receive a cancer diagnosis (**C**), assessed with flexible parametric modelling using restricted cubic splines including baseline SRH as a time-varying covariate. The model was adjusted for age, physical activity level, body mass index, smoking habits, alcohol consumption, duration of education, household income, and living with a spouse or partner.

Discussion

To the best of our knowledge, this is the first study to prospectively investigate the association between SRH and mortality separately among persons who did and did not receive a cancer diagnosis during follow-up using a multistate design. Compared to very good SRH, both good and poor baseline SRH was associated with increased all-cause mortality in our cohort of middle-aged to older women, especially in the subgroup of women who did not receive a cancer diagnosis during follow-up. For women who received a cancer diagnosis during follow-up, reporting poor SRH prior to diagnosis was associated with increased all-cause mortality; however, this relationship was weaker than that observed in women who remained cancer-free and that observed in the full cohort. Lower baseline SRH was also associated with increased incident cancer risk.

The association between SRH and mortality in the full cohort was influenced by modifiable lifestyle factors (physical activity level, BMI, smoking habits, and alcohol consumption) and socioeconomic position (education, household income, and living with a spouse or partner), but baseline SRH predicted all-cause mortality independent of all these factors.

The association between SRH and all-cause mortality has been well studied, with numerous population-based studies consistently reporting the ability of SRH to predict mortality across different countries and subpopulations.[2–4] Our study only provides estimates for this association in women. A large meta-analysis of eight large prospective cohort studies of elderly participants found that the association between SRH and mortality was consistent between men and women.[4]

In our survival models, we did not adjust for comorbidities when examining the association between baseline SRH and all-cause mortality. Our study did not aim to explain any underlying mechanisms in this association, and as SRH reflects perceived health status, we assumed that participants incorporated their disease status when evaluating their own health. Moreover, by including physical activity level, BMI, smoking status, and alcohol consumption in our models, we adjusted for health-related factors that affect both mortality and the risk of chronic conditions such as cardiovascular diseases and diabetes. The self-reporting of diseases implies that the condition was diagnosed by a physician, but SRH likely includes symptoms that have not been reported to or diagnosed by physicians and may thus include subclinical or undiagnosed portions of disease prevalence.[5,16] Stenholm et al studied repeated measurements of SRH in association with cause-specific mortality and found that SRH started to decline before cardiovascular disease was diagnosed.[16]

Baseline SRH was associated with cancer risk, after adjustment for modifiable lifestyle factors and variables related to socioeconomic position. SRH is impacted by modifiable lifestyle factors that are also linked to cancer risk, such as physical inactivity, obesity, smoking, and alcohol consumption. Most previous prospective studies of middle- and older-aged individuals concluded that SRH was not associated with cancer risk.[17–19] However, these studies all had smaller sample sizes and fewer cancer cases relative to ours. Roelsgaard et al concluded that a decrease in SRH did not predict cancer risk in a cohort of Danish female nurses over 44 years of age.[20] However, they reported a HR for cancer risk of 1.08 (95% CI 0.96–1.21), which indicates a positive association. Another Danish study of 7189 individuals (66% men) aged 48–62 years found an association between poor baseline SRH and cancer risk after adjusting for age, sex, BMI, smoking, alcohol intake, physical activity level, marital status, life satisfaction, and vitality.[21]

When separating women who received a cancer diagnosis from those who did not by including cancer diagnosis as a separate transition in a multistate survival model, SRH was an even stronger predictor of all-cause mortality in the subgroup of women who remained cancer-free during follow-up, also when compared to the entire cohort. This association may reflect mortality from chronic diseases with a high mortality risk, including cardiometabolic diseases, and adds value to SRH as a predictor of mortality, given the prevalence of individuals who will not receive a cancer diagnosis in their lifetime. Poor or very poor pre-diagnostic SRH was associated with increased mortality after cancer diagnosis. Our observation of a weaker association between SRH and mortality after cancer diagnosis suggests other and stronger predictors of mortality risk than SRH after a cancer diagnosis, compared to the cohort as a whole and to the women who stayed cancer-free during follow-up. First, the prognosis of cancer may be a stronger predictor of mortality than pre-diagnostic SRH for these women. In a systematic comparison of 5-year mortality predictors in middle-aged to older individuals in the UK Biobank study, Ganna and Ingelsson found that a previous cancer diagnosis was a stronger mortality predictor than SRH in women, but not in men, for whom SRH was the strongest mortality predictor.[22] Second, we did not incorporate changes in SRH or lifestyle after cancer diagnosis, as our aim was to evaluate the predictive value of pre-diagnostic SRH on mortality after a subsequent cancer diagnosis. Smoking cessation has been shown to improve survival in individuals with lung cancer,[23] which is

the second most common cancer among Norwegian women,[24] and several studies have shown that a significant proportion of cancer patients and survivors do indeed quit smoking and improve their diet.[25,26] On the other hand, reduced physical activity levels have been observed after cancer diagnosis,[25] and obesity has been linked to reduced overall survival in cancer patients.[27] Several trials have studied the effect of dietary and exercise interventions on weight loss in cancer patients. A recent systematic review and meta-analysis found that dietary interventions, both alone and in combination with exercise interventions, are effective for weight loss in patients with cancer.[28] It remains unclear if post-diagnosis weight reduction or other behavioral lifestyle changes improves prognosis among cancer patients.

There are few previous studies on the association between SRH and mortality in cancer patients. A retrospective study of 521 elderly patients with multiple myeloma found that low pre-diagnostic SRH was associated with increased all-cause mortality (HR 1.32, 95% CI 1.02–1.171) and multiple myeloma-specific mortality (HR 1.22, 95% CI 0.87–1.70).[8] Eng et al found that low SRH in combination with reduced walking ability at diagnosis was associated with reduced all-cause, but not cancer-specific, survival in women aged 65 years or older diagnosed with breast cancer. The estimated probabilities for 5- and 10-year survival were 0.86 and 0.65, respectively, for women with high SRH and without limited walking ability, and 0.71 and 0.30 for women with low SRH and limited walking ability.[29] Several population-based studies have assessed the association between SRH and cancer-specific mortality. Benjamins et al studied the association between SRH and cause-specific mortality, including cancer-specific mortality, and found that SRH predicted death from cancer.[30] In a large, pooled meta-analysis of eight cohort studies that included elderly participants (n=424,791), poor SRH was associated with cancer-specific mortality (HR 2.37, 95% CI 1.37–4.11).[4] In a recent study of 894 men and women aged 65 years and older, baseline SRH was not associated with cancer-specific mortality.[31] However, in the above-mentioned studies, information on cancer diagnosis was obtained from death certificates, instead of prospectively as a timely event in a survival analysis; thus, SRH may have been measured both before and after diagnosis. Thus, prospective population-based studies of the association between pre-diagnostic SRH and cancer-specific mortality are lacking. It has been suggested that declining SRH, as evaluated by repeated measurements, may predict mortality better than a single SRH measure,[32,33] warranting the inclusion of both pre- and post-diagnostic assessments of SRH in prospective studies on the relationships between SRH and mortality in people living with and beyond cancer.

Strengths and Limitations

The main strengths of this study are its large sample size, prospective design, and long follow-up period. The random selection of participants provided a national and population-based sample. Our study population included 110,104 women with a total follow-up time of 22 years, which provides a considerable number of cases to investigate for both cancer incidence and mortality. A validation study found that women in the NOWAC study had a slightly higher level of education compared to a random sample of women from the Norwegian population.[34] In addition, cancer incidence rates from the NOWAC cohort were identical to those reported to the Cancer Registry of Norway.[9] The NOWAC cohort is thus representative of middle-aged women in Norway and is most likely not prone to selection bias.

The NOWAC study includes self-reported data on modifiable lifestyle factors and socioeconomic position, which were used as confounders in our analyses. We used a four-item SRH scale that has been considered valid to measure health in older adults,[35] and the reported associations with mortality from other cohort studies are consistently similar.[2,3]

Several items in the NOWAC questionnaires have been validated, including the assessment of physical activity level,[36] self-reported BMI,[37] and smoking habits.[38] The use of the continuous scale (from 1 to 10) was found to be valid to rank physical activity levels in Norwegian women.[36] A validation study from the NOWAC cohort found self-reported height and weight valid to rank BMI.[37] A study of hypomethylated genes associated with smoking exposure found that hypomethylation status correlated with self-reported smoking status in the NOWAC post-genome cohort.[38] Self-reported alcohol consumption in the NOWAC cohort was very low and has not yet been validated, nor have the variables corresponding to socioeconomic position, which may be a source of social desirability bias.

In this study, we did not adjust for dietary information, which could be a source of residual confounding. However, the effect estimates for associations between dietary habits and cancer risk are generally small and cancer site-specific.

Cox regression models, mostly proportional hazard models, have been mostly used to study the predictive value of SRH on survival in recent publications. However, fitting Cox regression models with our data, violated the assumption of proportional hazards for SRH as the main exposure (p=0.0000 for Grambsch–Therneau test of scaled Schoenfeld residuals from a fitted Cox model). Therefore, we chose to use a flexible parametric model with restricted cubic splines that rests the assumption of proportional hazards throughout the study period. In addition, we included SRH as a time-varying covariate to allow the HRs to vary over time. Our splines regression plot for the association between SRH and all-cause mortality in the NOWAC cohort (Figure 4) shows that the HR estimates are stronger and have wider CIs at the start of follow-up for women who reported poor or very poor baseline SRH and stabilize with age. This is to be expected, as few participants had poor or very poor SRH, and even fewer died at the start of follow-up. The same was observed for associations between baseline SRH and cancer risk, and between baseline SRH and all-cause mortality in cancer-free women (Figures 5A and B). Reviews of other population-based studies found that the association between SRH and mortality was robust across different assessment methods.[2,3]

Conclusions and Implications

All categories lower than very good SRH reported at baseline predicted increased cancer risk and increased all-cause mortality during follow-up in our middle-aged to older Norwegian women, independent of lifestyle factors or socioeconomic position. Poor pre-diagnostic SRH was associated with increased all-cause mortality among women who later received a cancer diagnosis, suggesting that SRH is a useful instrument in epidemiological studies of cancer, and that it may be useful to healthcare providers as an assessment of a patient's overall health. All-cause mortality in people with cancer may be less linked to an unhealthy lifestyle than to comorbidities, such as cardiovascular disease, diabetes, or obesity. Prospective studies on the ability of SRH to predict site-specific cancer mortality and cancer-specific mortality are warranted.

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Disclosure

The authors report no competing interests in this work.

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