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Symptoms of Sleep Disordered Breathing and Risk of Cancer: A Prospective Cohort Study

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Study Objectives: Sleep disordered breathing (SDB) has been associated with oxidative stress, inflammation, and altered hormonal levels, all of which could affect the risk of cancer. The aim of the study is to examine if symptoms of SDB including snoring, breathing cessations, and daytime sleepiness affect the incidence of total cancer and subtypes of cancer.

Design: Prospective cohort study.

Setting: The third wave (1991-1993) of the Copenhagen City Heart Study.

Participants: There were 8,783 men and women in whom cancer had not been previously diagnosed.

Measurements and Results: Participants answered questions about snoring and breathing cessations in 1991-1993, whereas information about daytime sleepiness based on the Epworth Sleepiness Scale was collected in a subset of the participants (n = 5,894) in 1998. First-time incidence of cancer was followed until December 2009 in a nationwide cancer register. We found no overall association between symptoms of SDB and incident cancer. Yet, in the small group with high daytime sleepiness, we observed a surprisingly higher cancer incidence (hazard ratio = 4.09; 95% CI 1.58-10.55) in persons younger than 50 years. We also found a higher risk of virus/immune-related cancers (2.73; 1.27-5.91) and alcohol-related cancers (4.92; 1.45-16.76) among persons with daytime sleepiness. More SDB symptoms were associated with a higher risk of smoking-related cancers (P_{trend}: 0.04). Apart from these findings there were no clear associations between symptoms of sleep disordered breathing and cancer subtypes.

Conclusion: We found very limited evidence of relationship between symptoms of sleep disordered breathing and incidence of cancer.

Keywords: Cancer, cohort study, daytime sleepiness, impaired sleep, sleep disordered breathing

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INTRODUCTION

Sleep disordered breathing (SDB) is a prevalent condition in modern society, estimated to affect 24% of men and 9% of women.[1] SDB refers to a range of sleep disorders characterized by breathing cessations during sleep, often accompanied by snoring.[2] Most often the interruption of ventilation is caused by partial or complete closure of the upper airway, also known as obstructive sleep apnea.[3] Such interruptions will cause decreased blood oxygen saturation and sleep fragmentation, which in many instances will lead to daytime sleepiness.[4] SDB has been associated with reduced quality of life[5] and a higher risk of cardiometabolic disorders and all-cause mortality in a number of studies,[6-8] but studies assessing the relationship between SDB and cancer are few.[9-12]

Experimental and observational studies have shown that sleep impairment is associated with several factors related to cancer initiation and promotion such as inflammation,[13,14] oxidative stress,[15,16] hormonal levels,[17-19] and alterations of the immune system.[20-22] Moreover, intermittent hypoxia, similar to that experienced by patients with SDB, has been shown to enhance cancer progression in mice.[9,10] In humans, SDB has recently been associated with cancer mortality in a prospective cohort study.[12] The authors found that participants with severe SDB had an almost five times higher risk of cancer death than those free of SDB. Cancer mortality was used as the outcome measure in this study and it was therefore not possible to distinguish between the etiologic and prognostic role of SDB. That SDB may also be relevant for cancer etiology was recently emphasized by a prospective study,[11] in which they found that severity of SDB, based on the apnea-hypopnea index and percentage of the nighttime spent with SO_2 less than 90%, was associated with higher risk of incident cancer. This study included 4,910 patients investigated for suspected obstructive sleep apnea who were followed up for a median of 4.5 years, during which only 261 received a diagnosis of cancer, making it difficult to distinguish between cancer subtypes with different etiology. In contrast, the current study is population based, has a longer follow-up, and addresses subtypes of cancer in addition to total cancer incidence.

We hypothesize that SDB may affect cancer incidence through biological and probably also behavioral pathways. The objective of the current study is to determine the relationship between symptoms of SDB including snoring, breathing cessations and daytime sleepiness, and risk of all incident cancers as well as subtypes of cancer including alcohol-, smoking-, virus/immune-, and hormone-related cancers in a large prospective cohort study of 8,783 men and women.

A commentary on this article appears in this issue on page 1409.

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METHODS

Study Population

The Copenhagen City Heart Study (CCHS) is a Danish longitudinal cohort study initiated in 1976. An age-stratified sample of 19,698 men and women age 20 to 93 years was drawn from the Central Population Registry and invited to participate in the study. Of these, 14,223 individuals (72%) attended the first examination in 1976-1978. A physical examination was performed and the participants completed a comprehensive questionnaire regarding various risk factors. In the years 1981-1983, 1991-1993, and 2001-2003 the study population was expanded and additional study assessments were performed for both new and continuing study participants. A total of 10,135 persons participated in the third wave (1991-1993) of the study (response proportion: 61%) in which questionnaire information on snoring and breathing cessations was collected. The third wave was used as the baseline for the current study. Most of the participants were Caucasian. All participants gave written informed consent. More detailed description of the CCHS can be found elsewhere.[23] Participants in whom cancer was previously diagnosed at baseline (n = 730) or with invalid dates of outcome were excluded (n = 2). Also excluded were participants with missing information on any of the covariates: educational attainment (n = 113), smoking (n = 43), physical activity (n = 47), alcohol consumption (n = 75), marital status (n = 12), or body mass index (BMI; weight (kg)/height $(m)^2$) (n = 330). There were 4,860 women and 3,923 men (8,783 in total) who were eligible for the analyses of snoring and breathing cessations.

In January 1998, between waves, a questionnaire focusing on daytime sleepiness was sent to the 9,118 persons still alive from the third wave of the CCHS.[24] Of those invited, 6,794 persons returned the questionnaire (response proportion: 75%). The year 1998 was used as the baseline for analyses focusing on daytime sleepiness. Participants in whom cancer was diagnosed (n = 688) or who had missing information on covariates (n = 212) in the 1991-1993 CCHS questionnaire were excluded again, leaving 3,288 women and 2,606 men (5,894 in total) eligible for the daytime sleepiness analyses.

Symptoms of SDB

We addressed three symptoms of SDB: snoring, breathing cessations during sleep, and daytime sleepiness. Information on snoring and breathing cessations were assessed by the following two questions: Have you or your partner noticed that you are snoring during sleep? and: Have you or your partner noticed that you hold your breath for a long time ("stop breathing") during sleep?, with four possible responses: Seldom/never, Sometimes, Often/always, or I do not know.

Daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS), which is a validated eight-item scale developed to measure daytime sleepiness.[25] The items relate to the probability (0 = never, 1 = slight, 2 = moderate, 3 = high) of dozing in eight situations from everyday life. The eight scores are summed to obtain a single score in the range of 0-24. The ESS scores were split into the following categories for our analyses: 0-4, 5-9 (reference group), 10-15, and 16-24. The categorization and the choice of reference group was based on previous reports that the normal range is between 0-10,[25,26] combined with the finding that a very low score may indicate insomnia[25] and the fact that scores ≥ 16 were exclusively found in patients with moderate or severe SDB in one study.[25]

Finally, we combined snoring, breathing cessations, and daytime sleepiness into one composite measure of number of SDB symptoms. Points were obtained when reporting snoring sometimes or often/always, breathing cessations sometimes or often/always, and scoring ≥ 10 on the ESS, yielding a score ranging from 0 to 3. Two and three symptoms were combined into one category for the statistical analyses, as only 84 participants experienced all three symptoms. Participants who answered "I do not know" to the questions about snoring or breathing cessations and participants with missing information on any of the symptoms of SDB were not included in these analyses. Therefore only 3,647 men and women were eligible for analyses with number of SDB symptoms.

Covariates

Covariates included sex, age, BMI (< 25, 25-29, ≥ 30), alcohol consumption (< 1, 1-7, 8-14, 15-21, 22+ drinks/week), smoking (never-smoker, ex-smoker, smoker of 1-14 g/day, smoker of 15-24 g/day, and smoker of more than 24 g/day), educational attainment (< 8, 8-10, ≥ 11 years), physical activity in leisure time (sedentary or very light activity, 2-4 h of light activity per w, more than 4 h of light activity or 2-4 h of high-level activity, and more than 4 h of high-level activity per week), marital status (married/cohabitating, unmarried, separated/divorced, widowed), lung function (measured by spirometry at baseline and expressed as forced expiratory volume in 1 sec in percent of the predicted value), menopause (yes/no) and use of postmenopausal hormone therapy (yes/no). All covariates were measured at baseline in 1991-1993.

Follow-up

Participants were followed from the date of the third examination until the date of the first diagnosis of cancer (n = 1,985), death (n = 2,137), emigration out of Denmark (n = 105), or end of follow-up on December 31, 2009 (n = 4,556). Thus, fewer than 2% were lost to follow-up. Incidence of cancer and deaths were identified through linkage to nationwide hospital discharge and death registries, and the main outcomes of interest were all incident cancers, as well as smoking-related cancers (International Classification of Diseases [ICD] 7-codes 140, 141, 143-149, 150, 157, 160-162, 180, 181 and [ICD] 10-codes C0-C6.9, C9-C15.9, C25-C25.9, C30-C34.9, C38.4, C45, C46.2, C64-C68.9), alcohol-related cancers (ICD7-codes 141, 143-146, 148-150, 155, 161 and ICD10-codes C1-C6.9, C9-C15.9, C22-C24.9, C32-C32.9, C46.2), virus/immune-related cancers (ICD7-codes 155, 171, 191, 200-202, 204 and ICD10-codes C22-C24.9, C44-C44.9, C46, C53-C53.9, C82-C85.9, C91-C96.9), and hormone-related cancers (ICD7-codes 170, 172, 175, 177 and ICD10-codes C50-C50.9, C54-C54.9, C56-C57.4, C61-C61.9). These are main subtypes of cancer and it is worth noting that some cancers will not fit into any category, whereas others fit into more than

Table 1—Baseline characteristics of the 8,783 participants from the third wave of the Copenhagen City Heart Study

	Total population (n = 8,783)	1998 population (n = 5,894)	Number of SDB symptoms[b] (n = 3,647)		
			0 (n = 1,218)	1 (n = 1,759)	2-3 (n = 670)
Number of cancer cases (%)	1,985 (23)	1,097 (19)	171 (14)	350 (20)	131 (20)
Mean age at baseline (SD)	57 (15.3)	55 (15.0)	50 (17)	54 (14)	55 (13)
Mean BMI (SD)	26 (4.4)	25 (4.2)	24 (4)	26 (4)	27 (4)
Women, n (%)	4,860 (55)	3,288 (56)	784 (64)	877 (50)	219 (33)
Schooling < 8 years, n (%)	2,945 (34)	1,763 (30)	230 (19)	470 (27)	227 (34)
Physically inactive, n (%)	1,056 (12)	584 (10)	80 (7)	146 (8)	85 (13)
Living without partner, n (%)	3,759 (43)	2,352 (40)	441 (36)	404 (23)	147 (22)
High alcohol intake[a], n (%)	1,373 (16)	897 (15)	142 (12)	305 (17)	135 (20)
Current smoker, n (%)	4,293 (49)	2,733 (46)	450 (37)	868 (49)	364 (54)

[a]The Danish drinking limits in the 1990s were 14 drinks/week for women and 21 drinks/week for men. [b]Participants who answered "do not know" to the questions about snoring or breathing cessations and participants with missing information on any of the symptoms of SDB were not included in the analyses with number of SDB symptoms. Therefore only 3,647 men and women were eligible for these analyses. BMI, body mass index; SD, standard deviation; SDB, sleep disordered breathing.

one, e.g., smoking- and alcohol-related cancers. The cancers were included in all the categories that they fit into.

Statistical Analysis

We used the Cox proportional hazards model to assess the relationship between symptoms of SDB and cancer incidence. Age was included as the underlying time variable, which allowed for thorough adjustment for age. Due to similarity of effects in the initial sex-specific analyses the analyses were combined for women and men and a sex stratum variable was included to allow the baseline hazard to differ by sex.

Initially, we estimated the age-adjusted hazard ratios (HR) and their 95% confidence intervals (95% CI) for incidence of total cancer as well as subtypes of cancer in separate models including snoring, breathing cessations, daytime sleepiness, and number of SDB symptoms, respectively. We tested the assumption of proportional hazards and it was not met for the relationship between daytime sleepiness and total cancer, meaning that there was an interaction between daytime sleepiness and age as age was the underlying time variable. This analysis was therefore split into two age bands (younger than 50 years and 50 years or older), in which the assumption was met. Multivariate models were fitted to adjust for potential confounding from baseline covariates. Potential confounders were identified based on prior knowledge and the method of Directed Acyclic Graphs[27] and included age, sex, BMI, marital status, educational attainment, physical activity level, alcohol consumption, and smoking. These confounders were included in all multivariate analyses. Additional adjustment for lung function was performed in the smoking-related cancer analyses,[28,29] whereas menopausal status and postmenopausal hormone therapy use was included in the analyses of hormone-related cancers.[30-32]

In sensitivity analyses, we excluded the first 2 years of follow-up to prevent reverse causation (e.g., yet undiagnosed cancer causing daytime sleepiness). We also performed secondary analyses restricted to married/cohabitating participants (n = 5,024), as we were concerned that those who did not have a partner might not be aware of their snoring or breathing cessations.

RESULTS

Baseline Characteristics

At baseline, the 8,783 participants had a mean age of 57 years (range 21-93 years), 4,860 were women (55%) and 3,923 were men. Cancer was diagnosed in a total of 1,985 participants during an average follow-up time of 13 years. The most frequent cancers were virus/immune-related cancers (n = 559), followed by smoking-related cancers (n = 490), hormone-related cancers (n = 455) and alcohol-related cancers (n = 120). Baseline characteristics are shown in Table 1. Almost two in three participants (61%) experienced at least one symptom of SDB. Snoring was the most prevalent symptom (59%), followed by daytime sleepiness defined as an ESS score $\geq$ 10 (11%) and breathing cessations (9%). Those with symptoms of SDB were older, had a higher BMI, and were more likely to be men, have low education, be physically inactive, live with a partner, drink above the Danish sensible drinking limits (> 21 drinks/week for men and > 14 drinks/week for women), and be current smokers compared to participants with no symptoms. The 1998 population (n = 5,894) differed only in minor ways from the main population (n = 8,783) on these baseline variables. When comparing those with and without a partner, those who did not have a partner were much more likely to answer "I do not know" to the questions about snoring and breathing cessations, whereas the responses to the ESS were similar in the two groups.

Symptoms of SDB and Total Cancer Risk

There were no clear associations between snoring, breathing cessations, or the total number of SDB symptoms and total cancer incidence (Tables 2 and 3). However, high levels of daytime sleepiness (ESS score of 16-24) were associated with a higher cancer risk among younger (younger than 50 years) (HR = 4.09, 95% CI 1.58-10.55), but not older participants (0.87; 0.41-1.85). Nevertheless, there were no signs of a dose-response relationship between the severity of daytime sleepiness and the risk of total cancer, and the higher risk observed among the younger participants was only based on five cancer cases.

Table 2—Risk of total cancer associated with snoring and breathing cessations among the 8,783 Danish men and women from the third wave of the Copenhagen City Heart Study

Total cancer	Number of cases[a]	IR / 10,000 years	Age-adjusted HR (95% CI)	Multiple adjusted HR (95% CI)[b]
Overall population (n = 8,783)	1,985	175		
Snoring (n = 8,767)				
Seldom/rarely (n = 2,334)	436	138	1 (ref)	1 (ref)
Sometimes (n = 3,713)	874	180	1.03 (0.92;1.16)	0.99 (0.88;1.11)
Often/always (n = 1,429)	351	190	1.09 (0.95;1.26)	1.04 (0.90;1.21)
Do not know (n = 1,291)	317	215	1.03 (0.89;1.20)	0.99 (0.85;1.16)
Breathing cessations (n = 8,760)				
Seldom/rarely (n = 4,643)	992	161	1 (ref)	1 (ref)
Sometimes (n = 663)	152	179	0.99 (0.83;1.18)	0.96 (0.80;1.14)
Often/always (n = 103)	23	180	1.06 (0.70;1.61)	1.07 (0.70;1.62)
Do not know (n = 3,351)	809	193	1.05 (0.95;1.15)	1.03 (0.93;1.14)

[a]The total number of cancer cases was 1,985, but because of missing values, the number of cases does not add up to the total. [b]Adjusted for age, BMI, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status. CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Table 3—Risk of total cancer associated with daytime sleepiness and number of SDB symptoms among the 5,894 Danish men and women from the third wave of the Copenhagen City Heart Study who also responded in 1998

Total cancer	Number of cases[a]	IR / 10,000 years	Age-adjusted HR (95% CI)	Multiple adjusted HR (95% CI)[b]
1998 population (n = 5,894)	1,097	191		
Daytime sleepiness (ESS score) (n = 5,814)				
< 50 years of age (n = 2,008) (n = 2,003)				
0-4 (n = 755)	61	72	1.00 (0.72;1.41)	0.97 (0.69;1.36)
5-9 (n = 1,005)	77	68	1 (ref)	1 (ref)
10-15 (n = 228)	17	66	0.98 (0.58;1.65)	0.99 (0.58;1.68)
16-24 (n = 15)	5	317	3.83 (1.53;9.56)	4.09 (1.58;10.55)
≥ 50 years of age (n = 3,886) (n = 3,811)				
0-4 (n = 1,971)	497	281	1.07 (0.93;1.23)	1.03 (0.90;1.18)
5-9 (n = 1,457)	342	259	1 (ref)	1 (ref)
10-15 (n = 347)	83	274	1.12 (0.88;1.42)	1.10 (0.87;1.40)
16-24 (n = 36)	7	217	0.85 (0.40;1.80)	0.87 (0.41;1.85)
Number of SDB symptoms[c] (n = 3,647)				
0 (n = 1,218)	171	136	1 (ref)	1 (ref)
1 (n = 1,759)	350	202	1.22 (1.01;1.47)	1.18 (0.98;1.43)
2-3 (n = 670)	131	201	1.17 (0.92;1.48)	1.13 (0.89;1.44)
P_{trend}			0.14	0.27

[a]The total number of cancer cases was 1,097 in the 1998 population, but because of missing values, the number of cases does not add up to the total. [b]Adjusted for age, body mass index, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status. [c]Symptoms include snoring (sometimes or often/always), breathing cessations (sometimes or often/always) and ESS score ≥ 10. CI, confidence interval; ESS, Epworth Sleepiness Scale; HR, hazard ratio; IR, incidence rate; SDB, sleep disordered breathing. The 1998 population consisted of 2,008 individuals below the age of 50 years and 3,886 of 50 years and above. Of those, 2,003 and 3,811 individuals, respectively, reported valid information on the ESS.

Symptoms of SDB and Risk of Cancer Subtypes

The incidence of alcohol-related cancers was not associated with snoring, breathing cessations, or the number of SDB symptoms (Tables 4 and 5). Daytime sleepiness, however, with an ESS score in the range 16-24, was associated with a markedly higher risk of alcohol-related cancers (HR = 4.92, 95% CI 1.45-16.76), although with no exposure-dependent effect. Adjusting for alcohol intake continuously only changed the results marginally (results not shown).

Smoking-related cancers were not related to snoring, breathing cessations, or daytime sleepiness (Tables 4 and 5). However, an exposure-dependent association between number

Table 4—Risk of different subtypes of cancer associated with snoring and breathing cessations among the 8,783 Danish men and women from the third wave of the Copenhagen City Heart Study

	Alcohol-related		Smoking-related		Virus/immune-related		Hormone-related	
	N	Multiple adj. HR (95% CI)[a]	N	Multiple adj. HR (95% CI)[b]	N	Multiple adj. HR (95% CI)[a]	N	Multiple adj. HR (95% CI)[a]
Number of cases	120		490		559		455	
Snoring (n = 8,767[c])								
Seldom/rarely	18	1 (ref)	78	1 (ref)	134	1 (ref)	125	1 (ref)
Sometimes	50	1.09 (0.63;1.87)	212	1.10 (0.85;1.43)	243	1.01 (0.81;1.25)	200	0.83 (0.66;1.04)
Often/always	30	1.25 (0.69;2.29)	100	1.18 (0.87;1.61)	91	1.07 (0.81;1.42)	72	0.85 (0.63;1.14)
Do not know	22	1.59 (0.83;3.06)	88	1.24 (0.90;1.70)	89	1.04 (0.79;1.39)	58	0.60 (0.44;0.84)
Breathing cessations (n = 8,760[c])								
Seldom/rarely	56	1 (ref)	210	1 (ref)	306	1 (ref)	234	1 (ref)
Sometimes	6	0.46 (0.20;1.07)	50	1.10 (0.81;1.51)	30	0.72 (0.49;1.05)	30	0.94 (0.64;1.38)
Often/always	1	0.52 (0.07;3.78)	5	0.79 (0.32;1.92)	4	0.71 (0.26;1.92)	5	1.22 (0.50;2.97)
Do not know	57	1.32 (0.89;1.94)	213	1.16 (0.94;1.42)	216	0.96 (0.79;1.15)	185	0.96 (0.79;1.18)

[a]Adjusted for age, body mass index, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status. [b]Adjusted for age, body mass index, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status, lung function. [c]Participants with missing on lung function were excluded from the smoking-related analyses, hence the population was smaller in these: snoring (n = 8,761), breathing cessations (n = 8,664). adj, adjusted; CI, confidence interval; HR, hazard ratio.

Table 5—Risk of different subtypes of cancer associated with daytime sleepiness and number of SDB symptoms among the 5,894 Danish men and women from the third wave of the Copenhagen City Heart Study who also responded in 1998

	Alcohol-related		Smoking-related		Virus/immune-related		Hormone-related	
	N	Multiple adj. HR (95% CI)[a]	N	Multiple adj. HR (95% CI)[b]	N	Multiple adj. HR (95% CI)[a]	N	Multiple adj. HR (95% CI)[a]
Number of cases	61		257		324		259	
Daytime sleepiness (ESS score) (n = 5,814[c])								
0-4 (n = 2,726)	27	0.90 (0.52;1.56)	125	0.94 (0.71;1.23)	163	1.07 (0.84;1.36)	136	1.05 (0.81;1.36)
5-9 (n = 2,462)	26	1 (ref)	94	1 (ref)	121	1 (ref)	101	1 (ref)
10-15 (n = 575)	4	0.70 (0.24;2.00)	28	1.34 (0.88;2.05)	31	1.17 (0.78;1.73)	21	0.92 (0.57;1.47)
16-24 (n = 51)	3	4.92 (1.45;16.76)	2	1.02 (0.25;4.18)	7	2.73 (1.27;5.91)	1	0.49 (0.07;3.51)
Number of SDB symptoms[d] (n = 3,647[c])								
0	4	1 (ref)	25	1 (ref)	57	1 (ref)	47	1 (ref)
1	16	1.51 (0.49;4.66)	73	1.44 (0.90;2.29)	109	1.25 (0.89;1.74)	87	1.10 (0.76;1.59)
2-3	9	1.61 (0.47;5.53)	42	1.73 (1.03;2.91)	35	1.13 (0.72;1.76)	25	0.82 (0.49;1.36)
P_{trend}		0.49		0.04		0.46		0.55

[a]Adjusted for age, body mass index, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status. [b]Adjusted for age, body mass index, tobacco consumption, alcohol consumption, years of schooling, physical activity, marital status, lung function. [c]Participants with missing on lung function were excluded from the smoking-related analyses, hence, the population was smaller in these: daytime sleepiness (n = 5,774), symptoms (n = 3,616). [d]Symptoms include snoring (sometimes or often/always), breathing cessations (sometimes or often/always) and ESS score ≥ 10. adj, adjusted; CI, confidence interval; ESS, Epworth Sleepiness Scale; HR, hazard ratio; SDB, sleep disordered breathing.

of SDB symptoms and smoking-related cancers appeared when these measures were summed (P_{trend}: 0.04).

Virus/immune-related cancers were associated with daytime sleepiness, with participants who had an ESS score in the range 16-24 experiencing a higher risk of these cancers (HR = 2.73, 95% CI 1.27-5.91). None of the additional measures were related to the incidence of virus/immune-related cancers (Tables 4 and 5).

The risk of hormone-related cancers was in general not related to snoring, breathing cessations, nor daytime sleepiness, although participants who answered "I do not know" to the question about snoring had a lower risk (Tables 4 and 5). Adjustment for menopausal status and use of hormone replacement therapy among women only marginally affected the estimates (results not shown). The total number of SDB symptoms was not associated with the incidence of hormone-related cancers.

Analyses restricted to participants who were married or who had a cohabitating partner at baseline (n = 5,024) showed results quite similar to the main analyses (results not shown). Excluding the first 2 years of follow-up only marginally altered

the results, with some associations becoming slightly stronger (results not shown).

DISCUSSION

In this large study, with several measures of SDB symptoms and register-based information on cancer incidence, we found very limited evidence of an association between symptoms of SDB and incidence of cancer. Yet, in the small group with high daytime sleepiness (ESS ≥ 16), we observed a surprisingly high cancer incidence. Daytime sleepiness was related to a higher risk of total cancer among participants younger than 50 years, and to a higher incidence of alcohol- and virus/immune-related cancers. However, these associations must be interpreted cautiously because they were based on very few cases and no dose-response relation was evident. Apart from these findings, a dose-response association between the risk of smoking-related cancers and the number of SDB symptoms was also observed.

The findings of the current study do not convincingly support an association between symptoms of SDB and cancer incidence, although we did observe some associations between symptoms of SDB and different cancer subtypes. Campos-Rodriguez et al.[11] reported more consistent associations between measures of SDB and cancer incidence, although the association seemed to be limited to men and patients younger than 65 years. These differences in results might be due to differences in patient and population samples. But it could also be due to the different measures of SDB, where Campos-Rodriguez et al. used the apnea-hypopnea index and percentage of nighttime spent with SO_2 less than 90% compared to the self-reported measures SDB symptoms in the current study. In fact, the value of self-reported SDB symptoms as surrogates for SDB can be questioned.[33] Although daytime sleepiness measured by the ESS has previously been shown to discriminate well between persons with and without SDB and to correlate with the severity of SDB measured by polysomnography,[25] it is likely to be affected by misclassification. A review evaluating screening questionnaires for SDB found that symptom-based instruments had a mean sensitivity and specificity of 77% and 53%, respectively, in a nonpatient population.[33] This exposure misclassification may have biased our results toward null, and it is likely that more consistent and stronger associations between SDB and cancer incidence would have been found, if a more valid measure of SDB had been available. We supplemented the ESS with snoring and breathing cessations in a composite measure of SDB symptoms to increase the specificity, but when interpreting the results one should be aware that the included symptoms of SDB are not identical to SDB.

Nieto et al.[12] found a clear dose-response relation between severity of SDB and cancer mortality (P_{trend}: 0.005), and an almost five times higher risk of cancer death among participants with severe SDB compared with those free of SDB. The magnitude of these results made us wonder if SDB is a more important prognostic than etiologic factor for cancer, meaning that the incidence of cancer is not necessarily increased in patients with SDB, but that they may have a worse prognosis compared with people without SDB. We therefore performed a separate analysis with total cancer mortality as outcome and found a slightly stronger effect of the number of SDB symptoms on cancer mortality compared with cancer incidence (data not shown). Although the association was not of such magnitude as reported by Nieto et al.,[12] this might indicate that SDB is a stronger prognostic than etiologic factor in cancer. Further studies are needed to address this issue.

Other possible causes of impaired sleep such as short sleep duration (< 6 h) and night shift work have also previously been linked to a higher risk of overall cancer and hormone-related cancers, respectively.[34,35] These previous results on hormone-related cancer are in contrast to our results of no associations between symptoms of SDB and hormone-related cancers. To our knowledge, this is the first study to address cancer subtypes in relation to SDB. Investigations into the differences in effects of SDB on different cancer subtypes are therefore needed.

In the current study, age was found to modify the association between daytime sleepiness and total cancer risk, possibly indicating that SDB may have worse consequences in the young and middle-aged compared with the older participants. This is in line with the study by Campos-Rodriguez et al.,[11] who likewise reported SDB to more strongly affect cancer incidence in the younger age group (younger than 65 years).

We observed a higher risk of alcohol-related cancers associated with daytime sleepiness, which is likely due to residual confounding from alcohol misuse. It is possible that participants with high alcohol consumption obtain higher scores on the ESS due to their high consumption rather than due to SDB.

The association between number of SDB symptoms and smoking-related cancers has at least three possible explanations. One is that the SDB and the accompanying daytime sleepiness may increase the participants' cigarette consumption, hence also heightening the rate of smoking-related cancers. Residual confounding by smoking is a second explanation, as smoking is an established risk factor for SDB.[36] Third, the finding could be due to chance.

The risk of virus/immune cancers was higher in the presence of daytime sleepiness. Immune suppression represents a plausible explanation for this association. Sleep has been shown to support immune defense, and sleep deprivation has therefore been associated with a reduction of natural immune responses in experimental studies.[20,21] Such alterations of the immune system might increase the risk of virus/immune-related cancers as the immune system is involved in the defense against these cancers.[37]

Strengths and Limitations

To the best of our knowledge, this is the first study to also address cancer subtypes, when investigating the association between SDB and cancer incidence. The prospective design of the current study ensured temporality between the symptoms of SDB and cancer incidence, and the large sample size allowed us to address cancer subtypes separately. The third wave of the CCHS included information on important socioeconomic, demographic and, lifestyle factors, allowing for thorough adjustment for confounding. Linkage of civil registry numbers to a nationwide cancer register enabled identification of first-time hospital admission for cancer and allowed for nearly complete long-term follow-up.

Participants without a partner more often did not know if they snored or had breathing cessations during sleep, and a smaller proportion reported SDB symptoms compared with those who had a partner. This raised the concern that the amount of snoring and breathing cessations was underestimated among those

without a partner. However, when the analyses were restricted to participants who had a partner, we found results quite similar to the main analyses.

In summary, the current study did not convincingly support our hypothesis that SDB affects the incidence of cancer. The results were essentially negative and the few associations observed were most often based on very few cases. Misclassification of exposure due to self-report of SDB may, however, have biased our results in the null direction. The higher risk of virus/immune-related cancers among persons with daytime sleepiness may reflect an effect of SDB on this cancer subtype, with alterations of the immune system as a plausible pathway. Experimental studies to address more directly the associations between SDB and the function of the immune system are needed to support this hypothesis. Further, future prospective studies will benefit from addressing cancer subtypes in addition to total cancer.

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