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Joint tobacco smoking and alcohol intake exacerbates cancer risk in women– the Danish nurse cohort

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ABSTRACT

Purpose: To explore separate and combined tobacco and alcohol use and risk of overall, smoking-related, alcohol-related, breast and gynecological cancers in women.

Method: Questionnaires from 19,898 women in The Danish Nurse Cohort in 1993 were linked to registries on hospitalizations, death causes and migration until Dec 2016. Cancer risk by tobacco and alcohol was estimated using Cox proportional hazards models.

Results: 16,106 nurses, aged > 44 years (mean = 56), were eligible for analysis. Throughout 23 years (mean follow-up = 18.8 years) overall cancers counted 4,968. Of these, 1,897, 2,231, 1,407 and 579 events were smoking-related, alcohol-related, breast cancers and gynecological cancers. Increased risks of overall, smoking-related, and breast cancer were observed for current smoking and excess alcohol intake (> 14 units/week), separately, compared to never smoking and light drinking (1–7 units/week) respectively. Moderate drinking (8–14 units/week) increased the risk of alcohol-related and breast cancer. Additional risk increases were observed among smokers drinking alcohol above light levels for overall, smoking-related, alcohol-related and breast cancer (HR = 1.40, 95% CI:1.30–1.51, HR = 1.72, 95% CI:1.52–1.94, HR = 1.33, 95% CI:1.26–1.40, HR = 1.32, 95% CI:1.15–1.53, respectively), compared to non-smokers drinking lightly. These risks increased further for smokers drinking above moderate levels (HR = 1.49, 95% CI:1.36–1.63, HR = 1.97, 95% CI:171.-2.26, HR = 1.40, 95% CI:1.22–1.60, HR = 1.33, 95% CI:1.12–1.57, respectively). No significant associations were found for gynecological cancer.

Conclusions: Smoking and alcohol, both separately and combined, increased risks of overall, smoking-related, alcohol-related and breast cancer; combined use resulted in incremental risk increases. Co-use of smoking and alcohol represent an extensive threat to public health; thus, prevention could benefit from combined targeting.

1. Introduction

Tobacco and alcohol are carcinogenic agents for 18 human organ sites(IARC, 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012) and leading risk factors for cancer, disability and premature death(Forouzanfar et al., 2016; IARC, 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Stewart and Wild, 2014). Although the prevalence of smoking and alcohol intake has declined in Europe over the past decade, European countries continue to have the highest consumption rates in the world(Danish Health Authority, 2018; Geneva: World Health Organization, 2018; Griswold et al., 2018; World Health Organization, 2015, 2015). Moreover, while smoking and alcohol intake are still predominantly male phenomena in most parts of the world, a growing number of European countries report that women's intake now equal that of men(Danish Health Authority, 2018; Geneva: World Health Organization, 2018; Griswold et al., 2018; Hjerteforeningen, Sundhedsstyrelsen, 2019; World Health

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Table 1
Definitions of cancer outcomes based on the IARC list of human carcinogens (IARC, 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012).

Outcome	Cancer sites	ICD-8 Codes (1977–1993)	ICD-10 Codes (1994-)
Overall cancer	All	140–209	C00–C96
Smoking-related cancers	Malignant neoplasm of oral cavity, pharynx, nasopharynx, nasal cavity and paranasal sinus, larynx, oesophagus, lung, stomach, liver and bile duct, kidney, pancreas, colon and rectum, renal pelvis and ureter, uterine cervix, ovary, urinary bladder, leukaemia	140-149, 513–157, 160–162, 180, 183, 188–189, 204-207	C00–C16, C18–C25, C300, C31–C34, C53, C56, C64–C68, C91–C95
Alcohol-related cancers	Malignant neoplasm of oral cavity, pharynx, larynx, oesophagus, upper digestive tract, breast, liver and bile duct, colon and rectum	140-151, 1520(9), 153–156, 161, 174	C00–C24, C32, C50
Breast cancer	Malignant neoplasm of breast	174	C50
Gynecological cancers	Malignant neoplasm of vulva, vagina, uterus, ovary, other/unspecified genital organs, placenta	180–184	C51–C58

Organization, 2015, 2015). In Denmark, smoking rates have increased for the first time in 20 years, particularly among the young to middle-aged, and the smoking prevalence among young women aged 15 to 19 years now by far exceeds that of their male peers (60.5% vs 39.5%, respectively)(Danish Health Authority, 2018; Hjerteforeningen, Sundhedsstyrelsen, 2019). Furthermore, Danish students have the highest prevalence of alcohol intake (32%) in Europe(Group et al., n.d.). At worst, the development in Denmark and other European countries could indicate the beginning of a new trend toward increased use of tobacco and alcohol, especially driven by women.

Research suggests that biological, behavioral and social factors are responsible for gender-specific variations in smoking drivers and barriers to smoking cessation(Allen et al., 2014), and that women, more often than men, may become strongly addicted to smoking and find cessation difficult(Hjerteforeningen, Sundhedsstyrelsen, 2019; Smith et al., 2016). Moreover, evidence points to a greater susceptibility to smoking- and alcohol-related morbidity and mortality in women due to gender differences in the pathophysiological effects of tobacco and alcohol use(Allen et al., 2014; Erol and Karpyak, 2015; Wang et al., 2014). Tobacco and alcohol are most commonly studied as separate risk factors for cancer; however, these substances are often used in tandem (Bobo and Husten, 2000), emphasizing the relevance of studying their joint effect. With the gender-specific differences in vulnerability to smoking- and alcohol-related morbidity, it seems reasonable to hypothesize that women are at excess risk from combined tobacco and alcohol use.

The current increase in both smoking and alcohol intake, especially among European women, and the excess risk related to the female gender, underpins the need for gender-specific initiatives in research and prevention strategies. Thus, the present study was undertaken to explore the association between separate and combined use of tobacco and alcohol and the risk of overall, smoking-related, alcohol-related, breast and gynecological cancers in a homogeneous female population.

2. Methods

2.1. Study population

The Danish Nurse Cohort(Hundrup et al., 2012) comprising 23,170 female nurses who were above 44 years of age and registered members of the Danish Nursing Organization in 1993 (member rate ~95% of all Danish nurses). Questionnaires were sent by mail in 1993 and reached a response rate of 86% (n = 19,898). The questionnaires covered information on nurses' smoking and alcohol habits in 1993, along with other lifestyle factors, sociodemographic factors and information on health issues(Hundrup et al., 2012). Through individual participant linkage to the Danish nationwide Civil Registration System, questionnaire data were pooled with data from nationwide registries on dates of birth and death, migrations, hospitalization admissions (dates and diagnoses) and causes of death(Thygesen et al., 2011). The registries ensured no loss of follow-up, were fully updated and available until December 31st, 2016. Nurses were included in the present study if they had no prior history of cancer and had completed questionnaire data on the variables of interest.

2.2. Variables

Four exposure variables were defined for smoking and alcohol; two for their separate measures and two for combined use with alcohol intake set at different cut off values. Smoking was defined in categories of never/previous/current smoking, and alcohol intake in categories of abstinence/light/moderate/excessive intake; corresponding to no intake/1–7/8–14/ > 14 units/week (one unit equaling 12 g of ethanol). The two variables for combined use of smoking and alcohol each included four categories with combinations of smoking status (current smokers/non- or previous smokers) and weekly alcohol intake set at one of two cut off values ($\leq$7/ > 7 or $\leq$14/ > 14 units). Alcohol categories were based on the Danish Health Authority's recommendations for women which declare low disease risk at up to 7 units/week and high disease risk at above 14 units/weeks(Danish health Authority, n.d.). Respondents provided information on their intake of different alcoholic beverages; first, units consumed on the last weekday (Monday-Thursday), and; secondly, units consumed during the last weekend (Friday-Sunday). Since evidence suggests that cancer risk is comparable across types of alcoholic beverage(IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Marron et al., 2012; Purdue et al., 2009), alcohol intake was estimated across alcoholic beverages. Thus, a measure of weekly alcohol intake was estimated by ((total alcohol intake on the last weekday)*4) + (total alcohol intake throughout the last weekend).

Outcomes of interest were first-time hospital diagnosis or mortality from overall cancer, smoking or alcohol-related cancer, breast cancer and gynecological cancers (definitions in Table 1). Grouping of smoking- and alcohol-related cancers was done according to the International Agency for Research on Cancer's (IARC) list of cancer sites with sufficient evidence for tobacco and/or alcohol being causative carcinogens(IARC, 2018).

Confounding covariates were available from questionnaire data and mainly included categorical variables (Table 2): Body Mass Index (kg/m^2) (BMI) (< 18.5/18.5–30/$\geq$30), cohabitation/married, self-rated health (SRH), physical activity level, hormone replacement therapy, oral contraceptives, age at menarche ($\leq$12/13–15/$\geq$16), and parity. No. of births was included as a numeric variable. Data on age and comorbidities (diabetes, cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD)) were retrieved from Danish nationwide registries.

2.3. Statistical analysis

Baseline characteristics were compared across levels of smoking and alcohol use with Chi-square tests for categorized variables and one-way ANOVA for continuous variables.

Table 2
Baseline characteristics of participants by smoking status and alcohol intake, 1993.

Characteristics by smoking status

Variable	Level	Non-Smoker	Previous Smoker	Current Smoker	Total	P-value[a]
Number of participants	*N (%)*	5271 (32.7)	4744 (29.5)	6091 (37.8)	16106 (100)	
Age	*Mean (SD)*	55.0 (8.0)	57.7 (9.0)	56.0 (7.9)	56.2 (8.3)	< 0.001
Alcohol units/week	*Mean (SD)*	7.4 (8.8)	9.1 (9.1)	10.5 (10.8)	9.1 (9.8)	< 0.001
Body Mass Index	*Mean (SD)*	24.0 (3.5)	24.1 (3.5)	23.0 (3.3)	23.6 (3.4)	< 0.001
	Missing[b], *n*	43	46	48	137	
Age at menarche	*Mean (SD)*	13.6 (1.5)	13.8 (1.6)	13.7 (1.6)	13.7 (1.6)	< 0.001
	Missing[b], *n*	83	79	136	298	
Parity	*Yes, n (%)*	5011 (85.3)	4368 (81.7)	5690 (82.1)	15069 (83.0)	< 0.001
	No, n (%)	861 (14.7)	980 (18.3)	1239 (17.9)	3080 (17.0)	
	Missing[b], *n*	59	38	67	164	
Number of births	*Mean (SD)*	2.1 (1.2)	1.9 (1.2)	1.9 (1.2)	2.0 (1.2)	< 0.001
	Missing[b], *n*	59	38	67	164	
Cohabitation	*Yes, n (%)*	4060 (77.0)	3455 (72.8)	4127 (67.8)	11642 (72.3)	< 0.001
	No, n (%)	1211 (23.0)	1289 (27.2)	1964 (32.2)	4464 (27.7)	
	Missing[b], *n*	42	29	50	121	
Self-rated health	*Good or very good, n (%)*	4469 (84.8)	3902 (82.3)	4840 (79.5)	13211 (82.0)	< 0.001
	Moderate to very bad, n (%)	802 (15.2)	842 (17.7)	1251 (20.5)	2895 (18.0)	
	Missing[b], *n*	162	152	220	534	
Physical activity	*Low level, n (%)*	294 (5.6)	310 (6.5)	519 (8.5)	1123 (7.0)	< 0.001
	Moderate level, n (%)	3611 (68.5)	3260 (68.7)	4009 (65.8)	10880 (67.6)	
	High level, n (%)	1366 (25.9)	1174 (24.7)	1563 (25.7)	4103 (25.5)	
	Missing[b], *n*	71	71	119	261	
Diabetes	*Yes, n (%)*	40 (0.8)	38 (0.8)	37 (0.6)	115 (0.7)	0.44
	No, n (%)	5231 (99.2)	4706 (99.2)	6054 (99.4)	15991 (99.3)	
Cardiovascular diseases	*Yes, n (%)*	279 (5.3)	387 (8.2)	393 (6.5)	1059 (6.6)	< 0.001
	No, n (%)	4992 (94.7)	4357 (91.8)	5698 (93.5)	15047 (93.4)	
Chronic obstructive pulmonary disease	*Yes, n (%)*	46 (0.9)	85 (1.8)	76 (1.2)	207 (1.3)	< 0.001
	No, n (%)	5225 (99.1)	4659 (98.2)	6015 (98.8)	15899 (98.7)	

Characteristics by alcohol intake

Variable	Level	Abstinence	Light Intake	Moderate Intake	Excessive Intake	Total	P-value[a]
Number of participants	*N (%)*	2867 (17.8)	5952 (37.0)	3756 (23.3)	3531 (22)	16106 (100)	
Age	*Mean (SD)*	59.3 (9.3)	55.8 (8.1)	55.3 (7.9)	55.3 (7.8)	56.2 (8.3)	< 0.001
Body Mass Index	*Mean (SD)*	24.2 (4.0)	23.7 (3.4)	23.4 (3.2)	23.3 (3.1)	23.6 (3.4)	< 0.001
	Missing[b], *n*	51	43	23	20	137	
Age at menarche	*Mean (SD)*	13.7 (1.6)	13.7 (1.6)	13.7 (1.6)	13.6 (1.5)	13.7 (1.6)	0.17
	Missing[b], *n*	77	99	62	60	298	
Parity	*Yes, n (%)*	2598 (76.4)	5629 (84.7)	3562 (85.1)	3280 (83.8)	15069 (83.0)	< 0.001
	No, n (%)	801 (23.6)	1019 (15.3)	624 (14.9)	636 (16.2)	3080 (17.0)	
	Missing[b], *n*	39	56	35	34	164	
Number of births	*Mean (SD)*	1.9 (1.4)	2.0 (1.2)	2.0 (1.1)	2.0 (1.2)	2.0 (1.2)	< 0.001
	Missing[b], *n*	39	56	35	34	164	
Smoking status	*Non-smoker, n (%)*	1114 (38.9)	2213 (37.2)	1112 (29.6)	832 (23.6)	5271 (32.7)	< 0.001
	Previous smoker, n (%)	743 (25.9)	1764 (29.6)	1203 (32.0)	1034 (29.3)	4744 (29.5)	
	Current smoker, n (%)	1010 (35.2)	1975 (33.2)	1441 (38.4)	1665 (47.2)	6091 (37.8)	
Cohabitation	*Yes, n (%)*	1700 (59.3)	4417 (74.2)	2842 (75.7)	2683 (76.0)	11642 (72.3)	< 0.001
	No, n (%)	1167 (40.7)	1535 (25.8)	914 (24.3)	848 (24.0)	4464 (27.7)	
	Missing[b], *n*	26	42	30	23	121	
Self-rated health	*Good or very good, n (%)*	2104 (73.4)	4929 (82.8)	3189 (84.9)	2989 (84.7)	13211 (82.0)	< 0.001
	Moderate to very bad, n (%)	763 (26.6)	1023 (17.2)	567 (15.1)	542 (15.3)	2895 (18.0)	
	Missing[b], *n*	112	185	122	115	534	
Physical activity	*Light level, n (%)*	318 (11.1)	337 (5.7)	202 (5.4)	266 (7.5)	1123 (7.0)	< 0.001
	Moderate level, n (%)	1927 (67.2)	4034 (67.8)	2554 (68.0)	2365 (67.0)	10880 (67.6)	
	High level, n (%)	622 (21.7)	1581 (26.6)	1000 (26.6)	900 (25.5)	4103 (25.5)	
	Missing[b], *n*	109	80	49	23	261	
Diabetes	*Yes, n (%)*	34 (1.2)	40 (0.7)	27 (0.7)	14 (0.4)	115 (0.7)	0.003
	No, n (%)	2833 (98.8)	5912 (99.3)	3729 (99.3)	3517 (99.6)	15991 (99.3)	
Cardiovascular diseases	*Yes, n (%)*	273 (9.5)	368 (6.2)	221 (5.9)	197 (5.6)	1059 (6.6)	< 0.001
	No, n (%)	2594 (90.5)	5584 (93.8)	3535 (94.1)	3334 (94.4)	15047 (93.4)	
Chronic obstructive pulmonary disease	*Yes, n (%)*	57 (2.0)	65 (1.1)	37 (1.0)	48 (1.4)	207 (1.3)	0.001
	No, n (%)	2810 (98.0)	5887 (98.9)	3719 (99.0)	3483 (98.6)	15899 (98.7)	

[a] P-values for between group comparisons.
[b] Distribution of missing data on each covariate prior to exclusion (not included in the characteristics of the total population).

Cox proportional hazards (PH) models were used to assess associations between exposures and outcomes. Time to event was modelled with age as underlying time-scale from baseline on April 30th 1993 to end of follow-up on December 31st 2016. Participants were censored according to the first occurrence of emigration, other cause of death or end of follow-up. Furthermore, the models were stratified by birth cohort in 5-year intervals and adjusted for relevant confounders(Canchola et al., 1995). As this was a cohort study where the sample size was given in advance, no sample size calculation was conducted. Based on the number of events throughout the follow-up time, sufficient

statistical power for the main endpoints could be assumed.

Proportionality and nonlinearity assumptions were checked statistically and graphically using scaled Schoenfeld and Martingale residuals, respectively. Non-proportionality issues were solved by adding covariate*time(age) interactions or by stratifying on the violating covariate. In models where the exposure variable was the primary cause for violation, and interaction terms could not solve the issue, proportionality was further explored and dealt with in 5-year time-interval models. As expected, no. of births as a numeric variable tested non-linear. The covariate was, however, kept in a numeric form since categorizing no. of births did not improve the model significantly (ANOVA test) and the categorical variable "parity" (yes/no) provided assistant control.

All tests were two-sided and statistical significance was set at a p-value of < 0.05. SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria)(R Core Team (2018), 2018) were used for data management and statistical analyses.

2.4. Ethical considerations

The Danish Nurse Cohort Study was approved by the Scientific and Ethical Committee of Copenhagen and Frederiksberg Municipalities (Hundrup et al., 2012). The present study was approved by The Center for Data Reports in the Capital Region, Denmark (jr.no. VD-2018-338 and I-Suite no.: 6585).

3. Results

3.1. Population characteristics

Of the 19,898 cohort participants, the final study population comprised 16,106 (81%) female nurses aged 45–93 years (mean = 56) at baseline. Reasons for exclusion were history of cancer (n = 631) and missing data on exposures (n = 1,525) and other covariates (n = 1,636). In total, 8,527 participants (53%) completed the follow-up of 23 years (mean = 18.8), 4,968 were diagnosed with or died from cancer, and 2,611 were censored due to death of other causes (n = 2,373) or emigration (n = 238). Of cancer events, 1,897 and 2,231 were located in organs related to either smoking or alcohol, respectively, while 1,407 and 579 events were located to the female breast or genitals.

Table 2 shows baseline participant characteristics according to smoking status and alcohol intake. Grouped by smoking status, previous smokers were older and had more comorbidities than non-smokers and current smokers, while current smokers had a higher intake of alcohol, lower Body Mass Index (kg/m^2) (BMI), lower level of physical activity, lower self-rated health (SRH) and were more often non-cohabiting, compared to non- and previous smokers.

Compared to any level of alcohol intake, abstainers were older, had higher BMI and more comorbidity, lower levels of SRH and physical activity, and were more often non-smokers and non-cohabiting.

3.2. Smoking and risk of overall, smoking-related, breast and gynecological cancers

Results are presented with hazard ratios and 95% confidence intervals in Table 3. Compared to non-smokers, current smokers had significantly increased risk of overall cancer, smoking-related cancers and breast cancer, while previous smokers had significantly increased risk of smoking-related cancers. A major risk increase was found for current smokers, who had a 1.83-fold higher risk for smoking-related cancers after adjustment for confounding. No significant associations were detected for gynecological cancers.

Table 3
Smoking and risk of overall cancer, smoking-related cancers, breast cancer and gynecological cancers. Risk estimates in hazard ratios (HR) and 95% confidence intervals (CI).

		Overall Cancer			Smoking-related Cancers			Breast Cancer			Gynecological Cancers		
Smoking status	*N*	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[b] HR (95% CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)
Non-smoker	*5271*	*1445*	Ref.	Ref.	*453*	Ref.	Ref.	*420*	Ref.	Ref.	*206*	Ref.	Ref.
Previous	*4744*	*1429*	1.06 (0.99–1.15)	1.05 (0.97–1.13)	*518*	1.17 (1.03–1.32)	1.17 (1.03–1.33)	*418*	1.14 (0.99–1.31)	1.11 (0.96–1.27)	*179*	0.93 (0.76–1.14)	0.91 (0.74–1.11)
Current	*6091*	*2094*	1.37 (1.28–1.46)	1.32 (1.24–1.42)	*926*	1.89 (1.69–2.12)	1.83 (1.63–2.05)	*569*	1.27 (1.12–1.44)	1.19 (1.05–1.36)	*194*	0.86 (0.71–1.05)	0.84 (0.69–1.03)

[a] Age as time scale and stratified by birth cohort.
[b] Age as time scale and stratified by birth cohort. Adjusted for alcohol intake, BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy.
[c] Age as time scale and stratified by birth cohort. Adjusted for alcohol intake, BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy, oral contraceptive use, no. of births, age at menarche.

Table 4
Alcohol intake and risk of overall cancer, alcohol-related cancers, breast cancer and gynecological cancers. Risk estimates in hazard ratios (HR) and 95% confidence intervals (CI).

		Overall Cancer			Alcohol-related Cancers			Breast Cancer			Gynecological Cancers		
Alcohol Intake (units/week)	*N*	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[b] HR (95%CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	*No. of cases*	Crude[a,d] HR (95% CI)	Adjusted[c,d] HR (95% CI)	*No. of cases*	Crude[a,d] HR (95% CI)	Adjusted[c,d] HR (95% CI)
Abstinence	*2867*	*913*	1.07 (0.98–1.16)	1.04 (0.96–1.13)	*425*	1.19 (1.05–1.34)	1.16 (1.03–1.31)	*245*	1.10 (1.02–1.18)	1.08 (1.00–1.16)	*117*	1.15 (0.79–1.68)	1.13 (0.78–1.66)
Light (1–7 units)	*5952*	*1753*	Ref.	Ref.	*750*	Ref.	Ref.	*475*	Ref.	Ref.	*209*	Ref.	Ref.
Moderate (8–14 units)	*3756*	*1139*	1.04 (0.96–1.12)	1.02 (0.95–1.10)	*528*	1.13 (1.01–1.26)	1.11 (1.00–1.25)	*350*	1.18 (1.10–1.25)	1.16 (1.08–1.23)	*126*	0.75 (0.51–1.11)	0.76 (0.51–1.13)
Excessive (> 14 units)	*3531*	*1163*	1.19 (1.10–1.28)	1.14 (1.05–1.22)	*528*	1.25 (1.12–1.40)	1.22 (1.08–1.35)	*337*	1.23 (1.15–1.31)	1.18 (1.10–1.26)	*127*	0.74 (0.50–1.11)	0.75 (0.50–1.12)

[a] Age as time scale and stratified by birth cohort.
[b] Age as time scale and stratified by birth cohort. Adjusted for smoking, BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy.
[c] Age as time scale and stratified by birth cohort. Adjusted for smoking, BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy, oral contraceptive use, no. of births, age at menarche.
[d] Result derived from 5-year time interval model.

Table 5
Combined smoking and light alcohol intake (≤7 units/week) and risk of overall cancer, smoking- and alcohol-related cancers, breast cancer and gynecological cancers. Risk estimates in hazard ratios (HR) and 95% confidence intervals (CI).

		Overall Cancer			Smoking-related Cancers			Alcohol-related Cancers			Breast Cancer			Gynecological Cancers		
Smoking and alcohol intake	*N*	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[b] HR (95% CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	*No. of cases*	Crude[a,d] HR (95% CI)	Adjusted[c,d] HR (95% CI)	*No. of cases*	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	*No. of cases*	Crude[a,d] HR (95% CI)	Adjusted[c,d] HR (95% CI)
Non-smoker and light intake	*5834*	*1691*	Ref.	Ref.	*604*	Ref.	Ref.	*782*	Ref.	Ref.	*473*	Ref.	Ref.	*233*	Ref.	Ref.
Non-smoker and above light intake	*4181*	*1183*	1.00 (0.93–1.08)	1.01 (0.94–1.09)	*367*	0.89 (0.78–1.01)	0.90 (0.79–1.02)	*547*	0.98 (0.93–1.04)	0.99 (0.94–1.05)	*365*	1.07 (0.94–1.23)	1.08 (0.94–1.24)	*152*	0.66 (0.46–0.96)	0.67 (0.46–0.97)
Smoker and light intake	*2985*	*975*	1.24 (1.14–1.34)	1.22 (1.13–1.33)	*441*	1.58 (1.40–1.78)	1.53 (1.35–1.74)	*393*	1.04 (0.98–1.11)	1.03 (0.97–1.10)	*247*	1.08 (0.93–1.27)	1.06 (0.90–1.23)	*93*	0.89 (0.60–1.33)	0.90 (0.61–1.34)
Smoker and above light intake	*3106*	*1119*	1.42 (1.31–1.53)	1.40 (1.30–1.51)	*485*	1.76 (1.56–1.98)	1.72 (1.52–1.94)	*509*	1.34 (1.27–1.42)	1.33 (1.26–1.40)	*322*	1.36 (1.18–1.57)	1.32 (1.15–1.53)	*101*	0.72 (0.47–1.08)	0.71 (0.47–1.08)

[a] Age as time scale and stratified by birth cohort.
[b] Age as time scale and stratified by birth cohort. Adjusted for BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy.
[c] Age as time scale and stratified by birth cohort. Adjusted for BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy, oral contraceptive use, no. of births, age at menarche.
[d] Result derived from 5-year time interval model.

3.3. Alcohol intake and risk of overall, alcohol-related, breast and gynecological cancers

Results are shown in Table 4. Compared to light alcohol intake, both abstinence, moderate- and excessive alcohol intake were associated with significantly increased risk of alcohol-related cancers and breast cancer. Overall, excessive alcohol intake yielded the greatest risk increases with 1.14-, 1.22-, and 1.18-fold risk for overall cancer, alcohol-related cancers and breast cancer, respectively. No significant associations were found for gynecological cancers.

3.4. Combined smoking and light alcohol intake and risk of overall, smoking-related, alcohol-related, breast and gynecological cancers

Detailed results are presented in Table 5. Compared to non-smokers with a light alcohol intake, non-smokers with an alcohol intake above the light level were not associated significantly with any of the cancer outcomes (overall, smoking-related, alcohol-related, breast and gynecological cancer). However, current smokers had significantly increased risk of overall cancer and smoking-related cancer. The risk of smoking-related cancer increased from 1.53-fold in smokers with a light alcohol intake to 1.72-fold in smokers with a larger than light alcohol intake (adjusted). Alcohol-related cancer risk and breast cancer risk were increased by respectively 1.33- and 1.32-fold in smokers with an alcohol intake above the light level. No significant associations were found for the gynecological cancer outcome.

3.5. Combined smoking and moderate alcohol intake and risk of overall, smoking-related, alcohol-related, breast and gynecological cancers

Detailed results are presented in Table 6. Compared to non-smokers with alcohol intake at a moderate level, non-smokers with an alcohol intake above the moderate level were not at significantly increased risk of any of the cancer outcomes (overall, smoking-related, alcohol-related, breast and gynecological cancer). The risk of overall, smoking-related, and alcohol-related cancers was increased in current smokers with a moderate alcohol intake or less, and an additional risk increase was found for smokers with an alcohol intake above the moderate level; the risk of smoking-related cancers increased from 1.61- to 1.97-fold, and the risk of alcohol-related cancers increased from 1.13- to 1.40-fold. Current smoking combined with more than a moderate alcohol intake was associated with a significant 1.33-fold risk for breast cancer. No significant associations were found for gynecological cancers.

4. Discussion

In this cohort study including 16,106 female nurses we evaluated associations between smoking and alcohol intake, separately and combined, and overall, smoking-related, alcohol-related, breast and gynecological cancers. We found an increased risk of both overall cancer, smoking-related cancers and breast cancer among current smokers, while previous smokers had an increased risk of smoking-related cancers only. Excessive alcohol intake was associated with an increased risk of overall cancer, alcohol-related cancers and breast cancer. An increased risk of alcohol-related cancers and breast cancer was found for abstinence and moderate alcohol intake. Combined smoking and alcohol use carried an incremental risk increase for overall, smoking- and alcohol-related cancers, and breast cancer. Importantly, these risk estimates were doubled in smokers with an alcohol intake above a moderate level compared to smokers with a lower intake.

With an immense amount of studies confirming the association between tobacco and site-specific cancers, tobacco smoking is presently considered a causal pathway for at least 16 cancers in the human body (Anantharaman et al., 2011; Cheng et al., 2015; Gupta et al., 2009; Pang et al., 2015; Szymańska et al., 2011; Talamini et al., 2009; Zuo

Table 6
Combined smoking and moderate alcohol intake (≤14 units/week) and risk of overall cancer, smoking- and alcohol-related cancers, breast cancer and gynecological cancers. Risk estimates in hazard ratios (HR) and 95% confidence intervals (CI).

Smoking and weekly alcohol intake	N	Overall Cancer			Smoking-related Cancers			Alcohol-related Cancers			Breast Cancer			Gynecological Cancers		
		No. of cases	Crude[a] HR (95% CI)	Adjusted[b] HR (95% CI)	No. of cases	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	No. of cases	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	No. of cases	Crude[a] HR (95% CI)	Adjusted[c] HR (95% CI)	No. of cases	Crude[a, d] HR (95% CI)	Adjusted[c, d] HR (95% CI)
Non-smoker and moderate intake	8149	2329	Ref.	Ref.	798	Ref.	Ref.	1079	Ref.	Ref.	675	Ref.	Ref.	314	Ref.	Ref.
Non-smoker and above moderate intake	1866	545	1.07 (0.97–1.17)	1.07 (0.97–1.17)	173	1.00 (0.85–1.18)	1.01 (0.86–1.19)	250	1.05 (0.91–1.20)	1.05 (0.91–1.20)	163	1.07 (0.90–1.27)	1.06 (0.89–1.26)	71	0.66 (0.40–1.09)	0.66 (0.40–1.08)
Smoker and moderate intake	4426	1476	1.28 (1.20–1.37)	1.26 (1.18–1.35)	648	1.65 (1.49–1.83)	1.61 (1.44–1.78)	624	1.15 (1.04–1.27)	1.13 (1.02–1.25)	395	1.14 (1.01–1.29)	1.11 (0.98–1.26)	138	0.88 (0.63–1.24)	0.88 (0.63–1.24)
Smoker and above moderate intake	1665	618	1.52 (1.39–1.66)	1.49 (1.36–1.63)	278	2.03 (1.77–2.33)	1.97 (1.71–2.26)	278	1.43 (1.25–1.63)	1.40 (1.22–1.60)	174	1.37 (1.16–1.62)	1.33 (1.12–1.57)	56	0.85 (0.52–1.40)	0.84 (0.51–1.32)

[a] Age as time scale and stratified by birth cohort.
[b] Age as time scale and stratified by birth cohort. Adjusted for BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy.
[c] Age as time scale and stratified by birth cohort. Adjusted for BMI, physical activity, self-rated health, cohabitation, parity, hormone replacement therapy, oral contraceptive use, no. of births, age at menarche.
[d] Result derived from 5-year time interval model.

et al., 2017). There is, however, according to the International Agency for Research on Cancer (IARC), only limited evidence for tobacco as a carcinogenic agent for breast cancer and cancer of the endometrium (IARC, 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). Nonetheless, our findings indicate that female smokers are at significantly increased risk of breast cancer. This is in line with recent findings from the Women's Health Initiative study (Arthur et al., 2018b) and an increasing amount of studies and systematic reviews on the subject(Bérubé et al., 2014; Catsburg et al., 2015; Gaudet et al., 2017; Jones et al., 2017; Macacu et al., 2015; Sollie and Bille, 2017). Moreover, a recent study from the Danish Nurse Cohort published similar results(Andersen et al., 2017). Despite the fact that tobacco is an established risk factor for some gynecological cancers, such as cervical(Roura et al., 2014) and ovarian cancer(Arthur et al., 2018a; Jordan et al., 2006; Praestegaard et al., 2017), our analyses did not yield significant associations between tobacco and a composite outcome of gynecological cancers. The inclusion of all female genital cancers in our composite outcome definition could be a potential explanation.

Confirming findings from previous studies(Arthur et al., 2018b; Bagnardi et al., 2015, 2013; Choi et al., 2018; Ferrari et al., 2014; Griswold et al., 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; O'Donnell et al., 2015; Smyth et al., 2015), we found that, compared to light drinking, excessive drinking, but notably also moderate drinking, increased the risk of alcohol-related cancer and breast cancer, but not gynecological cancer. Although alcohol intake appears less risky than smoking (Anantharaman et al., 2011; Maas et al., 2016) and a cardio protective effect of low to moderate drinking is suggested by numerous studies (Griswold et al., 2018; O'Donnell et al., 2015; Ronksley et al., 2011), zero intake seems to carry the lowest risk of overall health loss (Griswold et al., 2018).

Tobacco and alcohol use are relatively easy to identify and monitor, and since they are closely associated and commonly used in combination on a daily and long-term basis(Miller and Gold, 1998), research on their joint effect on cancer risk is highly relevant. Nevertheless, the combined effect has mainly been studied in mixed gender case-control studies on upper digestive tract cancers, in which combined use increases the risk extensively(Anantharaman et al., 2011; Dal Maso et al., 2016; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Szymańska et al., 2011; Weikert et al., 2009). Our findings suggest that, compared to the risks associated with separate use, combined smoking and alcohol intake above light or moderate levels greatly increases the risks of overall cancer, smoking- and alcohol-related cancers, and cancers of the breast. Previous studies have not found evidence of interactions between tobacco and alcohol on risk of breast cancer(Hamajima et al., 2002; Suzuki et al., 2010). Therefore, to the best of our knowledge, this is the first study to infer additional breast cancer risk by combined use of alcohol and tobacco. A few studies have examined breast cancer risk by joint effects of modifiable risk factors, such as alcohol, smoking, BMI, physical activity and diet, and the findings consistently demonstrate that risk is extensively reduced by healthier lifestyle(Arthur et al., 2018b; McKenzie et al., 2015; Sanchez-Zamorano et al., 2011). Furthermore, one study found that 28.9% of all breast cancers in women could be prevented by minimizing obesity, smoking, alcohol intake, and hormone therapy with each of these risk factors contributing to reductions of 3–12%(Maas et al., 2016). Thus, from a public health perspective, it is imperative to analyze and evaluate the joint health impact of modifiable risk factors and to integrate and promote joint-factor prevention strategies.

The present findings emphasize the public health threat of joint smoking and alcohol and convey the important public health message that combined use infers incremental cancer risk. Thus, a need for combined prevention strategies is substantiated. Our findings furthermore present risk assessments for broad cancer outcomes, such as overall, smoking- and alcohol-related cancers, which could facilitate public health communication and promotion.

The suggested gender variations in motivational factors for substance uptake and cessation, and in susceptibility and morbidity outcomes(Allen et al., 2014; Erol and Karpyak, 2015; Hjerteforeningen, Sundhedsstyrelsen, 2019; Smith et al., 2016; Wang et al., 2014), further indicate that gender-oriented prevention strategies may be fundamental for success.

The present study has the advantages of a large homogenous female population, an exceptionally high response rate (86%), and complete follow-up due to nationwide registries on hospitalizations, death causes and migration. These are all important factors to minimize selection and information bias. However, as in any other cohort study exploring behavioral risk factors within a long follow-up period, there is a risk of lifestyle changes which potentially can yield imprecise risk measurements. Furthermore, the combined smoking and alcohol measure required unrefined groupings, e.g. joining non-smokers with previous smokers, and could thus result in somewhat vague risk assessments. Although smoking and alcohol drinking were socially accepted to greater extent in the 90's, underreporting is likely to have occurred and would result in misclassification bias and an overestimation of cancer risk. Misclassification bias and residual confounding, especially when exploring alcohol habits, is an ongoing challenge, since grouping of abstainers often include older, so-called sick quitters, including former problem drinkers and people who quit for health reasons. We were not able to detect and exclude former problem drinkers, and thus they would have been labelled as abstainers with the potential of introducing bias and overestimated the true risk for abstinence. The group of light alcohol intake was considered less prone to bias, and since > 50% of Danish women have a light alcohol intake(Danish Health Authority, 2018), light alcohol intake was the reference group in analyses on alcohol intake. Since no international consensus on recommended alcohol intake exists and recommendations vary between countries, we chose the alcohol limits recommended for women by the Danish Health Authority(Danish health Authority, n.d.).

5. Conclusion

In this large cohort study of 16,106 female nurses, we found that tobacco smoking and moderate to excessive alcohol intake each increased the risk of overall cancer, smoking- and alcohol-related cancers, and breast cancer, but not of gynecological cancers. Moreover, we found that exposure to both tobacco smoking and alcohol inferred an incremental risk of the same outcomes. Since combined and long-term use of tobacco and alcohol is common in many countries, the health risks associated with combined use should not be overlooked by clinicians, researchers or politicians in public health management and disease prevention. In fact, public health might very well benefit greatly from prevention strategies targeting women's use of smoking and alcohol in combination.

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Declaration of competing interests

None declared.

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