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ORIGINAL RESEARCH

Light to Moderate Alcohol Consumption and Cancer Incidence: The Norwegian Women and Health Cohort Study

Fjorida Llaha[1], Idlir Licaj[1], Ekaterina Sharashova[1], Pietro Ferrari[2], Marko Lukic[1], Kristin Benjaminsen Borch[1]

[1]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, 9019, Norway; [2]Nutrition and Metabolism Branch, International Agency for Research on Cancer (IARC), World Health Organization, Lyon, 69366, France

Correspondence: Fjorida Llaha, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Hansine Hansens veg 18, Tromsø, 9019, Norway, Email fjorida.llaha@uit.no

Purpose: To investigate the impact of light-moderate (up to 20 g/day) alcohol consumption on incidence of postmenopausal breast, kidney, lung, pancreatic, colorectal, postmenopausal ovarian and postmenopausal endometrial cancer among women.

Methods: Participants were 70,932 women aged 41–70 years, randomly recruited in the Norwegian Women and Health (NOWAC) cohort study from 1996 to 2004. We included women who reported that they consumed alcohol. Only postmenopausal women (N = 32,735) were included in the analyses for female cancers. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: The mean follow-up was 19 years. The estimated hazard ratio (HR) from each additional 12g/day of alcohol consumption for postmenopausal breast cancer was 1.20 (95% confidence intervals CI: 1.03 to 1.41), and for kidney cancer 0.42 (95% CI: 0.24 to 0.75). The corresponding estimates for postmenopausal breast cancer among women who used menopausal hormone therapy (MHT) were HR = 1.27, 95% CI: 1.05 to 1.54, and among women who never used MHT were HR = 1.12, 95% CI: 0.86 to 1.47. Compared to alcohol consumption of <3.5 g/day, consumption of 3.5–10 g/day revealed for lung cancer inverse association with risk of lung cancer among women who consumed primarily wine (HR = 0.65, 95% CI; 0.43 to 0.88), but not among other drinkers (HR = 1.10, 95% CI; 0.88 to 1.31). No associations were confined for pancreatic, colorectal, ovarian and endometrial cancers.

Conclusion: Women drinking light-moderate alcohol level had a higher risk of postmenopausal breast cancer and a lower risk of kidney cancer incidence. Our results do not support the threshold of up to 1 drink/day as a safe limit for breast cancer, especially for postmenopausal women who use MHT. The inverse relationship found for lung cancer could be explained by the healthier lifestyle correlated with this light-moderate drinking.

Keywords: alcohol, cancer prevention, women, cohort study

Introduction

Heavy alcohol consumption (≥50 g/day) has been linked to higher incidence of several cancers, including cancer of the colorectum, female breast, oral cavity, pharynx, larynx, liver, and esophagus, and possibly to a higher risk of cancer of the stomach, pancreas, lung, and gallbladder.[1,2] Alcohol may contribute to carcinogenesis through several mechanisms, including the inhibition of DNA methylation, induction of oxidative stress, enhancement of inflammation, and elevation of steroid hormone levels, which is particularly linked to an increased risk of breast cancer.[3] However, the impact on cancer of light (≤10g/day of ethanol or <1 drink/day) to moderate (10–20 g/day of ethanol or 1 to <2 drinks/day) of alcohol consumption, which is more typical among women, is less clear.

Meta-analyses of mainly cohort studies that have focused on the association between light and moderate alcohol consumption and cancer risk suggest a higher incidence of oral cavity, pharynx, esophagus, and female breast cancer.[1,4,5] Findings from recent studies showing a higher risk of breast cancer only for alcohol level exceeding 1 drink/day[6,7]

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maintain open the debate on a possible threshold. A recent analysis from the prospective UK Million Women Study, which predominantly includes women with moderate alcohol consumption, reported higher risk for pancreatic and colorectal cancer incidence by each additional daily drink, among drinkers.[8] Two meta-analyses of cohort studies made different conclusions about the relationship between light drinking and endometrial cancer incidence.[5,9] One supported the lower risk,[9] and the other did not.[5] Pooled analyses of case-control and cohort studies found lower risk for lung cancer incidence by light alcohol consumption, but different results regarding moderate alcohol consumption.[5,10] An analysis from the prospective UK Million Women Study in 2009 found lower risk for ovarian cancer incidence by light alcohol drinking,[11] although this was not replicated by later meta-analysis.[5] Previous publications have discussed the choice of exposure reference category as a potential factor contributing to different results among studies, and the bias in relation to the non-drinker reference category.[3,9,10]

Although the relationship between alcohol and cancer incidence has been extensively studied, including by many cohort studies, the role of different alcoholic drinks still needs to be elucidated. Some of these studies concluded that alcohol consumption, irrespective of the alcoholic drink, was related to the risk of cancer.[11–14] Yet, several studies have found differences,[10,15–20] arguing that the differences could partly be due to the lifestyle habits correlated with alcoholic drink choices, despite the adjustment for lifestyle factors in their analysis.[10] Inconsistencies exist regarding the impact of alcohol across strata of other key modifiable factors like smoking,[8,12,13,16,21] body mass index (BMI),[8,12,16,19,22,23] and menopausal hormone therapy (MHT) use.[8,22,24–30] Research in women conducting such analyses is available for female cancers, in particular for breast cancer,[8,12,22–30] but it remains scarce for other cancer sites.[8,21]

In addition to the above gaps, within the Norwegian context, it is important to continue investigating the impact of alcohol consumption on cancer among women due to the increased (age-standardized) incidence of overall cancer and alcohol use prevalence among Norwegian women.[31,32] The trends of other modifiable factors do not entirely explain the rising incidence of cancer. Smoking prevalence has consistently declined among Norwegian women over the past three decades,[33] and the use of MHT has decreased since 2002.[34,35] The rising trends of obesity has continued in women aged 40–49 years, but not among women 60–69 years.[36]

We aimed to investigate the impact of light to moderate alcohol consumption in middle-aged to older women who consumed alcohol on the incidence of common cancer sites including postmenopausal breast, kidney, lung, pancreatic, colorectal, postmenopausal ovarian and postmenopausal endometrial cancers. In addition, we aimed to investigate the impact in subgroups defined by the type of alcohol consumed, smoking status, BMI levels and MHT use. We used data from the Norwegian Women and Health (NOWAC) cohort study, characterized by low to moderate alcohol consumption.[37]

Materials and Methods

Study Population

Details of the NOWAC (previously named as Norwegian Women and Cancer) cohort study have been previously reported.[38] Shortly, 172,478 women were randomly recruited across Norway during 1991–2007. Women self-administered a paper-based questionnaire recording sociodemographic factors, lifestyle and medical history. Since we used dietary variables as covariates in our analyses (explained below), we included in this study the NOWAC sub-cohort (n = 95,937) who returned a detailed and similar food frequency questionnaire (FFQ) during 1996–2005 (herein baseline). We excluded women with prevalent cancer, those who died, emigrated, were pregnant or breastfeeding during exposure/alcohol recall period, or had missing alcohol data. In the NOWAC cohort, non-drinkers are more likely to report poor health status.[37] Adding that we could not differentiate between former drinkers and lifetime abstainers, we included only drinkers in this study to avoid comparison with non-drinkers who were possibly sick, therefore to mitigate abstainer bias.[39] The final sample was 70,932 women. The analyses for female cancers were restricted to postmenopausal women (n = 32,735), since we aimed to assess the effect modification by the use of MHT. Those with a history of oophorectomy and hysterectomy at baseline were excluded from the ovarian and endometrial cancer analyses, respectively. A detailed flow chart of the study participants is presented in supplemental file 1.

Ascertainment of Alcohol Consumption

In the NOWAC FFQs, women were asked whether they were alcohol abstainers; if not, they were asked about their average frequency consumption of wine, beer, spirits, and liqueurs during the past 12 months. The answers ranged from never/seldom to 2+ drinks/day. Alcohol consumption (in g/day) was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic drink, using average unit volume and ethanol concentration data from the Norwegian Weights and Measurement Food Table.[40] A value of 0 g/day was assigned to abstainers or never/seldom answers, and these were considered non-drinkers. In this study, consumption of liqueurs was not included in the total alcohol calculation as it was only surveyed in around 30% of this sample. Alcohol data in NOWAC measured by FFQ have demonstrated good reproducibility (correlation coefficient between FFQs = 0.72),[41] and validity (correlation coefficient between alcohol data measured by FFQ and those obtained from four 24-hour dietary recalls = 0.67).[40] We categorized alcohol consumption as low <3.5 g/day, light 3.5–10 g/day, moderate >10-20 g/day, and high >20 g/day. This categorization was based on the broad definition of light (<10 g/day of alcohol) and moderate consumption (10–20 g/day of alcohol),[4,5,42] and similar categorizations used in other women's cohort studies.[11,22,27] Following previous epidemiological studies,[43–45] drinkers were divided into two groups: wine drinkers, if ethanol from wine constituted ≥70% of their total ethanol consumption, and other drinkers otherwise. Our focus was on wine consumption given its particular increase in Norway,[46] and the possible low public awareness regarding its cancer-related risks, as found in studies from Australia and US.[47,48]

Assessment of Covariates

Several self-reported covariates were used in this study as explained below in the Statistical analysis section. A detailed description of covariate collection and computation is given in Supplemental file 2.

Ascertainment of Outcomes

Cancer diagnoses were coded according to the International Classification of Diseases, 10th Revision. We examined the seven most common cancers: breast (C50), colorectal (C18-20), lung (C34), kidney (C64), pancreatic (C25), ovarian (C56) and endometrial (C54). Cancer cases, emigrations and deaths were identified through the electronic linkage to the Cancer Registry of Norway and the National Population Register.

Statistical Analysis

In descriptive analyses, continuous variables were presented as means with standard deviations for normally distributed variables or as medians with interquartile ranges for skewed variables. Categorical variables were presented by frequency and percentage.

As a first step, we performed restricted cubic splines to model the shape of the relationship between alcohol consumption and cancer incidence (Supplemental file 3). From visual inspection of the restricted cubic splines analysis, we observed fair linear relationships, except for lung cancer. Therefore, for lung cancer, we performed only categorical exposure analysis. For other cancer sites, the primary analysis was the continuous exposure analysis of each 12 g/day alcohol (equivalent to one standard drink in Norway), with the categorical analysis provided as supplementary.

We used multivariable Cox proportional hazard models to calculate hazard ratios (HR) with 95% confidence intervals (CI). For each woman, we computed person-years of follow-up starting from the age at baseline until the attenuated age of diagnosis of any type of cancer, emigration, death, or end of study on 31 December 2020, whichever came first. Directed Acyclic Graphs (DAGs) were used as a conceptual tool to depict the relationships between observed and unobserved covariates, exposure, and outcomes. However, we cannot ensure a complete causal knowledge on the DAGs, therefore the modified disjunctive cause criterion was the main principle guiding the confounder selection.[49] To estimate the total effect, we controlled for each covariate that is a cause of the exposure, or of the outcome, or of both; excluding from this set any variable considered to be a mediator, and including covariates considered to be proxy for unmeasured confounders. The details of these assumptions and the DAGs are presented in Supplemental file 4. All models were adjusted for years of education (≤9, 10–12, 13–16, ≥17), smoking (never, pack-years in the following categories: 1–4,

5–9, 10–19, ≥20, and ever smokers with no information on pack-years), and physical activity level (1–4, 5–7, 8–10 scores). BMI (<25, 25–29.9, ≥30 kg/m2) was included in all models except for lung cancer. Parity (bearing child, not bearing child) and MHT use (never, former, and current) were included in the models for female cancers. For breast cancer, the parity covariate was computed as not bearing child, bearing child and age at first birth ≤30 years, and bearing child and age at first birth >30 years. Age at menarche (in years) and breastfeeding duration (0 months, <12 months, >12 months) were included in the models for postmenopausal breast and ovarian cancer. Oral contraceptive use (ever, never) was included in the models for postmenopausal ovarian and endometrial cancer. History of breast cancer in mothers and sisters (yes, no, I do not know) was included in the model for postmenopausal breast cancer. Fruit and vegetables intake in g/day (tertiles) was included in the models for lung and postmenopausal breast cancer. Red and processed meat intake in g/day (tertiles) was included in the models for lung and colorectal cancer. Calcium intake in mg/day (tertiles) was included in the models for colorectal and postmenopausal breast cancer. Fiber intake in g/day (tertiles) was included in the model for colorectal cancer. In addition, all analyses were stratified by year of birth (1927–1934, 1935–1944, 1945–1954, 1955–1957) to ensure that comparisons were made within women who were as similar as possible. Further, all models were adjusted for calorie intake from non-alcoholic sources in kj/day (tertiles) to separate as much as possible the effect of alcohol from the effect of body size and composition, physical activity, metabolic efficiency and overall diet quality.[50] We corrected the estimates for regression dilution bias, arising from variation over time or random measurement error of alcohol data.[51] A subset of women provided two repeated measures of alcohol data. The timeline between the repeated measures was on average six years. The average intake of repeated measure in g/day within each baseline quintiles of alcohol was used to calculate the regression dilution ratio (RDR = 0.84) according to MacMahon-Peto method,[52] (Supplemental file 5). Log HR estimates and the corresponding standard errors from dose analysis were divided by RDR to yield corrected HR and CI.

We estimated HR with 95% CI in subgroups defined by the alcohol consumed (wine drinkers and other drinkers), and potential effect modifiers including smoking status (ever and never smoker), BMI (<25 kg/m2 and ≥25 kg/m2), and MHT (ever and never user). Subgroup analyses by MHT use were done for female cancers, by smoking status for all cancer sites and by BMI for all cancer sites except lung cancer. These subgroup analyses were guided by evidence on key modifiable risk factors for each cancer site.[53] The subgroup analyses in ever smokers, ever users of MHT and women with BMI ≥25 kg/m2 were adjusted for their remaining initial categories. For example, the analysis in the subgroup of ever users of MHT was adjusted for former and current MHT use. Interaction terms assessed at multiplicative scale between alcohol and potential effect modifiers showed a p-value of >0.1, therefore not included in the main Cox models.

For colorectal cancer, we conducted an additional analysis by analyzing colon (C18) and rectal (C19, C20) cancer as separate outcomes.

We conducted sensitivity analyses. First, we restricted the analysis to more than 2 years of follow-up to address potential reverse causality. Further, to fully capture the impact of light to moderate alcohol consumption on cancer incidence, we excluded women with consumption of alcohol >20 g/day (n = 638, 1% of drinkers). Body weight and height have an independent impact on cancer risk.[53] Adjusting for BMI and not for its individual components may leave residual confounding. Adding the questionable relevance of BMI as an indicator of excessive body fatness,[54] we repeated the analyses adjusting for weight in kg (tertiles) and height in cm (tertiles) instead of BMI. All models were additionally adjusted for regions to account for potential variances of unmeasured lifestyle and medical behaviors that may have emerged due to differences in environmental conditions across Norway and the initial implementation of the mammography screening program in 1996.[55] The model for colorectal cancer was additionally adjusted for menopause status and MHT use (pre and perimenopausal, postmenopausal and never user of MHT, postmenopausal and former user of MHT, postmenopausal and current user of MHT) given the relationship between the use of MHT and the risk of colorectal cancer in postmenopausal women.[56] Last, we accounted for the competing risk of overall death according to the Fine and Gray method.[57]

All analyses were done on complete cases. For Cox models, a complete case analysis is not biased when the chance of being a complete case does not depend on the outcome.[58] We assumed this assumption was fulfilled since the exposure and all covariates were measured before the outcomes. However, to check if the exclusion of missing values would change the results, we re-ran the main analyses on the imputed data. Missing values were handled with multiple

imputations by chained equations method (20 imputed data sets) for the following covariates: smoking (1.2% of missing data among drinkers), level of education (4.5%), physical activity (7%), BMI (1.9%), fruits and vegetables intake (1.2%), red and processed meat (1.6%), and age at menarche (1.4%). Stata version 18.0 was used for all analyses and the codes are displayed on Supplemental file 13.

Language Used and Interpretation of the Findings

On the need to clarify the study purpose, the choice of the methods and assumptions, we used a causal language to formulate the study aim and throughout the Methods section.[59,60] Given the small identified effects and the acknowledged limitations of our study (explained below), we used more of an associational language to interpret our results.[59,60] For the interpretation of the results, we have focused on data compatibility using the point estimate and, particularly, the 95% CI (including its width and endpoints). We used STROBE for reporting guidelines (Supplemental file 6).

Results

In this study, which included only women who consumed alcohol, 58% of women reported low alcohol consumption, 32% reported light, 9% reported moderate, and 1% reported high alcohol consumption (Table 1). The proportion of women with the highest level of education, current smokers, and ever users of MHT, and the mean intake of red and processed meat, increased with increasing levels of alcohol consumption. Approximately 34% of women reported drinking primarily wine and were classified as wine drinkers. Wine drinkers compared to other drinkers reported lower calorie intake, higher levels of education and of physical activity, greater consumption of fruits and vegetables, lower intake of red and processed meats, were less likely to smoke, and more likely to have used MHT. During a mean follow-up of 19 years, 254 women developed pancreatic cancer, 226 kidney cancer, 1,378 colorectal cancer, 1,001 lung cancer, 1,531 of postmenopausal breast cancer, 214 of postmenopausal ovarian cancer, and 346 of postmenopausal endometrial cancer.

The estimated HR from each additional 12g/day of alcohol consumption for postmenopausal breast cancer was 1.20 (95% CI = 1.03 to 1.41, Figure 1). This association was particularly observed among wine drinkers (HR = 1.38, 95% CI = 1.06 to 1.80) and ever users of MHT (HR = 1.27, 95% CI = 1.05 to 1.54). The estimates in never users of MHT were HR = 1.12, 95% CI = 0.86 to 1.47, and in other drinkers were HR = 1.13, 95% CI = 0.93 to 1.38. The estimates were similar according to BMI levels (Figure 1). The estimates according to smoking were fairly similar but with low precision in never smokers, probably due to a small number of cases (Figure 1). The results from the categorical analysis were also more compatible with a higher risk (Supplemental file 7). Compared to low alcohol consumption, the estimates were HR = 1.11, 95% CI = 0.99 to 1.25 for light consumption, and HR = 1.24, 95% CI = 1.05 to 1.46 for moderate consumption.

For kidney cancer, the estimated HR from each additional 12g/day of alcohol consumption was 0.42 (95% CI = 0.24 to 0.75, Figure 2). This pattern of association was also observed across subgroup analyses, but with some differences in precision and magnitude. For example, the small number of cases among wine drinkers (n = 66) and never smokers (n = 59) yielded estimates with low precision in these subgroups. The magnitude of risk was larger among women with BMI ≥25 kg/m2 (HR = 0.34, 95% CI = 0.14 to 0.85) than women with BMI <25 kg/m2 (HR = 0.48, 95% CI = 0.23 to 1.03). Categorical analysis also revealed a lower risk (Supplemental file 7).

For lung cancer, compared to low alcohol consumption, the estimates for light consumption were HR = 0.94, 95% CI = 0.80 to 1.08, for moderate HR = 0.98, 95% CI = 0.80 to 1.20, and for heavy HR = 1.19, 95% CI = 0.74 to 1.90 (Figure 3). In ever smokers, these estimates were materially similar to the entire sample. The number of cases in never smokers was small (n = 62) and the CIs were substantially wide. For light drinking level, an inverse association pattern was confined among wine drinkers (HR = 0.70, 95% CI = 0.53 to 0.91), but not among other drinkers (HR = 1.08, 95% CI = 0.92 to 1.28). Among wine drinkers, the inverse association was less precise for moderate drinking levels (HR = 0.79, 95% CI = 0.39 to 1.18, Figure 3).

The analyses with exposure contrast per 12/day increase of alcohol yielded results with wide CIs and no specific association patterns were confined for pancreatic (HR = 1.07, 95% CI = 0.71 to 1.61), colorectal (HR = 1.06, 95% CI = 0.88 to 1.27), postmenopausal ovarian cancer (HR = 1.06, 95% CI = 0.67 to 1.67), and postmenopausal endometrial

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Table 1 Baseline Characteristics of the Study Population According to the Amount and Type of Alcohol Consumption. The Norwegian Women and Cancer Study 1996–2004

	By Category of Alcohol Consumption				By Type of Alcohol	
	Low (<3.5 g/Day)	Light (3.5 to 10 g/Day)	Moderate (>10 to 20 g/Day)	High (>20 g/Day)	Wine Drinkers	Other Drinkers
N (%)	35,525 (57.5)	19,907 (32.2)	5,737 (9.3)	587 (1)	20,970 (34.0)	40,786 (66.0)
Age, mean (SD)	50.9 (6.0)	50.6 (5.6)	50.7 (5.5)	51.9 (5.7)	51.8 (5.6)	50.3 (5.9)
Alcohol in g/day, median (IQR)	1.5 (0.9–2.21)	5.9 (4.9–7.5)	12.4 (11.4–14.4)	23.4 (22.7–26.5)	2.2 (0.9–6)	2.8 (1.5–6.1)
Percentage of ethanol from wine, median (IQR)					100 (81.9–100)	26.4 (0–45.2)
Calorie intake from non-alcoholic sources in kj/day, mean (SD)	1,665.3 (454.7)	1,651.9 (442.7)	1,638.6 (452.9)	1,592.1 (508.8)	1,628.5 (447.3)	1672.9 (452.7)
BMI in kg/m2, mean (SD)	24.8 (3.9)	24.1 (3.4)	24.0 (3.4)	24.5 (3.6)	24.4 (3.7)	24.6 (3.7)
Highest category of education (≥ 17 years of education), n (%)	4,250 (12.0)	3,635 (18.3)	1,264 (22.0)	151 (25.7)	4,048 (19.3)	5252 (12.9)
Lowest category of education (≤9 years of education), n (%)	10,421 (26.4)	3,476 (16.2)	819 (13.4)	76 (12.3)	3,609 (15.8)	11,174 (24.9)
Current smokers, n (%)	11,413 (32.1)	6,456 (32.4%)	2,277 (39.7)	295 (50.3)	5,888 (28.1)	14,553 (35.7)
Pack-year smoked in current smokers, mean (SD)	3.9 (1)	4 (1)	4.2 (0.9)	4.4 (0.8)	3.9 (1)	4 (1)
High level of physical activity (8–10 score), n (%)	5,245 (14.8)	3,031 (15.2)	780 (13.6)	70 (11.9)	3,373 (16.1)	5753 (14.1)
Age at menarche, mean (SD)	13.2 (1.1)	13.2 (1)	13.2 (1.1)	13.2 (1.2)	13.2 (1.2)	13.2 (1.0)
Ever use of OC, n (%)	22,628 (63.7)	11,900 (59.8)	3,226 (56.2)	276 (47)	11,380 (54.3)	26,650 (65.3)
Not bearing child, n (%)	2,623 (7.4)	1,692 (8.5)	676 (11.8)	103 (17.8)	1,849 (8.8)	3245 (7.9)
Breastfeeding duration in months, median (IQR)	11 (5–19)	11 (5–18)	10 (4–18)	10 (4–18)	11 (5–19)	10 (5–18)
Ever use of MHT, n (%)	11,300 (31.8)	7,019 (35.3)	2,178 (38)	260 (44.3)	7,833 (37.4)	12,924 (31.7)
Fruits and vegetables intake in g/day, mean (SD)	341.0 (197.4)	355.4 (195.8)	341.9 (197.1)	322.4 (209.9)	378.4 (206.7)	328.7 (189.7)
Red and processed meat intake in g/day, mean (SD)	49.3 (26.7)	50.1 (26.4)	52.7 (28.9)	53.2 (33.5)	46.4 (25.9)	51.7 (27.2)
Fiber intake in g/day, mean (SD)	21.6 (6.7)	21.3 (6.6)	20.4 (6.6)	18.5 (6.9)	21.6 (6.7)	21.3 (6.6)
Calcium intake in mg/day, mean (SD)	754.6 (311.8)	740.2 (296.3)	729.8 (302.5)	709.1 (330.1)	728.5 (298.7)	756.8 (309.7)

Note: These are the results after excluding the missing data for BMI, education, physical activty, smoking.

Abbreviations: IQR, interquartile range; BMI, body mass index; OC, oral contraceptive; MHT, menopausal hormone therapy.

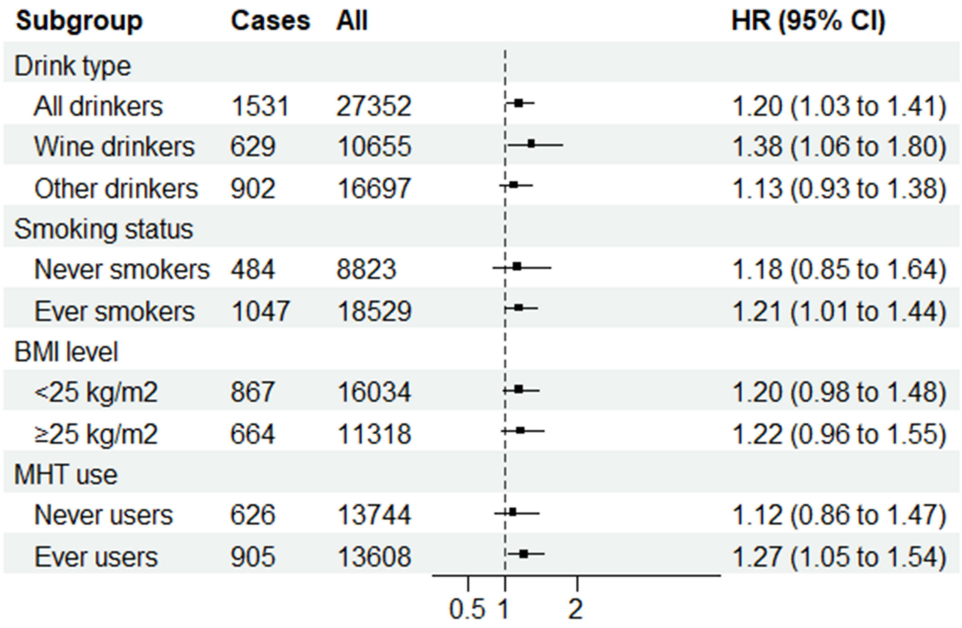

Figure 1 Hazard ratios (95% CIs) of postmenopausal breast cancer for each additional 12 g/day of alcohol consumption.
Notes: The Cox models with age as timescale were stratified by year of birth (1927–1934, 1935–1944, 1945–1954, 1955–1957) and adjusted for years of education (≤9, 10–12, 13–16, ≥17), smoking (never, pack-years in the following categories: 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years), physical activity level (1–4, 5–7, 8–10 scores), BMI in kg/m2 (<25, 25–29.9, ≥30), calorie intake from non-alcoholic sources in kj/day (tertiles), parity (not bearing child, bearing child and age at first birth ≤30 years, bearing child and age at first birth >30 years), menopausal hormone therapy use (never, former, and current), age at menarche (continuous), breastfeeding duration (0 months, <12 months, >12 months), history of breast cancer in mothers and sisters (yes, no, I do not know), fruit and vegetable intake in g/day (tertiles), and calcium intake in mg/day (tertiles). The subgroup analyses in ever smokers, ever users of menopausal hormone therapy and women with BMI ≥25 kg/m2 were adjusted for their remaining initial categories. For example, the analysis in ever users of menopausal hormone therapy was adjusted for former and current users' categories.

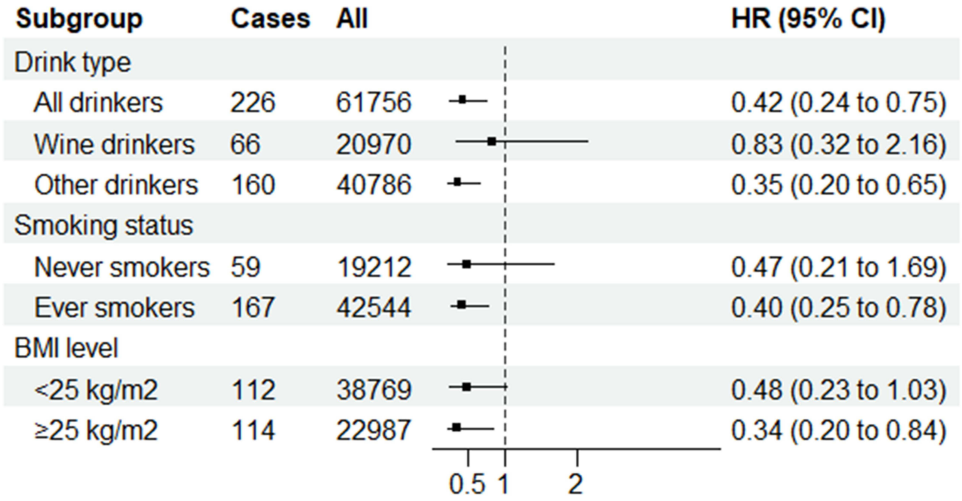

Figure 2 Hazard ratios (95% CIs) of kidney cancer for each additional 12 g/day of alcohol consumption.
Notes: The Cox models with age as timescale were stratified by year of birth (1927–1934, 1935–1944, 1945–1954, 1955–1957) and adjusted for years of education (≤9, 10–12, 13–16, ≥17), smoking (never, pack-years in the following categories: 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years), physical activity level (1–4, 5–7, 8–10 scores), BMI in kg/m2 (<25, 25–29.9, ≥30), and calorie intake from non-alcoholic sources in kj/day (tertiles). The subgroup analyses in ever smokers and women with BMI ≥25 kg/m2 were adjusted for their remaining initial categories. For example, the analysis in ever smokers was adjusted pack-years in categories 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years.

cancer (HR = 1.15, 95% CI = 0.81 to 1.64, Figure 4). Estimates with low precision were also observed across subgroup analyses for these cancer types (Supplemental file 8) and when investigating separate colon and rectum cancer (data not shown). One exception was the analysis for pancreatic cancer among other drinkers, yielding estimates close to the null

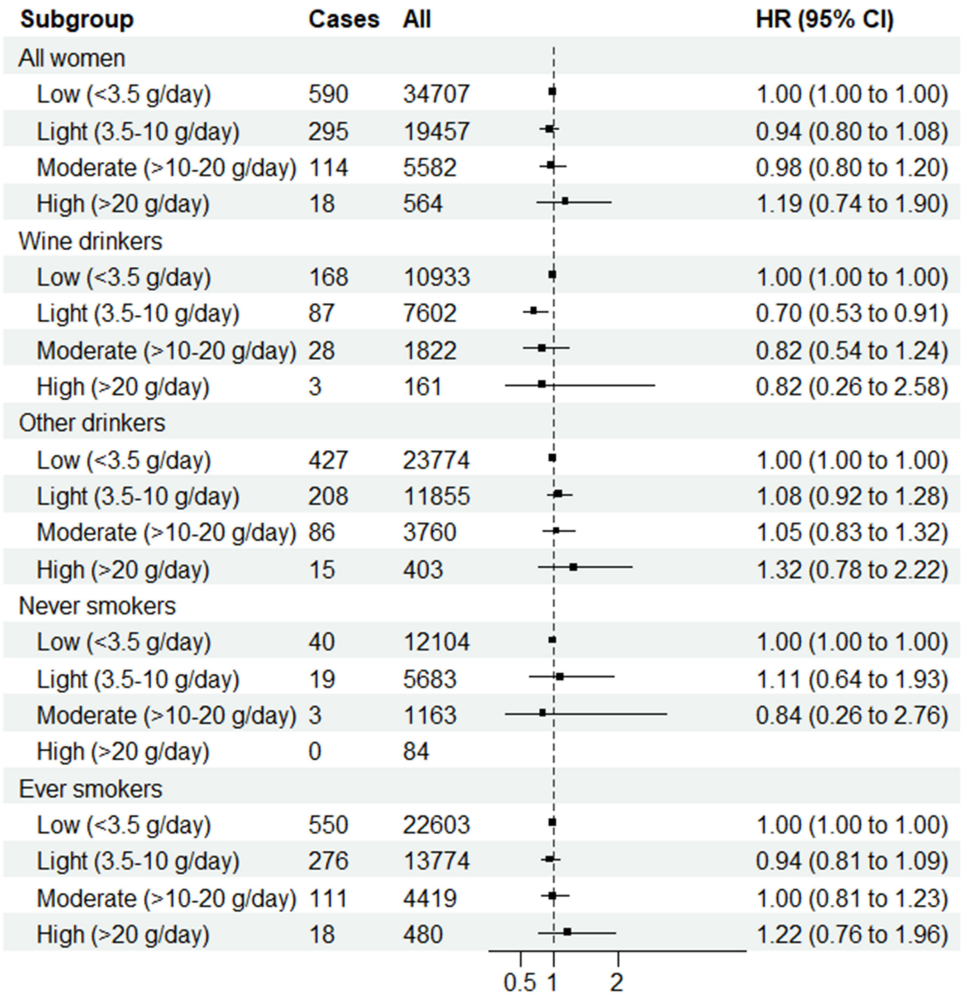

Figure 3 Hazard ratios (95% CIs) of lung cancer according to the categories of alcohol consumption.
Notes: The Cox models with age as timescale were stratified by year of birth (1927–1934, 1935–1944, 1945–1954, 1955–1957) and adjusted for years of education (≤9, 10–12, 13–16, ≥17), smoking (never, pack-years in the following categories: 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years), physical activity level (1–4, 5–7, 8–10 scores), calorie intake from non-alcoholic sources in kj/day (tertiles), fruit and vegetables intake in g/day (tertiles), and red and processed meat intake in g/day (tertiles). The subgroup analysis in ever smokers was adjusted pack-years in categories 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years.

(HR = 1.00, 95% CI = 0.90 to 1.10). No confirmative association patterns for these cancer sites were observed in the categorical analyses either (Supplemental file 7).

In the sensitivity analysis, the estimates remained materially similar when excluding women drinking >20 g/day of alcohol, excluding the first two years of follow-up, adjusting for body weight and height instead of BMI, additionally adjusting for region, accounting for competing risk by deaths, and additionally adjusting for menopause status and MHT use the analysis for colorectal cancer. Results were also similar in the imputed data (Supplemental file 9).

Post Hoc Analysis

The aim of our study was to investigate the impact of alcohol on the risk of cancer-specific sites, the most common. To have an overview of its impact on cancer, we posteriori estimated the HR with 95% CIs on the overall cancer incidence. This Cox model was stratified by year of birth and adjusted for all the covariates included in the cancer-specific analyses. In the complete case analysis (N = 60 4718, cases = 10,693) there was no evidence for an association between alcohol consumption and overall cancer risk, either in the continuous or categorical analysis. The estimates for each additional 12/day alcohol consumption were HR = 1.05, 95% CI = 0.98 to 1.19. Compared to low alcohol consumption, the

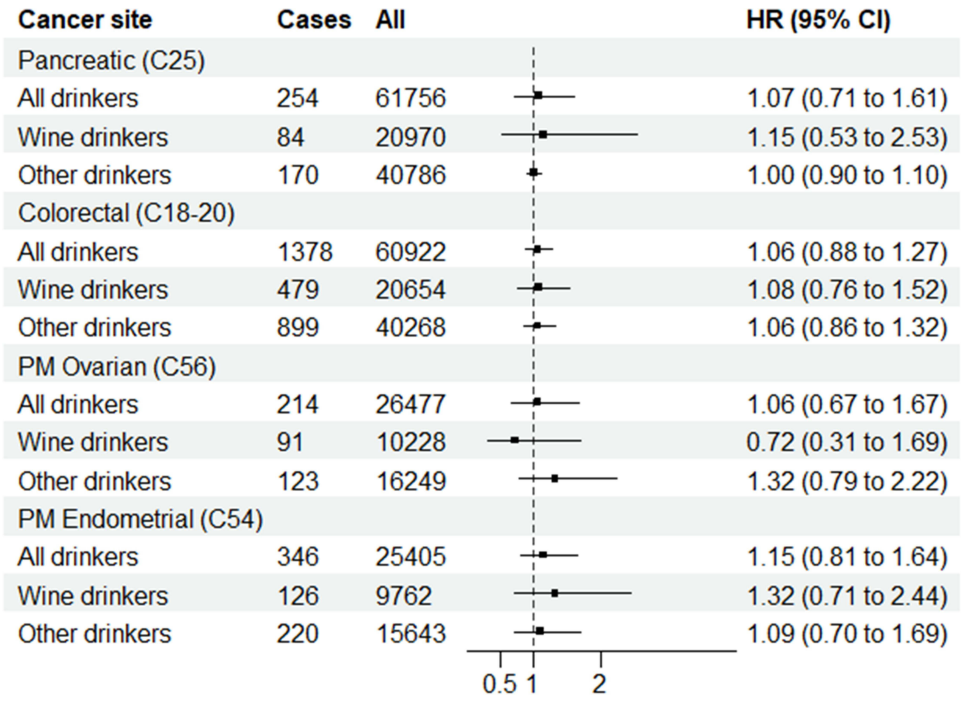

Figure 4 Hazard ratios (95% CIs) of pancreatic, colorectal, postmenopausal ovarian, and postmenopausal endometrial cancer for each additional 12 g/day of alcohol consumption.

Notes: The Cox models with age as timescale were all stratified by year of birth (1927–1934, 1935–1944, 1945–1954, 1955–1957) and adjusted for years of education (≤9, 10–12, 13–16, ≥17), smoking (never, pack-years in the following categories: 1–4, 5–9, 10–19, ≥20, and ever smokers with no information on pack-years), physical activity level (1–4, 5–7, 8–10 scores), BMI in kg/m2 (<25, 25–29.9, ≥30), and calorie intake from non-alcoholic sources in kj/day (tertiles). The Cox model for colorectal cancer was additionally adjusted for red and processed meat in g/day (tertiles), fiber intake in g/day (tertiles), and calcium intake in mg/day (tertiles). The Cox model for postmenopausal ovarian cancer was further adjusted for parity (not bearing child, bearing child), menopausal hormone therapy use (never, former, current), age at menarche (continuous), breastfeeding duration (0 months, <12 months, >12 months), and oral contraceptive use (never, ever). The Cox model for postmenopausal endometrial cancer was additionally adjusted for parity (not bearing child, bearing child), menopausal hormone therapy use (never, former, current), and oral contraceptive use (never, ever).

estimates for light, moderate and high were HR = 1.02, 95% CI = 0.98 to 1.07, HR = 1.04, 95% CI = 0.97 to 1.11, HR = 1.06, 95% CI = 0.86 to 1.28, respectively.

We performed restricted cubic spline analysis for breast cancer outcomes in subgroups of ever and never users of MHT (Supplemental file 10). The visual inspection of the cubic spline plots indicates higher risk in ever users of MHT, and the relationship appears to follow a linear pattern.

To assess how the covariates would change the estimates, we removed the covariates one by one from the main Cox models. We did this only for breast, kidney and lung cancer, for which an association was found (Supplemental file 11). We observed that most changes in the estimates for breast cancer occurred when removing BMI, smoking, MHT use and education. Most changes in the estimates for kidney cancer occurred when removing physical activity, BMI, smoking, and education. Most changes in the estimates for lung cancer occurred when removing smoking and education.

Discussion

Main Findings

In this study of middle-aged to older Norwegian women who mainly consumed alcohol at low (<3.5 g/day), light (3.5–10 g/day) and moderate levels (>10-20 g/day), followed-up for an average of 19 years, we estimated the risk of common cancer sites in the overall female population and in subgroups defined by the type of alcohol consumed, smoking status, BMI, and the use of MHT. In the analysis of each additional 12g/day of alcohol consumption, we found a higher risk for postmenopausal breast cancer and a lower risk of kidney cancer. For postmenopausal breast cancer, the higher risk was primarily observed among ever users of MHT and women who consumed primarily wine, named as wine drinkers. An inverse association for lung cancer risk was confined only among wine drinkers when comparing light alcohol

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consumption with low. No specific association patterns were observed for pancreatic, colorectal, postmenopausal ovarian and postmenopausal endometrial cancer.

Comparison with Other Studies and Possible Explanations

The evidence from observational studies linking alcohol consumption with a higher risk of breast cancer is abundant[5,8,11,12,14,26] although limited to Norwegian population.[61] Despite this overwhelming evidence, a causal relationship has not been supported by Mendelian randomization studies,[62,63] which offers a better way to test causality. We found an overall 11% higher hazard of developing breast cancer for light drinking and 24% higher for moderate consumption. Two meta-analyses of cohort and case-control studies, found for light drinking 4% and 9% higher risk, and for moderate drinking 13% and 23%.[2,5] Several cohort studies revealed an association with breast cancer regardless of the type of alcoholic drink consumed.[11,12,14] However, within the overall positive association between alcohol consumption (exposure contrast: per 10g/day) and breast cancer risk, an umbrella review of the evidence pointed out two particularly stronger associations: alcohol consumption and breast cancer risk among current users of MHT; and wine consumption and the risk of postmenopausal breast cancer.[64] This evidence was reflected in our results. Wine and other drinkers in our study differed in some characteristics. For example, among postmenopausal women, proportion of MHT ever users was 51% in wine drinkers and 46.4% in other drinkers. This imbalance might have contributed to the different results between wine and other drinkers, given that the use of MHT is suggested to be a strong determinant of postmenopausal breast cancer among NOWAC women.[65] Alcohol may increase breast cancer risk by elevating steroid hormone levels. A randomized trial of 51 postmenopausal women found that hormone levels increased after the consumption of 15 g/day or 30 g/day alcohol for 8 weeks.[28] Two meta-analyses of observational studies from 1998[28] and 2002[29] which found an overall 9% and 7.1% of higher risk for breast cancer with the exposure contrast per 10g/day alcohol consumption, reported close estimates across strata of never, past or current users of MHT. Later, cohort studies in postmenopausal women, including our own, confirmed this association only in ever or current users of MHT, with regard to the exposure contrast per 10g/day alcohol consumption,[26] when comparing light drinkers (3.4–9.9 g/day) to non-drinkers,[27] or when comparing low-moderate drinkers (<20 g/day) to non-drinkers.[30] Contrary, the late analysis from prospective UK Million Women Study with the exposure contrast per 1 drink/day, which overall found a higher risk of 12% for postmenopausal breast cancer, reported close estimates among users and never users of MHT.[8] A noteworthy data is also the higher average alcohol consumption among MHT users (4.6 g/day) in our study, compared to never users (3.7 g/day). The evidence from cohort studies also suggests that alcohol consumption amplifies the impact of MHT use on breast cancer.[30,66] A randomized trial of 12 postmenopausal women found a 3-fold increase of the steroid hormone levels by moderate alcohol consumption in women using MHT, and found no changes in women not using MHT.[67] Like other cohort studies,[8,12] our estimates were materially similar across BMI levels or smoke status.

The results for kidney cancer align with various cohort studies and meta-analyses.[5,8,11,16,18,19] Looking at the restricted cubic splines from our analysis (Supplemental file 4) and from other studies,[5,16,18] the lower risk relies on the levels of alcohol consumption >5-15 g/day. Some studies reported a greater association with wine consumption compared to other alcoholic drinks, particularly among women.[16,18,19] We did not find the same pattern, likely due to the small number of cases (n = 66) among wine drinkers. Our results in never smokers were also uncertain. However, other studies with more balanced distribution of cases and non-cases among never, former and current smokers found nearly similar estimates across all these subgroups,[8,16] Other cohort studies confined the lower risk in adults with overweight and reported no clear association in adults with normal weight, probably due to their small number of cases in this subgroup.[16,19] In our study, the magnitude of the association was greater in women with BMI ≥25 kg/m2 compared to women with BMI <25 kg/m2, suggesting some degree of effect modification by overweight/obesity. The lower risk of type 2 diabetes associated with moderate alcohol consumption, especially in women with BMI ≥25 kg/m2,[68] may explain these findings. Enhanced insulin sensitivity and the lower risk of diabetes are postulated as the mechanism related to the inverse association with kidney cancer.[68]

Brenner, Fehringer and colleagues[10,20] have previously highlighted two key issues—both of which we also support—before considering a causal interpretation of the inverse association between light-moderate alcohol consumption and the risk of lung cancer. These issues are the bias arising from the choice of non-drinkers as reference category, and the

healthier lifestyle correlated with light-moderate drinking. The pooled analyses of case-control and cohort studies from the International Lung Cancer Consortium and the SYNERGY study, with non-drinkers as reference category found 20% lower risk for light and moderate levels of alcohol consumption, in ever and never smokers.[10,20] A meta-analysis of 10 cohort studies, with non/occasional drinkers as reference category, found 9% lower risk of lung cancer by alcohol consumption at light levels, but null results at moderate levels.[5] An analysis from the prospective UK Million Women Study in 2009, with reference category women who consumed ≤2 drinks/week, found 9% lower risk only for the light level of drinking.[11] In our study, among wine drinkers the hazard for light drinking level was 30% lower. The previous pooled analyses[10,20] also found an inverse association for wine and liqueur consumption, but not for beer. Wine drinkers in our study were less likely to smoke and tended to have other healthier lifestyle habits and higher education level, which probably confounded the inverse association with lung cancer, despite the adjustment for these factors in the analysis. In a previous NOWAC study, an inverse association between a healthy lifestyle index and cancer incidence was observed mainly for lung cancer.[69] When alcohol component was excluded from the lifestyle index, the estimates were not attenuated, indicating that alcohol consumption did not contribute to this association.[69] The presence of flavonoids in wine, compounds characterized by antioxidant properties, has been postulated as a biological interpretation of this association.[10] However, this hypothesis remains questionable due to the low bioavailability of flavonoids and their high concentration needed to trigger biological effects.[70,71] There is no convincing evidence that the high intake of flavonoids provided by wine consumption reduces the risk of lung cancer.[72] Moreover, this hypothesis cannot explain the inverse association found with low-moderate liqueur consumption.[10,20]

The recent analysis (exposure contrast: per 1 drink/day) from the UK Million Women Study which excluded non-drinkers confined slightly higher risk for pancreatic (8% higher) and colorectal cancer (10% higher).[8] These differences from our findings might be due to their larger sample, higher average alcohol consumption (approximately 9.6 g/day), or their lack of control for dietary variables in the analysis. Most cohort studies and up-dated meta-analyses reported lack of association for pancreatic, colorectal, ovarian and endometrial cancer in women by light to moderate alcohol consumption.[5,15,24,73–75] Based on our results, we do not have evidence to oppose these findings.

Strengths and Limitations

The strengths of this study include the prospective design which largely mitigates differential recall for the exposure and covariates, large sample size, updated assessment of alcohol consumption, long follow-up, and the use of a high-quality national cancer registry to identify cases of cancer.[38] We adjusted for numerous potential confounders and many of them have demonstrated reliability in self-reported measures, for example, BMI, physical activity, smoking, or MHT use (Supplemental file 2). Overall, the relative validity of NOWAC FFQ is within the range observed in other European cohorts and considered adequate in ranking individuals according to dietary components.[40] This study has limitations. First, the results for pancreatic, colorectal, ovarian, endometrial cancer, and the results from some subgroups analyses had low precision and enabled us to infer firm conclusion about the presence or the lack of any association. The low precision was probably due to the small number of cases and the narrow variation in alcohol consumption. In the entire sample, only 6.1% consumed more than 12g/day (or 1 drink/day) and among postmenopausal women, only 5.8%. Second, without a gold standard for alcohol consumption assessment, the measurement error from self-reported data is likely present in this study, although probably non-differential between cases and non-cases. The use of repeated measures of alcohol in this study likely minimized the random measurement errors. The correction slightly attenuated the estimates away from the null, for example, by 4% for postmenopausal breast cancer and 7% for kidney cancer (Supplemental file 12). Although liqueur consumption was excluded from the total alcohol count as it was surveyed in only 30% of this study sample, this is unlikely to be an issue given the very low consumption in NOWAC (99% of drinkers consumed ≤1.13 g/day). Third, residual confounding is likely present due to unmeasured confounders. One common unmeasured covariate for the outcomes, except for breast cancer, is the lack of data on the family history of the respective cancer sites (supplemental file 4). We also lacked information on lifetime exposure to alcohol. Drinking history may influence both current drinking and lifetime cancer risk through cumulative exposure, and unmeasured confounding by prior alcohol consumption cannot be excluded. Another source of possible residual confounding might be due to measurement errors of self-reported covariates or due to their changes over time. However, the results from

previous NOWAC studies indicate that the individual changes in physical activity, BMI, diet, and smoking do not seem to have an impact on the breast, colorectal or overall cancer incidence, independent of their baseline values.[76] Measurement errors from dietary covariates might not be of significance as these covariates did not change the estimates when we removed them from the Cox models (Supplemental file 11). Caution should be taken when generalizing our finding to the wider female population. Although NOWAC was considered to have no major selection bias, women in NOWAC possessed slightly higher education than the source population.[77] They were similar with regard to lifestyle factors, and the incidence rates for all cancer sites in the NOWAC cohort were almost identical to those from the Norwegian Cancer Registry at the time of validation.[77]

Conclusion and Implication

Our results indicate that women drinking light-moderate alcohol level have a higher risk for postmenopausal breast cancer and a lower risk for kidney cancer incidence. The higher risk for breast cancer may be largely specific to postmenopausal women who used MHT. The findings from this study support the discussion that the inverse association for lung cancer risk by light-moderate drinking could be explained by the healthier lifestyle correlated with this pattern of drinking, rather than being a true causal relationship.

Although the identified possible effects of breast cancer in this study were small, the burden of breast cancer in women attributed to light-moderate alcohol consumption is a public health issue to be considered.[42] Our findings do not support the consumption of 1 drink/day (or 10–12 g/day) as a safe threshold for breast cancer occurrence. Therefore, we support the current reevaluation of the national guidelines changing the recommendation for Norwegian women who consume alcohol from "*do not exceed 10 g/day of alcohol intake*" to a safer message "drink as little as possible".[78] Individual decisions of women on the exact level of alcohol consumption should also account for MHT use, beyond other factors. The findings regarding the higher risk of breast cancer among women who consumed primarily wine may be a useful health message to contrast the specific low public awareness of wine-related cancer risks.[47,48] We recommend that public health efforts targeting alcohol reduction should clearly communicate that all types of alcoholic beverages, including wine, pose a risk of cancer development.

For future research, we propose two primary directions: to investigate the impact of light to moderate alcohol consumption—or within the range of 1 or 2 drinks/day—on breast cancer risk in women who have never used MHT; and to evaluate and quantify the interaction effects, especially on additive scale, of alcohol consumption and MHT use in breast cancer risk.

Ethics and Consent

All women in NOWAC gave informed consent and this present study was approved by the Regional Committee for Medical Research Ethics Northern Norway (no. 488563). The guidelines according to the Declaration of Helsinki were followed.

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All authors declare no known conflict of interest that could have influenced this work. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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