

Use of Oral Contraceptives, Alcohol, and Risk for Invasive Breast Cancer

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Abstract

The aim of our study was to examine how the use of oral contraceptives (OCs) interact with alcohol on breast cancer risk within the large prospective follow-up study, Norwegian Women and Cancer Study. Between 1991 and 1997, women aged 30 to 70 years were drawn at random from the central person register and mailed an invitation. Follow-up information was collected throughout 2001 by linkage to national registries. Only women ($n = 86,948$) with complete information on alcohol consumption and duration of OC use were included in the present analysis. A total of 1,130 invasive breast cancers were diagnosed during 618,638 person-years of follow-up. Consumption of ≥ 10.0 g/d alcohol was associated with a breast cancer relative risk (95% confidence interval) of 1.69 (1.32-2.15), consistent with a linear relationship (P for trend < 0.0001). Among alcohol consumers, an excess risk of breast cancer was observed

for total duration of OC use only among women who consumed < 5 g/d alcohol (P for trend = 0.0009). We observed a negative interaction between duration of OC use and alcohol consumption effects (P for interaction = 0.01). After stratification on menopausal status, the association between high alcohol intake and breast cancer was more prominent among postmenopausal women than among premenopausal women (P for heterogeneity = 0.01). No interaction between alcohol and duration of OC use were significant after stratification on menopausal status. Our findings in conjunction with biological data imply that alcohol and OCs have antagonistic effects on breast cancer risk through a common pathway. Whether the interactive effect differs according to menopausal status remains unclear and needs further investigations. (Cancer Epidemiol Biomarkers Prev 2004;13(8):1302-7)

Introduction

A direct association between moderate alcohol consumption and breast cancer incidence has been observed in most epidemiologic studies, although the association is less clear among premenopausal women than among postmenopausal women (1). The underlying mechanisms through which this occurs are not firmly established (2) but may include an influence on circulating levels of estrogens (3), immune function, enhanced permeability of chemical carcinogens, decreased absorption of essential nutrients (4), or through metabolism of alcohol to acetaldehyde, a known carcinogen (5).

Lifetime cumulative exposure to estrogens is known as the most important risk factor for breast cancer (6). In our previous study, breast cancer increased with increasing duration of use mostly due to estrogen component (7). For premenopausal women, alcohol intake has been associated with higher concentrations of estradiol, estrone, androstenedione, or testosterone as well as decreases in follicle stimulating hormone and 6-sulfatoxy-melatonin (2). In some cases, higher blood hormone

levels observed for alcohol consuming women were only observed in those using oral contraceptives (OCs; refs. 8, 9). Furthermore, blood levels of the reactive ethanol metabolite acetaldehyde are significantly elevated during the high estradiol phase of the menstrual cycle of women who consume alcohol (10). A case-control study has evaluated the modification of OC effect on breast cancer risk by different factors, notably alcohol, among young women (< 35 and < 45 years; ref. 11). Although statistical power was limited, authors conclude that an interactive effect of OCs with higher levels of alcohol consumption remains in interest. In postmenopausal women taking hormonal replacement therapy (HRT), acute ingestion of alcohol caused an average increase of 300% in estradiol levels compared with placebo (12). Among non-HRT users, only estrone sulfate and dehydroepiandrosterone (DHEA) sulfate concentrations increased when women consumed alcohol (13). Although early prospective studies have found a significant interaction between alcohol and HRT use (14, 15), a pooled analysis (1) as well as a more recent prospective study (16) agreed with previous case-control studies (17-21) to conclude that alcohol increased breast cancer risk independently of HRT use. Only one study, to our knowledge, found that alcohol increased breast cancer risk in postmenopausal women who ever used OCs but not in postmenopausal women who never used them (22). Finally, a recent meta-analysis found no strong evidence for interaction between alcohol and either exposure to OCs or HRT (23).

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The aim of our study was to examine how OC use or estrogen dose from OCs interact with alcohol on breast cancer risk within the large prospective follow-up study, Norwegian Women and Cancer Study (NOWAC).

Subjects and Methods

Norwegian Women and Cancer Study. Between January 1991 and January 1997, 179,388 women from the general population of Norway, aged 30 to 70 years, were invited to participate in the prospective population-based cohort NOWAC (24; see also <http://www.ism.uit.no/kk/e/>).

Women were sampled according to birth year from the national population register at Statistics Norway, which includes all residents who stay in Norway for >6 months. The tax authorities continuously update this registry. Each resident has a unique "birth number" (birth date plus person number including information about sex and an internal algorithm). In addition, the name, address, and citizenship are registered (25). The division for Sample Surveys at Statistics Norway did the sampling procedure. Before mailing, an identification number was attributed for each woman instead of the "birth number."

Due to constraints in practical workload, methodologic substudies (26), and financial support, the enrolment was separated into 24 different series of mailing over 7 years. Information was collected by postal questionnaires with one to two reminders. In the letter of information, a photo booklet in color of the 36 different OC brands ever sold in Norway from 1967 to 1991 was included; for each brand, the period of marketing was indicated to facilitate recall of brand names.

Follow-up information is collected by linkage to the national cancer registry, which is estimated to be almost complete (27), and to death certificates based on the unique national identification number.

The National Data Inspection Boards and Regional Ethical Committee for Medical Research approved the study design, and all women gave informed consent for the record linkages.

Questionnaires. The questionnaire that was applied in 1991 to 1992 contained 28 dietary questions including four questions on alcohol consumption. First, the participants were asked to indicate if they are teetotaler or not. Alcohol intake was recorded as the average frequency of intake of three types of alcoholic beverages (beer, wine, and spirits) over the preceding year. For each type of beverage, the predefined responses were in nine categories ranging from "almost never" to "6 to 10 glasses per day." From 1996, modifications have been done on the questionnaire, and the nine different answer categories were reduced to seven categories ranging from "almost never" to "≥1 glasses per day" because almost none of women were consuming >1 glass per day of each beverage. Alcohol consumption (in g/d of pure alcohol) was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage. The alcohol content was calculated as follows: one glass of wine (8.1 g ethanol per 100 g wine multiplied by 150 g), 12.15 g of ethanol; one glass of beer (3.5 g ethanol per 100 g

beer multiplied by 500 g), 17.5 g of ethanol; and one glass of spirit (33.6 and 52.1 g ethanol per 100 g spirits in a proportion of 95% and 5%, respectively, multiplied by 20 g), 6.9 g of ethanol. Women were categorized into four groups according to average daily alcohol intake: no alcohol, low intake [<2 drinks per week (0.1 to 4.9 g/d)], medium intake [2 to 3.9 drinks per week (5.0 to 9.9 g/d)], and high intake [≥ 4 drinks per week (≥ 10 g/d)].

In addition to the dietary questions, a wide range of nondietary questions were included in the NOWAC questionnaires. Concerning OC exposure, the questionnaires contained several general questions like age at first use, total duration of use, and current use. In addition, information about each specific period with one hormonal contraceptive brand was collected. Such a period was defined as any continuous use of one specified hormonal contraceptive brand. Eight different periods of use could be reported. Since the commercialization of the first combined OCs in 1965, two types of estrogens have been marketed in Norway: ethinyl estradiol and mestranol, which is converted at 70% in ethinyl estradiol. Therefore, we grouped mestranol and ethinyl estradiol together. We defined the term "estrogen dose from OCs" as the dose of estrogen (ethinyl estradiol or its equivalent in mestranol) of an OC brand used multiplied by the number of months it was used taken over all periods of use. To calculate estrogen dose from OCs and the total duration of OC use, only women with known brands for all user periods were included (76.6% of the OC users).

Samples for Analysis. Among the 179,388 women invited to participate, 102,443 were included in the NOWAC (crude response rate 57.1%; ref. 24). We excluded 10 women from follow-up: 7 had asked to be withdrawn from the study and 3 did not fill in the questionnaire. Women recruited in 1997 ($n = 5,933$) were also excluded because the questionnaire did not ask for alcohol intake. Among the 96,500 women, 2,785 women with prevalent cancer were removed from our analysis and 2,609 women had missing values for OC use status. In addition, we excluded ever users of OCs for whom duration of use was not informed ($n = 4,158$). Finally, it left us 86,948 women for our analysis. A total of 1,130 cases of breast cancer were diagnosed during 618,638 person-years of follow-up between 1991 and 2001.

Statistical Analysis. A Cox proportional hazard model was used to investigate the simultaneous effect of OC use, alcohol, and other risk factors on breast cancer incidence rate. In multivariate analyses, we adjusted for the following possible confounders: age, invitation to breast screening program defined according to age and county of residence, age at menarche, age at first birth and parity, family history of breast cancer in mother, menopausal status, use of HRT, and body mass index (BMI). We used a time-dependent variable for menopausal status giving all women who reached 50 years during follow-up postmenopausal status. Invitation to a screening program was also a time-dependent variable according to starting year of the screening program in specific geographic area and according to women's age (women aged >50 years are invited to do mammography). The number of subjects included in the separate analysis will vary somewhat due to item nonresponse. Tests for trend were calculated by introduction of ordinal

variables obtained by assigning consecutive integers to values of the categorized variable. In addition, relative risks (RRs) were compared by testing formally their heterogeneity.

A statistical interaction was evaluated by using a likelihood ratio test with a cross-product interaction term representing the two studied covariates. In statistical terms, an interaction between two factors is present when the effect of one factor on disease risk depends on the level of exposure to the other one. This definition depends on how effects on risk are measured (28). In our study, the measure of effect is the ratio of disease incidence between exposed and unexposed individuals. Therefore, statistical interaction is defined as a lack of fit to this multiplicative model (28). If the measure of effect were defined as a rate difference, interaction would be defined as a lack of fit to an additive model for the joint effects of the two risk factors.

Statistical analyses were done with the SAS software package, version 8.02.

Results

At baseline, few women reported drinking more than moderately in the previous year: for example, only 5.7% of the whole cohort drank ≥ 10 g/d (Table 1). Women in this latter category of drinking are younger and more likely to have ever used OCs and HRT (Table 1). Overall, nondrinkers had their first birth earlier and had more children. They also had higher BMI and less often family history of breast cancer among their first relatives (Table 1).

Table 2 shows the main effect of alcohol, OC ever use, and estrogen dose from OCs on risk of breast cancer. Risk of breast cancer increased with increasing values of all these three factors. Even a low consumption of alcohol significantly increased breast cancer risk compared with nonconsumers [RR 1.24, 95% confidence interval (95% CI) 1.06-1.44]. Consumption of ≥ 10 g/d alcohol was associated with a RR (95% CI) of 1.69 (1.32-2.15), consistent with a linear relationship (P for trend < 0.0001). Risk for breast cancer increased with both increasing total duration of OC use (P for trend = 0.01) and estrogen dose from OCs (P for trend = 0.01).

Table 2. RR for invasive breast cancer in NOWAC cohort by alcohol intake, total duration of OC use, and estrogen dose from OCs

	Cases (n)	Person-years	Multivariate RR*	P for trend
Alcohol intake (g/d) [†]				
None	244	168,312	1 (reference)	<0.0001
0.1-4.9	554	302,715	1.24 (1.06-1.44)	
5.0-9.9	188	86,213	1.35 (1.11-1.64)	
≥ 10.0	96	34,785	1.69 (1.32-2.15)	
OCs duration of use (y) [‡]				
Never	458	248,952	1 (reference)	0.01
0-4	361	198,871	1.19 (1.03-1.38)	
5-9	147	86,342	1.16 (0.95-1.41)	
≥ 10	116	57,856	1.29 (1.05-1.60)	
Estrogen dose from OCs (mg) ^{‡§}				
Never user	458	248,952	1 (reference)	0.01
0.1-49.9	188	107,700	1.26 (1.05-1.52)	
50.0-99.9	91	53,093	1.21 (0.96-1.54)	
≥ 100.0	80	38,675	1.28 (1.00-1.64)	

*Adjusted for effects of age, invitation to do breast screening, age at menarche, age at first birth and parity, family history of breast cancer in mother, menopausal status, HRT use, and BMI.

[†]Adjusted for duration of OC use.

[‡]Adjusted for alcohol intake.

[§]Progestagen-only users excluded.

To investigate the effect of combined alcohol and OC use, women were classified into 1 of 12 categories according to alcohol and OC use (Table 3). Compared with nondrinkers who never used OCs, long-time OC users (≥ 10 years) who consumed ≥ 10.0 g/d alcohol had an adjusted RR (95% CI) for breast cancer of 1.97 (1.13-3.43). The increased risk was approximately the same for women who were exposed to either of these factors alone (Table 3). Ever use and duration of OC use did not modify the relation between moderate and high alcohol intake and breast cancer risk, because the strength of the association with moderate and high alcohol consumption was consistent in never, short-term, and long-term users of OCs (P for heterogeneity = 0.35 and 0.96 for moderate and high alcohol consumption, respectively). Even low average alcohol intake significantly increased breast cancer risk, except for nonusers of OCs (P for

Table 1. Means and percentages of selected characteristics according to alcohol intake in women at baseline used for multivariate adjustment, NOWAC study

	Alcohol intake (g/d)				P
	None (n = 23,637)	0.1-4.9 (n = 42,689)	5.0-9.9 (n = 11,985)	≥ 10.0 (n = 4,773)	
Age at inclusion (y), mean (SD)	46.1 (9.4)	45.2 (8.6)	44.8 (7.7)	44.3 (7.4)	<0.0001
Age at menarche (y), mean (SD)	13.3 (1.4)	13.3 (1.4)	13.3 (1.3)	13.3 (1.4)	0.86
Age at first birth* (y), mean (SD)	23.8 (4.3)	23.6 (4.1)	24.3 (4.3)	24.2 (4.4)	<0.0001
Parity, mean (SD) [*]	2.7 (1.2)	2.4 (0.9)	2.2 (0.8)	2.2 (0.8)	<0.0001
BMI (kg/m ²), mean (SD)	24.2 (4.2)	23.6 (3.6)	23.0 (3.2)	22.8 (3.1)	<0.0001
No. of alcoholic beverage glasses per day, mean (SD)	0.0 (0.0)	0.1 (0.1)	0.6 (0.1)	1.3 (1.1)	<0.0001
OC ever use, %	40.8	57.4	65.5	71.2	<0.0001
Family history of breast cancer, %	4.4	4.4	4.9	6.0	<0.0001
Postmenopausal women, %	31.7	28.3	25.0	21.4	<0.0001
HRT ever use, [†] %	26.6	35.1	44.2	49.1	<0.0001

*Among parous women only.

[†]Among postmenopausal women only.

Table 3. RR for invasive breast cancer in NOWAC cohort by duration of OC use and alcohol use

Alcohol intake (g/d)	OC duration of use (y)	Cases (n)	Person-years	Multivariate RR*	P for trend
None	Never	139	93,518	1 (reference)	0.02
	0-9	82	64,271	1.15 (0.87-1.51)	
	≥10	23	10,523	1.99 (1.27-3.10)	
0.1-4.9	Never	214	118,665	1.19 (0.96-1.47)	0.0009
	0-9	278	153,204	1.56 (1.27-1.93)	
	≥10	62	30,846	1.73 (1.28-2.35)	
5.0-9.9	Never	76	27,428	1.72 (1.30-2.28)	0.18
	0-9	95	47,712	1.54 (1.18-2.01)	
	≥10	17	11,075	1.17 (0.71-1.95)	
≥10.0	Never	29	9,341	1.89 (1.26-2.82)	0.88
	0-9	53	20,026	2.02 (1.46-2.79)	
	≥10	14	5,418	1.97 (1.13-3.43)	

*Adjusted for effects of age, invitation to do breast screening, age at menarche, age at first birth and parity, family history of breast cancer in mother, menopausal status, HRT use, and BMI.

heterogeneity = 0.004). Among these low consumers of alcohol, breast cancer risk increased significantly with increasing total duration of OC use (P for trend = 0.0009). Only long-term OC users had a significant increased risk of breast cancer among nonconsumers of alcohol consistent with a dose-response effect (P for trend = 0.02; Table 3). Finally, we found a negative interaction between duration of OC use and levels of alcohol consumption (P = 0.01). Estrogen dose from OCs and alcohol consumption showed approximately the same results with a significant negative interaction between these two factors (P for interaction = 0.01).

We evaluated whether menopausal status at diagnosis modified the alcohol and breast cancer association. The interaction was statistically significant (P = 0.001). The effects of low and moderate intake of alcohol on breast cancer risk were not statistically different in premenopausal and postmenopausal women (P for heterogeneity = 0.36 and 0.10 for low and moderate intake of alcohol, respectively). In contrast, the association between high alcohol consumption and breast cancer was significantly

stronger among postmenopausal women (RR 2.20, 95% CI 1.62-3.00) than among premenopausal women (RR 1.20, 95% CI 0.82-1.75; P for heterogeneity = 0.01).

The results of the combined effects of alcohol and OC use to breast cancer according to menopausal status are shown in Table 4. A significant increased risk of breast cancer was found with increasing duration of OC use in premenopausal women who never drank alcohol (P for trend = 0.03) or drank ≤5 g/d alcohol (P for trend = 0.01). However, there was no significant interaction between alcohol and duration of OC use in this strata (P for interaction = 0.14). In postmenopausal women, a significant increased risk of breast cancer was found with duration of OC use in women who drank a little amount of alcohol (P for trend = 0.03); no significant interaction was found (P for interaction = 0.21).

Discussion

Long-term users of OCs (≥10 years) who consumed ≥10.0 g/d alcohol had almost a 2-fold increase risk for breast cancer compared with nonconsumers of alcohol who never used OCs. This increased risk was approximately the same when nondrinkers used OCs during a long time or when nonusers of OCs drank ≥10 g/d alcohol. First, among women consuming <5.0 g/d alcohol, the risk of breast cancer increased significantly with the total duration of OC use or with the estrogen dose from OCs. In contrast, among women consuming ≥5.0 g/d alcohol, duration of OC use and estrogen dose from OCs were not adding any excess risk of breast cancer compared with women consuming the same amount of alcohol and who never used OCs. Second, a negative interaction between alcohol and duration of OC use (or estrogen dose from OCs) was observed. Finally, the association between high alcohol intake and breast cancer was more prominent among postmenopausal women than among premenopausal women. No significant interaction between alcohol and duration of OC use was observed after stratification on menopausal status.

Limitations of the current study include imprecision in diet assessment and the reliance on a single assessment

Table 4. RR for invasive breast cancer in NOWAC cohort, by duration of OC use and alcohol use according to the menopausal status

Alcohol intake (g/d)	OC duration of use (y)	Premenopausal women			Postmenopausal women		
		Cases (n)	Person-years	RR* (95% CI)	Cases (n)	Person-years	RR*† (95% CI)
None	Never	51	29,140	1 (reference)	88	64,379	1 (reference)
	0-9	58	36,091	1.28 (0.87-1.86)	24	28,180	0.84 (0.53-1.32)
	≥10	14	6,141	1.96 (1.08-3.54)	9	4,381	1.89 (0.95-3.78)
0.1-4.9	Never	71	37,160	1.10 (0.77-1.58)	143	81,505	1.24 (0.95-1.61)
	0-9	158	83,626	1.43 (1.04-1.97)	120	69,578	1.65 (1.24-2.20)
	≥10	36	17,378	1.66 (1.08-2.55)	26	13,468	1.71 (1.10-2.67)
5.0-9.9	Never	26	7,949	1.65 (1.03-2.65)	50	19,479	1.76 (1.24-2.50)
	0-9	48	23,263	1.35 (0.91-2.01)	47	24,449	1.71 (1.19-2.46)
	≥10	6	5,640	0.72 (0.31-1.69)	11	5,434	1.68 (0.89-3.17)
≥10.0	Never	4	2,629	0.73 (0.27-2.03)	25	6,711	2.54 (1.62-3.98)
	0-9	24	9,843	1.58 (0.97-2.58)	29	10,183	2.51 (1.63-3.85)
	≥10	7	2,826	1.74 (0.78-3.84)	7	2,592	2.16 (1.00-4.69)

*Adjusted for effects of age, age at menarche, age at first birth and parity, family history of breast cancer in mother, and BMI.

†Adjusted for effects of invitation to do breast screening and HRT use.

of alcohol drinking habits during follow-up. However, if substantial misclassification has occurred, the likely effect would be to make detection of associations more difficult. Indeed, the studies with the longest duration since assessment of alcohol intake showed the weakest effect of alcohol on breast cancer (29), which suggests that recent exposure is more important than past exposure. In NOWAC, a follow-up questionnaire was sent in 1998 to the subsample of 46,978 women first recruited in 1991 to 1992. Information on consumption of alcohol was consistent in both questionnaires to within ~ 1 g/mo pure alcohol for 28.4% of the women included. Otherwise, 47.2% of the women tended to increase their total consumption of pure alcohol [mean (SD) 2.5 (2.5) g/d]. The effect of average consumption of >2 alcoholic drinks daily could not be adequately evaluated within our cohort, because only a few participants ($n = 443$) consumed that much alcohol.

Strengths of the current study include the strict definition of the population through the national population registers (24), large number of cases, completeness of follow-up through state-wide registers (mortality, migration, and cancer registers), assessment of diet before diagnosis of breast cancer, extensive data on OC brands used, and ability to adjust for multiple potential confounding factors.

If we assume that neither OC use nor alcohol consumption is preventive, the observed subadditivity (negative interaction) implies that competitive responders must be present (28). It is known that OCs increase cell proliferation in the human breast (30). The increased proliferation could occur not only due to synthetic estrogen exposure but also due to down-regulation of a biological factor that normally functions to inhibit proliferation (such as estrogen receptor β ; ref. 31). In parallel, the mechanism by which alcohol causes a rapid acute or chronic increase in circulating estrogens might be due to, for example, increased aromatization of testosterone to estradiol (31). In addition, a study in human breast cancer cell lines have shown that ethanol stimulates the transcriptional activity of the liganded estrogen receptor α , although it does not cause *de novo* activation of estrogen receptor α in the absence of the ligand (32). It is possible, therefore, that alcohol exposure increasing serum estrogen levels compensates the diminution of endogenous estrogen induced by OC use. Consequently, endogenous estrogen could regulate estrogen receptor α and β , which may reduce cell proliferation in the normal breast. It should also be noted that alcohol might have many other biological effects besides affecting circulating estrogen, which could also increase breast cancer (2).

Reports are inconsistent on the alcohol-related risk of breast cancer before and after the menopause. This may be due to methodologic issues or biological interactions (33). In the present study, the effect of high alcohol consumption on breast cancer risk was stronger among postmenopausal than among premenopausal women. Otherwise, it was no different relationship between alcohol and breast cancer risk according to the menopausal status, which agrees with the pooled analysis of the cohort studies (1). In contrast, one German case-control study (34) and the American cohort Nurses' Health Study II (35) concluded that there is unlikely to be

a large effect of moderate alcohol consumption on breast cancer among young women; however, the latter study did not exclude a modest effect. A review article on alcohol intake and late-stage promotion of breast cancer deduced that the increased risk of breast cancer with alcohol is considerably greater in postmenopausal women and that alcohol acts at a late stage in mammary carcinogenesis (36). No significant interaction between alcohol and OC use was observed in our study after stratification on menopausal status. Among premenopausal women, interaction between alcohol and OCs on breast cancer risk remains unclear (11). No strong evidence was observed in the recent meta-analysis conducted by the Collaborative Group on Hormonal Factors (23), although association between alcohol and breast cancer was stronger for postmenopausal women who had ever used OCs in the Netherlands cohort study (22). Overall, it is difficult to conclude due to lack of statistical power.

In conclusion, no excess risk of breast cancer was observed for total duration of OC use (or with estrogen dose from OCs) among women who consumed ≥ 5.0 g/d alcohol, whereas breast cancer risk increased with increasing duration of OC use (or with estrogen dose from OCs) among nonconsumers or low consumers of alcohol. Thus, our results support that alcohol and OCs have antagonistic effects on breast cancer risk through a common pathway. A possible stronger effect of high alcohol on breast cancer risk among postmenopausal women as well as the possible interaction between alcohol and duration of OC use according to menopausal status remain unclear and need further investigations.

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