

Wine, spirits, and beer intake and endometriosis risk among infertile women: results from a case control study

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Summary

Background: Alcohol consumption, a common habit worldwide, may affect estrogen levels. A relation between alcohol intake and endometriosis risk has been suggested. **Materials and Methods:** Case-control study including 80 infertile women with histologically confirmed endometriosis and 90 women, admitted for a wide spectrum of acute conditions unrelated to known potential risk factors for endometriosis, were interviewed using a structured questionnaire. Potential risk factors for endometriosis were analyzed using unconditional multiple logistic regression, fitted by the method of maximum likelihood. **Results:** Women with endometriosis were more educated and leaner. They also performed physical exercise during adolescence. The estimated odds ratios (ORs), in comparison with women reporting no alcohol intake, were 1.45 (95% confidence intervals (CIs) 0.76–2.78) for alcohol in general, 1.48 (95% CI 0.76–2.87) for women who drank wine, 1.29 (95% CI 0.65–2.58) for beer, and 1.30 (95% CI 0.56–3.03) for spirits. These findings were confirmed in strata of education, BMI, and leisure physical exercise during adolescence. **Conclusions:** This analysis, although based on a limited number of subjects, may offer some information about the suggested relation between endometriosis and alcohol intake.

Key words: Endometriosis; Alcohol consumption; Estrogen; Multiple logistic regression analysis.

Introduction

Alcohol consumption is a common habit worldwide. It is probably one of the most frequently ingested pharmacologically active substances in the world. The intake of alcohol may affect estrogen levels and potentially immunological mechanisms. Thus it is conceivable that it may have a role in endometriosis risk. In fact, alcohol intake increases circulating bioavailable estrogen level and this is believed to be one of the mechanisms underlying the association between alcohol consumption and estrogen-dependent diseases [1]. Furthermore, alcohol increases aromatase, interacts with luteinizing hormone production from the pituitary gland, resulting in increased estradiol release from the ovaries [2]. Long-term alcohol intake may also affect immune function and may regulate production of pro-inflammatory cytokines [3, 4].

The present authors have recently conducted a meta-analysis regarding the association between alcohol intake and risk of endometriosis. They found a significant association between alcohol consumption and endometriosis risk [5]. However, several points are still open to debate. The potential different effect of alcohol on the risk of infertility or pain associated endometriosis has not been adequately analyzed. It has been suggested that women with pelvic pain-related endometriosis may drink alcohol to alleviate pain [6]. Along this line, some studies have shown different effects of

alcohol on cases of endometriosis with infertility or pelvic pain [7, 8]. Thus it may be of interest to analyze the association between endometriosis and alcohol intake in women who had their work up for the diagnosis of endometriosis for infertility without pain. Furthermore, it has been suggested that the effect of wine or other source of alcohol intake may affect differently the endometriosis risk [9].

From February 2012 to May 2013 the authors conducted a small case control study on risk factors for endometriosis. Most of the interviewed women had work up for infertility. In order to offer information on the role of alcohol on the risk of endometriosis among women with infertility, they analyzed the association between alcohol intake and risk of endometriosis. Furthermore, they separately analyzed the effect of alcohol intake of wine, beer, and spirits on the risk of endometriosis.

Materials and Methods

Subjects were enrolled in a case-control study of endometriosis conducted at the San Raffaele Hospital and Policlinico of Milan in the period 2012–2013. Cases of endometriosis included 90 women (median age 35, range 19–49) with histologically confirmed, incident, i.e. laparoscopically diagnosed within the year before interview, endometriosis. Controls were 90 women (median age 35.5, range 17–76) admitted for a wide spectrum of acute conditions unrelated to known potential risk factors for endometriosis.

Revised manuscript accepted for publication January 26, 2016

Table 1. — *Distribution of cases of endometriosis and controls, according to selected factors.*

	Cases	Controls
Age (mean, standard deviation)	34.0 (6.4)	37.3 (9.8)
BMI, kg/m ²		
Normal weight	69 (88.5)	66 (76.7)
Overweight	9 (11.5)	20 (23.3)
Education (years)		
3-8	4 (5.0)	22 (25.9)
9-13	34 (42.5)	39 (45.9)
≥ 14	42 (52.5)	24 (28.2)
Smoking habits		
Never	49 (62.0)	60 (68.2)
Ever	30 (38.0)	28 (31.8)
Parity		
0	80 (100)	53 (58.9)
1	-	20 (22.2)
≥ 2	-	17 (18.9)
Miscarriage		
No	70 (87.5)	81 (90.0)
Yes	10 (12.5)	9 (10.0)
Menstrual cycles		
Regular	74 (92.5)	86 (95.6)
Irregular	6 (7.5)	4 (4.4)
Duration of menstrual cycles (days)		
1-3	11 (16.2)	4 (6.1)
4-6	45 (66.2)	51 (77.3)
≥ 7	12 (17.6)	11 (16.7)
Oral contraceptive use		
No	47 (58.8)	57 (63.3)
Yes	33 (41.2)	33 (36.7)
Leisure physical activity at age 12		
No	37 (46.2)	30 (33.3)
Yes	43 (53.8)	60 (66.7)
Alcohol intake		
No	37 (46.2)	49 (54.4)
≤ 1 per day	37 (46.2)	33 (36.7)
> 1 per day	6 (7.5)	8 (8.9)
Wine intake		
No	45 (56.2)	57 (63.3)
Yes	35 (43.8)	33 (36.7)
Beer intake		
No	53 (66.2)	64 (71.1)
Yes	27 (33.8)	26 (28.9)
Spirits intake		
No	65 (81.2)	76 (84.4)
Yes	15 (18.8)	14 (15.6)

sis. Of these, 7.8% had traumatic or non-traumatic orthopaedic conditions, 6.7% acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), 47.8% gynaecological benign conditions, and 11.1% ear, nose, and throat conditions, and 26.6% miscellaneous other illnesses (such as eye and dental disorders).

This case control study aimed to investigate the main lifestyle habits, that is, smoking, coffee intake, and alcohol consumption; the sample size was calculated to detect an OR of 2.0 (alpha=0.05 and beta=0.20) as statistically significant.

Less than 4% of cases and controls approached for interview refused to participate and the response rates did not vary across cases and controls. All interviews were conducted in hospital using a structured questionnaire which assessed personal characteristics and habits, anthropometric variables, education, and other socio-economic factors, general lifestyle habits, such as smoking, alcohol, coffee consumption, medical history, and dietary habits. Alcohol intake was investigated and assessed the daily consumption of wine, beer, and spirits. One dose of each kind of alcoholic beverage (125 ml of wine, 330 ml of beer, 30 ml of spirits) was intended to contain the same quantity of alcohol (12 mg of ethanol).

Normal weight was defined according to the World Health Organization [10]: women with body mass index (BMI) between 18.5 and 25.0 had normal weight, whereas women with BMI > 25.0 were overweight. The study was approved by the Hospital Institutional Review Boards. Signed informed consent was obtained by all women who were interviewed. Out of the 90 cases with endometriosis, 80 were identified during work up for infertility (median age 34, range 19-49). These cases were considered in the present report.

Odds ratios (ORs) for endometriosis, and the corresponding 95% confidence intervals (CIs) for levels of alcohol intake were computed. Furthermore, in order to take into account potential confounding factors, ORs were also computed using unconditional multiple logistic regression, fitted by the method of maximum likelihood. The factors included in the model were age and factors found to be associated with endometriosis risk in the crude analysis. These factors are listed in the footnote of the tables. Further, the authors analysed the effect of alcohol on endometriosis risk in strata of education, BMI, and physical activity, i.e. the factors found associated in the present analysis with endometriosis risk.

Results

Table 1 shows the distribution of the 80 cases and the 90 controls according to age, BMI, education, smoking habits, and lifelong menstrual history. As expected, women with endometriosis were more educated. In this sample, they also were leaner and performed less physical exercise during adolescence.

Table 2 shows the distribution of cases and controls with corresponding multivariate ORs in relation to alcohol intake in the whole series and in strata of selected covariates.

The estimated ORs, in comparison with women reporting no alcohol intake, were 1.48 (95% CI 0.68-2.79) in women reporting not more than one service per day and 1.16 (95% CI 0.31-4.28) in women reporting > one service, respectively (chi-square for trend = 0.44, *p* = 0.51, data not shown in table).

Among women who drank wine, the median intake was one service per week (interquartile range 1-3), and a similar result emerged also for beer and spirits. The median overall weekly intake was three services (IQR 2-7).

The increased risk of endometriosis among alcohol drinkers was confirmed in strata of education, BMI, and

Table 2. — Adjusted odds ratios (AORs) and 95% confidence intervals (95% CI) of endometriosis of daily intake of wine, beer, and spirits according to selected covariates.

	Cases	Controls	AOR (95% CI) Overall intake	AOR* (95% CI) Wine intake (ref=no.)	AOR* (95% CI) Beer intake (ref=no.)	AOR* (95% CI) Spirits intake (ref=no.)
Whole sample	43 (53.8)	41 (45.6)	1.45 (0.76–2.78)	1.48 (0.76–2.87)	1.29 (0.65–2.58)	1.30 (0.56–3.03)
Age (years)						
≤ 35	24 (55.8)	19 (42.2)	1.92 (0.72–5.15)	2.22 (0.80–6.22)	2.16 (0.73–6.39)	3.18 (0.81–12.46)
≥ 36	19 (51.4)	22 (48.9)	0.94 (0.37–2.39)	0.74 (0.29–1.89)	0.66 (0.24–1.81)	0.37 (0.10–1.40)
BMI (kg/m ²)						
Normal weight	36 (52.2)	29 (43.9)	1.42 (0.70–2.88)	1.51 (0.73–3.14)	1.47 (0.68–3.19)	1.44 (0.55–3.78)
Overweight	6 (66.7)	11 (55.0)	1.70 (0.29–9.78)	0.92 (0.15–5.62)	0.64 (0.11–3.75)	1.06 (0.16–8.38)
Education						
< 14	21 (55.3)	30 (49.2)	1.37 (0.59–3.20)	1.24 (0.52–2.95)	1.41 (0.56–3.53)	0.87 (0.28–2.68)
≥ 14	22 (52.4)	9 (37.5)	2.20 (0.73–6.62)	2.55 (0.79–8.28)	1.53 (0.47–4.97)	2.38 (0.49–11.48)
Leisure physical activity at age 12						
No	22 (59.5)	13 (43.3)	1.78 (0.54–5.84)	1.50 (0.45–4.93)	1.38 (0.33–5.72)	1.33 (0.27–6.48)
Yes	10 (52.6)	17 (41.5)	1.21 (0.53–5.75)	1.30 (0.56–3.06)	1.36 (0.59–3.15)	1.29 (0.44–3.76)

*Adjusted in turn for age, BMI, education, and physical activity during adolescence.

physical activity. Considering the different types of alcoholic beverages, the authors found similar results, except in overweight women.

Discussion

The results of this study confirm an association between alcohol intake and risk of endometriosis in infertile women. The effect was similar considering separately wine, beer or spirits intake. No clear trend in risk was observed with number of drinks per day. Interestingly the effect of alcohol was confined to normal weight women.

Before discussing the results of this study, we should consider the several potential biases of the study. Alcohol intake is more common in Italy in women with high education/income [11,12]. Likewise, high BMI, which is associated with high alcohol intake, was reported to lower the risk of diagnosis of endometriosis [13]. The potential confounding effect of these covariates was allowed for in the analysis, but there was no material modification in the pattern of risk estimates. This aspect is another point of interest of this study since only a few published studies included adjustment for these covariates [5].

There are problems of reliability and validity in the evaluation of alcohol intake. However, there is no reason to assume different recall on the basis of the disease status, as the association between endometriosis risk and alcohol intake is not a matter of public knowledge in Italy. Thus any misclassification should tend to reduce the estimated association. Moreover, the questionnaire showed a satisfactory reproducibility and validity [14].

The participation of cases and controls was almost complete. Controls were not examined by laparoscopy, so the authors cannot exclude that some may have had undiagnosed endometriosis. This can be considered a limitation

of this study, but the potential misclassification should only underestimate any difference between cases and controls.

Exclusion of controls with gynaecological conditions or reporting one or more birth from the analysis did not modify the risk estimates, giving reassurance that the medical conditions or the parity of controls did not influence the results.

The results of this study are in agreement with the general finding of the authors' previous meta-analysis. The specific interest of this study is the fact that it analysed the role of alcohol among infertile women. This analysis may help to consider the effect of alcohol without any potential confound effect due to the drinking of alcohol to alleviate pain [6].

Considering infertile women, however, it should be taken into account the fact that alcohol consumption has been also associated with infertility [8, 15]. Thus, it is possible that the association between alcohol drinking and endometriosis risk may be, at least in part, explained by the role of infertility. In the present analysis, however, when the authors considered among women aged 35 years or more as control only nulligravidae (a reasonable proxy in this class of age of infertile women), the association was confirmed.

In the present analysis, no clear dose-risk relationship emerged. This is consistent with the results of the quoted meta-analysis. A similar pattern of risk has been observed also for breast cancer.

Some researchers have suggested that drinks containing higher alcohol concentrations, i.e. liquors and spirits, could be more deleterious for alcohol-related diseases than drinks with lower alcohol concentrations, though the issue is still under discussion [16]. The only study that presented separately the effect of different alcoholic beverages showed a (positive) association only with wine drinking, in particular white wine [9]. The present authors did not find any dif-

ferences in the risk considering separately wine, spirit or beer intake.

Several biological explanations have been suggested to discuss the association between alcohol intake and endometriosis risk. First of all, alcohol has been shown to increase levels of endogenous estrogens [1,2]. Furthermore, alcohol intake may influence the immune response in various ways, affecting functions and mechanisms of both innate and acquired immunity [3, 4]. Alcohol is generally believed to suppress the immune response. Recent data also suggest that acute alcohol intake decreases inflammation and immunity whereas chronic exposure leads to opposite effects, inducing proinflammatory cytokine production in various cell types, as well as increasing lymphocyte proliferation and activation [4]. Therefore, since endometriosis is characterized by a chronic inflammatory reaction, alcohol-mediated effect may interfere with this phenomenon.

The observation in the present analysis, that the effect of alcohol intake on endometriosis risk was confined to normal weight women, may support the effect of alcohol on estrogen levels. In fact it is conceivable that in overweight (characterized by higher endogenous estrogen levels also in the premenopausal period), the effect of alcohol on estrogen levels is negligible.

In conclusion, this analysis, although based on a limited number of subjects, may offer some information about the suggested relation between endometriosis and alcohol intake.

Acknowledgements

This work was conducted within the framework of the activities of PRIN (Progetti di Ricerca di Interesse Nazionale).

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