Published in final edited form as:
Cancer Epidemiol. 2012 October ; 36(5): 458–460. doi:10.1016/j.canep.2012.06.007.

Higher alcohol intake may modify the association between mammographic density and breast cancer: An analysis of three case-control studies

Shannon M Conroy[3], **Karin Koga**[1], **Christy G. Woolcott**[2], **Timothy Dahl**[7], **Celia Byrne**[4], **Chisato Nagata**[5], **Giske Ursin**[6], **Martin J Yaffe**[8], **Celine M Vachon**[7], and **Gertraud Maskarinec**[1,*]

[1]University of Hawaii Cancer Center, Honolulu, HI, USA

[2]Dalhousie University, Halifax, NS, Canada

[3]Alberta Health Services, Calgary, AB, Canada

[4]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

[5]Gifu University Graduate School of Medicine, Gifu, Japan

[6]University of Oslo, Oslo, Norway

[7]Mayo Clinic, Rochester, MN, USA

[8]Sunnybrook Research Institute, Toronto, ON, Canada

Abstract

Alcohol consumption and mammographic density are established risk factors for breast cancer. This study examined whether the association of mammographic density with breast cancer varies by alcohol intake. Mammographic density was assessed in digitized images for 1,207 cases and 1,663 controls from three populations (Japan, Hawaii, California) using a computer-assisted method. Associations were estimated by logistic regression. When comparing ever to never drinking, mean density was similar and consumption was not associated with breast cancer risk. However, within the Hawaii/Japan subset, women consuming >1 drink/day had a non-significantly elevated relative risk compared to never drinkers. Also in the Hawaii/Japan population, alcohol intake only modified the association between mammographic density and breast cancer in women consuming >1 drink/day ($p_{interaction}$=0.05) with significant risk estimates of 3.65 and 6.58 for the 2nd and 3rd density tertiles as compared to 1.57 and 1.61 for never drinkers in Hawaii/Japan. Although these findings suggest a stronger association between mammographic density and breast cancer risk for alcohol consumers, the small number of cases requires caution in interpreting the results.

*Correspondence to Gertraud Maskarinec, MD, PhD University of Hawaii Cancer Center 1236 Lauhala Street, Honolulu, HI 96813 gertraud@cc.hawaii.edu.

Conflict of interest The authors declare no conflict of interest.

Keywords

breast cancer; alcohol; mammographic density; case-control study; pooling

Introduction

Mammographic density represents the proportion of radiologically dense stromal and epithelial tissue in the breast; it is one of the strongest predictors of breast cancer risk, conferring a 4–6 fold greater relative risk in women with high density [1]. Epidemiologic evidence suggests that alcohol consumption increases breast cancer; relative risks are elevated at levels as low as 1 drink/day [2]. Previous work described weak to moderate associations between alcohol intake and breast density in some [3, 4] but not all [5] studies and a lack of an interaction between alcohol and density on breast cancer risk [6]. Based on this evidence, we examined the potential effect modification of the association between mammographic density and breast cancer risk by alcohol consumption using a pooled dataset that described a 2-fold higher risk for breast cancer among women with >35% densities as compared to those with <20% densities [7].

Materials and Methods

As described elsewhere, we combined case-control data from four studies located in California, Hawaii, Japan, and Minnesota [7]. The studies were approved by their respective Institutional Review Boards. Since alcohol data were not available for Minnesota, the current analysis is based on three studies only. All breast cancer cases were newly diagnosed; controls were recruited from the general population in California, the Multiethnic Cohort in Hawaii, and screening participants in Japan [8–10]. Covariate information included ethnicity, menopausal status, hormone replacement therapy (HRT) use, family history of breast cancer, and body mass index (BMI). Alcohol intake was estimated from self-administered questionnaires in Hawaii and Japan [9, 10] and recorded as ever vs. never during face-to-face interviews in California [8]. For the combined dataset, intake was classified as ever vs. never (≥1 vs. <1 drink/month). For Hawaii and Japan only, the ever drinkers were divided into ≤1 and >1 drink/day.

After excluding women with missing information, digitized mammograms for 1,207 cases and 1,663 controls were available. Contralateral images were used for cases and randomly selected sides for controls. The size of the total breast and the dense area were determined by a single observer using Cumulus [7] and percent mammographic density was computed as their ratio. The reliability of the mammographic density measure was high (r=0.97).

Using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), we applied general linear models to examine the relation between alcohol intake and mammographic density in the controls. The association between mammographic density and breast cancer risk was represented by odds ratios (OR) with 95% confidence intervals (CI) estimated from unconditional logistic regression models adjusted for age at mammogram, menopausal status, HRT use, family history of breast cancer, and location/ethnicity (California/Caucasian, California/Asian, California/African American, Hawaii/Caucasian, Hawaii/Asian, Hawaii/other, Japan/Asian). To assess effect modification by alcohol intake, an interaction term between mammographic density and alcohol intake was included in the models. In addition to stratified analyses by alcohol use and location, models for Hawaii and Japan (N=2011) were repeated using the 3-level alcohol intake variable.

Results

Alcohol intake in this population was low; <50% of participants were classified as ever drinkers and only 10% of women in Hawaii and Japan consumed >1 drink/day (Table 1). Among controls, adjusted mean breast density did not differ between ever and never drinkers in the entire population (30.9% vs 31.2%; p=0.75) or in the Hawaii/Japan subset with respective means of 33.3%, 33.7%, and 30.9% (p=0.21) for the never, ≤1, and >1 drink/day categories. Alcohol drinking as dichotomous variable was not associated with breast cancer (OR=1.03, 95%CI: 0.87, 1.22) except in Japan (OR=1.58, 95%CI: 1.05, 2.39). However, for the 200 Hawaii/Japan women consuming >1 drink/day, the OR compared to never drinkers was 1.23 (95%CI: 0.86, 1.76).

The interaction between ever drinking and mammographic density was not significant ($p_{interaction}$=0.28); the breast cancer risk estimates (Table 2) in the highest density tertile were similar in drinkers and abstainers (OR=2.05; 95%CI: 1.47, 2.86 vs 1.61; 95%CI: 1.18, 2.19). Yet, in women from Hawaii and Japan who consumed >1 drink/day the interaction between alcohol intake and percent density was borderline significant ($p_{interaction}$=0.046); the ORs for the 2nd and 3rd tertile of percent density were 3.65 (95%CI: 1.30, 10.3) and 6.58 (95%CI: 2.28, 19.0) as compared to never drinkers in Hawaii/Japan. Similar results were obtained when breast density was modeled as a continuous variable expressed as standard deviation in controls.

Discussion

Consistent with the only previous study [6], alcohol consumption did not significantly modify the effect of mammographic density on breast cancer risk in this pooled analysis when comparing consumers and abstainers. In the Hawaii/Japan subset of women with more detailed alcohol intake information, the relative risk associated with mammographic density appeared to be greater in alcohol consumers with intakes above 1 drink/day than never drinkers but the small number of cases does not allow firm conclusions. Whereas the dichotomous model did not indicate an association between alcohol drinking and breast cancer, the relative risk was elevated for women consuming >1 drink/day without reaching statistical significance. This observation supports the idea of a threshold effect for alcohol suggested in previous reports [2].

Strengths of our study include assessing mammographic density with a computer assisted method that provides a continuous measure [1] and the standardization achieved by using one reader [7]. Potential limitations of our study are exposure assessment and recall bias in the case-control studies, differences in mammograms across locations, and potential confounding due to unmeasured participant characteristics. Due the original data collection in California, alcohol consumption had to be classified as ever vs. never. As in all epidemiologic studies, alcohol intake may have been underreported and selection bias may have resulted in study subjects who do not represent alcohol drinking patters in the general population, particular in Japan where controls were recruited from screening programs [10]. Heterogeneity as apparent in the significant association among Japanese women not seen in California and Hawaii question the combined analysis approach.

This pooled study suggests that postmenopausal women who consume >1 alcoholic drink/day may experience a stronger association between mammographic density and breast cancer risk than women consuming no or little alcohol. However, given the low level of alcohol consumption in this study population and the lack of dose information for one of the studies, this analysis had limited ability to model the exact relations between alcohol intake,

mammographic density, and breast cancer risk and the findings need to be interpreted with caution.

Acknowledgments

This research was supported by the National Cancer Institute, US Department of Health and Human Services, grant number R03 CA 135699. CGW and SMC were supported during the work on this project by postdoctoral fellowships on grant R25 CA 90956.

Abbreviations

BMI	body mass index
CC	craniocaudal
CI	confidence interval
HRT	hormone replacement therapy
MLO	mediolateral oblique
OR	odds ratio

References

1. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006; 15(6):1159–1169. [PubMed: 16775176]
2. Key J, Hodgson S, Omar RZ, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control. 2006; 17(6):759–770. [PubMed: 16783604]
3. Cabanes A, Pastor-Barriuso R, Garcia-Lopez M, et al. Alcohol, tobacco, and mammographic density: a population-based study. Breast Cancer Res Treat. 2011; 129(1):135–147. [PubMed: 21373874]
4. Vachon CM, Kushi LH, Cerhan JR, Kuni CC, Sellers TA. Association of diet and mammographic breast density in the Minnesota breast cancer family cohort. Cancer Epidemiol Biomarkers Prev. 2000; 9(2):151–160. [PubMed: 10698475]
5. Qureshi SA, Couto E, Hofvind S, Wu AH, Ursin G. Alcohol intake and mammographic density in postmenopausal Norwegian women. Breast Cancer Res Treat. 2012; 131(3):993–1002. [PubMed: 21993860]
6. Herrinton LJ, Saftlas AF, Stanford JL, Brinton LA, Wolfe JN. Do alcohol intake and mammographic densities interact in regard to the risk of breast cancer? Cancer. 1993; 71(10):3029–3035. [PubMed: 8490831]
7. Conroy SM, Woolcott CG, Koga KR, et al. Mammographic density and risk of breast cancer by adiposity: An analysis of four case-control studies. Int J Cancer. 2011
8. Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev. 2003; 12(4):332–338. [PubMed: 12692108]
9. Maskarinec G, Pagano I, Lurie G, Wilkens LR, Kolonel LN. Mammographic Density and Breast Cancer Risk: The Multiethnic Cohort. Am J Epidemiol. 2005; 162(8):743–752. [PubMed: 16150892]
10. Nagata C, Matsubara T, Fujita H, et al. Mammographic density and the risk of breast cancer in Japanese women. Br J Cancer. 2005; 92(12):2102–2106. [PubMed: 15956963]

Table 1

Characteristics of the study participants

Characteristic	Cases *N* = 1,207	Controls *N* = 1,663	*p-value* [b]
Location, %			
California	39.6	22.9	
Hawaii	49.0	39.6	
Japan	11.4	37.5	*<0.0001*
Ethnicity, %			
Caucasian	38.4	24.6	
Asian	38.0	56.0	
African American	16.9	9.2	
Other	6.7	10.2	*<0.0001*
Alcohol drinking status, %			
Never[a]	51.5	49.8	
Ever[a]	48.5	50.2	*0.36*
Alcohol consumption, %			
Never[a]	55.8	51.5	
≤1 drink/day[c]	32.5	39.5	
>1 drink/day[c]	11.7	9.0	*0.004*
Menopausal status/HRT use, %			
Premenopausal	29.0	36.4	
Postmenopausal/no HRT	34.7	34.9	
Postmenopausal/any HRT	36.3	28.7	*<0.0001*
Family history of breast cancer, %	15.7	8.5	*<0.0001*
Age at mammogram (years), mean (SD)	55.4 (11.0)	53.4 (10.5)	*<0.0001*
Body mass index (kg/m^2), mean (SD)	25.0 (5.1)	24.6 (5.0)	*0.04*
Percent dense area, mean (SD)	32.5 (17.5)	31.0 (18.4)	*0.03*

[a] Never = <1 drink/month; Ever = ≥1 drink/month.

[b] Obtained by χ^2-test for categorical variables and by *t*-test for continuous variables.

[c] Available for Hawaii and Japan only

Table 2

Mammographic density and breast cancer risk by alcohol drinking status

Alcohol status[a]	Percent density/Subgroup	Total Population			Japan/Hawaii subgroup		
		Cases	Controls	OR[b] (95% CI)	Cases	Contr	OR[b] (95% CI)
Never	<20%	175	288	1.00	105	213	1.00
	20–35	197	242	1.57 (1.16, 2.11)	138	206	1.49 (1.04, 2.13)
	>35	250	298	1.61 (1.18, 2.19)	164	241	1.68 (1.14, 2.46)
	1 SD (18.4%)[c]	622	828	1.21 (1.05, 1.39)	407	660	1.24 (1.05, 1.47)
Location (1 SD[c])	California (17.0%)	215	168	1.18 (0.94, 1.48)			
	Hawaii (17.5%)	356	395	1.29 (1.08, 1.55)			
	Japan (19.1%)	51	265	1.13 (0.70, 1.81)			
Ever	<20%	145	245	1.00	75	163	1.00
	20–35	173	256	1.48 (1.08, 2.03)	94	193	1.60 (1.05, 2.44)
	>35	267	334	2.05 (1.47, 2.86)	153	266	2.50 (1.60, 3.90)
	1 SD (18.4%)[c]	585	835	1.29 (1.12, 1.49)	322	622	1.33 (1.11, 1.60)
Location (1 SD[c])	California (17.0%)	263	213	1.26 (1.01, 1.58)			
	Hawaii (17.5%)	236	263	1.48 (1.18, 1.86)			
	Japan (19.1%)	86	359	1.04 (0.75, 1.45)			
High intake (>1 drink/day)[d]	<20%				17	34	1.00
	20–35				26	37	3.65 (1.30, 10.3)
	>35			NA	42	44	6.58 (2.28, 19.0)
	1 SD (18.6%)[c]				85	115	2.63 (1.62, 4.28)
Location (1 SC[c])	Hawaii (17.5%)				76	65	2.58 (1.54, 4.32)
	Japan (19.1%)				9	50	3.12 (0.89, 11.0)

[b] Odds ratios and 95% confidence intervals from logistic regression models adjusted for age at mammogram, BMI, menopausal status/HRT use, parity, age at first birth, family history of breast cancer, location/ethnicity.

[c] Per 1 SD difference in percent density among controls.

Cancer Epidemiol. Author manuscript; available in PMC 2013 October 01.

[d] Hawaii and Japan only