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Tobacco and Alcohol in Relation to Male Breast Cancer: An Analysis of the Male Breast Cancer Pooling Project Consortium.

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Abstract

Background: The etiology of male breast cancer is poorly understood, partly due to its relative rarity. Although tobacco and alcohol exposures are known carcinogens, their association with male breast cancer risk remains ill-defined.

Methods: The Male Breast Cancer Pooling Project consortium provided 2,378 cases and 51,959 controls for analysis from 10 case-control and 10 cohort studies. Individual participant data were harmonized and pooled. Unconditional logistic regression was used to estimate study design-specific (case-control/cohort) odds ratios (OR) and 95% confidence intervals (CI), which were then combined using fixed effects meta-analysis.

Results*:* Cigarette smoking status, smoking pack-years, duration, intensity, and age at initiation were not associated with male breast cancer risk. Relations with cigar and pipe smoking, tobacco chewing, and snuff use were also null. Recent alcohol consumption and average grams of alcohol consumed per day were also not associated with risk; only one sub-analysis of very high recent alcohol consumption (>60 grams/day) was tentatively associated with male breast cancer ($OR_{unexposed\ referent}$=1.29, 95%CI:0.97–1.71; $OR_{>0–<7\ g/day\ referent}$=1.36, 95%CI:1.04–1.77). Specific alcoholic beverage types were not associated with male breast cancer. Relations were not altered when stratified by age or body mass index.

Conclusions*:* In this analysis of the Male Breast Cancer Pooling Project we found little evidence that tobacco and alcohol exposures were associated with risk of male breast cancer.

Impact: Tobacco and alcohol do not appear to be carcinogenic for male breast cancer. Future studies should aim to assess these exposures in relation to subtypes of male breast cancer.

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Introduction

Male breast cancer is a rare malignancy with an age-adjusted incidence of less than 1 per 100,000 man-years in a vast majority of countries (1). This is in stark contrast to female breast cancer, which is much more common as evidenced by a female-to-male incidence rate ratio of 122 (1). Reasons for this sex disparity are likely related to differences in the numbers and types of cells available for carcinogenic transformation (2), menstrual cycle- and pregnancy-associated morphological changes in the breast tissue (3, 4), hormonal differences between women and men, and sex differences in breast cancer pathogenesis. Analysis of incidence rates (1) and risk factors (5-9) indicate some similarities between male and female breast cancer, yet the risk profile in men remains poorly elucidated, largely due to the paucity of studies each with a limited number of cases.

Tobacco smoking and alcohol consumption are each classified as a Group 1 carcinogen by the International Agency for Research on Cancer (10). Although the weak and inconsistent associations between tobacco smoking and female breast cancer risk have led most consensus panels to conclude a non-causal association, alcohol consumption has consistently shown a positive linear association with risk. However, the relations of these exposures with *male* breast cancer risk remain unknown. A number of individual studies of these associations were conducted, but most have been limited in their statistical power to elucidate these associations (5-8, 11-21). To overcome these limitations, we conducted an in-depth analysis of tobacco and alcohol exposures in relation to the risk of male breast cancer in the Male Breast Cancer Pooling Project (MBCPP)—an international consortium of case-control and cohort studies.

Materials and Methods

Study Population

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For the MBCPP, we identified all case-control studies as well as cohort studies with 10 or more cases of this rare malignancy. Studies were identified from literature searches in PubMed, citations within published manuscripts, and advertisement at the National Cancer Institute Cohort Consortium meetings (http://epi.grants.cancer.gov/Consortia/cohort.html). Although two case-control studies (16, 22) could not be included because data were no longer available, we secured the contribution of data from 11 case-control (5, 6, 12, 14, 15, 17, 21, 23-26) and 10 cohort (7, 8, 27-34) investigations. These studies contributed de-identified data following approved data sharing agreements, as well as NCI and study center institutional review board clearances. The case definition was any male breast cancer (ICD 10: C50) (35) reported via a cancer registry, medical record, death certificate, or self-report. Cancers were required to be incident (i.e., diagnosed after exposure ascertainment) for cohort studies, and with exposure ascertainment near cancer ascertainment for case-control studies. To maximize the number of cases, we included all male breast cancers, regardless of whether they were diagnosed as a first cancer or not. For cohort studies, we attempted to create nested case-control datasets with a 40:1 control-to-case ratio using incidence-density matching to retain balance between analytic efficiency and strong statistical power, especially for analyses of less common exposures (36). For these selected sets, controls were matched to cases on sex (male), race (study-specific categories), study center (for multi-center cohorts), date of birth (+/−1 year), date of entry (+/−1 year), and exit date (date last known alive and free of cancer [excluding non-melanoma skin cancer]) ≥ date of diagnosis of case. When matching controls to male breast cancer cases that were not first cancers, potential controls were not right-censored at diagnosis of cancer, as per the above exit date criterion. Matching for date of entry and of birth was relaxed in increments of +/−1 year until +/−3 years

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was reached. These methods were used for all cohort studies, with the only deviation being a 10:1 control-to-case ratio for the Kaiser Permanente Multiphasic Health Checkup Cohort (30).

Exposures

Cigarette smoking status (dichotomous: ever/never; categorical: current/former/never), duration (continuous and tertiles), intensity (cigarettes per day; continuous and tertiles), pack-years (continuous and quartiles [cigarettes per day / 20 * duration in years]), and age at initiation (continuous and tertiles) were harmonized and each assessed for their association with breast cancer. Harmonization means to standardize exposure variables across studies so that they are inferentially equivalent and conducive to a valid combined analysis (37). Having ever smoked cigars or pipes, chewed tobacco, or used snuff were each assessed as dichotomous exposures in relation to cancer risk. Cigarette smoking intensity, duration and age at initiation were additionally analyzed with adjustment for total exposure (pack-years) in an attempt to help discern whether these variables affect risk of cancer once the estimated effect of total exposure has been taken into account (38, 39).

Recent total alcohol consumption (per day) was assessed in grams using: a continuous metric; a categorical metric based on tertiles of the control distribution of exposed (0 grams [referent], >0–≤5.73, >5.73–≤21.65, and >21.65); "high-exposure" categorical metrics (0 grams [referent], >0–<7, 7–40/60/90, and >40/60/90); and these same categorical metrics with exclusion of unexposed individuals and use of the lowest exposed group as the referent. If average grams of alcohol consumed per day was not provided, we estimated this using the following drink-specific grams of alcohol per drink: light beer (2% abv) 5.18 g; ordinary beer (5% abv) 12.96 g; strong beer (7% abv) 18.14 g; wine 13.72 g; spirits 13.93 g. We also assessed whether recent beer, wine, or liquor exposure (each dichotomous) were associated with breast

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cancer. "Recent" was during the past year for most studies, but longer for a few other studies; for example, the European Multi-center Study (21) asked about alcohol consumption five years ago, while the U.S. National Follow-up Back Survey (14) and U.S. Multi-center Study (5) only had average consumption across the lifetime. All cut-points for categorization of exposures and covariates were based on the exposure distribution of control subjects combined across studies that were included in the analytic dataset for this study, except for the "high exposure" alcohol categorization.

Statistical Analysis

To standardize the methods and models for separate pooled analyses of case-control studies and cohort studies (nested case-control studies), we utilized unconditional logistic regression with adjustment for age (in tertiles) and study (categorical) to generate study design-specific odds ratios (OR) and 95% confidence intervals (CI). The study design-specific ORs and 95% CIs were combined using fixed effects meta-analysis to generate overall summary estimates of association (40). We assessed whether estimates (betas) deviated by more than 10% when individually adjusted for race, education, marital status, body mass index (BMI; kg/m^2), diabetes, family history of breast cancer, and ever having had children, as we considered these variables to be possible confounding factors of associations with tobacco and alcohol exposures and they were widely available from the studies included for analysis. We assessed whether tobacco smoking adjusted or stratified for alcohol consumption—and vice versa—affected the estimates attained. Using a pooled dataset that included both studies of case-control and cohort designs, we tested for interaction between tobacco smoking status (never/former/current) and recent alcohol consumption (categorical) in relation to male breast cancer risk.

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P values for heterogeneity were estimated using the likelihood ratio test comparing a base model to the same model with inclusion of an interaction term of exposure*study, within each of the pooled analyses of case-control studies and of cohort studies. Additional sensitivity analyses included stratification of the main results by median age of diagnosis; stratification of the main results by BMI (tertiles and WHO categories); re-analysis of all exposures with exclusion of the National Mortality Follow-back Survey (NMFS) (14), since age was age at death rather than at breast cancer diagnosis; and analyses focusing only on male breast cancers occurring as a first primary cancer. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and STATA 13.1 (StataCorp LP, College Station, TX). All statistical tests were two-sided. *P* values less than 0.05 were considered statistically significant.

Results

The 21 participating studies that comprise the MBCPP are shown in Supplementary Table 1 and were described previously (9). In brief, 11 case-control studies (5, 6, 12, 14, 15, 17, 21, 23-26) collectively contributed 1,190 cases and 4,531 controls, and 10 cohort studies (7, 8, 27-34) collectively contributed 1,215 cases and 47,482 controls. Combined, this provided a total of 2,405 male breast cancers and 52,013 controls for analysis. Three studies did not have information on tobacco or alcohol exposures (7, 24, 26) which precluded their inclusion in any of the analyses presented here. Thus there were 2,378 cases and 51,959 controls for analysis from 10 case-control and 10 cohort studies. Of this analytic population, the mean ages of cases and controls were 65.6 years (standard deviation [SD]=10.8) and 66.8 (10.5), respectively. The majority (85.7%) of subjects were white.

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None of the individual covariates of race, education, marital status, BMI, diabetes, family history of breast cancer, and ever having had children altered beta coefficients to any appreciable extent. In addition, adjustment of alcohol grams in the smoking status model, and adjustment of smoking status in the alcohol dichotomous and alcohol grams analyses had negligible effects on effect estimates. Therefore, the main results presented herein are adjusted only for age and study. Modeling age as a continuous, instead of categorical, variable did not materially affect the risk estimates.

Table 1 shows the summary estimates as well as study design-specific results. Ever (OR=0.99, 95%CI:0.86–1.13), former (1.07, 0.92–1.24), and current (0.86, 0.71–1.05) cigarette smoking were not associated with altered risks of male breast cancer. Although the case-control estimate for current vs. never cigarette smoking was statistically significantly reduced (OR=0.75, 95%CI:0.58–0.97), the estimate from the cohort studies did not support this association (1.08, 0.79–1.48), leading to a summary estimate that supported the null hypothesis. Similarly there were no associations with cancer risk observed for other metrics of cigarette smoking, including pack-years, duration, intensity, and age at initiation. When we additionally adjusted the latter three models for pack-years, the estimates were not materially altered (Supplemental Table 2). Analyses of ever having smoked cigars or pipes in relation to male breast cancer risk were—as per the above analyses—extremely well powered with ten studies and 600 cases. Yet these associations also indicated a lack of association with cancer risk. For the exposures tobacco chewing and snuff use, data were only available from case-control studies, yet they still provided close to 400 cases of this rare malignancy. The pooled case-control estimates for tobacco chewing (OR=1.10, 95%CI:0.72–1.68) and snuff use (0.97, 0.55–1.71) showed no association with male breast cancer risk.

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The summary estimates for alcohol exposures are presented in Table 2. Having recently consumed alcohol was not associated with cancer risk (OR=0.93, 95%CI:0.79–1.11) as was average alcohol consumption per 10 grams per day ($OR_{continuous}$=1.02, 95%CI:1.00–1.04). When analyzed as a categorical variable with cut-points based on quartiles of the control population, consuming more than 21.65 grams/day gave an odds ratio of 1.09 (0.88–1.34; Table 2), which increased to 1.16 (0.96–1.41) when using the lowest exposed group (>0–≤5.73 grams/day) as the referent instead of the unexposed (Supplementary Table 3). A similar, albeit stronger, association was observed when we assessed other high recent alcohol consumption groups such as >45 grams/day ($OR_{unexposed\ referent}$=1.16, 95%CI:0.90–1.49; $OR_{>0\text{–}<7\ g/day\ referent}$=1.21, 95%CI:0.97–1.52), >60 grams/day ($OR_{unexposed\ referent}$=1.29, 95%CI:0.97–1.71; $OR_{>0\text{–}<7\ g/day\ referent}$=1.36, 95%CI:1.04–1.77), and >90 grams/day ($OR_{unexposed\ referent}$=1.08, 95%CI:0.74–1.58; $OR_{>0\text{–}<7\ g/day\ referent}$=1.12, 95%CI:0.78–1.61) (Supplementary Table 3). However, none of the alcohol analyses provided evidence of dose-response and only one point estimate was statistically significant at α=0.05 (>60 grams/day vs. 0–<7 grams/day). Recent beer (OR=0.95, 95%CI:0.79–1.13), wine (1.06, 0.89–1.26), and liquor (0.89, 0.75–1.05) consumption were not associated with male breast cancer risk. Lastly, none of the p values for heterogeneity by study were deemed to be statistically significant (p=0.05) after false-discovery rate adjustment (41).

The age-stratified analyses did not provide evidence for any overt effect-modification by age (Table 3). There were tentative inverse associations of recent alcohol consumption and recent beer consumption with risk of male breast cancer in younger males, but confidence intervals were wide and considerably overlapping with those of the estimates for older males. Similar observations were seen for average grams of alcohol consumed per day. Analyses stratified by BMI (Table 4) did not provide evidence for effect modification; although estimates

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for tobacco chewing and recent liquor consumption appeared to differ by BMI tertile, confidence intervals were wide and considerably overlapped. Estimates for alcohol consumption did not vary across strata of tobacco smoking, although there was tentative evidence that current tobacco smoking was inversely associated with male breast cancer (OR=0.49, 95%CI:0.26–0.96) in those who reported no recent alcohol consumption. However, there was no evidence for an interaction between tobacco smoking status and alcohol consumption in relation to male breast cancer (p=0.58)

Sensitivity analyses that separately excluded the National Mortality Follow-back Survey (14) and male breast cancers that were not first cancers did not materially alter the results (not shown).

Discussion

International collaboration through the MBCPP has provided the opportunity for an in-depth and statistically well-powered assessment of tobacco and alcohol exposures in relation to the risk of male breast cancer. After pooling, harmonization and analysis of individual participant data from 20 studies, we find little evidence that these exposures are associated with the risk of developing male breast cancer.

Tobacco smoking—and cigarette smoking in particular— has been associated with increased risk of various cancers including lung, bladder, liver, various upper respiratory sites, myeloid leukemia, stomach and colorectal (10, 42-44). Tobacco smoke contains several carcinogens (45, 46) and is classified by the International Agency for Research on Cancer as *carcinogenic to humans* (Group 1) (10, 43). With regard to female breast cancer, tobacco smoking has often been associated with very slight increases in risk (risk ratios between 1.1 and

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1.3), but the inconsistent and weak associations have led most (10, 43 , 44, 47, 48), but not all (49, 50), consensus summary reports to conclude that the evidence is insufficient to support a causal relationship. The principal concerns of most positive prior studies are residual confounding leading to false-positive results, and the inability to test effect modification, whereby subpopulations at risk cannot be identified. Suspected effect-modifiers that might define these subpopulations include carcinogenic susceptibility (e.g., germline genetic, oxidative stress capacity), hormonal status (e.g., menopause, parity) and heterogeneous disease (e.g., tumor subtype) (10). There is evidence that supports the plausibility of causality—such as detection of tobacco smoke constituents in breast tissue, fluid and milk, and *in vitro* carcinogenic transformation of human breast epithelial cells—but the epidemiological evidence has been typically adjudged to be too weak to endorse causality (10). It is possible that reduced circulating estradiol concentrations caused by tobacco smoking in premenopausal women (51, 52) could counteract the known carcinogenic effects of tobacco smoke. It is of interest that male tobacco smokers have higher circulating concentrations of estradiol (53-55), akin to a similar phenomenon observed for post-menopausal women even after adjustment for BMI (56).

Historically, men have smoked more than women in the US, yet since 1965 the prevalence of smoking has been declining and converging between the sexes (57). However, any effect conferred by cigarette smoking on breast cancer risk is likely to be modified by sex, given that sex steroid hormones are central to the etiopathogenesis of this malignancy and that circulating concentrations differ greatly between men and premenopausal women. Moreover, incidence rates of female breast cancer are universally much greater than equivalent rates for males, with the average incidence rate ratio being 122 female breast cancers for every male breast cancer (1). Although there are various factors that cause this imbalance, the most obvious

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are the sex differences in breast tissue in terms of amount, type, and temporal changes, and differences in sex hormone levels. Indeed, it appears that tobacco smoking might primarily be associated with female breast cancer when exposure is during breast development, given findings of stronger associations in women who smoked prior to menarche or 11 or more years before first birth (58). Given these sex differences, we may not expect the strength—or even presence—of an exposure-breast cancer association to be the same in men as it is for women. In additional support of our null results are two further studies that were not included in the MBCPP but that also failed to find an association between tobacco smoking and male breast cancer risk (11, 16). Lastly, other tobacco use—including cigar and pipe smoking, chewing, and snuff use—was also not associated with male breast cancer risk in our analysis. These results further substantiate the null associations with cigarette smoking exposures.

Alcohol consumption was officially recognized to be carcinogenic to humans since an initial IARC Working Group review in 1987 (59). Alcohol consumption increases risk of many malignancies including liver, oropharyngeal, esophageal squamous cell carcinoma, and colorectal cancers (10). Alcohol consumption is also considered a Group 1 carcinogen for female breast cancer; the associated excess risk is modest—between 7 and 13% per 10g alcohol increase per day (about one drink), but the trend is monotonic (60-62). This association does not differ by alcoholic beverage types, nor is it modified by folate intake, menopausal status, or BMI, there is insufficient and inconsistent evidence as to whether associations vary by menopausal hormone therapy, tumor receptor status, or histological subtype (10).

There was little evidence that alcohol consumption was associated with male breast cancer in this analysis, and this is also true of two other studies that were not included in the MBCPP consortium (11, 18). High recent alcohol consumption (>60 grams/day) provided the strongest estimate of association (OR=1.36, 95%CI:1.04–1.77, p=0.02) when compared with a lower exposed group (>0–<7 grams/day) but the lack of dose-response may reduce the likelihood of this being a causal effect. On the other hand, one might expect that the weak, but well-established, effect of alcohol consumption on female breast cancer risk should also be observed in male breast cancer. The mechanism of the relationship between alcohol consumption and female breast cancer risk remains unknown, but the primary hypothesis is that ethanol increases estrogen concentrations, thereby activating cellular proliferation (10, 63, 64). In men, there is evidence both for (65, 66) and against (54) associations between alcohol consumption and circulating sex steroid hormone concentrations. Additional hypotheses surround local CYP2E1 metabolism of ethanol to acetaldehyde which is genotoxic and clastogenic and may also cause increased reactive oxygen species, altered epigenetic states, and modified cell cycling (10, 63, 64).

Strengths of this analysis include: the large number of male breast cancers available for analysis; use of individual participant data which permitted combined analyses with comparable variables—a feature not available in meta-analyses that use only published estimates of risk; and, no statistical evidence for heterogeneity after false-discovery rate adjustment(41). Limitations of our study include: exposures being elicited through questionnaires and thus prone to recall and interviewer biases, although tobacco (67, 68) and alcohol (69) exposures have been shown to be reliably recalled and this was supported by similar estimates of risk from both cohort and case-control study designs; some of the exposures were worded slightly differently across studies and included slight variations in time, which could have impacted the results; data on passive tobacco smoking was not available across studies, thus we could not account for such in our analyses;

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and stratification by potential effect modifiers of germline genetic polymorphism, tumor receptor subtype, or tumor histology was not possible due to unavailability of this information.

In this large, pooled analysis of the MBCPP, we find little evidence that tobacco and alcohol exposures are associated with the risk of male breast cancer.

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Table 1. Associations between tobacco exposures and male breast cancer risk

Exposure		Meta-Analysis					Case-Control Studies					Cohort Studies				
		Studies	**Cases**	**Controls**	**OR (95% CI)**	**p**	**Studies**	**Cases**	**Controls**	**OR (95% CI)**	**p**	**Studies**	**Cases**	**Controls**	**OR (95% CI)**	**p**
Cigarette Smoking Status	Never	18	414	6,236	*referent*		9	282	980	*referent*		9	132	5,256	*referent*	
	Ever	18	1,012	13,227	0.99 (0.86, 1.13)	0.85	9	734	2,784	0.95 (0.80, 1.13)	0.57	9	278	10,443	1.05 (0.84, 1.29)	0.69
p value for heterogeneity											*0.27*					*0.77*
Cigarette Smoking Status	Never	16	341	6,155	*referent*		7	209	899	*referent*		9	132	5,256	*referent*	
	Former	16	576	9,722	1.07 (0.92, 1.24)	0.40	7	364	1,471	1.09 (0.89, 1.34)	0.40	9	212	8,251	1.04 (0.83, 1.30)	0.75
	Current	16	205	3,192	0.86 (0.71, 1.05)	0.15	7	139	1,009	0.75 (0.58, 0.97)	0.03	9	66	2,183	1.08 (0.79, 1.48)	0.64
p value for heterogeneity											*0.41*					*0.68*
Cigarette Smoking Pack-Years	0	18	414	6,236	*referent*		9	282	980	*referent*		9	132	5,256	*referent*	
	>0 to ≤10	18	103	1,690	0.92 (0.71, 1.19)	0.52	9	65	436	0.84 (0.60, 1.17)	0.29	9	38	1,254	1.06 (0.70, 1.61)	0.77
	>10 to ≤30	18	165	2,518	0.92 (0.74, 1.15)	0.48	9	112	737	0.84 (0.64, 1.11)	0.22	9	53	1,781	1.10 (0.75, 1.60)	0.63
	>30	18	198	2,492	0.95 (0.77, 1.18)	0.65	9	154	833	0.95 (0.73, 1.23)	0.68	9	44	1,659	0.96 (0.65, 1.43)	0.85
p value for heterogeneity											*0.002*					*0.88*
	continuous	12	466	6,700	1.00 (1.00, 1.00)	0.93	6	331	2,006	1.00 (1.00, 1.01)	0.75	6	135	4,694	1.00 (0.99, 1.01)	0.69
p value for heterogeneity											*0.02*					*0.70*
Cigarette Smoking Duration	>0 to ≤20	12	165	2,432	*referent*		6	110	647	*referent*		6	55	1,785	*referent*	
	>20 to ≤35.5	12	177	2,556	0.94 (0.74, 1.19)	0.61	6	128	824	0.95 (0.71, 1.27)	0.72	6	49	1,732	0.93 (0.63, 1.38)	0.71
	>35.5	12	182	2,251	0.90 (0.70, 1.16)	0.42	6	146	827	0.89 (0.66, 1.20)	0.44	6	36	1,424	0.93 (0.59, 1.47)	0.76
p value for heterogeneity											*0.07*					*0.55*
	continuous	12	524	7,239	0.99 (0.99, 1.00)	0.16	6	384	2,298	0.99 (0.99, 1.00)	0.18	6	140	4,941	1.00 (0.98, 1.01)	0.61
p value for heterogeneity											*0.03*					*0.88*
Cigarette Smoking Intensity	>0 to ≤15.5	14	251	5,855	*referent*		6	118	806	*referent*		8	133	5,049	*referent*	

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	>15.5 to ≤25.4	14	165	1,920	1.19 (0.93, 1.52)	0.17	6	138	743	1.31 (0.98, 1.74)	0.07	8	27	1,177	0.92 (0.57, 1.47)	0.73
	>25.4	14	186	3,881	1.11 (0.90, 1.37)	0.32	6	87	505	1.13 (0.81, 1.58)	0.46	8	99	3,376	1.10 (0.84, 1.44)	0.49
p value for heterogeneity											*0.09*					*0.15*
	continuous	14	602	11,656	1.00 (1.00, 1.01)	0.53	6	343	2,054	1.00 (1.00, 1.01)	0.39	8	259	9,602	1.00 (0.99, 1.01)	0.97
p value for heterogeneity											*0.34*					*0.81*
Age of Smoking Initiation	>0 to ≤16	12	186	2,717	*referent*		6	146	922	*referent*		6	40	1,795	*referent*	
	>16 to ≤20	12	194	2,933	1.09 (0.87, 1.36)	0.47	6	140	888	1.03 (0.79, 1.35)	0.84	6	54	2,045	1.24 (0.82, 1.89)	0.31
	>20	12	140	2,179	1.04 (0.80, 1.35)	0.79	6	97	483	0.97 (0.71, 1.32)	0.85	6	43	1,696	1.22 (0.75, 2.00)	0.42
p value for heterogeneity											*0.17*					*0.30*
	continuous	12	520	7,829	1.01 (0.99, 1.02)	0.48	6	383	2,293	1.00 (0.99, 1.02)	0.85	6	137	5,536	1.01 (0.99, 1.04)	0.31
p value for heterogeneity											*0.18*					*0.78*
Cigar Smoking Status	Never	10	475	9,470	*referent*		4	236	688	*referent*		6	239	8,782	*referent*	
	Ever	10	131	2,395	1.05 (0.84, 1.31)	0.70	4	75	231	1.21 (0.86, 1.69)	0.27	6	56	2,164	0.93 (0.69, 1.26)	0.65
p value for heterogeneity											*0.05*					*0.38*
Pipe Smoking Status	Never	10	457	9,089	*referent*		4	223	690	*referent*		6	234	8,399	*referent*	
	Ever	10	153	2,803	0.97 (0.78, 1.20)	0.77	4	93	237	1.12 (0.80, 1.55)	0.52	6	60	2,566	0.87 (0.65, 1.16)	0.34
p value for heterogeneity											*0.09*					*0.67*
Tobacco Chewing Status	Never	-	-	-	-	-	3	369	1,252	*referent*		-	-	-	-	-
	Ever	-	-	-	-	-	3	32	92	1.10 (0.72, 1.68)	0.67	-	-	-	-	-
p value for heterogeneity											*0.35*					-
Snuff Status	Never	-	-	-	-	-	2	376	762	*referent*		-	-	-	-	-
	Ever	-	-	-	-	-	2	21	34	0.97 (0.55, 1.71)	0.91	-	-	-	-	-
p value for heterogeneity											*0.85*					-

Abbreviations: CI, confidence interval; OR, odds ratio; p, p value.

Table 2. Associations between alcohol consumption exposures and male breast cancer risk

Exposure		Meta-Analysis					Case-Control Studies					Cohort Studies				
		Studies	**Cases**	**Controls**	**OR (95% CI)**	**p**	**Studies**	**Cases**	**Controls**	**OR (95% CI)**	**p**	**Studies**	**Cases**	**Controls**	**OR (95% CI)**	**p**
Alcohol, recent consumption	No	17	211	3,497	*referent*		9	131	416	*referent*		8	80	3,081	*referent*	
	Yes	17	1,221	14,653	0.93 (0.79, 1.11)	0.43	9	921	3,544	0.87 (0.69, 1.09)	0.23	8	300	11,109	1.02 (0.79, 1.32)	0.87
p value for heterogeneity											*0.81*					*0.77*
Alcohol, average consumption (grams/day)	0	14	180	3,339	*referent*		7	101	392	*referent*		7	79	2,947	*referent*	
	>0 to ≤5.73	14	294	4,415	0.94 (0.76, 1.16)	0.57	7	203	574	0.95 (0.71, 1.27)	0.72	7	91	3,841	0.93 (0.68, 1.27)	0.65
	>5.73 to ≤21.65	14	306	4,430	0.91 (0.74, 1.13)	0.41	7	210	832	0.94 (0.70, 1.25)	0.66	7	96	3,598	0.89 (0.65, 1.21)	0.46
	>21.65	14	327	4,413	1.09 (0.88, 1.34)	0.44	7	241	1,676	1.02 (0.77, 1.36)	0.88	7	86	2,737	1.17 (0.85, 1.60)	0.33
p value for heterogeneity											*0.38*					*0.90*
	continuous per 10 g	14	1,107	16,597	1.017 (0.998, 1.037)	0.09	7	755	3,474	1.020 (0.990, 1.041)	0.20	7	352	13,123	1.020 (0.990, 1.051)	0.26
p value for heterogeneity											*0.19*					*0.58*
Beer, recent consumption	No	10	236	5,254	*referent*		5	131	793	*referent*		5	105	4,461	*referent*	
	Yes	10	483	9,368	0.95 (0.79, 1.13)	0.55	5	294	2,082	0.81 (0.63, 1.04)	0.09	5	189	7,286	1.11 (0.87, 1.42)	0.42
p value for heterogeneity											*0.83*					*0.21*
Wine, recent consumption	No	10	250	5,782	*referent*		5	131	769	*referent*		5	119	5,013	*referent*	
	Yes	10	463	8,804	1.06 (0.89, 1.26)	0.49	5	287	2,067	1.02 (0.80, 1.30)	0.88	5	176	6,737	1.11 (0.87, 1.41)	0.42
p value for heterogeneity											*0.91*					*0.11*
Liquor, recent consumption	No	10	300	6,523	*referent*		5	160	1,084	*referent*		5	140	5,439	*referent*	
	Yes	10	412	8,081	0.89 (0.75, 1.05)	0.16	5	258	1,767	0.84 (0.67, 1.06)	0.14	5	154	6,314	0.94 (0.74, 1.20)	0.63
p value for heterogeneity											*0.12*					*0.08*

Abbreviations: CI, confidence interval; OR, odds ratio; p, p value.

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Table 3. Associations between tobacco and alcohol exposures and male breast cancer risk stratified by median age at diagnosis

Exposure		Age < Median (<66 years)					Age ≥ Median (≥66 years)				
		Studies	Cases	Controls	OR (95%CI)	p value	Studies	Cases	Controls	OR (95%CI)	p value
Cigarette Smoking Status	Never	18	226	2,531			18	188	3,705		
	Ever	18	529	5,330	0.93 (0.77, 1.12)	0.42	18	483	7,897	1.04 (0.86, 1.26)	0.67
Cigarette Smoking Status	Never	16	178	2,487			16	163	3,668		
	Former	16	263	3,392	1.05 (0.85, 1.31)	0.64	16	313	6,330	1.07 (0.86, 1.32)	0.54
	Current	16	133	1,757	0.84 (0.65, 1.09)	0.18	16	72	1,435	0.89 (0.65, 1.21)	0.45
Cigarette Smoking Pack-Years	0	18	226	2,531			18	188	3,705		
	>0 to ≤10	18	57	781	0.79 (0.56, 1.12)	0.19	18	46	909	1.12 (0.76, 1.65)	0.57
	>10 to ≤30	18	93	1,166	0.84 (0.62, 1.13)	0.25	18	72	1,352	1.06 (0.75, 1.48)	0.76
	>30	18	113	1,038	0.96 (0.71, 1.28)	0.76	18	85	1,454	0.95 (0.69, 1.33)	0.78
	continuous	*12*	*263*	*2,985*	*1.00 (1.00, 1.01)*	*0.39*	*12*	*203*	*3,715*	*1.00 (0.99, 1.00)*	*0.41*
Cigarette Smoking Duration	>0 to ≤20	12	102	1,181			12	63	1,251		
	>20 to ≤35.5	12	102	1,272	0.89 (0.66, 1.22)	0.48	12	75	1,284	0.98 (0.68, 1.42)	0.92
	>35.5	12	86	809	1.04 (0.74, 1.46)	0.81	12	96	1,442	0.77 (0.53, 1.12)	0.18
	continuous	*12*	*290*	*3,262*	*1.00 (0.99, 1.01)*	*0.73*	*12*	*234*	*3,977*	*0.99 (0.98, 1.00)*	*0.02*
Cigarette Smoking Intensity	>0 to ≤15.5	14	119	2,201			14	132	3,654		
	>15.5 to ≤25.4	14	102	892	1.32 (0.94, 1.84)	0.11	14	63	1,028	1.06 (0.74, 1.53)	0.76
	>25.4	14	94	1,467	1.09 (0.80, 1.48)	0.58	14	92	2,414	1.14 (0.85, 1.52)	0.38
	continuous	*14*	*315*	*4,560*	*1.00 (0.99, 1.01)*	*0.56*	*14*	*287*	*7,096*	*1.00 (0.99, 1.01)*	*0.79*
Age of Smoking Initiation	>0 to ≤16	12	119	1,310			12	67	1,407		
	>16 to ≤20	12	97	1,300	0.95 (0.70, 1.29)	0.75	12	97	1,633	1.29 (0.91, 1.82)	0.15
	>20	12	71	778	0.94 (0.67, 1.34)	0.75	12	69	1,401	1.17 (0.79, 1.76)	0.43
	continuous	*12*	*287*	*3,388*	*1.00 (0.98, 1.02)*	*0.88*	*12*	*233*	*4,441*	*1.01 (0.99, 1.03)*	*0.25*
Cigar Smoking Status	Never	10	225	3,305			10	250	6,165		
	Ever	10	54	767	1.08 (0.76, 1.56)	0.66	10	77	1,628	1.04 (0.78, 1.38)	0.79
Pipe Smoking Status	Never	10	215	3,159			10	242	5,930		
	Ever	10	64	937	0.90 (0.64, 1.26)	0.54	10	89	1,866	1.04 (0.79, 1.38)	0.77
Tobacco Chewing Status	Never	3	223	770			3	146	482		
	Ever	3	18	51	1.15 (0.66, 2.03)	0.62	3	14	41	1.03 (0.54, 1.96)	0.93

Snuff Status	Never	2	230	477			2	146	285		
	Ever	2	11	18	1.05 (0.48, 2.28)	0.91	2	10	16	0.91 (0.40, 2.10)	0.83
Alcohol, recent consumption	No	17	98	1,186			17	113	2,311		
	Yes	17	672	6,424	0.77 (0.60, 0.99)	0.04	17	549	8,229	1.09 (0.86, 1.37)	0.46
Alcohol, average consumption (grams/day)	0	14	86	1,136			14	94	2,203		
	>0 to ≤5.73	14	146	1,626	0.80 (0.58, 1.09)	0.16	14	148	2,789	1.08 (0.81, 1.44)	0.62
	>5.73 to ≤21.65	14	165	1,843	0.79 (0.59, 1.08)	0.14	14	141	2,587	1.05 (0.78, 1.41)	0.76
	>21.65	14	199	2,293	0.90 (0.67, 1.22)	0.50	14	128	2,120	1.29 (0.95, 1.73)	0.10
	continuous	*14*	*596*	*6,898*	*1.00 (1.00, 1.00)*	*0.26*	*14*	*511*	*9,699*	*1.00 (1.00, 1.01)*	*0.16*
Beer, recent consumption	No	10	120	1,880			10	116	3,374		
	Yes	10	255	4,291	0.79 (0.61, 1.01)	0.06	10	228	5,077	1.13 (0.88, 1.44)	0.35
Wine, recent consumption	No	10	116	2,115			10	134	3,667		
	Yes	10	260	4,042	1.03 (0.80, 1.32)	0.84	10	203	4,762	1.10 (0.87, 1.40)	0.43
Liquor, recent consumption	No	10	146	2,573			10	154	3,950		
	Yes	10	230	3,589	0.85 (0.67, 1.07)	0.17	10	182	4,492	0.93 (0.74, 1.18)	0.56

All models were adjusted for age (continuous) and study (categorical). Abbreviations: CI, confidence interval; OR, odds ratio.

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Table 4. Associations between tobacco and alcohol exposures and male breast cancer risk stratified by body mass index (kg/m²)

		BMI Tertile 1 (<24.56)					BMI Tertile 2 (≥24.56–<27.38)					BMI Tertile 3 (≥27.38)				
Exposure		**Studies**	**Cases**	**Controls**	**OR (95%CI)**	**p value**	**Studies**	**Cases**	**Controls**	**OR (95%CI)**	**p value**	**Studies**	**Cases**	**Controls**	**OR (95%CI)**	**p value**
Cigarette Smoking Status	Never	18	149	2,215			18	122	2,025			18	138	1,847		
	Ever	18	317	4,085	0.89 (0.71, 1.11)	0.31	18	330	4,319	1.16 (0.91, 1.48)	0.22	18	330	4,461	0.86 (0.68, 1.10)	0.23
Cigarette Smoking Status	Never	16	120	2,176			16	104	2,005			16	112	1,827		
	Former	16	160	2,708	0.97 (0.74, 1.26)	0.80	16	189	3,238	1.22 (0.93, 1.60)	0.15	16	206	3,530	0.96 (0.73, 1.25)	0.74
	Current	16	72	1,244	0.75 (0.54, 1.05)	0.10	16	66	992	1.07 (0.76, 1.52)	0.69	16	60	846	0.80 (0.56, 1.16)	0.25
Cigarette Smoking Pack-Years	0	18	149	2,215			18	122	2,025			18	138	1,847		
	>0 to ≤10	18	35	547	0.89 (0.57, 1.38)	0.59	18	44	555	1.38 (0.89, 2.13)	0.15	18	22	538	0.65 (0.38, 1.10)	0.11
	>10 to ≤30	18	54	806	0.94 (0.63, 1.39)	0.76	18	54	873	0.97 (0.65, 1.46)	0.90	18	53	767	0.85 (0.57, 1.27)	0.42
	>30	18	67	773	0.94 (0.64, 1.40)	0.78	18	65	781	1.11 (0.75, 1.64)	0.59	18	55	870	0.72 (0.48, 1.06)	0.10
	continuous	*12*	*156*	*2,126*	*1.00 (0.99, 1.01)*	*0.94*	*12*	*163*	*2,209*	*1.00 (0.99, 1.01)*	*0.54*	*12*	*130*	*2,175*	*1.00 (0.99, 1.01)*	*0.85*
Cigarette Smoking Duration	>0 to ≤20	12	57	756			12	58	807			12	46	808		
	>20 to	12	50	779	0.82	0.36	12	65	885	0.95	0.79	12	54	831	0.96	0.85

	≤35.5				(0.54, 1.25)					(0.63, 1.43)					(0.63, 1.47)	
	>35.5	12	67	796	0.88 (0.58, 1.35)	0.57	12	63	710	0.88 (0.57, 1.35)	0.55	12	46	665	0.92 (0.57, 1.47)	0.73
	continuous	*12*	*174*	*2,331*	*1.00 (0.98, 1.01)*	*0.55*	*12*	*186*	*2,402*	*0.99 (0.98, 1.00)*	*0.18*	*12*	*146*	*2,304*	*1.00 (0.98, 1.01)*	*0.60*
Cigarette Smoking Intensity	>0 to ≤15.5	14	81	1,835			14	88	1,958			14	73	1,890		
	>15.5 to ≤25.4	14	50	663	1.04 (0.66, 1.63)	0.88	14	60	652	1.16 (0.76, 1.77)	0.50	14	48	545	1.48 (0.94, 2.35)	0.09
	>25.4	14	54	932	1.14 (0.76, 1.70)	0.53	14	59	1,186	1.14 (0.78, 1.66)	0.51	14	68	1,663	1.08 (0.76, 1.55)	0.66
	continuous	*14*	*185*	*3,430*	*1.00 (0.99, 1.02)*	*0.50*	*14*	*207*	*3,796*	*1.00 (0.99, 1.02)*	*0.55*	*14*	*189*	*4,098*	*1.00 (0.99, 1.01)*	*0.73*
Age of Smoking Initiation	>0 to ≤16	12	55	886			12	63	889			12	60	865		
	>16 to ≤20	12	72	988	1.45 (0.97, 2.17)	0.07	12	63	994	0.91 (0.61, 1.37)	0.65	12	52	862	0.99 (0.66, 1.49)	0.95
	>20	12	42	720	1.01 (0.63, 1.62)	0.96	12	59	715	1.32 (0.84, 2.07)	0.23	12	35	704	0.83 (0.50, 1.36)	0.45
	continuous	*12*	*169*	*2,594*	*1.00 (0.98, 1.03)*	*0.90*	*12*	*185*	*2,598*	*1.01 (0.99, 1.03)*	*0.45*	*12*	*147*	*2,431*	*1.01 (0.98, 1.03)*	*0.69*
Cigar Smoking Status	Never	10	171	2,896			10	140	3,041			10	151	3,310		
	Ever	10	28	564	0.84 (0.53, 1.32)	0.45	10	48	800	1.16 (0.80, 1.69)	0.43	10	49	958	1.10 (0.75, 1.61)	0.61
Pipe Smoking Status	Never	10	154	2,654			10	138	2,946			10	152	3,254		

	Ever	10	48	838	0.79 (0.53, 1.16)	0.23	10	54	883	1.18 (0.81, 1.71)	0.38	10	46	1,023	0.98 (0.66, 1.45)	0.92
Tobacco Chewing Status	Never	3	121	498			3	121	373			3	115	331		
	Ever	3	11	35	1.15 (0.56, 2.35)	0.70	3	14	23	1.83 (0.90, 3.71)	0.10	3	5	33	0.37 (0.14, 0.98)	0.05
Snuff Status	Never	2	137	338			2	111	207			2	116	183		
	Ever	2	4	14	0.52 (0.16, 1.67)	0.27	2	8	12	1.05 (0.41, 2.71)	0.91	2	8	7	1.43 (0.49, 4.13)	0.51
Alcohol, recent consumption	No	17	66	1,124			17	65	1,074			17	73	1,207		
	Yes	17	408	4,915	0.96 (0.71, 1.30)	0.82	17	393	4,853	0.92 (0.67, 1.25)	0.58	17	386	4,514	0.95 (0.70, 1.28)	0.73
Alcohol, average consumption (grams/day)	0	14	58	1,045			14	58	1,014			14	57	1,189		
	>0 to ≤5.73	14	105	1,332	1.02 (0.70, 1.49)	0.91	14	92	1,413	0.86 (0.59, 1.25)	0.42	14	88	1,563	0.95 (0.65, 1.39)	0.80
	>5.73 to ≤21.65	14	100	1,543	0.80 (0.55, 1.16)	0.24	14	100	1,473	0.90 (0.62, 1.31)	0.60	14	99	1,294	1.04 (0.72, 1.52)	0.82
	>21.65	14	102	1,408	1.02 (0.70, 1.50)	0.90	14	106	1,508	1.04 (0.71, 1.52)	0.85	14	107	1,379	1.26 (0.87, 1.83)	0.22
	continuous	*14*	*365*	*5,328*	*1.00 (1.00, 1.00)*	*0.87*	*14*	*356*	*5,408*	*1.00 (1.00, 1.00)*	*0.98*	*14*	*351*	*5,425*	*1.00 (1.00, 1.01)*	*0.01*
Beer, recent consumption	No	10	71	1,642			10	78	1,645			10	79	1,830		
	Yes	10	153	2,861	0.93 (0.68, 1.28)	0.67	10	168	3,094	1.02 (0.75, 1.39)	0.90	10	148	3,207	0.91 (0.67, 1.24)	0.54
Wine, recent	No	10	80	1,71			10	78	1,78			10	84	2,13		

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consumption				2					2					7		
	Yes	10	142	2,770	0.98 (0.72, 1.33)	0.88	10	164	2,956	1.14 (0.84, 1.55)	0.41	10	143	2,886	1.10 (0.81, 1.48)	0.54
Liquor, recent consumption	No	10	104	2,049			10	89	2,096			10	97	2,216		
	Yes	10	117	2,444	0.70 (0.52, 0.94)	0.02	10	152	2,640	1.16 (0.86, 1.56)	0.33	10	131	2,818	0.86 (0.64, 1.14)	0.30

All models were adjusted for age (continuous) and study (categorical). Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

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