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ORIGINAL PAPER

The individual and combined effects of alcohol consumption and cigarette smoking on site-specific cancer risk in a prospective cohort of 26,607 adults: results from Alberta's Tomorrow Project

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Abstract

Purpose Alcohol consumption and cigarette smoking increase the risk of developing several cancers. We examined the individual and synergistic effects of these modifiable lifestyle factors on overall and site-specific cancer risk.

Methods Baseline participant data were acquired from Alberta's Tomorrow Project (ATP). Adults 35–69 years old who consented to data linkage and completed relevant questionnaires were included ($n = 26{,}607$). Incident cases of cancer up to December 2017 were identified via linkage to the Alberta Cancer Registry. Associations between alcohol consumption, cigarette smoking, and cancer risk were examined using adjusted Cox proportional hazard models. Non-linear effects were estimated using restricted cubic splines. Interactions between alcohol and tobacco were examined through stratified analyses and inclusion of interaction terms in relevant models.

Results A total of 2,370 participants developed cancer during the study follow-up period. Cox proportional hazard models found no statistically significant associations between alcohol consumption and incidence of all cancers among males (hazard ratio [HR] 1.14, 95% confidence interval [CI] 0.93–1.40) and females ([HR] 0.89, 95% confidence interval [CI] 0.73–1.10), though a modest and positive association was observed in both males and the entire cohort using cubic splines. Smokers were at an increased risk of developing all cancers (female current smokers: [HR] 1.72, 95% [CI] 1.49–1.99, male current smokers: [HR] 1.24, 95% [CI] 1.03–1.49) with the strongest association observed between current smokers and lung cancer (males: [HR] 11.33, 95% [CI] 4.70–27.30, females: [HR] 23.51, 95% [CI] 12.70–43.60). A 3-way interaction model showed an additive effect between alcohol as a continuous variable (g/day) and pack-years (PYs) consumed for all, colon, and prostate cancers. A "U-shaped" multiplicative interaction was observed for breast cancer ($p = 0.05$).

Conclusions Alcohol consumption was minimally associated with all-cancer risk. Cigarette smoking clearly increased all-cancer risk, with females being more affected than males. Combined use of alcohol and tobacco increased the risk of developing all, colon, and prostate cancers. A "U-shaped" multiplicative interaction was observed for breast cancer when alcohol and tobacco were used in combination.

Keywords Alcohol consumption · Cigarette smoking · Cancer risk · Cohort · Alberta's Tomorrow Project

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Introduction

The annual number of cancer cases in Canada is predicted to increase by 84% in males and 74% in females through 2032 [1]. Although these increases are mainly attributable to an aging population and population growth, an increase in the incidence rates for many cancers has also been observed. These findings highlight the need for more etiologic research to identify risk factors that can be modified to reduce cancer burden. There is strong and consistent evidence that modifiable lifestyle risk factors such as cigarette smoking and alcohol consumption are associated with cancer incidence [2–7]. The synergistic effect of alcohol and tobacco is widely accepted for cancers of the upper aerodigestive tract [8–11], but there remain uncertainties regarding the magnitude of these effects at other cancer sites, and there is limited evidence for Canadian populations.

According to a 2015 Health Canada Report, almost 80% of Canadians (22 million) consumed alcohol in 2012 [11]. Classified as a Group 1 carcinogen by the International Agency for Research on Cancer in 1988, alcohol has been associated with increased risk of colorectal, female breast, oral cavity, pharynx, larynx, liver, and esophageal cancers [3, 8]. Variable by region, it is estimated that in 2012, 1.6–3.5% of cancer cases in Alberta and 2–4% of cases in Ontario were attributable to alcohol consumption [12, 13]. Although excessive alcohol intake is widely accepted as a cancer risk factor, evidence shows that light-to-moderate drinking can increase or decrease cancer incidence depending on the cancer type, reaffirming the need for site-specific analyses [14]. Distinguishing effects by type of alcohol consumed (i.e., beer, wine, and liquor) is also necessary to understand these associations by cancer site [15].

Tobacco smoke is known to contain carcinogens that lead to altered oncogene and tumor-suppressor gene expression in DNA, thereby increasing risk of cancer [16]. Specifically, cigarette smoking is associated with increased risk of lung, breast, kidney, pancreas, liver, bladder, multiple upper respiratory and digestive tract, myeloid leukemia, and colorectal cancers [7, 9, 17–19]. Smoking was estimated to attribute for approximately 15.7% of all cancers in Alberta in 2012 [20] and according to the World Health Organization, tobacco use is the most important and avoidable risk factor for cancer, responsible for roughly 22% of all cancer deaths [2, 21].

While smoking and alcohol consumption are hypothesized to have a synergistic impact on increasing overall cancer risk, less research has quantified the combined effects of alcohol and tobacco consumption at multiple primary cancer sites in large prospective analyses. Therefore, the aim of this study was to analyze the individual and synergistic effects of alcohol consumption and cigarette smoking on total and site-specific cancer incidence using data from a large prospective cohort study based in Alberta, Canada.

Methods

Study population

Participant data were acquired from Alberta's Tomorrow Project (ATP), a population-based prospective cohort study. Established in 2001, the aim of this cohort study is to measure the association between modifiable lifestyle factors and chronic disease outcomes. Detailed information regarding ATP's recruitment and enrolment, data collection, data input and cleaning, and statistical analysis has been published elsewhere [22]. Briefly, men and women aged 35–69 years were recruited via eight waves of random digit dialing during the first phase of this cohort from 2001 to 2008. Eligibility requirements included having not been previously diagnosed with cancer (excluding non-melanoma skin cancer), plans to reside in Alberta for at least one year, and the ability to complete written questionnaires in English. For these analyses, baseline participants who consented to data linkage, completed the Health and Lifestyle Questionnaire (HLQ), the Past Year Physical Activity Questionnaire (PYTPAQ), and the Canadian Diet History Questionnaire I (CDHQ-I) were included ($n = 26{,}607$). A total of 2,370 participants (1,012 males and 1,358 females) developed cancer during the study follow-up period, which was a mean of 7.2 years for cancer cases, 12.9 years for non-cancer cases, and 12.3 years for all baseline participants (Fig. 1). Ethical approval was granted by the Health Research Ethics Board of Alberta Cancer Committee and the University of Calgary Conjoint Health Research Ethics Board [22].

Data collection: questionnaires

The HLQ captured data pertaining to the participant's demographics, personal and family health and medical history, cancer screening tests, anthropometrics, and lifestyle factors including tobacco use and secondhand smoke exposure. Specifically, we were interested in the smoking status of participants (never, former, or current smoker) and cigarette pack-years (PYs) (cigarettes per day/20 × duration in years) consumed. The CDHQ-I was a detailed food frequency questionnaire that included questions on the frequency and portion size of beer, wine/wine coolers, and liquor/mixed drinks intake during the previous 12 months. The CDHQ-I data were analyzed using Diet*Calc, version 1.4.2 (Canadian version) software to obtain the nutrient and food group

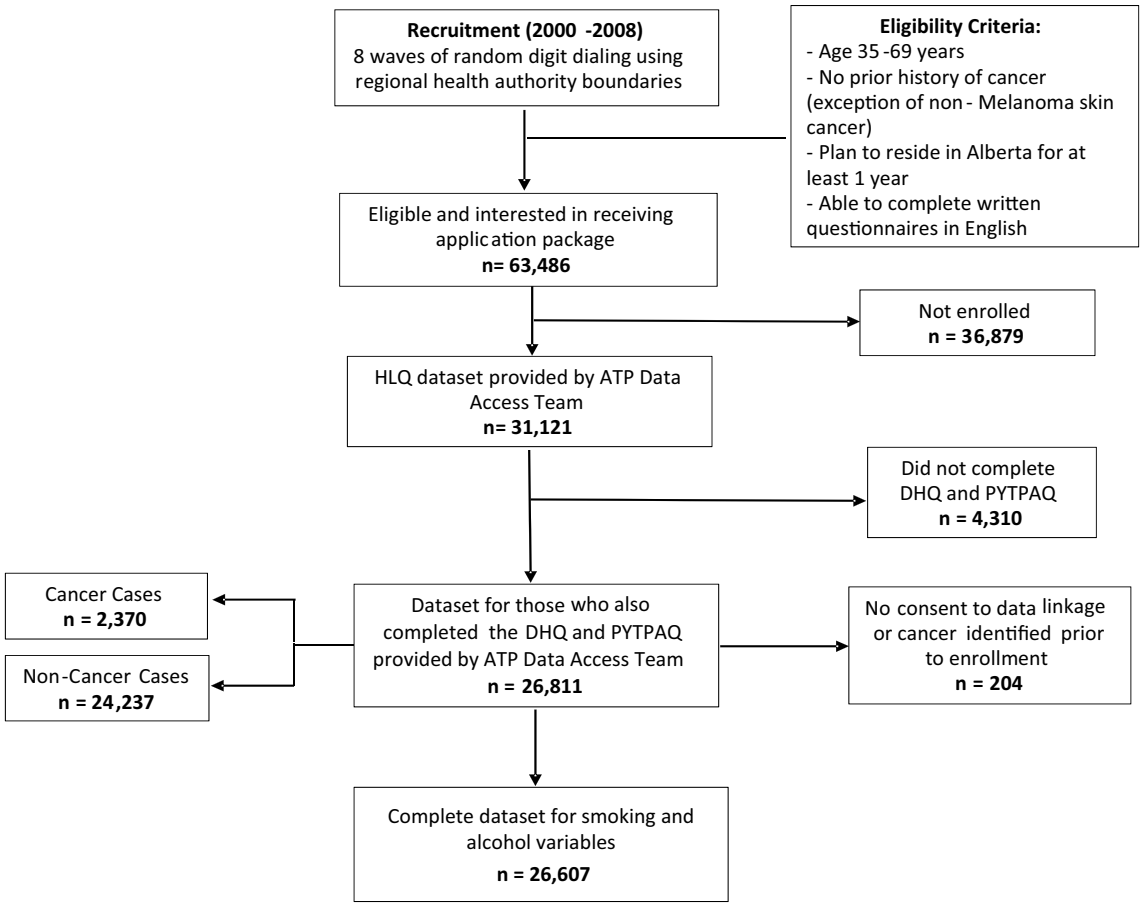

Fig. 1 Study flow diagram

variables. Lastly, the PYTPAQ captured the frequency, duration, and intensity of occupational, household, and recreational activities done in the previous 12 months. For this analysis, total physical activity levels of participants were used (MET-hours/week) as a covariate. Other covariates adjusted for include age, body mass index (BMI (kg/m^2)), cancer screening tests (prostate cancer for males, breast cancer for females, and colon cancer for both sexes), education level (high school or less/some post-high school/post-high school certificate or degree), marital status (married or living with someone/divorced, separated or widowed/single), menopausal status (female breast cancer only), and total household income ($0–$49,999/$50,000–$99,999/≥$100,000 CDN). If any covariates were missing for a given participant, this individual was removed from the multivariable-adjusted analyses.

Cancer registry linkage

Incident, primary cancers were identified through data linkage with the Alberta Cancer Registry (ACR) using participants' Personal Health Numbers up to 6 December 2017. The coding of new cancer cases by site was based on the *International Classification of Diseases for Oncology, Third Edition* [23]. The ACR has consistently achieved ≥ 95% cancer case ascertainment [24].

We considered all incident cancer cases identified through data linkage with the ACR, as well as eight site-specific cancers with greater than 100 incident cases: breast (pre- and postmenopausal analyzed separately), colon (includes cancers of the colon, rectum, and rectosigmoid junction), prostate, lung, endometrial, Non-Hodgkin lymphoma, leukemia, and hematological cancers (includes Hodgkin lymphoma, Non-Hodgkin lymphoma, leukemia, multiple myeloma and plasmacytoma, and other hematopoietic and reticuloendothelioma cancers).

Statistical analysis

Cox proportional hazard regression models were used to assess the relationship between cancer incidence, alcohol consumption, and cigarette smoking. Participants' follow-up time was calculated from their exact age at entry into the study (time of HLQ completion) to their exact age when

first-site cancer was diagnosed, or until the follow-up time ended (time of data linkage with ACR in December 2017). Age-adjusted, multivariable-adjusted, and latency multivariable-adjusted (follow-up time ≥ 2.00 years) models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for daily alcohol consumed (non-drinkers, < 1 drink, ≥ 1 drink), smoking status of participants (never, former, current), and PYs of cigarettes consumed (0 PYs, < 10 PYs, 10– < 20 PYs, ≥ 20 PYs). In our analyses, we converted total daily alcohol consumed (grams) into a categorical variable using the Canadian standard of 13.6 g of ethanol in a standard drink [25]. Approximately 82% of the participants in this cohort reported being non-drinkers or consuming < 1 drink/day, so having a relatively low value (≥ 1 drink/day) for our highest drinking category was necessary to maintain greater statistical power when stratifying by sex across nine cancer sites. We also created restricted cubic spline plots using the continuous version of the exposure variables to further examine the associations. To examine the joint effects of alcohol and tobacco, we examined stratified analyses and created joint exposure variables across categories of smoking and drinking for cancer sites with more than 150 cancer cases (all, colon, breast, lung, and prostate cancers). We evaluated the presence of interactions between alcohol and tobacco consumption by creating multiplicative terms between alcohol category and smoking group category variables. Interaction terms between alcohol and tobacco were retained in the model if the p value for the interaction term was < 0.1. We also examined a three-way effect modification between continuous alcohol intake (g/day) with PYs of smoking overall and across cancer sites. The presence of non-linear effects was determined using a test of non-linear spline terms where the non-linear term was retained in the model if $p < 0.1$. We also tested for the presence of interactions between non-linear terms for alcohol and tobacco. Non-linear analyses were performed using the RMS package in R. Independent sensitivity analyses were performed additionally adjusting for food energy consumption (kilocalories) and underweight participants (BMI < 18.5) (results not shown).

Results

Among males ($n = 10{,}026$), the mean total daily alcohol intake was slightly higher for cancer cases than non-cases (17.6 g vs. 16.7 g), whereas for females ($n = 15{,}581$), non-cases had higher mean values (6.5 g vs. 5.9 g) (Table 1). Males and females who developed cancer were more frequently former or current smokers than non-cases (males: 66.6% vs. 57.1%, females: 60.2% vs. 52.8%). Cancer cases also reported a higher percentage of participants consuming ≥ 20 PYs compared to non-cases: 33.9% vs. 22.4% for males and 28.2% vs. 15.3% for females, respectively. The non-cases were younger, more educated, had a higher total household income, lower BMI, and were frequently premenopausal (females only) at baseline compared to the cancer cases.

Alcohol

There were not statistically significant associations between total alcohol consumption and cancer risk for any site using categorical variables (Table 2). When alcohol was analyzed as a continuous variable, a moderate, non-linear, and positive association was observed between alcohol and all-cancer risk in males and the entire cohort with no association observed among females (Fig. 2). There was a strong, inverse association between total alcohol consumption and endometrial cancer incidence in the age-adjusted model (HR 0.25, 95% CI 0.10–0.64); however, the multivariable-adjusted model was no longer statistically significant (HR 0.44, 95% CI 0.17–1.16). A moderate and positive association was observed for alcohol consumption and colon cancer incidence in the male population ($P_{trend} < 0.05$ for both the age-adjusted, and multivariable-adjusted models), however, this effect was attenuated when using the latency multivariable-adjusted model ($P_{trend} = 0.12$).

When examining these associations by beverage type, there were no statistically significant associations observed for males or females for beer or liquor consumption and all-cancer incidence; however, there was a strong, inverse association observed among female wine drinkers with all-cancer incidence ($P_{trend} < 0.01$) (Supplementary Tables 1–3).

Smoking

Among males, a moderate and positive association between all cancer incidence was observed for current smokers versus never smokers and all-cancer incidence in the multivariable-adjusted model (HR 1.24, 95% CI 1.03–1.49) (Table 3). When combined with former smokers, these findings suggest being an ever smoker is associated with overall cancer incidence in the male population ($P_{trend} = 0.10$). Among females, current smoking was strongly associated with an increase in all-cancer incidence using the multivariable-adjusted model (HR 1.72, 95% CI 1.49–1.99). Both male and female former smokers were at an increased risk of developing lung cancer, however, the strongest associations were observed in current smokers (HR 11.33, 95% CI 4.70–27.30 for males; HR 23.51, 95% CI: 12.70–43.60 for females). Inverse associations were observed among prostate ($P_{trend} < 0.05$) and endometrial ($P_{trend} < 0.05$) cancer for ever smokers and cancer incidence (Table 3).

Higher levels of smoking increased all-cancer risk in both males and females (Table 4). Smoking ≥ 20 PYs marginally

Table 1 Characteristics of Alberta's Tomorrow Project study population ($n=26,607$) with baseline questionnaire data from Phase I (2000–2008)

	Male cancer ($n=1,012$)	Male non-cancer ($n=9,014$)	Female cancer ($n=1,358$)	Female non-cancer ($n=15,223$)
Follow-up time (years)	7.2 (4.0)	13.0 (2.5)	7.2 (4.0)	12.8 (2.5)
Age (years)	57.3 (8.2)	50.3 (9.0)	55.6 (9.1)	50.5 (9.1)
Body mass index (kg/m^2)	28.8 (4.8)	28.0 (4.4)	28.3 (6.4)	27.2 (5.9)
Underweight–overweight (< 30.0 kg/m^2)	66.3% ($n=671$)	72.9% ($n=6,570$)	67.5% ($n=917$)	74.4% ($n=11,321$)
Obese (≥ 30.0 kg/m^2)	33.5% ($n=339$)	26.9% ($n=2,423$)	32.0% ($n=435$)	25.4% ($n=3,865$)
Mean total physical activity (MET-hours/week)	151.8 (74.3)	173.8 (74.9)	145.6 (68.7)	157.3 (65.0)
Mean daily alcohol intake (g)	17.6 (41.3)	16.7 (45.5)	5.9 (13.8)	6.5 (19.8)
Mean daily beer intake (g)	7.7 (27.7)	9.1 (35.4)	1.4 (5.6)	1.75 (13.3)
Mean daily wine intake (g)	3.4 (10.0)	2.8 (6.9)	2.8 (10.1)	3.0 (7.6)
Mean daily liquor intake (g)	6.5 (26.4)	4.8 (24.1)	1.6 (6.5)	1.8 (10.6)
Non-drinkers	14.8% ($n=150$)	13.1% ($n=1,181$)	20.6% ($n=279$)	16.7% ($n=2,548$)
< 1 drink (0.01–13.59 g) daily	55.0% ($n=557$)	58.2% ($n=5,246$)	68.1% ($n=925$)	71.2% ($n=10,843$)
≥ 1 drink (13.60 + g) daily	30.2% ($n=305$)	28.7% ($n=2,585$)	11.3% ($n=153$)	12.1% ($n=1,826$)
Marital status				
Married or living with someone	84.4% ($n=854$)	83.2% ($n=7,497$)	72.3% ($n=982$)	76.4% ($n=11,623$)
Divorced, separated or widowed	10.6% ($n=107$)	10.3% ($n=926$)	21.7% ($n=295$)	18.4% ($n=2,796$)
Single	5.0% ($n=51$)	6.6% ($n=590$)	5.9% ($n=80$)	5.3% ($n=803$)
Education				
High school or less	32.8% ($n=332$)	24.2% ($n=2,178$)	34.9% ($n=474$)	29.5% ($n=4,487$)
Some post-high school	18.3% ($n=185$)	18.3% ($n=1,652$)	23.0% ($n=313$)	21.8% ($n=3,323$)
Post-high school certificate or degree	48.9% ($n=495$)	57.5% ($n=5,183$)	42.0% ($n=571$)	48.7% ($n=7,412$)
Total household income				
$0–$49,999	32.4% ($n=328$)	23.0% ($n=2,070$)	45.1% ($n=613$)	34.3% ($n=5,217$)
$50,000–$99,999	42.8% ($n=433$)	44.5% ($n=4,008$)	36.5% ($n=496$)	39.1% ($n=5,947$)
≥ $100,000	22.9% ($n=232$)	31.2% ($n=2,811$)	14.8% ($n=201$)	23.8% ($n=3,626$)
PYs of smoking	15.7 (19.0)	10.3 (15.0)	12.5 (16.7)	7.5 (12.2)
0 PYs consumed	35.8% ($n=362$)	46.4% ($n=4,179$)	42.1% ($n=572$)	50.4% ($n=7,665$)
0.1 to < 10.0 PYs consumed	17.3% ($n=175$)	18.2% ($n=1,645$)	16.9% ($n=230$)	22.4% ($n=3,416$)
10.0 to < 20.0 PYs consumed	13.0% ($n=132$)	13.0% ($n=1,170$)	12.7% ($n=173$)	11.9% ($n=1,812$)
20.0 + PYs consumed	33.9% ($n=343$)	22.4% ($n=2,020$)	28.2% ($n=383$)	15.3% ($n=2,330$)
Smoking status				
Never	33.4% ($n=338$)	42.9% ($n=3,866$)	39.7% ($n=539$)	47.0% ($n=7,162$)
Former	46.9% ($n=475$)	39.2% ($n=3,534$)	36.7% ($n=499$)	36.2% ($n=5,518$)
Current	19.7% ($n=199$)	17.9% ($n=1,609$)	23.5% ($n=319$)	16.6% ($n=2, 531$)
Self-reported colon cancer screening				
Yes	46.4% ($n=469$)	39.7% ($n=3,575$)	49.0% ($n=666$)	42.6% ($n=6,486$)
No	53.6% ($n=543$)	60.3% ($n=5,439$)	51.0% ($n=692$)	57.4% ($n=8,737$)
Self-reported breast cancer screening				
Yes	N/A	N/A	98.4% ($n=1,336$)	97.5% ($n=14,838$)
No	N/A	N/A	1.6% ($n=22$)	2.5% ($n=383$)
Self-reported prostate cancer screening				
Yes	88.1% ($n=892$)	74.7% ($n=6,730$)	N/A	N/A
No	11.9% ($n=120$)	25.3% ($n=2,283$)	N/A	N/A
Menopausal status				
Premenopausal	N/A	N/A	31.8% ($n=432$)	52.6% ($n=8,015$)
Postmenopausal	N/A	N/A	68.2% ($n=926$)	47.4% ($n=7,207$)

Means and standard deviations are reported for continuous variables and proportions; sample sizes are reported for categorical variables

Table 2 Associations between overall alcohol consumption (drinks/day) and cancer incidence among males ($n = 10{,}026$) and females ($n = 16{,}581$)

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
All-cancer								
Non-drinkers	150	1.0 (Ref.)	143	1.0 (Ref.)	279	1.0 (Ref.)	261	1.0 (Ref.)
< 1 drink	557	1.01 (0.84, 1.21)	550	1.04 (0.86, 1.25)	925	0.90 (0.79, 1.03)	890	0.92 (0.80, 1.06)
≥ 1 drink	305	1.12 (0.92, 1.36)	299	1.14 (0.93, 1.40)	153	0.90 (0.74, 1.10)	150	0.89 (0.73, 1.10)
P for trend		0.19		0.16		0.21		0.24
Prostate cancer								
Non-drinkers	60	1.0 (Ref.)	57	1.0 (Ref.)	–	–	–	–
< 1 drink	239	1.09 (0.82, 1.45)	236	1.12 (0.84, 1.51)	–	–	–	–
≥ 1 drink	102	0.95 (0.69, 1.30)	100	1.00 (0.71, 1.39)	–	–	–	–
P for trend		0.56		0.80	–	–	–	–
Breast cancer—premenopausal								
Non-drinkers	–	–	–	–	27	1.0 (Ref.)	24	1.0 (Ref.)
< 1 drink	–	–	–	–	144	1.06 (0.70, 1.60)	140	1.13 (0.73, 1.75)
≥ 1 drink	–	–	–	–	24	1.01 (0.58, 1.75)	23	1.01 (0.56, 1.81)
P for trend	–	–	–	–		0.96	–	0.97
Breast cancer—postmenopausal								
Non-drinkers	–	–	–	–	64	1.0 (Ref.)	62	1.0 (Ref.)
< 1 drink	–	–	–	–	192	0.91 (0.69, 1.21)	185	0.88 (0.66, 1.18)
≥ 1 drink	–	–	–	–	32	0.94 (0.62, 1.45)	31	0.90 (0.57, 1.40)
P for trend	–	–	–	–	–	0.68	–	0.62
Endometrial cancer								
Non-drinkers	–	–	–	–	31	1.0 (Ref.)	26	1.0 (Ref.)
< 1 drink	–	–	–	–	89	0.74 (0.49, 1.12)	79	0.90 (0.57, 1.41)
≥ 1 drink	–	–	–	–	5	0.25* (0.10, 0.64)	5	0.44 (0.17, 1.16)
P for trend	–	–	–	–		< 0.01		0.16
Colon cancer								
Non-drinkers	9	1.0 (Ref.)	9	1.0 (Ref.)	25	1.0 (Ref.)	25	1.0 (Ref.)
< 1 drink	41	1.25 (0.61, 2.58)	41	1.21 (0.59, 2.51)	71	0.79 (0.49, 1.25)	68	0.79 (0.49, 1.25)
≥ 1 drink	33	2.04† (0.97, 4.27)	32	1.93† (0.91, 4.10)	13	0.88 (0.44, 1.75)	13	0.86 (0.39, 1.86)
P for trend		< 0.05		< 0.05		0.55		0.31
Lung cancer								
Non-drinkers	15	1.0 (Ref.)	13	1.0 (Ref.)	37	1.0 (Ref.)	34	1.0 (Ref.)
< 1 drink	35	0.68 (0.37, 1.24)	34	0.79 (0.42, 1.51)	78	0.66* (0.45, 0.98)	74	0.59* (0.39, 0.90)
≥ 1 drink	24	0.95 (0.50, 1.81)	23	0.91 (0.45, 1.83)	21	1.12 (0.65, 1.91)	21	0.72 (0.41, 1.25)
P for trend		0.90		0.92		0.79		0.15
Leukemia								
Non-drinkers	5	1.0 (Ref.)	5	1.0 (Ref.)	9	1.0 (Ref.)	8	1.0 (Ref.)
< 1 drink	33	1.72 (0.67, 4.42)	32	1.56 (0.61, 4.04)	32	0.98 (0.47, 2.07)	31	1.10 (0.50, 2.43)
≥ 1 drink	16	1.68 (0.61, 4.59)	15	1.42 (0.50, 3.97)	3	0.56 (0.15, 2.07)	3	0.61 (0.16, 2.35)
P for trend		0.43		0.68		0.48		0.62
Non-Hodgkin lymphoma								
Non-drinkers	9	1.0 (Ref.)	9	1.0 (Ref.)	13	1.0 (Ref.)	12	1.0 (Ref.)
< 1 drink	27	0.77 (0.36, 1.63)	27	0.80 (0.38, 1.72)	29	0.62 (0.32, 1.21)	29	0.74 (0.37, 1.48)
≥ 1 drink	17	0.97 (0.43, 2.18)	17	1.14 (0.50, 2.63)	5	0.65 (0.23, 1.84)	5	0.89 (0.30, 2.63)
P for trend		0.88		0.59		0.26		0.64
Hematological cancers								
Non-drinkers	14	1.0 (Ref.)	14	1.0 (Ref.)	23	1.0 (Ref.)	21	1.0 (Ref.)
< 1 drink	60	1.10 (0.61, 1.97)	59	1.07 (0.60, 1.93)	63	0.76 (0.47, 1.23)	62	0.87 (0.52, 1.44)

Table 2 (continued)

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
≥ 1 drink	35	1.29 (0.69, 2.40)	34	1.29 (0.68, 2.44)	8	0.58 (0.26, 1.31)	8	0.70 (0.30, 1.62)
P for trend		0.37		0.37		0.15		0.40

$^{**}p < 0.01$, $^{*}p < 0.05$, $^{\dagger}p < 0.10$

[a]Adjusted for age (continuous), sex (for non-sex-specific cancers), marital status (married or living with someone/divorced, separated, or widowed/single, never married), highest level of education (high school or less/some post-high school education/post-high school certificate or degree), total household income ($0 to $49,999/$50,000 to $99,999/≥ $100,000), smoking status (current/former/never), PYs of cigarettes (0 PYs, < 10 PYs, 10 to < 20 PYs, ≥ 20 PYs), BMI (underweight-overweight, obese), menopausal status (pre-menopause/post-menopause) (breast cancer only), history of breast cancer screening (yes/no) (breast cancer only), history of colon cancer screening (yes/no), and history of prostate cancer screening (yes/no) (prostate cancer only)

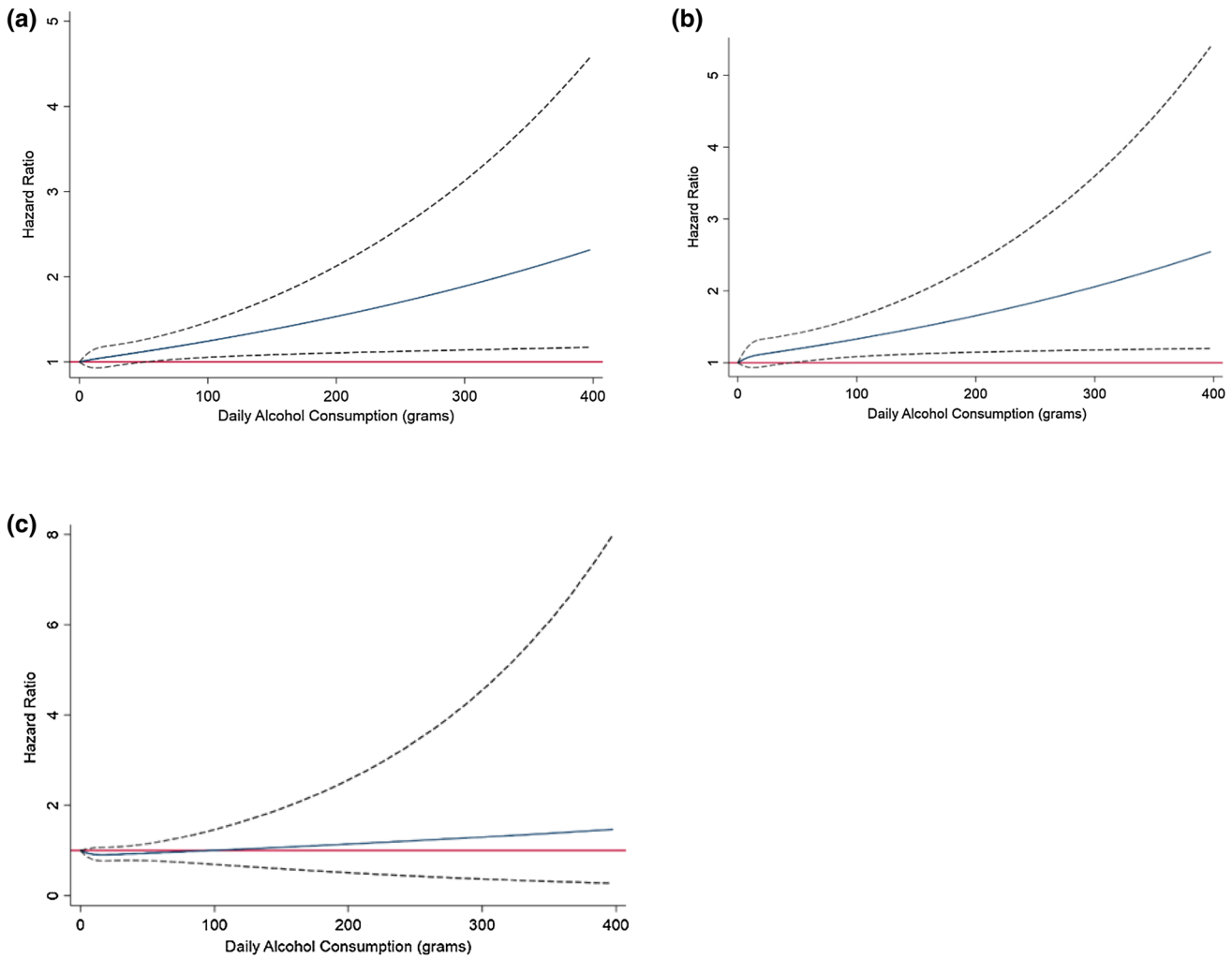

Fig. 2 Cancer incidence and alcohol consumption. **a** Effect of alcohol consumption on all-cancer risk among all participants adjusted for covariates. **b** Effect of alcohol consumption on all-cancer risk among males adjusted for covariates. **c** Effect of alcohol consumption on all-cancer risk among females adjusted for covariates

increased females risk of developing premenopausal breast cancer ($P_{trend} = 0.08$) and dramatically increased their risk of developing colon cancer ($P_{trend} < 0.01$). Risk of developing lung cancer was significantly increased by smoking ≥ 20 PYs compared to non-smokers for both males (HR 10.16, 95% CI 4.29–24.04) and females (HR 20.05, 95% CI: 10.92–36.70).

Table 3 Associations between smoking status and cancer incidence among males ($n = 10{,}026$) and females ($n = 16{,}581$)

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
All-cancer								
Never	338	1.0 (Ref.)	333	1.0 (Ref.)	539	1.0 (Ref.)	517	1.0 (Ref.)
Former	475	1.06 (0.92, 1.22)	467	1.02 (0.88, 1.18)	499	1.11† (0.99, 1.26)	481	1.11† (0.98, 1.26)
Current	199	1.31** (1.10, 1.56)	192	1.24* (1.03, 1.49)	319	1.73** (1.51, 1.99)	303	1.72** (1.49, 1.99)
P for trend		< 0.05		0.10		< 0.01		< 0.01
Prostate cancer								
Never	162	1.0 (Ref.)	158	1.0 (Ref.)	–	–	–	–
Former	189	0.86 (0.69, 1.06)	186	0.85 (0.69, 1.06)	–	–	–	–
Current	50	0.69* (0.50, 0.95)	49	0.70* (0.51, 0.98)	–	–	–	–
P for trend		< 0.05		< 0.05	–	–	–	–
Breast cancer—premenopausal								
Never	–	–	–	–	87	1.0 (Ref.)	83	1.0 (Ref.)
Former	–	–	–	–	71	1.16 (0.85, 1.59)	70	1.23 (0.89, 1.70)
Current	–	–	–	–	37	1.23 (0.84, 1.80)	34	1.19 (0.79, 1.80)
P for trend	–	–	–	–		0.23		0.23
Breast cancer—postmenopausal								
Never	–	–	–	–	123	1.0 (Ref.)	119	1.0 (Ref.)
Former	–	–	–	–	120	1.09 (0.85, 1.41)	115	1.07 (0.82, 1.38)
Current	–	–	–	–	45	1.03 (0.73, 1.45)	44	1.07 (0.75, 1.53)
P for trend		–		–		0.63		0.61
Endometrial cancer								
Never	–	–	–	–	75	1.0 (Ref.)	66	1.0 (Ref.)
Former	–	–	–	–	35	0.57** (0.38, 0.85)	31	0.56** (0.36, 0.86)
Current	–	–	–	–	15	0.57* (0.33, 0.99)	13	0.59† (0.32, 1.09)
P for trend	–	–	–	–		< 0.05		< 0.05
Colon cancer								
Never	23	1.0 (Ref.)	23	1.0 (Ref.)	42	1.0 (Ref.)	42	1.0 (Ref.)
Former	44	1.43 (0.86, 2.39)	44	1.30 (0.77, 2.18)	44	1.25 (0.82, 1.91)	43	1.24 (0.81, 1.91)
Current	16	1.55 (0.82, 2.94)	15	1.32 (0.67, 2.59)	23	1.65† (0.99, 2.74)	21	1.48 (0.86, 2.54)
P for trend		0.12		0.31		0.07		0.14
Lung cancer								
Never	6	1.0 (Ref.)	6	1.0 (Ref.)	13	1.0 (Ref.)	12	1.0 (Ref.)
Former	29	3.22** (1.33, 7.77)	28	2.81* (1.15, 6.84)	41	3.71** (1.99, 6.92)	38	3.80** (1.98, 7.27)
Current	39	14.71** (6.2, 34.8)	38	11.33** (4.7, 27.3)	82	22.1** (12.3, 39.7)	79	23.51** (12.7, 43.6)
P for trend		< 0.01		< 0.01		< 0.01		< 0.01
Leukemia								
Never	18	1.0 (Ref.)	18	1.0 (Ref.)	17	1.0 (Ref.)	16	1.0 (Ref.)
Former	26	1.18 (0.64, 2.18)	25	1.29 (0.69, 2.41)	20	1.41 (0.74, 2.70)	19	1.54 (0.79, 3.03)
Current	10	1.23 (0.57, 2.67)	9	1.46 (0.64, 3.34)	7	1.20 (0.50, 2.90)	7	1.41 (0.57, 3.50)
P for trend		0.54		0.32		0.41		0.25
Non-Hodgkin lymphoma								
Never	20	1.0 (Ref.)	20	1.0 (Ref.)	26	1.0 (Ref.)	26	1.0 (Ref.)
Former	27	1.14 (0.64, 2.07)	27	1.05 (0.57, 1.91)	17	0.78 (0.42, 1.44)	16	0.74 (0.39, 1.38)
Current	6	0.67 (0.27, 1.66)	6	0.64 (0.25, 1.62)	4	0.46 (0.16, 1.32)	4	0.46 (0.16, 1.35)
P for trend		0.73		0.59		0.15		0.13
Hematological cancers								
Never	39	1.0 (Ref.)	39	1.0 (Ref.)	45	1.0 (Ref.)	44	1.0 (Ref.)
Former	54	1.17 (0.77, 1.77)	53	1.16 (0.75, 1.78)	37	0.99 (0.64, 1.53)	35	0.99 (0.63, 1.55)

Table 3 (continued)

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
Current	16	0.91 (0.51, 1.63)	15	0.96 (0.52, 1.76)	12	0.78 (0.41, 1.49)	12	0.85 (0.44, 1.63)
P for trend		0.88		0.79		0.59		0.72

$^{**}p<0.01$, $^{*}p<0.05$, $^{\dagger}p<0.10$

[a]Adjusted for age (continuous), sex (for non-sex-specific cancers), marital status (married or living with someone/divorced, separated, or widowed/single, never married), highest level of education (high school or less/some post-high school education/post-high school certificate or degree), total household income ($0 to $49,999/$50,000 to $99,999/≥ $100,000), alcohol consumption (grams of ethanol per day), BMI (underweight-overweight, obese), menopausal status (pre-menopause/post-menopause) (breast cancer only), history of breast cancer screening (yes/no) (breast cancer only), history of colon cancer screening (yes/no), and history of prostate cancer screening (yes/no) (prostate cancer only)

A significantly increased risk of lung cancer was observed in females but not in males when smoking 10 to < 20 PYs (HR 7.46, 95% CI: 3.61–15.41). For prostate cancer, a moderate and inverse association was found between higher PYs consumed and cancer incidence compared to baseline ($p=0.03$). For endometrial cancer, a strong and inverse association with cancer incidence was found with < 10 PYs of exposure compared to the non-smoking reference group (HR 0.38, 95% CI 0.20–0.72). This association became less statistically significant and more positive in the highest PYs category compared to baseline for multivariable-adjusted models (HR 0.50, 95% CI 0.28–0.89) with an overall $P_{trend}<0.05$.

Synergistic effects of smoking and alcohol consumption

For males, HRs in all categorical analyses of alcohol/PYs were greater than the reference category (non-drinkers and non-smokers) with statistically significant risks observed where ≥ 20 PYs were consumed ($p=0.02$) (Table 5). Among all categories for males and females where PYs exceeded ≥ 20, a statistically significant and positive association between alcohol/PYs and all cancer incidence was observed with risk estimates between 1.55 and 1.80 ($P_{trend}<0.01$). In analyses using the continuous form of the variables, a " U-shaped" multiplicative effect was observed for alcohol/PYs and breast cancer ($p=0.05$) (Supplementary Fig. 1b), whereas for colon and prostate cancer, suggestion of an additive effect was observed (Supplementary Figs. 1c and 1d).

Discussion

Among participants of Phase I of the Alberta's Tomorrow Project cohort, alcohol was associated with colon cancer risk among men, showing evidence of a dose–response relationship. Wine was the only beverage type with a significant impact on all-cancer risk, with a 24% reduced risk in females. As expected, cigarette smoking appeared to have a greater impact on cancer risk in comparison to alcohol, affecting multiple cancer sites and overall cancer risk.

There is established evidence for the effect of alcohol's causal association with cancers of the upper aerodigestive tract, liver, colorectum, and female breast [18]. Several studies have also determined a dose–response relationship with these site-specific cancers showing that excessive drinking is more detrimental compared to light-to-moderate consumption [26, 27]. In the current study, we found no linear association between overall alcohol consumption and all-cancer risk in females. However, when examining non-linear effects, we observed a moderately positive association between alcohol intake and all cancer risk for the entire population and in males only. These discrepant effects across sex might arise because males reported a much higher mean daily alcohol intake (17.6 g among cancer cases) compared to the female participants (5.9 g among cancer cases) and had higher tendencies towards risky patterns of use [28].

Consuming < 1 drink/day was associated with a decreased incidence of female lung cancer, while drinking ≥ 1 drink/day was associated with an increased incidence of male colon cancer. No associations between alcohol consumption and leukemia, non-Hodgkin lymphoma, hematological cancers or cancers of the prostate, and endometrium were observed which aligns with the current literature. Our findings for a lack of association between alcohol consumption and breast cancer incidence are not supported by the existing literature [2, 18]. A possible explanation is that female average alcohol intake was low (5.9 g/day in cancer cases and 6.5 g/day in non-cancer cases). In addition, having a large range of alcohol intakes in the highest drinking category (≥ 1 drink/day) combined with a small sample size may have resulted in a decreased ability to detect smaller effect sizes. For lung and colon cancer, our findings are similar to those found in a recent study where there was a decreased incidence of lung cancer in both males and females consuming ≤ 1 drink/day, and an increased incidence of colon cancer in males consuming ≤ 2 drinks/day [[15]]. Interestingly, we found that beer consumption was significantly associated with an increased risk of developing female lung cancer,

Table 4 Association between PYs of tobacco consumed and cancer incidence among males (n = 10,026) and females (n = 16,581) who completed the HLQ, PYTPAQ, DHQ, and consented to data linkage

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
All-cancer								
No PYs	362	1.0 (Ref.)	357	1.0 (Ref.)	572	1.0 (Ref.)	547	1.0 (Ref.)
< 10 PYs	175	1.06 (0.89, 1.27)	172	1.04 (0.87, 1.25)	230	0.95 (0.81, 1.10)	223	0.97 (0.83, 1.13)
10 to < 20 PYs	132	1.08 (0.89, 1.32)	129	1.04 (0.85, 1.27)	173	1.30** (1.10, 1.54)	162	1.27** (1.07, 1.52)
20 + PYs	343	1.27** (1.09, 1.48)	334	1.19* (1.02, 1.39)	383	1.77** (1.56, 2.02)	370	1.77** (1.54, 2.02)
P for trend		< 0.01		< 0.05		< 0.01		< 0.01
Prostate cancer								
No PYs	171	1.0 (Ref.)	167	1.0 (Ref.)	–	–	–	–
< 10 PYs	78	0.99 (0.76, 1.29)	77	0.99 (0.75, 1.29)	–	–	–	–
10 to < 20 PYs	52	0.89 (0.65, 1.21)	50	0.87 (0.63, 1.19)	–	–	–	–
20 + PYs	100	0.76* (0.59, 0.97)	99	0.76* (0.58, 0.98)	–	–	–	–
P for trend		< 0.05		< 0.05	–	–	–	–
Breast cancer—premenopausal								
No PYs	–	–	–	–	93	1.00 (Ref.)	89	1.00 (Ref.)
< 10 PYs	–	–	–	–	49	1.13 (0.80, 1.60)	48	1.17 (0.82, 1.67)
10 to < 20 PYs	–	–	–	–	23	1.08 (0.75, 1.70)	21	1.05 (0.65, 1.70)
20 + PYs	–	–	–	–	30	1.51* (1.00, 2.29)	29	1.57* (1.02, 2.43)
P for trend	–	–	–	–		0.08		0.08
Breast cancer—postmenopausal								
No PYs	–	–	–	–	131	1.00 (Ref.)	127	1.00 (Ref.)
< 10 PYs	–	–	–	–	56	1.05 (0.77, 1.44)	55	1.06 (0.77, 1.45)
10 to < 20 PYs	–	–	–	–	32	1.02 (0.69, 1.50)	29	0.96 (0.64, 1.45)
20 + PYs	–	–	–	–	69	1.13 (0.84, 1.51)	67	1.13 (0.83, 1.53)
P for trend	–	–	–	–		0.45		0.52
Endometrial cancer								
No PYs	–	–	–	–	82	1.0 (Ref.)	72	1.0 (Ref.)
< 10 PYs	–	–	–	–	12	0.34** (0.18, 0.62)	11	0.38** (0.20, 0.72)
10 to < 20 PYs	–	–	–	–	16	0.83 (0.49, 1.42)	14	0.82 (0.46, 1.47)
20 + PYs	–	–	–	–	16	0.53* (0.31, 0.92)	14	0.50* (0.28, 0.89)
P for trend	–	–	–	–		< 0.05		< 0.05
Colon cancer								
No PYs	26	1.0 (Ref.)	26	1.0 (Ref.)	42	1.0 (Ref.)	42	1.0 (Ref.)
< 10 PYs	15	1.26 (0.67, 2.39)	15	1.21 (0.64, 2.30)	15	0.85 (0.47, 1.54)	15	0.87 (0.48, 1.58)
10 to < 20 PYs	13	1.47 (0.76, 2.87)	13	1.35 (0.69, 2.64)	17	1.77* (1.01, 3.11)	16	1.68[†] (0.94, 3.01)
20 + PYs	29	1.48 (0.87, 2.54)	28	1.24 (0.71, 2.18)	35	2.14**(1.36, 3.36)	33	2.04** (1.28, 3.26)
P for trend		0.13		0.42		< 0.01		< 0.01
Lung cancer								
No PYs	6	1.0 (Ref.)	6	1.0 (Ref.)	14	1.0 (Ref.)	12	1.0 (Ref.)
< 10 PYs	5	1.78 (0.54, 5.85)	5	1.75 (0.53, 5.75)	4	0.72 (0.24, 2.19)	3	0.64 (0.18, 2.26)
10 to < 20 PYs	3	1.44 (0.36, 5.76)	3	1.32 (0.33, 5.28)	21	6.96** (3.54, 13.69)	19	7.46** (3.61, 15.41)
20 + PYs	60	12.56** (5.40, 29.23)	56	10.16** (4.29, 24.04)	97	17.01** (9.71, 29.80)	95	20.05** (10.92, 36.7)
P for trend		< 0.01		< 0.01		< 0.01		< 0.01
Leukemia								
No PYs	21	1.0 (Ref.)	21	1.0 (Ref.)	17	1.0 (Ref.)	16	1.0 (Ref.)
< 10 PYs	13	1.39 (0.70, 2.78)	13	1.50 (0.75, 3.00)	12	1.68 (0.80, 3.52)	11	1.75 (0.81, 3.79)
10 to < 20 PYs	8	1.16 (0.51, 2.62)	8	1.31 (0.58, 3.00)	5	1.27 (0.47, 3.45)	5	1.46 (0.53, 4.03)
20 + PYs	12	0.82 (0.40, 1.69)	10	0.84 (0.38, 1.84)	10	1.52 (0.69, 3.32)	10	1.76 (0.79, 3.96)

Table 4 (continued)

	Males				Females			
	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]	Cases	Age-adjusted	Cases	Multivariable-adjusted[a]
P for trend		0.62		0.78		0.31		0.17
Non-Hodgkin lymphoma								
No PYs	23	1.0 (Ref.)	23	1.0 (Ref.)	26	1.0 (Ref.)	26	1.0 (Ref.)
< 10 PYs	13	1.28 (0.65, 2.53)	13	1.27 (0.64, 2.51)	10	0.92 (0.44, 1.91)	10	0.95 (0.46, 1.97)
10 to < 20 PYs	6	0.81 (0.33, 1.98)	6	0.73 (0.29, 1.80)	4	0.68 (0.24, 1.94)	4	0.68 (0.23, 1.95)
20 + PYs	11	0.71 (0.34, 1.47)	11	0.61 (0.29, 1.30)	7	0.69 (0.30, 1.59)	6	0.58 (0.24, 1.44)
P for trend		0.30		0.15		0.31		0.20
Hematological cancers								
No PYs	45	1.0 (Ref.)	45	1.0 (Ref.)	45	1.0 (Ref.)	44	1.0 (Ref.)
< 10 PYs	27	1.36 (0.84, 2.19)	27	1.40 (0.86, 2.26)	22	1.16 (0.70, 1.94)	21	1.19 (0.70, 2.00)
10 to < 20 PYs	14	0.96 (0.53, 1.75)	14	0.96 (0.52, 1.77)	9	0.87 (0.42, 1.78)	9	0.92 (0.45, 1.90)
20 + PYs	23	0.75 (0.45, 1.26)	21	0.71 (0.41, 1.21)	18	1.03 (0.60, 1.79)	17	1.04 (0.58, 1.84)
P for trend		0.25		0.20		0.99		0.96

$^{**}p < 0.01$, $^{*}p < 0.05$, $^{\dagger}p < 0.10$

[a]Adjusted for age (continuous), sex (for non-sex-specific cancers), marital status (married or living with someone/divorced, separated, or widowed/single, never married), highest level of education (high school or less/some post-high school education/post-high school certificate or degree), total household income ($0 to $49,999/$50,000 to $99,999/≥ $100,000), alcohol consumption (grams of ethanol per day), BMI (underweight-overweight, obese) menopausal status (pre-menopause/post-menopause) (breast cancer only), history of breast cancer screening (yes/no) (breast cancer only), history of colon cancer screening (yes/no), and history of prostate cancer screening (yes/no) (prostate cancer only)

Table 5 Combined effects of alcohol and PYs of smoking and cancer incidence among males ($n = 10{,}026$) and females ($n = 16{,}581$)

	Multivariable-adjusted							
	Cases	No PYs	Cases	< 10 PYs	Cases	10 to < 20 PYs	Cases	20 + PYs
Males								
All-cancer								
Non-drinkers	51	1.0 (Ref.)	20	1.14 (0.68, 1.91)	15	1.16 (0.65, 2.07)	57	1.49* (1.02, 2.18)
< 1 drink	226	1.21 (0.89, 1.64)	91	1.15 (0.82, 1.63)	72	1.25 (0.87, 1.79)	161	1.34† (0.98, 1.84)
≥ 1 drink	80	1.27 (0.89, 1.81)	61	1.45* (1.00, 2.11)	42	1.23 (0.81, 1.85)	116	1.51* (1.09, 2.11)
P for trend								< 0.01
P-interaction								0.02
Females								
All-cancer								
Non-drinkers	133	1.0 (Ref.)	36	1.00 (0.69, 1.45)	18	0.98 (0.60, 1.60)	74	1.71** (1.29, 2.27)
< 1 drink	391	0.93 (0.76, 1.14)	154	0.85 (0.68, 1.08)	114	1.15 (0.90, 1.48)	231	1.55** (1.24, 1.91)
≥ 1 drink	23	0.52** (0.33, 0.82)	33	0.92 (0.63, 1.35)	30	1.35 (0.91, 2.01)	64	1.80** (1.34, 2.43)
P for trend								< 0.01
P-interaction								< 0.01

$^{**}p < 0.01$, $^{*}p < 0.05$, $^{\dagger}p < 0.10$

[a]Adjusted for age (continuous), sex (for non-sex-specific cancers), marital status (married or living with someone/divorced, separated, or widowed/single, never married), highest level of education (high school or less/some post-high school education/post-high school certificate or degree), total household income ($0 to $49,999/$50,000 to $99,999/≥ $100,000, BMI (underweight-overweight, obese)

while consuming < 1 drink/day of wine or liquor decreased female lung cancer risk, suggesting beverage type might play a role in the etiology of this disease. Female wine drinkers also had a 24% risk reduction for all cancers. The possible mechanisms behind these associations include the presence of flavonoids and resveratrol in red wine, which is thought to reduce cancer risk by inhibiting certain metabolic processes [29, 30].

In this cohort, we found a significantly increased risk of all cancers in current smokers, female former smokers, males with ≥ 20 PYs consumed, and females with ≥ 10 PYs consumed. These results suggest both a dose–response relationship and the possibility that cigarette smoking has a slightly greater effect on female cancer risk. We also observed that consuming ≥ 10 PYs was associated with increased female colon cancer risk. The strongest site-specific association observed among all analyses was between smoking and lung cancer with a substantially increased risk in males and females smoking ≥ 20 PYs.

The current literature is inconsistent in identifying increased cancer risk among female smokers compared to male smokers [31, 32]. Based on our findings that female current smokers and females smoking ≥ 10 PYs have higher HRs for all cancers and lung cancer compared to males, coupled with the findings that female never smokers had a higher incidence of cancer compared to males, we can conclude that females have a higher absolute risk and susceptibility to the effects of lung carcinogens. Continued research is required to clarify the varying magnitude of effect caused by cigarette smoking based on sex and the potential for other influencing factors such as genetics, age that smoking was initiated, and specific histological types. Our finding that cigarette smoking has a protective effect against endometrial cancer is consistent with existing literature [33–35]. Interestingly, one study using EPIC cohort data found that among premenopausal women, long-term smokers were at a two-fold greater risk of developing endometrial cancer compared to never smokers, while postmenopausal women had a 30% risk reduction [36]. Although body mass index was adjusted for in our analyses, effect modification and residual confounding is still possible given the established inverse association between smoking and BMI, and the positive association between BMI and endometrial cancer. Future research should clarify the interactions and associations between endometrial cancer, smoking, excess adiposity, and menopausal status.

Inconsistency exists in the literature when assessing the relationship between smoking and prostate cancer risk. In agreement with our findings, the 2017 UK Biobank cohort observed that smoking reduced men's risk of developing prostate cancer by 7–15% depending on smoking status (former vs. current) [37]. However, a pooled data analysis of 24 cohort studies found that all smokers were at an increased risk of developing prostate cancer compared to non-smokers [38].

Alcohol and smoking are most strongly associated with cancers of the upper aerodigestive tract with ample evidence to suggest that when combined, these risk factors act in a multiplicative way. However, less is known about the combined effect of alcohol and smoking at other primary cancer sites and this study is among the first to systematically investigate the presence of non-linear multiplicative effects between alcohol and tobacco in a prospective cohort study. Our findings suggest that alcohol and smoking have an additive effect on all, colon, and prostate cancer risk. However, it seems that this interaction is not observed unless excessive amounts of alcohol and PYs are consumed (≥40 PYs and ≥ 50 g of alcohol daily). The Singapore Chinese Health Study in 2007 also found an additive effect of alcohol and tobacco use on rectal cancer, but found no significant effect on colon cancer. These differences may be attributed to the different biological mechanisms tobacco carcinogens have on the tissues of the colon and rectum [39]. For breast cancer, a "U shape" association was observed (supplementary Fig. 1b) as moderate alcohol consumption and minimal tobacco use was associated with lower cancer incidence; this interaction rapidly changes in a multiplicative fashion when alcohol consumption and PYs increase. Lastly, we observed no synergistic effect between alcohol, PYs consumed, and lung cancer incidence, suggesting that tobacco use is the strongest etiologic driver for increased lung cancer risk [40]. A previous study looking at the synergistic effects of alcohol and tobacco consumption found similar results related to lung cancer risk [38].

This study has several strengths worth mentioning. First, the prospective cohort study design supported our ability to examine longitudinal relationships between smoking, alcohol consumption, and cancer incidence. Second, we utilized questionnaires previously shown to be valid and reliable, allowing us to examine detailed information pertaining to smoking habits, alcohol consumption, and numerous confounders. Third, we examined for the presence of non-linear effects using restricted cubic spline terms within interaction terms and considered the synergistic effects of alcohol and tobacco use which provides enhanced insight into the nature of these findings.

Despite these strengths, there are a few limitations that should be acknowledged when considering the results of this study. First, all the data were acquired from participant questionnaires. Although the questionnaires were valid and reliable, using self-reported data likely resulted in underestimations of cigarette smoking and alcohol consumption due to social desirability bias, which may have introduced non-differential misclassification bias. Second, smaller sample sizes for individual analyses were the result of conducting nine site-specific analyses, stratifying by sex, and stratifying alcohol consumption by beverage type. This level of stratification reduced the statistical power to detect effects. Also, since most study participants consumed less alcohol compared to the overall Canadian population in 2012, the representativeness of our sample is slightly skewed. Generalizing our results to the public, we may consider the possibility of even stronger associations between alcohol, tobacco, and cancer incidence given a different sample population

where alcohol consumption was higher. Lastly, although we were able to adjust for several sociodemographic, lifestyle, and health-related variables, the possibility of residual and unmeasured confounding remains. Previous studies have observed that the effects of alcohol can vary depending on an individual's overall dietary intake which was not adjusted for in the current study. We did perform additional sensitivity analyses for food energy consumption (kilocalories) and the adjustment did not meaningfully impact the main findings (results not shown). An important mechanism linking diet and cancer is the direct link between diet and obesity which is often the strongest non-tobacco modifiable risk factor for several cancers. We did adjust our primary analyses for BMI and we performed additional sensitivity analyses including those with low BMI (<18.5) in our analyses and did not observe meaningful impacts on the main findings (results not shown). Examining the impact of specific foods and nutrients on the associations with alcohol and tobacco was beyond the scope of these analyses. Hormone replacement therapy, oral contraceptive use, distribution of adipose tissue, and the presence of diabetes were also not adjusted for and might have an effect on the association between smoking and endometrial cancer.

Alcohol and tobacco use are modifiable lifestyle factors that strongly influence cancer incidence depending on frequency of use, duration of use, and cancer site. Often, excessive use of one of these risk factors is positively associated with the other, which can further exacerbate and compound chronic disease risk. Future research efforts should continue assessing the combined consumption patterns of alcohol and tobacco and the potential for synergistic impact. Additional research of the impact of alcohol among former smokers is needed to reduce cancer risk post successful smoking cessation. Also, a better understanding is required concerning the differential impact of alcohol and tobacco on men and women, along with the possible biological or sociocultural mechanisms behind these interactions.

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