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Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States)

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Data from a population-based study of newly diagnosed cases of prostate cancer ($n = 362$) and age-matched controls ($n = 685$) conducted in Utah (United States) between 1983 and 1986 were used to determine if cigarette smoking, alcohol, coffee, tea, caffeine, and theobromine were associated with prostate cancer risk. These factors were examined since their use differs in the Utah population, which is comprised predominantly of members of the Church of Jesus Christ of Latter-day Saints (LDS or Mormon), from most other populations. Pack-years of cigarettes smoked, alcohol intake, and consumption of alcohol, coffee, tea, and caffeine were not associated with prostate cancer risk. Compared with men with very low levels of theobromine intake, older men consuming 11 to 20 and over 20 mg of theobromine per day were at increased risk of prostate cancer (odds ratio [OR] for all tumors = 2.06, 95 percent confidence interval [CI] = 1.33-3.20, and OR = 1.47, CI = 0.99-2.19, respectively; OR for aggressive tumors = 1.90, CI = 0.90-3.97, and OR = 1.74, CI = 0.91-3.32, respectively). We present biological mechanisms for a possible association between prostate cancer and theobromine. This finding needs further exploration in studies with a wider range of theobromine exposures and more men with aggressive tumors.

Key words: Alcohol, caffeine, coffee, males, prostate cancer, smoking, theobromine, tea, United States.

Introduction

Little is known about the etiology of prostate cancer despite the fact that several analytic studies have been conducted to determine its origins.[1-3] In Utah (United States), prostate cancer is the most commonly occurring cancer among men and, unlike many other cancers where the Utah population is considered one of low risk, the incidence rate of prostate cancer is higher than that observed throughout most areas of the US.[4] In 1985, a population-based case-control study was conducted in Utah to identify environmental factors associated with prostate cancer. In this paper, we evaluate the associations between cigarette smoking, and consumption of alcohol, coffee, tea, caffeine, and theobromine. These factors are examined since the Utah population is predominantly Mormon, or members of the Church of Jesus Christ of Latter-day Saints, a religion which proscribes smoking and consumption of alcohol and of coffee and tea, which are major contributors in most populations to caffeine and theobromine intake. Examination of these factors in this population has been shown to have utility in identification of risk factors for other cancers.[5,6]

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Table 1. Prostate cancer risk associated with cigarette smoking by age, Utah

Pack-years	≤67 Years				>67 years			
	Cases	Controls	OR[a]	(CI)[b]	Cases	Controls	OR[a]	(CI)[b]
All tumors								
0	79	184	1.00	(referent)	88	149	1.00	(referent)
1-28.6	44	96	1.07	(0.71-1.59)	44	80	0.93	(0.62-1.40)
>28.6	56	105	1.24	(0.86-1.80)	47	65	1.22	(0.81-1.85)
P value for linear trend			0.34				0.50	
Aggressive tumors								
0	18	184	1.00	(referent)	23	149	1.00	(referent)
1-28.6	9	96	0.96	(0.43-2.09)	11	80	0.89	(0.43-1.81)
>28.6	11	105	1.07	(0.51-2.22)	15	65	1.50	(0.77-2.88)
P value for linear trend			0.96				0.38	

[a] OR = odds ratio.
[b] CI = 95% confidence interval.

Materials and methods

White men, aged 45 to 74 years and living in Salt Lake, Davis, Utah, and Weber counties in Utah were eligible for inclusion in this study. All cases were histologically confirmed, first-primary prostate cancer. Cases diagnosed between 1 January 1984 and 15 November 1985 were identified through a rapid reporting system which is used to abstract cases from pathology laboratories. Controls were matched to cases by five-year age categories. Controls less than 65 years of age were selected by random-digit dialing (RDD)[7,8] and controls over 65 were selected from lists provided by the Health Care Financing Administration (social security). The completion rate for cases was 77.4 percent and for controls it was 76.9 percent. A detailed description of study methods and methods used to calculate study completion rates have been published.[1]

The reference period for the study was the three years prior to diagnosis or onset of symptoms for cases and the three-year period prior to interview for controls. A quantitative food-frequency questionnaire was used to ascertain the frequency and amount of alcohol, coffee, and tea consumed.[9] The Utah State University nutrient-database was used to obtain levels of caffeine and theobromine intake from all foods listed on the 183 food frequency questionnaires. Caffeine and theobromine levels in the database were from the US Department of Agriculture food composition tables, Handbook 8. The major sources of caffeine and theobromine in this population were colas, coffee, tea, and chocolate. Participants were asked if they ever smoked cigarettes, the quantity usually smoked, and the number of years that they smoked cigarettes. Using this information, number of pack-years smoked was determined.

Information about tumors was obtained from the Utah Cancer Registry. Using information on stage and histology, we estimated tumor aggressiveness. Aggressive tumors were defined as undifferentiated localized tumors and well-differentiated to undifferentiated regional or distant tumors. This was done to discriminate better between cases and controls since autopsy studies have estimated that as many as 50 percent of men in the population have undiagnosed prostate tumors at the time of death.[10,11] It also was of interest to determine if risk factors for prostate cancers differed by tumor aggressiveness.

Statistical methods

Associations were evaluated by age (≤67 and >67 years) and by tumor aggressiveness using odds ratios (OR) and corresponding 95 percent confidence intervals (CI) derived by the Cornfield method.[12] Age 67 was used as a stratification point since examination of data by smaller age groups indicated that effects may change between 65 and 70 years of age. Additionally, since 50 percent of the cases in this study were 67 or less years of age and 50 percent were over 67 years of age, we were able to maximize our power to examine age effects by using age 67 as a stratification point. Crude ORs are presented since adjustment for other factors including dietary intake, body size, age within strata, and demographic characteristics did not alter these associations. Four cases and six controls were not included in the analyses because interviewers felt that the data were unreliable.

Results

Cigarette smoking as assessed by pack-years smoked, was not associated with prostate cancer risk (Table 1), although a slight elevation in risk was observed for

Table 2. Prostate cancer risk associated with alcohol consumption by age, Utah

	≤67 Years				>67 years			
	Cases	Controls	OR[a]	(CI)[b]	Cases	Controls	OR[a]	(CI)[b]
All tumors								
Total alcohol								
None	90	210	1.00	(referent)	121	196	1.00	(referent)
Any	89	175	1.19	(0.87-1.63)	58	98	0.96	(0.67-1.36)
Wine								
None	130	262	1.00	(referent)	140	239	1.00	(referent)
Any	49	123	0.80	(0.57-1.14)	39	55	1.21	(0.80-1.83)
Beer								
None	114	260	1.00	(referent)	142	224	1.00	(referent)
Any	65	125	1.19	(0.85-1.65)	37	70	0.83	(0.56-1.25)
Spirits								
None	105	236	1.00	(referent)	134	211	1.00	(referent)
Any	74	149	1.12	(0.81-1.54)	45	83	0.85	(0.59-1.24)
Aggressive tumors								
Total alcohol								
None	16	210	1.00	(referent)	31	196	1.00	(referent)
Any	22	175	1.65	(0.89-3.08)	18	98	1.16	(0.65-2.06)
Wine								
None	27	262	1.00	(referent)	36	239	1.00	(referent)
Any	11	123	0.87	(0.44-1.70)	13	55	1.57	(0.82-2.97)
Beer								
None	24	260	1.00	(referent)	38	224	1.00	(referent
Any	14	125	1.21	(0.64-2.29)	11	70	0.93	(0.47-1.79)
Spirits								
None	20	236	1.00	(referent)	36	211	1.00	(referent)
Any	18	149	1.42	(0.77-2.63)	13	83	0.92	(0.49-1.72)

[a] OR = odds ratio.
[b] CI = 95% confidence interval.

older men with aggressive tumors (OR = 1.50, CI = 0.77-2.88). The most frequent type of alcohol consumed was spirits, with approximately 15 percent of both cases and controls reported having drunk more than two 1.5 oz shots of hard liquor per week. Approximately 11 percent of cases and controls drank more than two 12 oz beers per week, and 10 percent of controls and seven percent of cases drank more than two 6 oz glasses of wine per week. Assessment of alcohol intake (Table 2) among men who had aggressive tumors showed a nonstatistically significant increased risk from total alcohol consumption among younger men (OR = 1.65, CI = 0.89-3.08) and from wine consumption for older men (OR = 1.57, CI = 0.82-2.97). No significant associations were observed between consumption of coffee, tea, and caffeine and prostate cancer risk (Table 3). Among older men, consumption of theobromine was associated with an increased risk of prostate cancer. This association was observed for all tumors as well as for more aggressive tumors. However, the confidence intervals generally include one, possibly from limited numbers of men in the higher consumption categories. A significant linear trend was observed only between theobromine intake and risk of prostate cancer in older men ($P = 0.04$).

Discussion

While prostate cancer rates are high in Utah compared with other areas of the US, environmental factors which are different in Utah because of the religious beliefs of much of the population do not appear to influence risk of the disease. In this study, 75 percent of both cases and controls stated that they were members of the Church of Jesus Christ of Latter-day Saints, approximately half of whom are active church members.

We believe, and have shown in other reports,[1,9] that examination of tumors by degree of aggressiveness is informative since tumor aggressiveness more clearly discriminates cases from controls. However, we have limited statistical power to evaluate associations with aggressive tumors, and findings therefore should be interpreted with this in mind.

Few positive associations were detected in this

Table 3. Prostate cancer risk associated with coffee, tea, caffeine and theobromine consumption by age, Utah

	≤67 Years				>67 years			
	Cases	Controls	OR[a]	(CI)[b]	Cases	Controls	OR[a]	(CI)[b]
All tumors								
Coffee (cups/wk)								
0	77	170	1.00	(referent)	84	137	1.00	(referent)
1-20	48	106	0.99	(0.68-1.47)	54	81	1.09	(0.73-1.61)
>20	54	109	1.09	(0.75-1.60)	41	76	0.88	(0.58-1.34)
P value for linear trend			0.73				0.63	
Tea (cups/wk)								
0	116	242	1.00	(referent)	127	202	1.00	(referent)
1-5	23	64	0.75	(0.47-1.20)	16	28	0.90	(0.47-1.75)
>5	40	79	1.06	(0.72-1.57)	36	64	0.90	(0.59-1.36)
P value for linear trend			0.94				0.57	
Caffeine (mg/day)								
≤50	85	187	1.00	(referent)	100	157	1.00	(referent)
51-250	37	91	0.90	(0.59-1.35)	39	63	0.97	(0.64-1.48)
>250	57	107	1.17	(0.81-1.69)	40	74	0.85	(0.56-1.28)
P value for linear trend			0.54				0.47	
Theobromine (mg/day)								
≤10	87	184	1.00	(referent)	83	175	1.00	(referent)
11-20	41	96	0.90	(0.61-1.34)	45	46	2.06	(1.33-3.20)
>20	51	105	1.03	(0.71-1.50)	51	73	1.47	(0.99-2.19)
P value for linear trend			0.99				0.04	
Aggressive tumors								
Coffee (cups/wk)								
0	15	170	1.00	(referent)	22	137	1.00	(referent)
1-20	13	106	1.39	(0.67-2.87)	15	81	1.15	(0.60-2.22)
>20	10	109	1.04	(0.47-2.26)	12	76	0.98	(0.48-1.98)
P value for linear trend			0.93				0.95	
Tea (cups/wk)								
0	22	242	1.00	(referent)	31	202	1.00	(referent)
1-5	8	64	1.38	(0.60-3.03)	6	28	1.40	(0.55-3.40)
>5	8	79	1.11	(0.50-2.44)	12	64	1.22	(0.62-2.37)
P value for linear trend			0.77				0.59	
Caffeine (mg/day)								
≤50	19	187	1.00	(referent)	26	157	1.00	(referent)
51-250	11	91	1.19	(0.57-2.46)	14	63	1.34	(0.74-2.73)
>250	8	107	0.74	(0.32-1.63)	9	74	0.73	(0.38-1.43)
P value for linear trend			0.50				0.61	
Theobromine (mg/day)								
≤10	18	184	1.00	(referent)	22	175	1.00	(referent)
11-20	12	96	1.28	(0.62-2.61)	11	46	1.90	(0.90-3.97)
>20	8	105	0.78	(0.34-1.74)	16	73	1.74	(0.91-3.32)
P value for linear trend			0.61				0.11	

[a] OR = odds ratio.
[b] CI = 95% confidence interval.

study. Although an increased risk for prostate cancer was observed among younger men who drank alcohol and among older men who drank wine, these associations were not statistically significant and may be spurious. Lack of an association between alcohol consumption and prostate cancer has been reported in at least four other studies.[2,13–15] Similarly, coffee, tea, and cigarette smoking have not been associated with prostate cancer in some studies.[2,13,15,16] although in others, associations between prostate cancer and black tea[17] and cigarette smoking[18] have been observed.

We believe that the major finding from the current study is that theobromine may increase risk of prostate cancer in older men. However, as noted in Table 3, this association is not linear for aggressive tumors, which may reflect our small numbers. While this association may be spurious, support for its plausibility can be found in the literature.

Theobromine has been shown to be genotoxic.[19,20] Like caffeine, it potentiates DNA damage by various carcinogens in human cells.[19] In one study of Chinese hamsters, sister chromatid exchange (SCE) was used as

a measure of DNA damage.[21] Theobromine was found to produce a higher and more linear rate of SCE damage than caffeine. SCE effects were observed with caffeine only when doses above a threshold of 150 mg/kg body weight were applied.[19] Theobromine also has been shown to cause testicular atrophy and spermatogenic cell abnormalities in rats.[20] While theobromine is present in tea, cocoa powder is about two percent theobromine, and therefore individuals who consume chocolate or cocoa may consume hundreds of milligrams of theobromine per day. Consumption of chocolate and cocoa do not violate the Mormon dietary restrictions.

In addition to a direct effect, theobromine could act indirectly in the etiology of prostate cancer in conjunction with hormones. We have shown in studies of twins in Utah that theobromine was associated inversely with levels of plasma androstanediol glucuronide and testosterone glucuronide.[22] Theobromine was the only significant dietary factor associated with testosterone glucuronide and explained 10 percent of its variance. It is unclear, however, what role testosterone glucuronide may play in the etiology of prostate cancer.

Little is known about the etiology of prostate cancer. We do not know if theobromine contributes to prostate cancer risk, although there are suggestions from this study that an association may exist. This finding, given the biological feasibility of an association, deserves further evaluation.

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