



BLADDER CANCER AND THE CONSUMPTION OF ALCOHOLIC BEVERAGES IN SPAIN

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The relationship between bladder cancer and alcohol consumption was investigated in a case-control study conducted in 506 patients (453 males and 53 females) with diagnoses of papillary urothelial carcinoma during 1978-1982 at « La Paz » hospital (Madrid), and an equal number of controls matched for age, sex and date of admission to the hospital. The results showed that the risk of bladder cancer does not increase with the intake of beer, wine and spirit beverages. However, a high risk of bladder cancer was associated with consumption of wine mixed with « gaseosa » (a refreshment beverage consisting of carbonated water plus artificial sweeteners).

INTRODUCTION

The association between bladder cancer and consumption of substances such as coffee and artificial sweeteners has been studied in considerable depth (6, 7, 8, 11, 12, 25). However, little attention has been devoted to the possible effects of alcohol consumption on bladder cancer. Most of these studies have failed to find any association (10, 13, 16, 26, 30). However, an increased risk of bladder cancer associated with alcoholic beverage intake has been reported in smokers but not in non-smokers, suggesting a synergistic effect (23).

Ethanol probably acts as a carcinogen on tissues with which it comes into direct contact, such as the mucosa of the digestive tract (2, 9, 23, 28, 29) and the liver parenchyma (12). In addition, ethanol seems to enhance the risk of cancer in other tissues such as the breast (21) and pancreas (5). This synergistic effect of alcohol has been explained by three mechanisms: a) alcohol

may serve as a solvent for carcinogens (23), b) alcoholic beverages may be contaminated with carcinogenic impurities (20), and c) nutritional deficiencies may be associated with alcohol use (18).

Since about 2% of alcohol ingested is excreted in the urine (14) the mucosa of the bladder is directly exposed to ethanol and is also subject to some of the above-mentioned indirect mechanisms.

This report describes a case-control study on the effects of consumption of alcoholic beverages (some combined with a refreshment beverage known as « gaseosa ») on bladder cancer in Spain.

MATERIALS AND METHODS

The case-group consisted of 506 patients (453 males and 53 females) who were diagnosed as suffering from papillary urothelial carcinoma at « La Paz » hospital (Madrid, Spain) in 1978-1982. The control-group included an equal number of

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individuals from the same hospital, whose diseases were neither malignant or benign tumors nor diseases assumed to be related to bladder cancer, such as cirrhosis or urologic diseases. The controls were matched for age (year of age \pm 0.5), sex and date of admission to the hospital, and selected through random sample. The data related to social class have previously been reported (1); no association between bladder cancer and any social class was found (Table 1). The percentage distributions of the patients and controls into different social classes were similar to those found in the normal Spanish population within these age groups.

The questionnaire included questions on the use of coffee and other drinks, artificial sweeteners, cigarette smoking, and occupational and residential histories. The questions on consumption of alcoholic beverages were placed in the middle of the questionnaire, immediately after questions on a variety of non-alcoholic beverages. The subjects were asked to estimate separately the number of « servings » of 1) beer, 2) spirits, 3) wine, and 4) wine mixed with « gaseosa » (50% of each beverage) consumed in a typical week during the winter one year previously. « Gaseosa » is a frequently consumed refreshment beverage in Spain and consists of carbonated water plus artificial sweeteners. A serving was defined as a can, bottle or draught of beer, a 44.4 ml (1.5-ounce) jigger of spirits, a 118.3 ml (4-ounce) glass of wine, and 236.6 ml (8-ounce) glass of wine mixed with gaseosa. The average alcohol consumption and patterns of drinking over time were also investigated.

The association between alcohol consumption and bladder cancer was assessed by the BMDP programs 1D, (27), 2D (7), and 4F (4). To assess the results the maximum error likelihood accepted was 5% ($P < 0.05$).

RESULTS

No significant differences with regard to alcohol consumption were found between bladder cancer patients and controls in males or in females (Table 2). The minimum number of servings ingested by consumers was 7 servings per week.

The relationship between bladder cancer and amount of alcohol consumed in different age groups of males is shown in Table 3. Since the number of female alcohol consumers was low in both the bladder cancer and control groups, the classification of alcohol consumers into categories could not be established for females. A significant association between bladder cancer and alcohol consumption was found, only in the group of males younger than 60 years of age who consumed more than 41 servings/week.

The same results were obtained when the years

TABLE 1.
Bladder cancer and social class.

| MALES | | | | |
|--------------|-------|------------|------------|-----|
| Social class | Cases | | Controls | |
| | No. | percentage | percentage | No. |
| low | 25 | 7.1 | 10.5 | 37 |
| middle-low | 264 | 74.8 | 76.2 | 269 |
| middle-high | 52 | 14.7 | 10.2 | 36 |
| high | 12 | 3.4 | 3.1 | 11 |
| total | 353 | 100 | 100 | 353 |
| FEMALES | | | | |
| Social class | Cases | | Controls | |
| | No. | percentage | percentage | No. |
| low | 9 | 17 | 22.6 | 12 |
| middle-low | 42 | 79.2 | 71.7 | 38 |
| middle-high | 2 | 3.8 | 5.7 | 3 |
| high | 0 | 0 | 0 | 0 |
| total | 53 | 100 | 100 | 53 |

TABLE 2.
Bladder cancer and alcohol consumption.

| | Cases | | Controls |
|--------------|----------------------|--------------|----------|
| | No. observed | No. expected | No. |
| Males | | | |
| non-drinkers | 71 | 78.5 | 86 |
| drinkers | 282 | 274.5 | 267 |
| | $\chi^2 = 2.43$ n.s. | | |
| | Cases | | Controls |
| | No. observed | No. expected | No. |
| Females | | | |
| non-drinkers | 43 | 39.5 | 36 |
| drinkers | 10 | 13.5 | 17 |
| | $\chi^2 = 0.38$ n.s. | | |

of alcohol consumption in different age groups were studied (Table 4).

The stratification of male bladder cancer patients and their controls in relation to the number of cigarettes and the amount of alcohol consumed weekly showed no association between bladder cancer and alcohol consumption in smokers (Table 5). No association was observed when the alcohol drinking and non-drinking male patients and their controls were stratified according to years of smoking (Table 6).

TABLE 3. — Bladder cancer and amount of alcohol consumed in males distributed by age groups.

| Servings/week | Males younger than 60 years of age | | | | | Males from 60 to 70 years of age | | | | | Males older than 70 years of age | | | | |
|---------------|------------------------------------|-------|------|------------|---------------|----------------------------------|-------|------|------------|---------------|----------------------------------|-------|------|------------|---------------|
| | case | cont. | O.R. | conf. int. | χ^2_{MH} | case | cont. | O.R. | conf. lim. | χ^2_{MH} | case | cont. | O.R. | conf. int. | χ^2_{MH} |
| non-drinkers | 21 | 34 | 1 | | | 24 | 28 | 1 | | | 26 | 24 | 1 | | |
| 7-13 | 21 | 21 | 1.6 | 0.7-3.6 | 2.7 | 19 | 19 | 1.2 | 0.5-2.7 | 0.13 | 12 | 17 | 0.65 | 0.25-1.65 | 0.82 |
| 14-27 | 22 | 30 | 1.2 | 0.5-2.6 | 0.19 | 33 | 31 | 1.24 | 0.6-2.6 | 0.33 | 50 | 40 | 1.15 | 0.6-2.3 | 0.16 |
| 28-41 | 14 | 9 | 2.5 | 0.9-6.8 | 3.3 | 17 | 22 | 0.9 | 0.4-2.1 | 0.06 | 14 | 20 | 0.6 | 0.3-1.55 | 0.93 |
| > 41 | 31 | 15 | 3.3 | 1.5-7.6 | 8.5 | 38 | 31 | 1.4 | 0.7-2.9 | 0.93 | 11 | 12 | 0.8 | 0.3-2.3 | 0.1 |

TABLE 4. — Bladder cancer and years of alcohol consumption in males distributed by age groups.

| Years alcohol consumption | Males younger than 60 years of age | | | | | Males from 60 to 70 years of age | | | | | Males older than 70 years of age | | | | |
|---------------------------|------------------------------------|-------|------|------------|---------------|----------------------------------|-------|------|------------|---------------|----------------------------------|-------|------|------------|---------------|
| | case | cont. | O.R. | conf. int. | χ^2_{MH} | case | cont. | O.R. | conf. int. | χ^2_{MH} | case | cont. | O.R. | conf. int. | χ^2_{MH} |
| 0 | 21 | 34 | 1 | | | 24 | 28 | 1 | | | 26 | 24 | 1 | | |
| 0-10 | 10 | 11 | 1.47 | 0.53-4.06 | 0.55 | | | | | | 8 | 7 | 1.05 | 0.33-3.35 | 0.08 |
| 11-20 | 20 | 17 | 1.9 | 0.82-4.43 | 2.23 | 4 | 3 | 1.5 | 0.32-7.65 | 0.29 | | | | | |
| 21-30 | 58 | 47 | 2 | 1.03-3.79 | 4.1 | | | | | | | | | | |
| 31-40 | | | | | | 80 | 76 | 1.22 | 0.65-2.30 | 0.41 | 19 | 25 | 0.7 | 0.31-1.58 | 0.72 |
| 41-50 | | | | | | 23 | 24 | 1.12 | 0.5-2.46 | 0.07 | 39 | 34 | 1.05 | 0.51-4.23 | 0.02 |
| > 50 | | | | | | | | | | | 21 | 23 | 0.84 | 0.37-1.9 | 0.17 |

TABLE 5. — Bladder cancer and amount of alcohol consumed in smokers distributed by number of cigarettes/week consumed.

| Servings/week | Number of cigarette/week consumed | | | | | | | | |
|---------------|--|----------|-------------------------|----------|------|---|----------|------|--|
| | Non-smokers | | Less than 140 cig./week | | | More than 140 cig./week | | | |
| | Cases | Controls | Cases | Controls | O.R. | Cases | Controls | O.R. | |
| non-drinkers | 13 | 47 | 20 | 24 | 1 | 38 | 15 | 1 | |
| 7-13 | 10 | 32 | 15 | 15 | 1.2 | 27 | 10 | 1.06 | |
| 14-27 | 11 | 49 | 38 | 36 | 1.26 | 56 | 16 | 1.38 | |
| 28-41 | 1 | 21 | 17 | 20 | 1.02 | 27 | 10 | 1.06 | |
| 41 | 6 | 20 | 28 | 24 | 1.4 | 46 | 14 | 1.3 | |
| | O.R. global = 1.24 c. i. 95% (0.64-2.39) $\chi^2_{MH} = 0.4$ | | | | | O.R. global = 1.23 c. i. 95% (0.62-2.42) $\chi^2_{MH} = 0.36$ | | | |

TABLE 6. — Bladder cancer and alcohol consumption in males distributed by years of cigarette consumption.

| alcohol consumption | Years of cigarette smoking | | | | | | | | | |
|---------------------|----------------------------|----------|--------------------|----------|---------------------|----------|---------------------|----------|--------------------|----------|
| | Non-smokers | | Less than 20 years | | From 21 to 30 years | | From 31 to 40 years | | More than 40 years | |
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| non-drinkers | 13 | 47 | 8 | 7 | 14 | 10 | 6 | 2 | 30 | 20 |
| drinkers | 28 | 122 | 24 | 30 | 50 | 40 | 125 | 35 | 55 | 40 |

$\chi^2_{MH} = 0.0006$

TABLE 7.
Bladder cancer
and consumption of wine plus « gaseosa ».

| MALES | | | |
|---------------|-------|----------|------|
| Servings/week | Cases | Controls | O.R. |
| non-drinkers | 278 | 332 | 1 |
| 21-27 | 36 | 11 | 3.9 |
| 28-41 | 28 | 8 | 4.18 |
| > 41 | 11 | 2 | 6.56 |

O.R. global = 4.26 (c. i. 2.56-7.09)

$\chi^2_{MH} = 35.1$ (p 0.001)

FEMALES

| wine + « gaseosa » | Cases | Controls |
|--------------------|-------|----------|
| non-drinkers | 48 | 47 |
| drinkers | 5 | 6 |

O.R. = 0.8 (c. i. 0.35-4.4)

$\chi^2_{MH} = 0.1$

TABLE 8.
Bladder cancer and consumption
of wine plus « gaseosa » in smoker males.

| wine + « gaseosa » | Smokers | | Non-smokers | |
|--------------------|---------|----------|-------------|----------|
| consumption | Cases | Controls | Cases | Controls |
| non-drinkers | 252 | 169 | 1 | 26 |
| 21-27 | 29 | 7 | 2.78 | 7 |
| 28-41 | 22 | 6 | 2.46 | 6 |
| > 41 | 9 | 2 | 3.01 | 2 |

O.R. global = 2.6 (c. i. 1.47-4.9) $\chi^2_{MH} = 44$ (p 0.001)

Interaction between consumption of « wine + gaseosa » and smoking

| consumption of wine + « gaseosa » | Non-smokers | Smokers |
|-----------------------------------|---------------------------|-------------------------------|
| non-drinkers | 1 | 9.35 |
| | (26/163) | c. i. 5.92-14.77 (252/169) |
| drinkers | 15.67 | 22.07 |
| | c. i. 5.58-44.04 (5/6) | c. i. 12.43-50.5 (0/15) |

Rothman test of synergy for the multiplicative effect $S=1.04$. Numbers in parentheses refer to case/controls

The study of by beverage type revealed an increased risk of bladder cancer in males consuming more than 21 servings per week of wine mixed with « gaseosa ». Such an association was not found in females (Table 7). A progressive increase in the O.R.s with the increases in the

amount of wine mixed with « gaseosa » ingested can be observed in male patients.

The risk of bladder cancer appeared increased in male smokers who drank wine mixed with « gaseosa » (Table 8). The interaction between cigarette smoking and consumption of wine mixed with « gaseosa » in the generation of bladder cancer was more than additive and did not reach statistical significance when we tested the multiplicative effect with the Rothman test of synergy (22).

DISCUSSION

It has been suggested that, if alcohol itself is not a bladder carcinogen, it might still act as a cocarcinogen in interaction with some other risk factors (2, 3, 9, 15, 19, 24), principally tobacco (10, 12). The results of this study suggest that the consumption of alcoholic beverages (with the exception of wine mixed with « gaseosa ») does not increase the risk of bladder cancer. Although alcohol consumption appeared to be associated with the disease in a small group of males younger than 60 years of age who consumed more than 41 servings/weeks, such an association was not observed in other categories. In this study, drinkers of wine with gaseosa are grouped with alcohol drinkers in general, and they are probably responsible for the above-mentioned association. This finding agrees with the results of Thomas *et al.* (26) in the United States, who also reported a lack of synergism between alcohol consumption and the smoking habit.

Although the number of females studied is not high enough to confirm the validity of our conclusions, the number of males constitutes a reasonably high proportion of all incident cases in the geographic area of Madrid, and the controls constitute a probability sample of the population from which the cases come. These are reasons for being confident about the accuracy of the data on alcohol consumption in the study. The interviews were conducted by medical staff at the hospital, and the questions about alcohol consumption were mixed with questions about beverages of all kinds. The orientation of the interview was towards matters pertaining to artificial sweetener use, occupation, and cigarette-smoking rather than alcohol drinking. This may have helped to minimize the problem of the subjects being wary about the questions related to alcohol consumption.

In contrast to the other alcoholic beverages studied, the mixture of wine and « gaseosa » increases the risk of bladder cancer. There are no previous epidemiological reports on the consumption of « gaseosa ». Wine with « gaseosa » might exert its noxious effect through two mechanisms: a) the wine used for this mixture is usually of lower quality and contains higher amounts of

impurities than consumed alone; and b) « gaseosa » is sweetened with saccharin (60%) and cyclamate (40%). Either the impurities contained in the wine or the artificial sweeteners added to the « gaseosa » might be responsible for its carcinogenic effect rather than alcohol itself. It is also possible that this sweetened beverage could enhance the action of alcohol, though such relationship has not been found with other artificial sweeteners, or that impurities in the wine could be converted into carcinogenic substances upon contact with the « gaseosa ». These possible causes should be investigated in further epidemiologic studies.

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