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Fluid intake and clinicopathological characteristics of bladder cancer: the West Midlands Bladder Cancer Prognosis Programme (BCPP).

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Abstract

Introduction

Between 10 and 20% of bladder cancer (BC) patients who are diagnosed with non-muscle-invasive bladder cancer will progress to muscle-invasive disease. Risk of progression depends on several factors at diagnosis including age, tumour stage, grade, size and number, and the presence or absence of carcinoma in situ (CIS). Fluid intake may be related to these factors.

Materials and Methods

Data of 1,123 participants from the West Midlands Bladder Cancer Prognosis Programme (BCPP) were used. Data collection was via a semi-structured questionnaire, and case report forms were used to collect clinicopathological data. Fluid intake was measured for six main categories: alcoholic fluids, hot fluids, fruit fluids, milk, fizzy drinks, and water, and converted into quintile variables. Multilevel mixed-effects linear regression was performed for every beverage category per clinicopathological variable and corrected for age, gender and smoking status.

Results

Age at diagnosis was distributed differently amongst those in different total fluid intake quintiles (predicted means 71.5, 70.9, 71.5, 69.9, and 67.4 respectively) and showed a significant inverse linear trend in alcohol ($p<0,01$), hot fluids ($p<0,01$), and total fluids intake ($p<0,01$), in non-muscle-invasive bladder cancer (NMIBC) patients.

Conclusion

Our results suggest an inverse association for alcohol intake and total fluid intake with age at diagnosis. These results should be confirmed by future studies, alongside a possible (biological) mechanisms that could influence tumour growth, and the effect of micturition frequency.

Background

Bladder cancer (BC) is the tenth most common cancer in the UK. With 10,063 new cases diagnosed in 2014, the BC incidence in the UK is about 28 cases every day (1); the total number of BC patients make up 3% of the total cancer cases (1). BC occurs more often in the elderly (2) and, due to the increasingly elderly population, will likely form a large burden on healthcare systems in the future. BC also has the largest per- patient lifetime cost of all cancers (3, 4, 5) and recurs often (6, 7). At presentation, 70-75% of patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC: stages Ta/T1/Tis) (6, 7). NMIBC recurs in 50%-70% of cases (6); 10%-20% of cases will progress to muscle-invasive bladder cancer (MIBC: stages T2-T4) (6, 8) and may ultimately die from disease (9). Five year survival rates for MIBC are 27-50% (10).

The urogenous contact hypothesis assumes that a high total fluid intake dilutes the urine concentration and increases the frequency of urination, which in turn reduces the time carcinogens in the urine are in contact with the bladder urothelium (11). This should lead to a decreased risk of BC (12, 13). Literature regarding the association between total fluid intake and BC risk is inconsistent (14, 15). In a systematic review done by Brinkman and Zeegers (15), ten out of twenty studies that investigated the influence of total fluid intake reported a statistically significant association, of which six reported a positive association and four a negative association with bladder cancer risk. In the Health Professionals Follow-Up Study, Michaud et al. (16) reported a significant decreased risk of BC in men with a high total fluid intake, whilst other observational studies did not report any statistically significant association (17, 18).

Progression risk depends on several factors at diagnosis including age, tumour stage, grade, size and number, and the presence or absence of carcinoma in situ (CIS) (19, 20). The impact of fluid intake on these clinicopathological factors is still not clear, as this has not yet been researched (21). NMIBC and MIBC are two very different version of BC, with a different treatment and prognosis each. We will therefore look at them separately, as to not let the results be influenced by any unknown confounder.

This study is the first attempt to investigate whether fluid intake is associated with either favourable or unfavourable clinicopathological factors at diagnosis.

Materials and Methods

The West Midlands Bladder Cancer Prognosis Programme (BCPP)

The BCPP is an ongoing multi-centre epidemiological prospective cohort study with 1550 participants recruited from ten different hospitals in the West Midlands. The aim of the BCPP is to gather information on determinants of BC and its prognosis. Participants were eligible if cystoscopy findings were suggestive of BC. Patients who were previously diagnosed with cancer of the urethra, bladder, ureter, or renal pelvis within the last decade were excluded from the cohort, as well as patients who were infected with HIV. Details of the BCPP cohort have been published previously (22). The study protocol was approved by the Nottingham Multi-centre Research Ethics Committee (06/MRE04/65), and written informed consent was obtained from all participants.

Dietary Intake assessment (of Fluid intake assessment)

All data were collected prospectively. Baseline data collection was done with the use of a semi-structured questionnaire administered by research nurses prior to initial treatment for BC (transurethral resection, TURBT, in most cases). This questionnaire collected information concerning socio-demographic data, medical history, environmental exposures, use of medications, diet, smoking behaviour, health related quality of life, and social support. Research nurses also collected data on subsequent tumour histopathology and treatment with dedicated case report forms (CRFs). For fluid intake, participants were asked what their consumption for a certain type of drink was during the past year (never or less than once per month, 1-3 per month, once per week, 2-4 per week, 5-6 per week, and at least once per day), as well as their average overall daily consumption (average number of drinks per day). For each type of consumption, a standard amount in millilitres (ml) was assumed as follows (alcoholic drinks based on The Chief Medical Officers' Low risk unit guidelines (23)): a glass of (fortified) wine amounts to 175ml, a pint of beer or a cider amounts to

568ml, spirits and liqueurs amount to 25ml, a cup of hot fluid (tea, coffee, hot chocolate, Ovaltine and Horlicks, and soup) amounts to 237ml, and a glass of fruit fluid (squashed fruit or pure fruit juice), milk, fizzy drinks, and water all amount to 284ml. Fluid types were divided into six main categories: Alcoholic fluids (wine/champagne, fortified wine, beer, cider, spirits, and liqueurs), hot fluids (tea, coffee, hot chocolate, Ovaltine and Horlicks, and soup), fruit fluids (squashed fruit or pure fruit juice), milk, fizzy drinks, and water. A total fluid intake variable was created by taking the sum of the mentioned categories.

Outcome assessment

Participants were separated into either NMIBC or MIBC groups based on histopathological TNM classification at diagnosis (24). Participants with stage Ta, T1 and Tis were coded as NMIBC, whilst participants with T2+ were categorized as MIBC. This information, along with grade (1973 classification), the number of tumours visible, the presence or absence of concomitant CIS, and the size of the largest tumour, was gathered by the research nurses after initial resection. Age at diagnosis was calculated by subtracting the date of birth of the participant with the date of the cystoscopy results.

Statistical analyses

A quintile variable was created consisting of 5 groups per beverage type for all beverage categories and for total fluid intake. Descriptive statistics compared age at diagnosis, NMIBC or MIBC cases, stage, grade, tumour size (cm), number of tumours, and smoking status per quintile of total fluid intake. Smoking status was included since smoking is a significant contributor towards the development of bladder cancer as well, as prognosis (25). A multilevel mixed-effects linear regression was performed for every beverage category (alcohol, hot fluids, fruit fluids, milk, and water) per clinically relevant variable (age at diagnosis, grade, stage, number of tumours, size of largest tumour) with the exception of concomitant (CIS). The relationship between different types of drinks and fluid intake categories with each clinicopathological characteristic of BC was investigated by calculating

predicted means for different types and amounts of fluid intake. After testing for heterogeneity, some analyses appeared to use heterogenic data, so a random intercept was added for all analyses to be consistent. This was done to correct for potential clustering of patients in hospital areas. Tests for linear trend over quintile categories were performed by linear regression analysis using the quintile categories as dummy variables.

Age at diagnosis, gender, and smoking status were corrected for in all regression models, where applicable. Since alcohol is expected to already show effects in small quantities compared to non-alcohol drinkers (26, 27), an extra group was created consisting of all non-alcohol drinkers, which served as the reference group for the analyses of all alcohol consumption. For every other beverage type, the lowest category was used as the reference group (Never/less than once per month), with an exception for tea and coffee. Since tea and coffee are widely consumed in large quantities, the reference group for these types was the highest category (at least once per day). Sensitivity analyses were done by running the regression analyses for patients aged 75 and above exclusively. We calculated predicted means for each clinical outcome per fluid intake group with 95% confidence intervals (CIs).

In addition to the multilevel linear regression models, we also created a logistic regression model for each quintile variable, which investigated the likelihood of being diagnosed with MIBC compared to NMIBC at initial diagnosis. We used Odds Ratios (OR) to represent the chance of being diagnosed with MIBC compared to NMIBC. The lowest beverage intake group was used as the reference group for each quintile variable. Stata/SE 14.2 was used to perform all statistical analyses and a p value of <0.05 was considered statistically significant. However, since no statistical corrections were done for multiple comparisons, we will focus our discussion on results with p-values less than 0.001.

Results

Participant selection and descriptive statistics

Out of all 1550 eligible participants, 276 (18%) participants were excluded because they did not subsequently have BC (n=273) or had missing stage data (n=3). Another 122 (8%) participants were excluded due to missing data: missing data for fluid intake (n=1) or missing information, regarding the date at which the questionnaire was filled in to calculate their age at diagnosis (n=121). Another 29 participants were excluded because their fluid intake could not be calculated or was too low to be a realistic amount of fluid (<0,5L per day in total). Eventually, 1,123 participants were eligible for analysis. For some participants, grade information was not available (n=22). However, because all other information was available, these participants were still included in the analyses.

Table 1 of the appendix shows the demographics and clinicopathological data of all participants with BC per quintile for total fluid intake with each quintile representing a higher daily fluid intake. Overall, the quintiles do not seem to have a different distribution of clinical parameters. The gender ratio is a 1:4 female to male ratio across all quintiles, with a total of 240 (21%) females and 883 (79%) males included in the study. Age at diagnosis is distributed differently (p=0.007) amongst participants in the total fluid quintiles (mean age 71.5, 70.9, 71.5, 69.9, and 67.4 respectively), showing an inverse trend. The ratio of NMIBC to MIBC was consistent across all quintiles.

Fluid intake and clinicopathological factors for NMIBC and MIBC patients

The results of the multilevel mixed-effects linear regression models are discussed below. Additional results concerning the clinicopathological factors grade, stage, and the number of tumours, along with the results for the logistic regression and sensitivity analyses for concomitant carcinoma in situ (CIS), can be found in the supplemental data.

Total beverage and total fluid quintiles

Age at diagnosis

The results for age at diagnosis can be found in table 2. Inverse linear trends were observed for alcohol intake, hot fluid intake, fizzy drink intake, and total fluid intake ($p<0.001$, 0.001, $p<0.001$, and 0.001 respectively) for NMIBC patients: higher fluid intake was associated with lower age at diagnosis. These inverse trends can also be seen for MIBC patients and alcoholic beverages, fruit fluids, fizzy drinks, and total fluid intake ($p<0.001$, 0.017, $p<0.001$, and 0.012 respectively). The intake of hot fluids almost showed a non-significant positive trend,; higher hot fluid intake was associated with a higher age at diagnosis. The trends for total alcohol intake and total fluid intake can be seen in figure 1.

Tumour size

The results for tumour size can be found in table 3. There is a significant ($p=0.013$) positive linear trend for hot fluids in NMIBC patients; the more hot fluids are consumed, the larger the tumour will be at diagnosis. For MIBC patients, there do not seem to be any statistically significant linear trends. However, there do seem to be trends in hot fluids, fruit fluids, and total fluid intake ($p=0.089$, 0.072, and 0.101 respectively).

Individual beverages concerning age at diagnosis and tumour size

Age at diagnosis

In supplemental 1, results can be seen for the different types of alcoholic drinks, as well as different beverages for hot fluids in NMIBC patients. There seems to be an inverse linear trend ($p=0.016$) for the intake of wine and/or champagne and age at diagnosis. This appears to be the case for beer,

cider, and liqueur as well. All hot fluids seem to have a significant linear trend (p=0.028, p=0.008, p<0.001 and p<0.001), with the exception of coffee (p=0.362). Most of these trends seem to be positive; the more one consumes the higher the age at diagnosis. This is observed in tea, hot chocolate, ovaltine and horlicks, and soups. However, these positive trends are not observed for total hot fluids intake in table 2.

Tumour size

The results for the association between hot fluid beverages and the size of the largest tumour at diagnosis in NMIBC and MIBC patients can be found in supplemental 5. For NIMBC patients, there do not seem to be any statistically significant linear trends. However, there appears to be a positive linear trend for tea consumption (p=0.061). For MIBC patients, there did not seem to be any linear trends with tumour size.

Discussion

In the present study age at diagnosis, grade, stage, number of tumours at diagnosis, the presence or absence of concomitant CIS, and the size of the largest tumour at diagnosis were observed in NMIBC and MIBC patients across fluid intake categories. Based on our results, linear trends are observed between fluid intake and two cliniciopathological factors: age at diagnosis and tumour size.

The inverse association between alcohol & total fluid intake with age at diagnosis

Alcohol intake

Clear inverse linear trends can be seen for total alcohol and total fluid intake in NMIBC patients, as seen in the tables as well as the graphs in figure 1. Similar trends can be seen when looking at the separate drinks for alcohol consumption; inverse trends are observed for wine and champagne, beer, cider, and liqueur. When we compared this to the individual beverages for MIBC patients, a similar pattern can be observed: the predicted mean of age at diagnosis is highest in the non-alcohol drinker group and lower for all following alcohol drinker quintiles (these results can be found in the supplemental 1). A higher alcohol beverage intake seems to indicate a BC diagnosis at an earlier age.

Literature to date is divided regarding the effects of alcohol on bladder cancer, with most studies concluding alcohol consumption to have no association (26-30) with bladder cancer, whereas other studies suggest a slight increase in risk for bladder cancer for men (31, 32). Our findings therefore do not fall in line with the majority of scientific findings. Several possible explanations for the observed association between alcohol and age at diagnosis are given in literature. It could be possible that the reference group might be different from alcohol group, or some form of unmeasured confounding, could explain the difference between alcohol drinker and non-alcohol drinker. The reference group for example, consists of non-alcohol drinkers. This is potentially a very select group and could differ from the rest of the population: only 17% of adults aged 16 and over in England said that they had not consumed alcohol in the past year or said that they are a non-drinker in 2015 (33).When we compared the non-drinker group versus the drinkers, they did not seem to differ across demographic

statistics. Another explanation could be the effect ethanol has on several mechanisms related to carcinogenesis. Ethanol slows down protein synthesis, which may inhibit cell repair mechanisms, resulting in malignant changes (34, 35). Ethanol also improves permeability to carcinogens, which may cause increased carcinogenic activity (35-38), and may increase cell proliferation (35, 36, 38, 39).

Total fluid intake

Literature regarding the association of total fluid intake and bladder cancer risk is also divided, with some studies concluding an inverse association (19, 40), no association (18, 21, 41, 42), and some concluding a positive association (43- 46). We hypothesized that the urogenous-contact hypothesis could explain the positive association between high total fluid intake and bladder cancer risk: exposure of the bladder wall to highly concentrated urine containing carcinogenic substances would increase the risk for developing bladder cancer (15, 16, 47). Based on this hypothesis, expected results for a higher fluid intake would therefore lead to a higher amount of micturition, which would cause less (concentrated) exposure to the bladder wall, resulting in a decreased risk for BC. However, our results suggest an inverse effect on at least two of the clinicopathological factors of BC. In the first instance higher fluid intake was significantly associated with lower age at diagnosis. This observed trend could be the natural decline in fluid intake with age - the elderly are known to drink less and are vulnerable to dehydration (48). However, this trend does not seem to explain our data when comparing our results with the total fluid intake of a subset of participants who were not diagnosed with BC. The age of non-BC participants seemed to only decrease in the highest quintile of fluid intake, instead of a trend throughout the quintiles (data not shown).

Another possible explanation for our results could be that the frequency of micturition is more important than total fluid intake (49). This explanation is supported by a case-control done by Silverman et al, in which an inverse trend in bladder cancer risk was found with higher frequencies of micturition, regardless of amount of fluid intake (50). How this could affect the cliniciopathological

factors of BC, however, has not been researched yet as of now. Unfortunately, the frequency of micturition was not covered by the BCPP questionnaires.

The positive association between hot fluid intake and the size of largest tumour at diagnosis

Our results suggest that the consumption of hot fluids is associated with tumour size at diagnosis: the higher the hot fluid consumption, the larger the tumour at diagnosis. However, individual drink types within total hot fluid consumption do not show this trend. Based on the current literature, it is not yet clear how this association could be explained. Therefore, it is likely that these findings are random, as there is no obvious causative relationship to explain these results. The size differences reported are within the same EAU clinicopathological category for tumour size and are not likely to influence clinical decision-making to the discussion

Limitations and recommendations for future studies

This is the first study to have prospectively investigated fluid consumption and tumour characteristics at the time of diagnosis. Most studies focus on BC aetiology or prognosis but very few, if any, have examined clinically relevant factors at the time of diagnosis. Since these clinicopathological characteristics of the disease are the most important predictors of BC prognosis, examining them at the time of diagnosis provides insight into how fluid intake might influence outcomes. However, since this is a cross-sectional analysis without the use of control group, the observed trends in relation to clinicopathological characteristics of cancer patients are difficult to interpret due to possible reverse causality. Another limitation of this study is the way the amount of fluids from beverages was measured. This was not done by measuring the amount in millilitres, but by asking the number of consumptions based on the past year in a questionnaire at diagnosis. The amount of beverages consumed could therefore be overestimated or underestimated due to recall bias. Since beverage intake was measured in 'consumptions', the assumptions made for the millilitres per beverage could differ from reality. It should also be taken into consideration that all multilevel linear

regressions were corrected for age, gender, and smoking status only; they were not corrected for possible concomitant carcinoma in situ (CIS), since for a lot of cases (n= 356) it was unclear whether a person had concomitant CIS. However, in order to estimate the impact this might have had, we did a sensitivity analysis for concomitant CIS in the NMIBC group. This analysis showed there was a difference between patients with concomitant CIS and patients without concomitant CIS; the trends we observed appeared to be more clear in patients without concomitant CIS compared to patients with concomitant CIS, but we do not see this difference in the overall analyses results. This could be due to a large difference in patient size (n=759 without CIS and n=117 with CIS). Therefore, our findings are more applicable towards patients without concomitant CIS. Furthermore, no statistical correction was done for multiple comparisons. Although there are a large number of comparisons due to all the different types of drinks, we focus our conclusions mainly on the quintile variables. Additionally, only groups with a very low p-value ($p < 0,001$) were considered to support our explanations.

Based on these results, we recommend future research to investigate the association of hot fluid intake alongside (biological) mechanisms that could influence tumour growth. The effect of micturition frequency should also be further examined, as this could explain the effect we found for total beverage fluid intake and alcohol intake.

Conclusion

The results of this study suggest an inverse association between alcohol intake and age at diagnosis, and a possible inverse association between total fluid intake and age at diagnosis. Although the results from this study are inconclusive towards the association of fluid intake from beverages and bladder cancer and should therefore be confirmed by future studies, they do support an association between fluid intake and clinicopathological factors important in determining prognosis for bladder cancer patients.

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