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ORIGINAL COMMUNICATION

Fluid intake and risk of bladder and other cancers

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There are appreciable differences in total fluid intake at the individual and population level, and substantial difficulties in obtaining valid measures of fluid intake. Epidemiological studies have examined the association between fluid intake and different types of cancer. For bladder cancer, fluid consumption has been associated with a moderate increase of risk in some studies, including a multicentric case–control study from the United States, based on about 3000 cases, with a decrease in others, including the Health Professional Follow-up study, or with no material association. The evidence, therefore, is far from consistent. Sources and components of fluids were also different across different types studies. From a biological point of view, a decreased fluid intake could result in a greater concentration of carcinogens in the urine or in a prolonged time of contact with the bladder mucosa because of less frequent micturition. Carcinogenic or anticarcinogenic components of various beverages excreted in the urine may also play a role in the process. It has been suggested that fluid consumption has a favorable effect on colorectal cancer risk. Fluid intake may reduce colon cancer risk by decreasing bowel transit time and reducing mucosal contact with carcinogens. Low fluid intake may also compromise cellular concentration, affect enzyme activity in metabolic regulation, and inhibit carcinogen removal. However, epidemiological data are inadequate for evaluation. Data are sparse and inconsistent for other neoplasms, including breast cancer. The fluid constituent of foods, confounding, interactions and possible influences of specific types of beverages should be investigated further. In conclusion therefore the association between total fluid intake and cancer risk remains still open to debate.
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Introduction

Fluid intake plays an important role in digestion, absorption, transportation and metabolism of nutrients. Water is also the medium for the elimination of toxins and waste products, and plays a fundamental role in most biochemical reactions and in macromolecule structure.

Several ecological studies considered the role of water as a carrier of carcinogens, as a consequence of chlorination or industrial contamination (Cantor *et al*, 1987, 1998; Bitterman *et al*, 1991; Shannon *et al*, 1996; Wilkens *et al*, 1996; Stookey *et al*, 1997). However, the relation between fluid intake and the risk of cancer has not been adequately evaluated, probably also because of the difficulties in assessing and quantifying total fluid intake (Jones & Ross, 1999).

Among various sites, bladder cancer received the most attention. Relevant findings on bladder and selected other neoplasms will be reviewed below.

Cancer of the bladder and lower urinary tract

The causes of bladder cancer, including cigarette smoking and occupational exposure to aromatic amines, are at least in part related to direct contact of the bladder urothelium with carcinogens excreted in the urine (Silverman *et al*, 1996; Negri & La Vecchia, 2001). Animal experiments have suggested that the frequency of urination is inversely related to the levels of potential carcinogens in the urothelium (Kadlubar *et al*, 1991). It has been reported that patients with urinary tract cancer consumed significantly smaller quantities of fluids compared to healthy controls (Bitterman *et al*, 1991). Fluid intake may also dilute metabolites in the urine and increase the frequency of voiding, thus reducing the time of contact of carcinogens with the bladder epithelium (Braver *et al*, 1987).

Tables 1 and 2 give the main results of selected case–control and cohort studies of various measures of fluid intake and bladder cancer risk.

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Table 1 Relationship between total fluid intake and bladder cancer in selected case–control studies

Reference, country	*Cases*[a]	*Sex*	*Fluid intake category*	*OR (95% CI)*	*Type of fluid*	*Observations*
Wynder *et al* (1963), New York	300	M	Not reported	No association	Total fluid	Total fluid includes tea, coffee and alcohol
	70	F	Not reported			
Dunham *et al* (1968), Louisiana	334	M	Not reported	No association	Total fluid	Total fluid includes alcoholic and nonalcoholic beverages, and various types of coffee
	159	F	Not reported			
Claude *et al* (1986), Germany	340	M	>2.0 *vs* ≤2.0 (l/day)	4.4 (2.3–8.2) $P<0.001$	Total fluid	Daily fluid intake includes coffee, tea, beer, wine and high-proof spirits. OR of 2.3 for high consumption of coffee, 2.1–2.8 for high consumption of beer
	91	F	>2.0 *vs* ≤2.0 (l/day)	4.0 (0.5–30.3)		
Jensen *et al* (1986), Denmark	40	M	0–0.99 (l/day)	1.0	Total fluid	Total fluid intake includes coffee, tea, beer, soft drinks. RR of bladder cancer for coffee drinking was not significant. A significant association was found for tea drinking
	121		1–1.99	0.9 (0.6–1.4)		
	66		2–2.99	1.3 (0.8–2.1)		
	33		3–3.99	2.0 (1.1–3.8)		
	20		4+	3.3 (1.4–7.4) $P<0.001$		
	26	F	0–0.99 (l/day)	1.0		
	51		1–1.99	1.1 (0.6–1.9)		
	10		2–2.99	1.3 (0.5–3.2)		
	4		3–3.99	1.8 (0.4–7.4)		
	0		4+			
Cantor *et al* (1987), USA	326	M	≤0.80 (l/day)	1.0	Tap water	Beverages from tap water were considered, including coffee, tea, reconstituted frozen juice and tap water *per se*
	366		0.81–1.12	1.12 (0.9–1.4)		
	404		1.13–1.44	1.24 (1.0–1.5)		
	441		1.45–1.95	1.39 (1.2–1.7)		
	498		≥1.96	1.47 (1.2–1.8) $P<0.0001$		
	120	F	≤0.80 (l/day)	1.0		
	139		0.81–1.12	0.99 (0.7–1.3)		
	116		1.13–1.44	0.90 (0.7–1.2)		
	141		1.45–1.95	1.13 (0.8–1.5)		
	144		≥1.96	1.29 (0.9–1.8)		
Slattery *et al* (1988), USA	70	M/F	≤289 (ozs/week)	1.00	Total fluid	Total fluid intake was calculated by adding together fluids from all sources (one ounce (oz) equals 28.4 g). Specific fluids related to bladder cancer risk were milk (RR 0.64) and coffee, intake (1.60), alcohol and tea at high levels (103 g/week) in non smokers (respectively OR 2.37, 2.25)
	69		290–387	0.91 (0.60–1.36)		
	68		388–488	0.84 (0.56–1.27)		
	85		489–653	1.20 (0.79–1.80)		
	108		>653	1.36 (0.89–2.07)		
	73	M/F	≤8 (8-oz.glass/week)	1.00	Water	
	86		9–15	1.10 (0.74–1.65)		
	58		16–22	0.88 (0.57–1.39)		
	77		23–33	1.10 (0.72–1.67)		
	124		>33	1.15 (0.79–1.69)		
Risch *et al* (1988), Canada	826	M	1 (l/day) increase	1.00 (0.92–1.09)	Total fluid	Total fluid intake includes soda, coffee, tea, milk, cocoa, nondiet soft drinks, beer, spirits, wine and orange juice. No relation for any type of coffee
		F		1.25 (0.98–1.60)		
Kunze *et al* (1992), Germany	307	M	1.1–2.0 (l/day)	1.6 (1.2–2.3)	Total fluid	Total fluid intake includes all nonalcoholic and alcoholic beverages. Habitual drinking of coffee was found to be associated with bladder cancer only for high consumption (OR for ≥1 l/day was 2.5). Reference category <1.1 l/day (115 male and 69 female cases)
	80		2.1–3.0	2.7 (1.6–4.4)		
	29		3.1+	4.9 (2.0–12.3)		
	64	F	1.1–2.0 (l/day)	1.2 (0.6–2.1)		
	11		2.1+	0.9 (0.3–2.5)		
Vena *et al* (1993), USA	49	M	1(lowest quartile)	1.00	Total fluid	Total fluid intake includes alcoholic beverages, bottled beverages, soda, milk coffee, tea, all juices and glasses of tap water
	95		2	2.60 (1.18–5.73)		
	76		3	3.68 (1.65–8.20)		
	131		4(highest quartile)	6.30 (2.82–14.08) $P<0.001$		

Table 1 Continued

Reference, country	*Cases*[a]	*Sex*	*Fluid intake category*	*OR (95% CI)*	*Type of fluid*	*Observations*
	75		1(lowest quartile)	1.00	Tap water	
I	71		2	1.32 (0.72–2.42)		
	68		3	1.63 (0.90–2.95)		
	137		4(highest quartile)	2.62 (1.53–4.47) $P<0.001$		
Wilkens *et al* (1996), Hawaii	195	M	1 (lowest quartile)	1.0	Total fluid	Total fluid includes coffee, black and green tea, soda, beer, spirits, wine, fruit juice, cocoa, water and milk. Tap water includes water, coffee, tea and cocoa. Total fluid consumed in 24 h was calculated as the sum of the daily intake of all beverages
			2	1.2 (0.7–2.1)		
			3	1.2 (0.7–2.0)		
			4 (highest quartile)	1.4 (0.8–2.6)		
			1 (lowest quartile)	1.0	Tap water	
			2	0.6 (0.3–1.0)		
			3	0.8 (0.4–1.3)		
			4 (highest quartile)	0.9 (0.6–1.6)		
			1 (lowest quartile)	1.0	Water	
			2	1.2 (0.7–2.0)		
			3	1.0 (0.6–1.8)		
			4 (highest quartile)	1.2 (0.7–1.9)		
	66	F	1 (lowest quartile)	1.0	Total fluid	
			2	0.6 (0.3–1.5)		
			3	0.4 (0.2–1.1)		
			4 (highest quartile)	0.3 (0.1–0.8) $P=0.01$		
			1 (lowest quartile)	1.0	Tap water	
			2	0.4 (0.2–1.0)		
			3	0.6 (0.3–1.5)		
			4 (highest quartile)	0.2 (0.1–0.6) $P<0.01$		
			1 (lowest quartile)	1.0	Water	
			2	0.7 (0.3–1.7)		
			3	1.0 (0.4–2.2)		
			4 (highest quartile)	0.4 (0.2–1.1)		
Bruemmer *et al* (1997), USA	44	M	≤ 7 (cups/day)	1.0	Total fluid	Liquid from tap includes water, coffee, decaffeinated coffee and tea. A moderate positive association for the use of decaffeinated coffee. An inverse association was found for soft drinks
	40		>7–9	0.8 (0.4–1.5)		
	49		>9–12	0.9 (0.5–1.6)		
	69		>12	1.0 (0.5–1.7)		
	38		≤ 5 (cups/day)	1.0	Tap water	
	65		>5–8	1.1 (0.6–2.0)		
	42		>8-10	1.7 (0.9–3.3)		
	57		>10	1.0 (0.5–1.7)		
	4	F	$\leq$ 7 (cups/day)	1.0	Total fluid	
	17		>7–9	4.2 (1.3–14.1)		
	22		>9–12	5.6 (1.7–18.6)		
	17		>12	4.7 (1.4–15.8) $P=0.02$		
	7		≤ 5 (cups/day)	1.0	Tap water	
	21		>5–8	1.2 (0.4–3.6)		
	11		>8–10	0.8 (0.3–2.5)		
	21		>10	1.5 (0.5–4.3)		
Cantor *et al* (1998), USA	157	M/F	$<$ 2.08 (l/day)	1.00	Total fluid	Total fluid includes beverages using tap water (water *per se*, coffee, hot and iced tea, reconstituted fruit juices, fruit drinks from powdered mixes and soups from concentrate or dry mix) and other beverages
	215		2.08 to <2.72	1.49 (1.1–2.0)		
	192		2.72 to <3.46	1.13 (0.9–1.5)		
	212		$\geq$ 3.46	1.14 (0.9–1.4)		
	347		Unknown			
Bianchi *et al* (2000), USA	1452	M/F	<2.6 (l/day)	1.0	Total fluid	Total fluids includes water, coffee, tea, fruit juices/drinks, soups, milk, soft drinks and alcoholic beverages. The crude OR is given
			≥ 2.6	1.32 (1.16–1.51)		
Geoffroy-Perez and Cordier (2001), France	103	M	≤ 8300 (ml/week)	1.00	Total fluid	Total fluid includes nonalcoholic drinks such as tap water, coffee, tea, bottled water, juice, milk and alcoholic beverages such as wine and beer
	87		8301–10 400	0.87 (0.58–1.30)		
	122		10 401–12 900	1.13 (0.76–1.67)		
	145		12 901–16 800	1.41 (0.96–2.08)		

Table 1 Continued

Reference, country	*Cases*[a]	*Sex*	*Fluid intake category*	*OR (95% CI)*	*Type of fluid*	*Observations*
	126		>16 800	1.07 (0.72–1.59)		
	19		Unknown			
	25	F	≤7300 (ml/week)	1.00		
	21		7301–9900	0.70 (0.30–1.65)		
	32		9901–12 800	1.17 (0.51–2.72)		
	26		>12 800	0.96 (0.42–2.22)		
	2		Unknown			

[a]Number of cases as reported in the original articles.

Table 2 Relationship between total fluid intake and bladder cancer in selected cohort studies

Reference, country	*Cases*	*Sex*	*Fluid intake category*	*RR (95% CI)*	*Type of fluid*	*Observations*
Mills *et al* (1991), USA	52	M/F	Not reported	≅1	Water	Californian 7th-day Adventist Health Study Cohort, including 34 198 subjects.
				>1 (not significant)	Total fluid	Total fluid consumption was created by summing individual consumption of 17 beverages. Sweetened real fruit juices showed significantly decreased risk with increasing consumption (relative risk 0.28 for daily consumption). Caffeine drinks and cola beverages had a relative risk greater than 1
Michaud *et al* (1999), USA	61	M	<1290 (ml/day)	1.0		Health Professionals Follow-up Study over a period of 10 y among 47 909 participants
	54		1290-1674	0.84 (0.58–1.21)		
	57		1675-2050	0.89 (0.62–1.29)		
	47		2051-2531	0.70 (0.47–1.04)		
	33		>2531	0.51 (0.32–0.80) P=0.004		
Zeegers *et al* (2001), The Netherlands	569	M/F	1 (lowest quintile)	1.00	Total fluid	Netherlands Cohort study of 58 279 men and 62 573 women. Total fluid consumption includes fluids from 19 specific beverages. Total water intake was calculated for beverages and food
			2	0.83 (0.55–1.25)		
			3	0.74 (0.48–1.13)		
			4	1.04 (0.69–1.56)		
			5 (highest quintile)	0.91 (0.65–1.29)		
			1 (lowest quintile)	1.00	Total water	Total water intake includes water from food and beverages
			2	0.80 (0.57–1.11)		
			3	0.86 (0.61–1.21)		
			4	0.91 (0.63–1.30)		
			5 (highest quintile)	0.94 (0.64–1.39)		

In a hospital-based case–control study conducted in New York (Wynder *et al*, 1963), including 370 cases of bladder cancer and an equal number of controls, no significant differences between cases and controls were reported for total fluid intake, as well as alcohol, tea and coffee consumption.

Likewise, a hospital-based case–control study from New Orleans, Louisiana (Dunham *et al*, 1968), including 493 cases of bladder cancer and 527 controls, found no material association with the amount of total daily fluid ingested, including alcoholic or nonalcoholic beverages, and various types of coffee.

In a German hospital-based case–control study (Claude *et al*, 1986), including 431 cases of bladder cancer and 431 controls, the odds ratio (OR) for a daily fluid intake of more than 21 *vs* up to 21 was around 4 for both sexes, although the estimates were significant only for male patients (OR, 4.4; 95% confidence interval (CI), 2.3–8.2). The ORs for drinking coffee, black tea, beer, wine and spirits were above unity in both sexes.

A population-based case–control study from Denmark (Jensen *et al*, 1986), based on 371 cases of bladder cancer and 771 controls, included information on coffee, tea and other beverages. There was an excess of risk for both total daily fluid intake and non-cola soft drinks, which was however significant only for male subjects (OR, 3.3; 95% CI, 1.4–7.4). Coffee was not significantly associated with bladder cancer risk. A significant association was found between bladder cancer and tea among men (OR, 2.1; 95% CI, 1.3–3.4) (not shown in the table), in the absence, however, of a linear trend in risk. Thus, the interpretation of the few apparent associations remains open to discussion.

Beverage intake, and specifically type of water source, was investigated in a large, multicentric population-based case–control study, conducted by the US National Cancer Institute (NCI) (Cantor *et al*, 1987), based on 2166 male and 689 female cases of bladder cancer and 3892 controls. The risk of bladder cancer increased with intake of tap water. For tap water consumption, the OR increased with daily intake, with an OR of 1.47 (95% CI, 1.2–1.8) among men and 1.29 (95% CI, 0.9–1.8) among women for the highest *vs* the lowest consumption quintile. The OR for the highest *vs* the lowest quintile of tap water consumption was 1.43 (95% CI, 1.23–1.67) for both sexes combined (not shown in the table). The risk gradient was restricted to persons with at least a 40-y exposure to chlorinated surface water, and was not found among long-term users of nonchlorinated ground water. The distinction of total fluid intake into its tap and non-tap water components indicated that the risk was primarily associated with tap water. The trend in risk was significant for both sexes combined, and for men only.

In a population-based case–control study conducted in Utah on 419 cases of bladder cancer and 889 controls (Slattery *et al*, 1988), total fluid intake was not related to bladder cancer. Specific fluids related to bladder cancer were milk (OR, 0.64; 95% CI, 0.42–0.98) and caffeinated coffee (OR, 1.60; 95% CI, 1.00–2.56). Alcohol showed a nonsignificant associaton only for relatively high levels (ie over 3.64 ounces or 103 g per week, OR, 2.11; 95% CI, 0.83–5.37); likewise, tea consumption in nonsmokers was associated with bladder cancer risk (OR, 2.25; 95% CI, 1.29–3.91). Both associations were apparently—though not significantly—stronger in ever-smokers compared to never-smokers. Thus, selected types of fluids appears to play a role in the development of bladder cancer—although subgroup analyses should be taken with due caution—while total fluid intake was not associated with risk (Table 1).

In a population-based case–control study (Risch *et al*, 1988) on dietary factors and bladder cancer, including 826 cases and 792 controls from different cities of Canada, a measure of total fluid intake was obtained by adding the reported daily consumption of several beverages, including diet soda, coffee, tea, milk, cocoa, nondiet soft drinks, beer, spirits, wine and orange juice. The average fluid intake was 2.13 l/day for male subjects and 1.55 l/day for female subjects. The OR for an increase of intake of 1 l/day was 1.00 (95% CI, 0.92–1.09) for male subjects and 1.25 (95% CI, 0.98–1.60) for female subjects.

A hospital-based case–control study from Germany (Kunze *et al*, 1992), based on 675 cases and 675 controls, analyzed total fluid intake, including alcoholic and nonalcoholic beverages. In men, the OR was 4.9 (95% CI, 2.0–12.3) for more than 3 l/day. By contrast, in women there was no relation between total fluid consumption and bladder cancer. In multivariate analysis, no significant additional effect of fluid intake was observed after accounting for coffee and beer. Thus, either some constituent of coffee and beer plays a role in bladder carcinogenesis, or total fluid intake was appreciably influenced by the amount of coffee and beer consumed.

Fluid intake and consumption of specific beverages were investigated in a population-based case–control study of 351 cases of bladder cancer and 855 controls from several New York state counties (Vena *et al*, 1993). Information on fluid consumption included alcoholic beverages, bottled beverages, soda, milk, coffee, tea, juices and tap water. Tap water was also a component of coffee, tea and juices. The total fluid consumption was associated with bladder cancer risk: the multivariate OR was 6.30 (95% CI, 2.82–14.08) for the highest quartile of fluid consumption for subjects below 65 y of age. The tap water component was associated with increased risk, and there was a positive dose–response relation.

In a case–control study of bladder cancer conducted on Oahu, Hawaii, from 1979 to 1986 (Wilkens *et al*, 1996), based on 261 cases and 522 controls, there was a strong inverse relation with total fluid intake among women (OR for the highest to lowest quartile 0.3; 95% CI, 0.1–0.8). Tap water showed a protective effect too (OR, 0.2; 95% CI, 0.1–0.6). The association was apparently stronger in smokers, and was present also when alcoholic beverages were excluded. Fluid intake showed no association among men, and several subgroup analyses were inconclusive.

In a population-based study including 262 bladder cancer cases and 405 controls from Western Washington (Bruemmer *et al*, 1997), there was a positive association among women between total fluid intake (OR, 4.7; 95% CI, 1.4–15.8), decaffeinated coffee (OR, 2.1; 95% CI, 0.8–5.3), and the incidence of bladder cancer. However, among men, there was an inverse relation between the consumption of soft drinks and bladder cancer (OR, 0.4; 95% CI, 0.2–1.1). No association was found between the incidence of bladder cancer and the intake of water, coffee, tea, diet soft drinks, alcohol or tap water for either sex.

In a population-based case–control study of 1123 cases of bladder cancer and 1983 controls from Iowa (Cantor *et al*, 1998), risk by intake level of all beverages and tap water from chlorination sources was evaluated. All beverages consumption was calculated by adding the contributions of several types of beverages. There was little association with all types of beverages (OR, 1.14; 95% CI, 0.9–1.4) for both sexes combined, or for beverages based on tap water only.

A study of 1452 bladder cancer cases and 2434 population controls from the Iowa Cancer Registry (Bianchi *et al*, 2000) found no consistent relation between tea intake and bladder cancer (OR, 0.9; 95% CI, 0.7–1.1 for >2.6 cups per day). An inverse relation with tea was apparent for drinkers of 2.6 or more liters of fluid per day. The crude OR for ≥2.6 *vs* <2.6 l of fluids per day was 1.32 (95% CI, 1.16–1.51). The interpretation of the apparent interaction between tea and bladder cancer remains, however, unclear.

A hospital-based case–control study from France (Geoffroy-Perez & Cordier, 2001), including 765 cases of bladder cancer, found no consistent association (OR, 1.07; CI, 0.72–1.59) with fluid intake among men. A positive association was reported for nonalcoholic drinks, coffee, tea and tap water, bottle water, juice and milk. No association was found among women.

Results from the California Seventh-day Adventist Health Study, a cohort investigation of 34 198 individuals, including 52 cases of bladder cancer (Mills *et al*, 1991), reported that total fluid intake (based on 17 different types of beverages) was associated with increased risk, although not significant. The risks were above unity for alcohol (relative risk (RR), 1.46; 95% CI, 0.44–4.85) as well as regular coffee drinking (RR, 1.99; 95% CI, 0.91–4.34).

The relation between total fluid intake and the risk of bladder cancer was examined over a period of 10 y in the Health Professionals Follow-up Study, based on a cohort of 47 909 male subjects, and 252 incident cases of bladder cancer (Michaud *et al*, 1999). Information on total fluid intake was derived from the reported frequency of consumption of 22 types of beverages. The daily fluid intake was inversely associated with bladder cancer risk: the multivariate RR was 0.51 (95%, CI; 0.32–0.80) for the highest quintile of total daily fluid intake (>2531 ml/day) as compared to the lowest one (<1290 ml/day). The consumption of water was associated with a reduced risk (RR, 0.49; 95% CI, 0.28–0.86 for ≥1440 ml *vs* <240 ml/day), as did the consumption of other fluids (RR, 0.63; 95% CI, 0.39–0.99 for >1831 ml *vs* 735 ml/day). Thus, it is unlikely that an anticarcinogenic substance was present in any particular beverage. The authors were, however, unable to assess accurately the sources of water consumed.

In a cohort study of 58 279 men and 62 573 women from the Netherlands, including 569 cases of bladder cancer (Zeegers *et al*, 2001), the RR for the highest *vs* the lowest quintile of total fluid consumption was 0.91 (95% CI, 0.65–1.29) for both sexes combined. Neither fluid consumption from beverages only, nor total water intake from food and beverages combined was associated with the incidence of bladder cancer.

Epidemiological data on fluid intake and bladder cancer are therefore inconclusive, although some of the more recent and valid studies, including the American Health Professional Cohort investigation (Michaud *et al*, 1999), suggest a possible inverse relation. However, the large multicentric NCI coordinated study of bladder cancer (Cantor *et al*, 1987) found a direct relation between fluid intake from tap water and bladder cancer risk. The interpretation of such inconsistent findings remains unclear.

Several hypotheses have been suggested to explain a possible relation between fluid intake and bladder cancer risk. The urogenous contact hypothesis (Braver *et al*, 1987) implies that prolonged contact of carcinogens in the urine with the urothelium increases bladder cancer risk. A higher fluid intake may cause prolonged contact with urine-borne carcinogens through distension of the bladder (Kunze *et al*, 1992). A high volume of total fluid may increase the workload of the bladder, while certain types of fluids may contain carcinogenic or chemopreventive substances (Slattery *et al*, 1988). In contrast, lower fluid intake could result in a greater concentration of carcinogens in the urine, or in prolonged contact with the bladder mucosa because of less frequent micturition (Braver *et al*, 1987; Kadlubar *et al*, 1991).

If water requirement-dependent mechanisms are important in carcinogenesis, combining water and diuretic beverages could reduce the observable effects. This is, therefore, a possible—though complex—explanation for the lack of effect of total beverages consumption in several studies.

Additional investigations would be required to evaluate the temporal and quantitative relation between fluid consumption and the risk of bladder cancer. There is also evidence that chronic inflammation, caused either by infections or by stones, has a role in the promotion of bladder cancer (Kunze *et al*, 1992; Burin *et al*, 1995), and a considerable fluid intake may reduce the risk of kidney stones (Pak, 1998) and hence possibly bladder cancer risk. The role of urinary tract stones on bladder carcinogenesis in humans remains, however, unclear (La Vecchia & Airoldi, 1999).

The source of drinking water may also be important. Several case–control studies supported an association between consumption of water from public sources and increased risk of bladder cancer. Some studies found that tap water with chlorine—and hence containing chlorination byproducts—may increase the risk of bladder cancer (Wilkins & Comstock, 1981; Gottlieb & Carr, 1982; Zierlier *et al*, 1986, 1988; Cantor *et al*, 1987, 1998; McGeehin *et al*, 1993; Koivusalo *et al*, 1994; King & Marrett, 1996; Kiemeney & Schoenberg, 1996; Freedman *et al*, 1997). Arsenic in drinking water has also been associated with increased risk of bladder cancer (Chen *et al*, 1986, 1992; Wu *et al*, 1989; Bates *et al*, 1995; Hopenhayn-Rich *et al*, 1996; Chiou *et al* 2001), but it is unclear whether the levels of arsenic in drinking water from developed countries have any meaningful effect. It is also uncertain whether the apparent association reflects inadequate allowance for social class correlates of bladder cancer, since bladder cancer risk is elevated in smokers and in workers exposed to occupational carcinogens—and hence in lower social class individuals (La Vecchia *et al*, 1989, 1990; Silverman *et al*, 1996; Negri & La Vecchia, 2001).

Thus, the epidemiological evidence from cohort and case–control studies on fluid intake and bladder cancer risk remains controversial. At least seven case–control and one cohort studies found risks above unity, two case–control and one cohort studies found a moderate inverse association and two case–control and one cohort studies reported no association.

Colorectal and other cancers

Colorectal cancer is the third most common cancer among men (after lung and prostate) and the second most frequently occurring cancer in women (after breast cancer) (Schottenfel & Fraumeni, 1996). The role of diet in colorectal cancer risk has been widely investigated, but analyses based on dietary factors have often overlooked nonnutrient dietary components, including water and fluids in general. Water intake is rarely measured, although it plays a relevant role in digestion and gut function. Approximately 80–200 ml water is lost daily through feces. With lower water intake, the fluid content of feces is reduced, and this may lead to reduced fecal output and constipation. Animal experiments suggest that this could increase colorectal neoplasm incidence (Long & Shannon, 1983; Metheny & Snively, 1983). Thus, increasing water intake may reduce colorectal cancer risk by decreasing bowel transit time, which would in turn reduce mucosal contact with carcinogens, or by decreasing the concentration of carcinogenic compounds in the water phase (Shannon *et al*, 1996). The issue, however, remains open to discussion (Dukas *et al*, 2000).

Several ecological studies considered the potential role of water as a carrier of carcinogens, mainly as a consequence of chlorination or industrial contamination (Shy, 1985; Young *et al*, 1987; Howe *et al*, 1989; Neutra & Ostro, 1992). However, at a 1992 symposium on the potential effect of

Table 3 Relationship between total fluid intake and colorectal and breast cancer in selected case–control studies

Reference, country	*Cancer site*	*Cases*[a]	*Sex*	*Fluid intake category*	*OR (95% CI)*	*Type of fluid*	*Observations*
Shannon *et al* (1996), USA	Colon	69	M	1 (lowest quartile)	1.00	Total nonalcoholic beverages	Total nonalcoholic beverages include water, caffeinated and decaffeinated coffee, caffeinated and herbal tea and a variety of soda beverages, some of which contained caffeine
		73		2	1.18 (0.70–1.99)		
		52		3	0.87 (0.51–1.49)		
		57		4 (highest quartile)	0.82 (0.48–1.42)		
		84		0–2 (glasses/day)	1.00	Water	
		63		>2.0–3.0	0.94 (0.57–1.54)		
		59		>3.0–5.0	0.80 (0.49–1.31)		
		32		>5.0	0.68 (0.38–1.22)		
		55	F	1 (lowest quartile)	1.00	Total nonalcoholic beverages	
		48		2	0.99 (0.56–1.76)		
		51		3	0.92 (0.52–1.62)		
		39		4 (highest quartile)	0.70 (0.38–1.26)		
		104		0–2 (glasses/day)	1.00	Water	
		28		>2.0–3.0	0.72 (0.39–1.33)		
		26		>3.0–5.0	0.41 (0.23–0.71)		
		28		>5.0	0.55 (0.31–0.99) $P=0.004$		
Slattery *et al* (1999), USA	Colon	722	M/F	≤2.0 (glasses/day)	1.00	Water	Total non alcoholic beverages include water, caffeinated and decaffeinated coffee, caffeinated and herbal tea and a variety of soda beverages some of which contained caffeine
		328		2.1–3.0	0.99 (0.83–1.19)		
		296		3.1–4.0	1.01(0.84–1.22)		
		325		4.1–6.0	0.81 (0.68–0.97)		
		322		>6.0	0.95 (0.79–1.14)		
		365		≤5.3	1.00	Total fluid	
		468		5.4–7.3	1.27 (1.05–1.53)		
		422		7.4–9.4	1.02 (0.84–1.24)		
		373		9.5–12.4	0.95 (0.78–1.16)		
		365		>12.4	0.86 (0.70–1.06) $P=0.04$		
Tang *et al* (1999), Taiwan	Colorectum	50*	M	1 (lowest tertile)	1.0	Water	Water sources included fountain water, underground water, well water, mineral water and distilled water. Among men, OR for rectal cancer was 0.08 (0.02–0.35) $P=0.0005$
		25		2	0.73 (0.32–1.65)		
		13		3 (highest tertile)	0.25 (0.10–0.61) $P=0.002$		
		30	F	1 (lowest tertile)	1.0	Water	
		24		2	0.84 (0.24–1.21)		
		13		3 (highest tertile)	0.55 (0.23–1.33)		
Stookey *et al* (1997), UK	Breast	44	F	Any water intake/ week	0.21 (0.07–0.62)	Water	The risk estimate was adjusted for age, height, exercise, family history, hormone replacement therapy use, endogenous estrogen exposure, oral contraceptive use, and tea, coffee and alcohol consumption

[a]Number of cases as reported in the original articles.

drinking water (Neutra & Ostro, 1992), the general consensus was that the evidence for source of water as a risk factor for colon cancer was not convincing.

The main results from analytical studies, including information on fluid intake and colorectal cancer, are given in Table 3. In a study from Seattle (Shannon *et al*, 1996), based on 444 cases of colon cancer and 414 population controls, there was a strong inverse relation between water intake (glasses of water per day) and risk of colon cancer among women (OR, 0.55; 95% CI, 0.31–0.99, for >5 *vs* ≤ 2 glasses/day). Among men, there was a 32% decreased risk with increasing water consumption (>5 *vs* ≤ 2 glasses/day), although the estimate was not significant. ORs were closer to unity for total nonalcoholic beverages (Shannon *et al*, 1996).

A population-based case–control study, including 1993 cases of colon cancer and 2410 controls from California, Utah and Minnesota (Slattery *et al*, 1999), examined specific types of fluids, that is, water and methylxanthines-containing beverages (coffee, tea, cola). Among men, coffee drinking was associated with a reduced risk of colon cancer (OR, 0.71; 95% CI, 0.53–0.96), and high water intake was protective for distal cancers (OR, 0.68; 95% CI, 0.49–0.96). In women, no important differences were observed. The total fluid and water intakes were also inversely associated with colon cancer among men who smoked, high consumers having approximately half the risk of low consumers. The inverse relation with coffee, however, may be related to specific components and/or metabolic effects of coffee (IARC, 1991; Tavani & La Vecchia, 2000).

A hospital-based case–control study conducted in Taiwan (Tang *et al*, 1999) on 163 subjects with histologically confirmed colorectal cancer and 163 hospital controls found an inverse relation between water intake and colorectal cancer among men. This was stronger for rectal cancer (OR, 0.08; 95% CI, 0.02–0.35) (not shown in the table). Similar, but not significant, trends were seen among women.

The association between fluid intake and colorectal cancer risk, if any, is unlikely to be due to differences in the source of water consumed, since the evidence for source of water as a risk factor for colorectal cancer is limited and inconsistent (Neutra & Ostro, 1992). There might also be an association between water consumption and other unidentified lifestyle or dietary factors that influence the risk of colorectal cancer (Tang *et al*, 1999).

Stookey *et al* (1996) reported the results of a pilot case–control study of breast cancer, including 44 cases and 55 controls. The risk of breast cancer was apparently reduced (multivariate OR, 0.21; 95% CI, 0.07–0.62). Considering the small sample size of that study, any interpretation remains, however, uncertain.

Conclusions

The issue of fluid and cancer has not been adequately assessed, even for the most widely investigated sites, such as bladder and colorectal neoplasms. For bladder cancer, the total fluid consumption has been associated with decreased risk in some studies (Dunham *et al*, 1968; Wilkens *et al*, 1996; Michaud *et al*, 1999), with a direct trend in risk in others (Claude *et al*, 1986; Jensen *et al*, 1986; Cantor *et al*, 1987, 1998; Kunze *et al*, 1992; Vena *et al*, 1993; Bruemmer *et al*, 1997; Bianchi *et al*, 2000), and with no excess risk (Wynder *et al*, 1963; Slattery *et al*, 1988; Risch *et al*, 1988; Mills *et al*, 1991; Zeegers *et al*, 2001).

Epidemiological evidence for colorectal is also limited. A protective role of fluid consumption on colorectal cancer has been suggested in a few case–control studies (Shannon *et al*, 1996; Tang *et al*, 1999; Slattery *et al*, 1999), but the evidence remains inconclusive. Data are scattered, and hence largely uninterpretable, for other neoplasms.

To provide meaningful results, reliable and valid instruments should be introduced to measure fluid intake in epidemiological studies (Gofti-Laroche *et al*, 2001). This is a particularly difficult task, since the fluid component of foods should also be considered (Franceschi *et al*, 1993, 1995; Decarli *et al*, 1996). Moreover, the separation of the effect of total fluid intake from that of individual beverages is difficult. The problem is conceptually similar to that of separating the effect of energy intake from that of various nutrients, and statisticians could take advantage from the vast literature on the topic (Willett, 1998).

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