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DIET, TOBACCO AND UROTHELIAL CANCER

A 14-year follow-up of 16477 subjects

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Abstract

Urothelial cancer has been linked with tobacco, phenacetin-containing analgesics and some industrially-related carcinogens. Carotene has been suggested as reducing the risk of urothelial cancer but there is not much information on the relation between diet and the incidence of human urothelial cancer. Furthermore, the magnitude of the risk of urothelial cancer for pipe smokers remains unclear. In a 14-year follow-up of 16477 Swedish twins the rate ratio of urothelial cancer (with 95% confidence interval) for subjects with a moderate/high intake of pork and beef respectively was 1.6 (1.0–2.7) and 1.6 (1.0–2.6). Meat consumption is widespread in Western populations. If the finding is supported by further data, a possible etiologic factor associated with the consumption of beef and pork would account for a substantial proportion of the cases of urothelial cancer. The rate ratio for men smoking a pipe/cigars, but not cigarettes, was 3.3 (95% confidence interval 1.5–7.4).

Key words: Bladder neoplasms; urothelial cancer, diet, meat, tobacco, cohort study.

Urothelial cancer originates in the mucosa of the lower urinary tract; the renal pelvis, urether, urinary bladder and urethra. Most cases of urothelial cancer primarily affect the urinary bladder and cancer at this site is globally a common malignant neoplasm (21).

In some countries bilharzia is an important etiologic factor for cancer of the urinary bladder but most bilharzia-induced neoplasms are squamous cell carcinomas. In countries with a low prevalence of bilharzia, cigarette smoking is the dominating known risk factor for cancer in the lower urinary tract and almost all malignant neoplasms at these sites are urothelial cancer (19). Industrially-related carcinogens and phenacetin-containing analgesics are other potential hazards for urothelial cancer (11, 14). However, the proportion of the population exposed to these risk factors, and consequently the attributable proportion of urothelial cancer, is usually low.

It has been suggested that carotene reduces the incidence of urothelial cancer and a high intake of carrots and green vegetables has been associated with a decreased risk of bladder cancer (8, 16). A high intake of meat has been associated with an increased risk of other cancers, such as cancer of the colon and pancreas (10, 20), but there is not much information on the relation between diet and the incidence of human urothelial cancer.

A recent suggestion that pipe/cigar smokers only face a 20–40% increased incidence of bladder cancer as compared to non-smokers (7) is in contrast with the ratio of 2 to 3 that is most often estimated for current cigarette smokers. It is unclear whether varying carcinogenicity in the tobaccos used or diverse smoking characteristics could explain the differences in the magnitude of the rate ratio.

The aim of the present study was to identify dietary factors that might be risk indicators for urothelial cancer and to estimate the increased risk for smokers of a pipe/cigars and cigarettes.

Material and Methods

The study cohort comprised the 16477 subjects who answered a postal questionnaire 1967–68. This was sent to 21152 individuals born 1886–1925, who were included in a population-based register of Swedish twins (3).

Information on diet, tobacco, and alcohol consumption was obtained from the 1967–68 questionnaire. The sub-

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jects related their intake of the food items shown in Table 1 to the total amount of food ingested, using the categories 'large proportion', 'medium proportion', 'low proportion' and 'no intake'. In the analysis, subjects who reported a high and/or a moderate intake (large and/or medium proportion) were compared with subjects who reported no or low intake ('unexposed').

Current smokers were divided into smokers of a pipe/cigars only and cigarette smokers (1–9, 10+ cigarettes/day). Ex-smokers were those who 'had ever smoked more than 5 packets of cigarettes or 50 cigars or 3 packets of pipe tobacco' and were not current smokers. Comparisons were made with persons not included in any smoking category.

Cancer incidence data were obtained from the National Swedish Cancer Registry. The notification to the Registry of all newly-diagnosed malignant diseases was compulsory for almost all physicians in Sweden during the study period. Anatomic site coding followed a modified version of the 7th revision of the International Classification of Diseases, ICD 7 (25). The follow-up included all cases of cancer in the renal pelvis (180.1) and the urinary organs (181) that were notified 1969–1982 and *not* reported as adenocarcinoma. Date of death for deceased individuals was extracted from the nationwide Cause-of-Death Registry. The above mentioned registers and the twin register use a 10-digit civil registration number, unique for each Swedish citizen, facilitating the computerized record linkage which was used for the analysis.

For each variable studied, person-years were calculated for the exposed and unexposed subjects. Deceased individuals contributed half a person-year for the year of death. The rate ratio was calculated with adjustment for age in 3 categories, gender and, in some computations, tobacco smoking (never smoked, ex-smoker and current smoker). The strata were summarized using a modification of the method proposed by Mantel-Haenszel (23). A 95% test-based confidence interval was constructed according to Miettinen (17).

Results

The 14-year follow-up of this cohort includes 206720 person-years, 87909 for men and 118811 for women. 17 female and 63 male cases of urothelial cancer occurred in the renal pelvis (5 cases), urether (4 cases), urinary bladder (70 cases) and urethra (1 case). No twin pair contained two cases of urothelial cancer.

Table 2 shows a rate ratio 50–70% above unity for subjects with a moderate or high intake of pork or beef. When subjects with moderate-high intake were considered together in one group (not shown in table), the rate ratio (with 95% confidence interval) associated with pork consumption was 1.6 (1.0–2.7), with beef consumption 1.6 (1.0–2.6) and with cured meat 1.1 (0.6–1.8). The rate ratios were similar among current smokers, those who had ever smoked as well as those who had never smoked. Adjustment for smoking in addition to age and gender changed the estimates by less than 0.1.

Subjects with a moderate/high intake of both pork and beef (Table 3) had a rate ratio of 2.2. Men with both exposures (not shown in table) had a rate ratio (with 95% confidence interval) of 2.0 (0.9–4.4) and women a rate ratio of 3.0 (0.7–12.5). 7 male and 2 female cases reported low or no intake for both pork and beef and information

Table 1

Eight different kinds of food items. Translation of the Swedish terms used in a questionnaire 1967–1968

Pork (pork chop, ham, bacon, etc.)
Beef and similar items
Sausage, minced meat and other cured meats and foodstuffs
Fruit and vegetables
Fish and shellfish
Farinaceous food (porridge, pancake, spaghetti, macaroni, etc.)
Egg and egg-dishes
Potatoes

Table 2

Number of cases (n) and rate ratio (PR) with 95% confidence interval (95% CI) for subjects with a high or moderate intake of certain food items as compared to individuals with low or no intake (adjusted for age and gender). Information on intake of respective food item missing for 6 cases on pork, 9 cases on beef and 5 cases on cured meat

	Intake	n	RR	95% CI
Pork	High	7	1.7	0.7–4.1
	Moderate	47	1.6	1.0–2.6
	Low-None	20	1.0	–
Beef	High	4	1.5	0.5–4.2
	Moderate	46	1.6	0.9–2.7
	Low-None	21	1.0	–
Cured meat	High	6	1.1	0.4–2.9
	Moderate	50	1.2	0.7–2.0
	Low-None	19	1.0	–

Table 3

Number of cases (n) and rate ratio (RR) with 95% confidence interval (95% CI) for subjects with a high/moderate intake of both pork and beef as compared to individuals with low or none intake (unexposed), adjusted for age and gender. Subjects with a high/moderate intake of pork but low/none intake of beef, a high/moderate intake of beef but low/none intake of pork, and with missing information for either one or both exposures are also shown

Exposure	n	RR	95% CI
Both pork and beef	39	2.2	1.1–4.4
Pork but not beef	11	1.5	0.6–3.7
Beef but not pork	10	1.5	0.6–3.8
Unexposed	9	1.0	–
Missing information	11	1.8	0.7–4.1

Table 4

Number of cases (n) and rate ratio (RR) with 95% confidence interval (95% CI) for men in certain smoking categories as compared to those who have never smoked (adjusted for age). Information on smoking habits missing for one male case

	n	RR	95% CI
1–9 cigarettes/day	14	4.5	2.1—9.9
10+ cigarettes/day	13	4.7	2.0–10.8
Pipe and/or cigar only	16	3.3	1.5–7.4
Ex-smokers	11	1.9	0.8–4.7
Ever smoked	54	3.3	1.7–6.7
Never smoked	8	1.0	-

was missing for 6 male and 5 female cases for either one or both exposures.

The rate ratio (with 95% confidence interval) for subjects exposed to fruit and vegetables (not shown in table) was 1.0 (0.6–1.6), to fish 1.3 (0.8–2.2), to farinaceous food 0.9 (0.5–1.4), to egg and egg dishes 1.0 (0.6–1.6) and to potatoes 0.8 (0.5–1.5). The figures were adjusted for age and gender.

Four female cases reported as current smokers of cigarettes and the remaining 13 cases stated that they had never smoked. This (not shown in table) gives a rate ratio (with 95% confidence interval) of 1.6 (0.5–5.2) for women who had ever smoked. Current smokers of cigarettes among men (Table 4) had a rate ratio of 4.5 or more, depending on the number of cigarettes smoked per day, while male smokers of a pipe/cigar had a rate ratio of 3.3.

Discussion

The present findings suggest an increased incidence of urothelial cancer after a moderate or high intake of pork or beef as compared with unexposed subjects. Adjustment for smoking made little difference to the estimate of rate ratio, indicating little or no confounding by smoking habits. Occupation and intake of analgesics are other potential confounding factors. We find it unlikely that these risk factors would substantially change the estimates of rate ratio. Also, there is no reason to believe that the fallacies in the identification of urothelial cancer should be differential between any of the groups studied. A possible non-differential misclassification of exposure, i.e. consumption of pork and beef, would tend to bias the rate ratio towards unity. Hence, if this is not a chance finding, the increased incidence could be explained by some factor(s) related to a moderate or high intake of pork or beef.

In a German case-referent study of cancer in the lower urinary tract (5) male subjects eating meat frequently had an estimated rate ratio (with 95% confidence interval) of 1.0 (0.7–1.4) while female subjects had an estimated rate ratio of 1.5 (0.8–2.9). In the present study the rate ratio for women exposed to both pork and beef was higher than that for men, 3.0 versus 2.0, but the estimate was very unstable since only 2 female cases reported as unexposed. In the German study high fat consumption is suggested as being related to the risk of cancer in the lower urinary tract. A possible high intake of fat among frequent consumers of pork and beef could thus increase the incidence of urothelial cancer. Another explanation could be that intake of the carcinogens in browned material formed during cooking (13, 24) influences the risk of urothelial cancer. The population controls in a recent case-referent study from Stockholm (20) consumed a large part of their beef and pork fried or grilled. Mutagenic activity has been detected in the urine of subjects having consumed a meal of fried pork or bacon (1).

The data contain scant information on the possible dose-response relation of urothelial cancer after exposure to pork or beef. There is almost certainly a substantial amount of non-differential misclassification between the categories moderate and high intake. Furthermore, the estimates of the rate ratio, especially for high intake, are unstable due to the small numbers.

An inverse relation between the intake of carotene and urothelial cancer has been suggested (8, 16). In the present study, consumption of yellow and green vegetables rich in carotene could not be separated from consumption of other vegetables and fruit. This implies a considerable non-differential misclassification, giving a bias of the rate ratio towards unity, which may explain the absence of association in our data.

Sixteen male cases stated that they were smoking a pipe/cigar only, giving a rate ratio (with 95% confidence interval) of 3.3 (1.5–7.4). The degree of misclassification from cigarette smoking before or after 1967–68 is probably low; in a random sample of the Swedish population, only 14% of the pipe smokers in 1963 had changed to cigarettes in 1969 (4).

IARC:s Scientific Committee (12) has found conflicting evidence of the role of pipe smoking in the etiology of bladder cancer. A recent suggestion (7) that pipe and cigar smokers only face a 20 to 40% higher incidence of urinary bladder cancer than non-smokers is based mostly on American studies. Our finding, together with others (2, 18), suggests that the proportion of pipe smokers in a population is causally related to the rate of urothelial cancer and that pipe smokers in Scandinavia have an increased incidence of urothelial cancer of a higher magnitude than do American pipe smokers. Similarly, Scandinavian pipe smokers seem to have an increased incidence of lung cancer of a higher magnitude than do American pipe smokers (2, 6). Hartge et al. (7) and Howe et al. (9) report a higher incidence for pipe smokers who inhale deeply than for other pipe smokers. Carstensen et al. (2) estimated the proportion of deep inhalers among pipe smokers in Sweden at 85% while 4% of pipe smoking controls in the case-referent study in the USA (7) reported

deep inhalation. While varying proportions of deep inhalers among the pipe smoking populations of the USA and Scandinavia could explain some of the differences in risk of urothelial cancer, it remains unclear whether other smoking characteristics or undetected confounding influence the results.

Pipe and cigar smokers were not separated in the study. According to the smoking survey in 1963 (4), pipe smokers far outnumber smokers of cigars. Hence, the results for smokers of a pipe/cigars refer mainly to pipe smoking.

Fallacies in the identification of urothelial cancer include missed diagnosis, treating papillomas without taking a histological specimen and not reporting these or other diagnosed cases as urothelial cancer to the National Swedish Cancer Registry. When examining death certificates, Mattsson & Wallgren (15) in 1978 found 49 cases of cancer in the urinary bladder (3.1% of all reported cases in Sweden 1978) that should have been included in the Cancer Registry. The non-differential misclassification introduced from the above mentioned sources is negligible.

The material was too small to analyze by different sites. Urothelial cancer is morphologically identical irrespective of the site of origin and is not seldom seen multifocally (22). Although the effect might be different at different sites, a carcinogen probably operates on the mucosa in the whole of the lower urinary tract. Thus, we chose a priori to include all reported cases of urothelial cancer.

The twin pairs are dissolved in the analysis. All cases of urothelial cancer occurred in different twin pairs and using a more sophisticated statistical technique would not change the point estimates of the rate ratio or influence the confidence limits substantially.

The consumption of beef and pork is widespread in Western populations. Hence, a possible etiologic factor associated with the consumption of beef and pork would contribute a substantial proportion of the cases of urothelial cancer. These associations are further examined in an ongoing case-referent study of urothelial cancer in Stockholm. There is persuasive evidence of a causal association between cigarette smoking and urothelial cancer. However, changing from cigarettes to pipe, and adopting the smoking characteristics pervading among pipe smokers in Scandinavia, probably has little, if any, preventive effect on the risk of urothelial cancer.

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