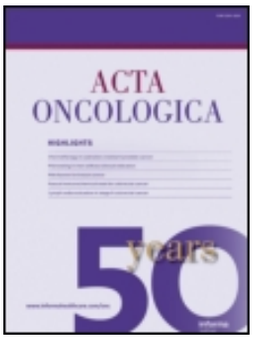

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ORIGINAL ARTICLE

Changes in alcohol intake and risk of upper digestive tract cancer

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Abstract

Introduction. Alcohol intake measured at one point in time is a strong predictor for later development of cancer of the oral cavity, pharynx, larynx and esophagus. In this prospective cohort study, we examined whether changes in individual alcohol intake resulted in subsequent altered risk of these cancers. *Material and methods.* In the Copenhagen City Heart Study we assessed alcohol intake among 4 896 men and 6 239 women who participated at both the first (1976–1978) and second (1981–1983) examination of the study. Alcohol intake changes on risk of upper digestive tract cancer 1981–2002 were examined by a Cox model adjusted for potential confounders. *Results.* Despite a small number of cases (n = 105), alcohol intake increase >14 drinks/week was associated with significantly elevated risk (hazard ratio = 2.5; 95% confidence interval, 1.1–5.3), while suggestively decreased risk was observed for persons lowering alcohol intake >7 drinks/week (0.5; 0.1–2.5). The trend test was highly significant ($p < 0.0001$). *Conclusions.* These findings support public health messages of not increasing alcohol intake and lowering consumption among people with high alcohol intake.

High intake of alcohol and tobacco smoking are the most important known risk factors for cancers of the oral cavity, pharynx, larynx and esophagus (upper digestive tract cancer) [1–3]. Although it is well-known that lifestyle factors such as alcohol intake do change over time [4,5], epidemiological studies of the effect of alcohol intake on the risk of upper digestive tract cancer are usually based on only one alcohol intake measurement [2,3,6]. Whether changing drinking habit actually results in altered risk, remains uncertain. To the authors' knowledge the association between changes in alcohol intake and upper-digestive tract has only been studied in case-control studies [7–14], while no prospective cohort studies from a general population with exposure information collected before the diagnosis of disease have been used. The present prospective cohort study examined whether individual changes in alcohol intake affected the subsequent risk of oral cavity, pharynx, larynx and esophagus cancer.

Materials and methods

The investigation was carried out in the Copenhagen City Heart Study, a large prospective cohort study initiated in 1976. In 1976–78 a cohort of 19 698 individuals from central Copenhagen was invited to a health examination and to fill in a questionnaire concerning health behaviour. The sample was randomly selected within age strata from a population of 90 000 inhabitants living in this well-defined area [15]. At the first examination 14 223 subjects participated (72%) and the cohort was re-examined in 1981–83 where 11 135 participated in their second examination. All participants gave written consent and the ethics committee for Copenhagen and Frederiksberg, Denmark, approved the study (no. 100.2039/91).

At first examination, the participants were asked in multiple-choice format to describe their intake of alcoholic drinks classed as beverages containing 9–13 grams of alcohol equivalent to one bottle of beer, glass of wine, or measure of spirits. The type-specific alcohol intake was added up to the aggregate intake of alcohol intake in drinks per week as previously described [16]. At the second examination the type-specific average number of beverages a week was reported, which was then added up to an aggregate intake. At neither examination was information on drinking history obtained.

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Changes in alcohol were included as the difference between the aggregated alcohol intake at second and first examination. The participants were then divided into six groups: major decrease (reduction of more than 7 drinks/week); minor decrease (1–6 d/w); steady consumption equalling $+/-1$ drink; minor increase (1–6 d/w); moderate increase (7–14 d/w) and a major increase (increase of >14 drinks/week). We adjusted for initial alcohol intake as a categorical variable, because it was expected that an initial high intake influenced the subsequent risk of cancer despite a decrease in intake. We used the Wald-test with five degrees of freedom to test for significance and supplemented with a trend-test where changes in alcohol intake was included continuously.

Smoking, sex, educational level, average income and body mass index were included as potential confounders on the background of previous studies showing that these variables were independent risk factors of upper digestive tract cancer [17–19]. These covariates, except sex, could change between first and second examination. Especially changes in smoking habits may be an important confounder, because it may be associated with changes in alcohol intake and with cancer risk. We therefore adjusted for changes in smoking habits included in six categories (sustained never smokers, sustained ex-smokers, smokers that quit between examinations, sustained light smokers (1–14 cigarettes/day), sustained heavy smokers (≥ 15 cigarettes/day) and heavy smokers that reduced consumption by at least 25%).

By means of the personal identification number linkage with the National Central Person Registry and the Danish Cancer Registry was obtained. This number has been assigned to all residents of Denmark since April 1, 1968. Vital status of each member of the cohort was followed in the National Central Person Registry. Information on cancer occurrence until December 31, 2002 among the study subjects was obtained through linkage to the files of the Danish Cancer Registry, which has collected information on all individuals in Denmark with a diagnosis of cancer since 1943. Comprehensive evaluation has shown that the Registry is 95–99% complete and valid [20,21].

We classified cancers according to the modified Danish version of the International Classification of Diseases, 7th revision, categorised as tongue (141.0, 141.1, 141.8), oral cavity (143.0, 144.0, 144.2), pharynx (145.0, 145.8, 146.0, 146.4, 147.0, 148.0), larynx (161.0, 161.1) and esophagus (150.0–150.2). The included diagnoses codes only consisted of sites previously shown to be associated with alcohol intake (e.g. sarcomas and melanomas were not included), which implied that the outcome consisted of only alcohol-associated malignancies. Until the end of 2002 the cohort experienced 118 alcohol-associated upper digestive tract cancers of which 11 were diagnosed before the second examination and therefore excluded. Of the remaining cases diagnosed after the second examination, 90 tumours were squamous cell carcinomas (84%), 11 were adenocarcinomas (10%), four were other rare carcinomas (4%) and two tumours were not histological confirmed malignant lesions (2%). Two participants developing squamous cell carcinomas of the tongue and esophagus had missing values on alcohol intake at first examination. A total of 105 cases were therefore included in the analysis.

A Cox regression was performed by using SAS/STAT software version 8.2 [22] to estimate the relative risk of upper digestive tract cancer by considering changes in alcohol intake, while taking potential confounding variables into account. Because age is a strong predictor of upper digestive tract cancer, age was used as the time scale with delayed entry, thereby adjusting for age. We examined the proportional hazard assumption for all factors included in the Cox model by plots of log(time) by log(-log(survival probability)). None of these tests indicated violation of the assumption. All p-values are from two-sided tests.

Follow-up started at the date of the second examination in 1981–83, until December 31, 2002, diagnosis of cancer, either upper digestive tract cancer or any other cancer (other than non-melanoma skin cancer), or date of death, emigration or disappearance, whichever came first. Participants with missing data on alcohol intake at first or second examination or diagnosis of any cancer (except non-melanoma skin cancer) before baseline (second examination) were excluded.

Results

The potentially confounding factors at first examination (sex, age, smoking, educational level, average income and body mass index) were unequally distributed on the six categories of changes in alcohol intake (Table I). Men and smokers both increased and decreased alcohol intake to a higher degree than women and non-smokers, while participants with lower average income and education level had more stable alcohol intake. The mean age was lowest for persons who increased or decreased alcohol intake, while differences for BMI did not show a systematic relationship. The age span ranged from 20.6 to 93.2, while the inter-quartile range was 44.4–60.3. Alcohol intake increased during follow-up with median alcohol intake increasing from 3.6 drinks/week at first examination to 4.0 drinks/week at second examination and the alcohol distribution

Table I. Characteristics of all subjects at the first examination by changing alcohol intake, Copenhagen City Heart Study, Denmark, 1976–78.

Changes in alcohol intake drinks/week	Females (number)	Males (number)	Age (mean)	Smoking (% smokers)	Income (% <4 000 DKK)	BMI (mean kg/m^2)	Educational level (% <8 years)
≤ −7	140	266	48.5	60.8	19.4	24.9	53.2
−6.9–1	1 600	1 146	51.2	59.0	23.2	25.2	61.0
−0.9–0.9	2 178	729	54.0	55.5	33.8	25.2	70.9
1–6.9	1 188	1 023	52.0	62.2	19.1	24.8	57.8
7–14	371	609	52.0	69.1	18.7	25.0	56.0
>14	193	912	50.6	77.2	15.8	25.7	60.1

was wider at second examination than at first examination.

A positive association between high alcohol intake at the second examination (baseline) and risk of upper digestive tract cancer was observed with significantly increased risk for alcohol intake above 42 drinks/week and a highly significant trend ($p < 0.0001$) (Table II).

The incidence of upper digestive tract cancer was associated with changing alcohol intake relative to stable alcohol intake adjusted for initial alcohol intake, changes in smoking habits and sex (Table III). A major increase of more than 14 drinks/week of alcohol was associated with a significantly elevated risk (hazard ratio (HR) = 2.5; 95%CI, 1.1–5.3) and participants with a decrease of more than 7 drinks/week had a not statistically significant lowered relative risk (0.5; 0.1–2.5) although only based on two cases. The trend test was highly significant ($p < 0.0001$). Further controlling for educational level, average income and body mass index at first examination or adjustment for all confounders at both first and second examination did not change the risk estimates of changes in alcohol intake (not shown). Furthermore, the results were not influenced by excluding abstainers (<1 drink/week) at either first or second examination (not shown).

By adjusting for alcohol intake at first examination we assumed no interaction between initial alcohol intake and changes in alcohol intake. We compared the estimates of changes in alcohol intake for persons with initial low and high alcohol intake, where the association was slightly stronger for persons initially drinking above 7 drinks/week, while persons initially drinking below 6 drinks/week did not have a positive effect of a minor decrease in alcohol intake.

Alternatively to adjust for alcohol intake at first examination, by adjusting for alcohol intake at second examination the risk of changes in alcohol intake and risk of upper digestive tract cancer remained (not shown) although attenuated and not statistically insignificant ($p = 0.91$). The test for trend was of borderline statistical significance ($p = 0.08$).

Table II. Alcohol intake at second examination and risk of upper digestive tract cancer, Copenhagen City Heart Study, Denmark, 1981–2002.

Alcohol intake (drinks/week)[a]	HR (95%CI)[b]
<1	1.00[c]
1–6	0.6 (0.3–1.3)
7–14	1.1 (0.6–2.1)
15–21	1.0 (0.4–2.1)
22–41	1.2 (0.5–3.1)
42–68	2.5 (1.3–5.0)
69+	3.3 (1.2–9.6)
Common test[d]	p = 0.002
Trend-test[e]	p < 0.0001

[a]Adjusted for age (underlying time-scale), sex, smoking, educational level, average income and body mass index.
[b]HR, hazard ratio; 95%CI, 95% confidence interval.
[c]Reference category.
[d]χ^2-statistics with 6 degrees of freedom.
[e]χ^2-statistics with 1 degrees of freedom.

Table III. Changing alcohol intake and the hazard ratio of upper digestive tract cancer, Copenhagen City Heart Study, Denmark, 1981–2002.

Changes in alcohol intake (drinks/week)[a]	(cases/person years at risk)	HR (95% CI)[b]
≤7	(2/6 617)	0.5 (0.1–2.5)
−6.9–1	(22/43 514)	1.2 (0.5–2.7)
−0.9–0.9	(14/44 491)	1.0[c]
1–6.9	(20/34 595)	1.3 (0.6–2.7)
7–14	(12/14 735)	1.4 (0.6–3.3)
>14	(35/16 142)	2.5 (1.1–5.3)
Common test[d]		p = 0.024
Trend-test[e]		p < 0.0001

[a]Adjusted for age (underlying time-scale), initial alcohol intake, sex and changes in smoking.
[b]HR, hazard ratio; 95%CI, 95% confidence interval.
[c]Reference category.
[d]χ^2-statistics with 5 degrees of freedom.
[e]χ^2-statistics with 1 degrees of freedom.

Discussion

In this prospective cohort study, we confirmed the positive association between alcohol intake and upper digestive tract cancer and added that a major increase in alcohol intake above 14 drinks/week was associated with significantly increased risk, while a suggestive decreased risk was observed for persons lowering their alcohol intake more than 7 drinks/week. The trend test for changes in alcohol intake was highly significant. These results points to a dose-response relationship between changes in alcohol intake and the incidence of the cancer disease under study.

To the best of our knowledge no other prospective cohort study has investigated the association between changes in alcohol intake and subsequent risk for upper digestive tract cancer, but eight studies did evaluate the effect of alcohol cessation on the risk of esophagus cancer [7–10,14] and cancer of the mouth and pharynx [11–13]. However, all of these studies were case-control studies and, in addition, seven of these studies included hospital-based controls [7–11,13,14]. Hospital-based studies may be more prone to selection bias compared to population-based studies, because the exposure distribution among controls may differ from the exposure distribution in the target population. Furthermore, differential recall of past alcohol exposure between cases and controls may also bias the results in case-control studies. Although the incidence rates of these cancers in general were higher in the countries in which these studies were carried out compared to Denmark [7–14], the results in all of the studies except the study with fewest cases [14] were in line with our results.

Our study had several advantages including our ability to adjust for initial alcohol intake, thereby taking into account the effect of alcohol intake before the changes appeared. Alternatively, we adjusted for alcohol intake at the second examination, where the estimates of alcohol intake changes attenuated, although the trend remained. Both results thereby supported that changes in alcohol intake affected the risk of upper digestive tract cancer, but that this effect primarily was attributable to alcohol intake at the second examination. This supports that the risk of upper digestive tract cancer is modifiable. Furthermore, we used highly valid data from the Danish Cancer Registry to obtain information of morbidity of these diseases [20,21]. All cases were verified by a histological examination minimising the influence of misclassification of the cancers under study.

Participants in this prospective study were asked twice about their intake of alcohol before the follow-up period for cancer was initiated. Self-reported alcohol consumption might underestimate the true intake [23], which may influence changes in alcohol intake. However, validation studies comparing self-administered questionnaire with intake assessed by detailed diet records showed high correlation above 0.80 and mean and standard deviation almost identical by the two methods [24,25]. The information on alcohol intake in Copenhagen City Heart Study has previously been characterised and discussed [16], where it was shown that alcohol intake was quite stable within strata of age, smoking habits and body mass index between the two examinations. Changes in alcohol intake may have occurred at any time between first and second examination, and those reporting a stable intake may have experienced changes as well. Additionally, the analyses did not include information about alcohol consumption at a later time point than the second examination. However, due to non-differential misclassification these potential differences in exposure among members of the same category would tend to bias the observed differences in cancer incidence towards the null.

In conclusion, in this large prospective population-based cohort study including two measurements of alcohol consumption and with more than 20 years of follow-up for cancer, we showed that an increase or decrease in alcohol intake influenced the relative risk for cancers of the upper digestive tract. These findings support that preventive public health messages concerning alcohol intake and advice focusing on lowering alcohol consumption in relation to the risk for these malignant diseases are justified.

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