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# Coffee intake and oral—oesophageal cancer: follow-up of 389 624 Norwegian men and women 40–45 years

# A Tverdal<sup>1</sup>, V Hjellvik<sup>\*,1</sup> and R Selmer<sup>1</sup>

Department of Pharmacoepidemiology, Norwegian Institute of Public Health, PO Box 4404, Nydalen, Oslo NO-0403, Norway

BACKGROUND: The evidence on the relationship between coffee intake and cancer of the oral cavity and oesophagus is conflicting and few follow-up studies have been done.

Methods: A total of 389 624 men and women 40-45 years who participated in a national survey programme were followed with respect to cancer for an average of 14.4 years by linkage to the Cancer Registry of Norway. Coffee consumption at baseline was reported as a categorical variable (0 or <1 cup, 1-4, 5-8, 9+ cups per day).

RESULTS: Altogether 450 squamous oral or oesophageal cancers were registered during follow-up. The adjusted hazard ratios with I-4 cups per day as reference were 1.01 (95% confidence interval: 0.70, 1.47), 1.16 (0.93, 1.45) and 0.96 (0.71, 1.14) for 0 or < I cup, 5-8 and 9+ cups per day, respectively. Stratification by sex, type of coffee, smoking status and dividing the end point into oral and oesophageal cancers gave heterogeneous and non-significant estimates.

CONCLUSION: This study does not support an inverse relationship between coffee intake and incidence of cancer in the mouth or oesophagus, but cannot exclude a weak inverse relationship.

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The evidence regarding the effect of coffee on cancer of the mouth, pharynx and larynx is judged as 'limited – no conclusion' (World Cancer Research Fund, 2007). Coffee is not mentioned among the food and nutritional factors that may modify the risk of cancer in the oesophagus. However, high-temperature drinks are judged as 'limited – suggestive' in increasing the risk (World Cancer Research Fund, 2007). A recent prospective study from Japan found an inverse relationship between coffee dose and the risk of oral, pharyngeal and oesophageal cancers (Naganuma *et al*, 2008). One prospective study from Norway found no relationship, whereas another study found an inverse relationship between coffee consumption and incidence of cancer in the buccal cavity and pharynx (Jacobsen *et al*, 1986; Stensvold and Jacobsen, 1994). The Japanese and the two Norwegian studies are the only prospective studies on this subject as far as we know.

Some case-control studies have found an inverse relationship (Tavani et al, 2003; Rodriguez et al, 2004), but not all (La Vecchia et al, 1989; Pintos et al, 1994). An update on coffee and cancer risk concluded that 'epidemiological data indicate an inverse relation between coffee, liver and probably oral and oesophageal cancers' (La Vecchia and Tavani, 2007). A recent pooled analysis of nine case-control studies of head and neck cancers with 5139 cases concluded with a support of the hypothesis of an inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx (Galeone et al, 2010a). So did a meta-analysis by Turati et al (2011) based on 2633 cases. These

cancers are serious with a 5-year relative survival of <10% for oesophageal cancer and around 50% for oral cancer in Norway (Cancer Registry of Norway, 2010). It is thus of great importance to obtain evidence of preventive measures of these cancers. We conducted a prospective study, including close to 400 000 participants aged 40-45 years.

## MATERIALS AND METHODS

### Study population

During 1985–1999, a cardiovascular survey programme was carried out in Norway. All men and women aged 40–42 years were invited. All counties, except for the capital Oslo, were visited every third year and each time a new cohort aged 40–42 was invited. In a few counties, a sample of people aged 43–45 years was invited. The attendance rate declined from close to 80% in the beginning down to nearly 60% at the end. Altogether 395 291 individuals participated in the surveys. We excluded 4603 who were registered as having cancer before attending the screening. In addition, 1064 did not answer the coffee questions, leaving 389 624 for analysis. Of these, 130 593 (33%) answered the question on alcohol, which was introduced in 1994.

## Variables

The study protocol was the same throughout the study period. Height and weight were measured to the nearest centimetre and half kilo. Underwear, stockings and trousers were allowed, but not shoes.



The questionnaire included questions on coffee consumption, smoking habits, cardiovascular history, diabetes history and physical activity. From 1994, questions about alcohol consumption were included and from 1997, a question about the consumption of fruit and vegetables was included. The questions about coffee were 'How many cups of coffee do you usually drink a day?' with preset categories; none or <1, 1-4, 5-8, 9+ cups. What type of coffee do you usually drink each day?' with preset categories; boiled coffee, filtered coffee, instant coffee, decaffeinated coffee and don't drink coffee. From 1994, the questions were changed to 'How many cups of boiled coffee do you usually drink a day?' and 'How many cups of other types of coffee do you usually drink a day?' The participants filled in the actual number of cups. We categorised the number of cups according to the preset categories 0 or <1, 1-4,5-8 and 9+ cups per day, coded as 1, 2, 3, 4, respectively. We then categorised the subjects into drinkers of boiled coffee and drinkers of other types. Note that drinkers of boiled coffee may also drink other types, whereas the 'other types' group does not include any boiled coffee drinkers.

The question on physical activity during leisure time had four alternatives from sedentary to intensive. However, during 1994–1997 ( $\sim$  22% of the study population), we asked about the number of hours of strenuous activity (sweating/out of breath) with four categories from none to 3+ hours per week. We have defined those in the lowest category of either question as sedentary.

The questions on alcohol read 'How many glasses of (1) beer (2) wine (3) spirits do you usually drink every 2 weeks?'. For each type, the actual number of glasses was filled in. In addition, there was a question on teetotalism (yes, no). In Norway, an alcohol unit is defined as 15 ml (12.8 g). This corresponds to a bottle (33 cl) of beer (4.5%), a glass (15 cl) of wine (12.0%) and a small glass (4 cl) of spirits (40%). We estimated the number of units per month by adding the number of glasses stated and multiplying by 2. We defined the categories as follows: (1) teetotaller, (2) not teetotaller, but 0 units per month, (3) <10 units per months and (4) 10 + units per month.

We defined five smoking categories as follows: (1) never smokers, (2) ex-smokers, (3) 1-19 cigarettes per day, (4) 20+ cigarettes per day and (5) others. People who smoked a pipe or cigars, but not cigarettes, made up the 'others' group.

Body mass index was categorised as < 20, 20 – 24, 25 – 29, 30 + kg m<sup>-2</sup>.

Information on educational level was collected from a national register in Statistics Norway by linkage as described beneath (end points). High education was defined as 13 or more years of education.

## Statistical analysis

The participants accrued person years from the date of their examination during the national survey to the date of first cancer, death, emigration or 31 December 2007.

Hazard ratios were estimated by Cox proportional hazards regressions with person years as the time variable. Smoking, body mass index, alcohol consumption and coffee intake were entered as dummy variables, according to the abovementioned categorisation and with never smokers,  $<20\,\mathrm{kg}\,\mathrm{m}^{-2}$ , teetotallers and 1–4 cups per day, respectively, as reference categories. When testing for trend, coffee was entered as a continuous variable coded as 1, 2, 3, 4. Equality of means or proportions across coffee groups was tested by analysis of variance or by  $\chi^2$  statistics from contingency tables, respectively. *P*-values <0.05 were considered statistically significant and all tests were two sided.

This study has a 90% power to detect a hazard ratio of 0.83 between two adjacent coffee groups. When taking the correlation between the coffee and smoking groups into account, the power is reduced to 87% when smoking is adjusted for. The power is 90% to detect a hazard ratio of 0.77 on half the study population.

## **End points**

Information on cancer was taken from the Cancer Registry of Norway by linkage using the encrypted personal identification number attributed to each inhabitant in Norway.

We used malignant neoplasm of buccal cavity or oesophagus (ICD-7 140-148, 150) as end point, restricted to squamous cell carcinoma (morphology codes 8050-8080, International Classification of Diseases for Oncology, Edition 3), which made up 93% of all cancers in mouth and oesophagus. We also did separate analyses for squamous cancers in the oesophagus (ICD-7 150) and in the mouth (ICD-7 140-148).

Altogether 450 people had cancer of the buccal cavity or oesophagus, distributed as cancer of lip (n=61), tongue (n=85), salivary gland (n=33), floor of mouth (n=28), other parts of mouth or unspecified (n=36), oral mesopharynx (n=88), nasopharynx (n=5), hypopharynx (n=16), pharynx unspecified (n=2) and oesophagus (n=96). In multivariate analyses, there were 446 end points due to missing information on confounders in some individuals. In the subgroup who had answered the alcohol questions, there were 75 end points, 74 in multivariate analyses.

## **RESULTS**

Table 1 shows baseline characteristics of age, smoking habits, body mass index and for the relevant subgroup, alcohol intake. Men were in the majority in the highest coffee consumption group and in the minority in the other coffee groups. About 20% smoked in the lowest coffee dose group increasing to >70% among people who drank nine or more cups per day. The proportion of boiled coffee use and daily smoking increased with the number of cups, whereas the proportion with high education decreased to less than half in the highest as compared with the lowest coffee dose group. The proportion of physically active people was also lowest in the highest coffee dose group. Alcohol consumption did not vary

Table I Baseline characteristics

	0, < I cup per day	I –4 cups per day	5–8 cups per day	9+ cups per day
N	41 454	153 376	150724	44 070
Age (mean)	41.3	41.4	41.4	41.4
Men, %	46.0	43.4	49.4	61.1
Boiled, %	4.4	26.4	31.0	36.3
High education, %	30.4	28.7	20.4	12.1
Physically active, %	78.3	81.6	78.4	69.7
Smoking, %				
Never	45.9	39.3	25.2	13.7
Ex	34.7	33.0	25.4	14.7
<20 cig	14.5	23.0	37. I	40.7
20+ cig	4.6	4.4	11.5	30.5
Smoke, not cig	0.2	0.3	0.5	0.5
BMI (kg m <sup>-2</sup> ), %				
<20	5.3	4.7	4.5	4.5
20-24	49.7	52.0	49.4	46.2
25-29	33.5	34.4	37.4	39.2
30+	11.5	8.8	8.6	10.1
Alcohol, %				
N (with info on alcohol)	14812	48 445	49 361	17975
Teetotallers	19.3	8.6	6.6	6.0
0 units per month	29.0	20.3	21.6	24.4
< 10 units per month	27.3	34.9	31.5	28.1
10+ units per month	24.0	36.0	40.2	41.4

Abbreviations: BMI = body mass index; cig = cigarettes. Men and women 40-45 years.

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much in the three upper coffee groups, whereas the consumption of alcohol was less in the 0 or <1 cup group.

The hazard ratios varied between 0.96 and 1.16 in the coffee groups with no distinct trend (Table 2). Stratification by sex, smoking and type of coffee revealed no distinct pattern. It is noted, however, that there is a positive trend among the non-smokers with a P-value for the trend slightly smaller than 0.05. However, this could be expected by chance when doing multiple testing, and testing for interaction between smoking (yes/no) and coffee consumption gave no significance (P = 0.08).

The lack of a consistent trend with coffee dose persisted when specifically using oral and oesophageal cancers as end point (Table 3).

Additional adjustment for alcohol in the subsample with information on alcohol consumption (the 33% of the study population, which entered in the period 1994–1999) had virtually no impact on the coffee-cancer association (Table 4).

Information on fruit and vegetables was available for 17% of the study population (those who were examined in 1997–1999). The proportion who consumed fruit/vegetables daily varied marginally between the three lowest coffee dose groups, whereas the proportion in the 9+ cups was lower in both men and women (data not shown).

#### DISCUSSION

In this large study of middle-aged men and women, we found no relationship between coffee dose and cancer of the buccal cavity, pharynx and oesophagus.

There have been some studies on this topic, but with ambiguous results. In a recent update from 13 studies, La Vecchia and Tavani (2007) reported that 12 of these found no association between coffee intake and cancers of the oral cavity, pharynx and oesophagus.

On the other hand, in a short report from two case-control studies, it was concluded that 'coffee may decrease the risk of oral/ pharyngeal and esophageal cancer'. A coffee dose of 3 + cups was compared with <1 cup per day (Tavani *et al*, 2003).

Cancer in the oral cavity and oesophagus is a rare disease in young people. Rodriguez *et al* (2004) found that high consumption of coffee (3 + cups per day) was inversely related to risk of oral and pharyngeal cancer below age 46. Interestingly, this study revealed an inverse relationship with body mass index, but as the authors state, this may be due to reverse causation.

A recent prospective study from Japan found 50% lower risk for oral, pharyngeal and oesophageal cancers for users of  $\geqslant 1$  cup per day as compared with no users (Naganuma *et al*, 2008). The

**Table 2** Adjusted HR<sup>a</sup> with 95% CI of squamous oral-oesophageal cancer by daily coffee consumption

	0, < I cup	I-4 cups	5-8 cups	9+ cups	HR per I unit	P-trend
All						
Cases	35	139	207	69		
Pyrs	580 385	2213629	2 184 454	619 489		
HR	1.01	Ref	1.16	0.96	1.02	0.79
95% CI	(0.70, 1.47)		(0.93, 1.45)	(0.71, 1.31)	(0.90, 1.14)	
Men						
Cases	30	87	148	60		
Pyrs	271 137	975 204	1 089 176	379 842		
HR	1.33	Ref	1.24	1.11	1.01	0.88
95% CI	(0.88, 2.02)		(0.95, 1.63)	(0.78, 1.58)	(0.88, 1.16)	
Women						
Cases	5	52	59	9		
Pyrs	309 248	1 238 424	1 095 277	239 647		
HR	0.42	Ref	1.04	0.57	1.03	0.78
95% CI	(0.17, 1.05)		(0.71, 1.53)	(0.27, 1.20)	(0.82, 1.30)	0.7.0
Non-smokers						
Cases	18	77	66	15		
Pyrs	466 172	I 586 749	1091824	172 339		
HR	0.78	Ref	1.14	1.51	1.22	0.043
95% CI	(0.47, 1.30)		(0.82, 1.59)	(0.87, 2.64)	(1.01, 1.47)	
Smokers						
Cases	17	62	141	54		
Pyrs	114 212	626 880	1 092 630	447   50		
HR	1.43	Ref	1.19	0.87	0.91	0.24
95% CI	(0.84, 2.45)		(0.88, 1.61)	(0.60, 1.27)	(0.79, 1.06)	
Boiled coffee						
Cases	2	39	74	32		
Pyrs	30 669	611247	703 807	231 139		
HR	0.88	Ref	1.26	1.17	1.10	0.40
95% CI	(0.21, 3.64)		(0.85, 1.87)	(0.71, 1.92)	(0.88, 1.39)	0.10
Other coffee						
Cases	33	100	133	37		
Pyrs	549715	1 602 381	I 480 646	388 350		
HR	1.01	Ref	1.11	0.83	0.98	0.73
95% CI	(0.68, 1.51)	i (Ci	(0.85, 1.54)	(0.56, 1.24)	(0.85, 1.12)	0.75

Abbreviations: CI = confidence interval; HR = hazard ratios; Pyrs = person years. <sup>a</sup>Adjusted for sex (except when stratified by sex), daily smoking (except in non-smokers), body mass index and education.



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Table 3 Adjusted HR<sup>a</sup> with 95% CI of subtypes of squamous oral—oesophageal cancer by daily coffee consumption

	0, < l cup	I-4 cups	5-8 cups	9+ cups	HR per I unit	P-trend
Buccal						
Cases	29	114	158	53		
Pyrs	580 385	2213629	2 184 454	619 489		
HR	1.03	Ref	1.12	0.96	1.01	0.92
95% CI	(0.68, 1.55)		(0.88, 1.44)	(0.68, 1.36)	(0.88, 1.15)	
Oesophagus						
Cases	6	25	49	16		
Pyrs	580 385	2 213 629	2 184 454	619 489		
HR	0.93	Ref	1.34	0.97	1.06	0.67
95% CI	(0.38, 2.26)		(0.82, 2.18)	(0.50, 1.88)	(0.82, 1.36)	

Abbreviations: CI = confidence interval; HR = hazard ratios; Pyrs = person years. \*Adjusted for sex, daily smoking, body mass index and education.

**Table 4** Adjusted HR with 95% CI of squamous oral-oesophageal cancer by daily coffee consumption in the subgroup where questions on alcohol were included

	0-4 cups	5+ cups	P-value
Cases	28	46	
Pyrs	648 566	704   46	
HR <sup>a</sup>	Ref	0.98	0.93
95% CI	_	(0.59, 1.61)	
HR with alcohol units <sup>b</sup>	Ref	0.98	0.94
95% CI	_	(0.59, 1.62)	

Abbreviations: CI = confidence interval; HR = hazard ratios; Pyrs = person years.  $^a$ Adjusted for sex, daily smoking, body mass index and education.  $^b$ Adjusted for sex, daily smoking, body mass index, education and alcohol consumption.

exposure groups in that study (never use, occasional use and  $\geqslant 1$  cup per day) are practically non-overlapping with the exposure groups in our study. The Japanese study compares low dose with no dose, whereas our study compares high dose with low dose.

Quite recently, a study of pooled individual-level data from nine case-control studies was published (Galeone et al, 2010a). The findings supported the hypothesis of an inverse association between caffeinated coffee drinking and oral and pharyngeal cancer. The odds ratio of >4 cups per day vs zero cups per day varied between 0.5 and 0.7 in various strata of geography, education, tobacco consumption, alcohol consumption and vegetable and fruit intake, which are quite consistent results. The authors claimed that recall bias of coffee consumption was not likely, as coffee consumption was not known to be related to head and neck cancers. On the other hand, recall bias on smoking habits and alcohol intake may well have taken place. It is hard to assess the impact on the risk estimates of recall bias of confounders. A meta-analysis by Turati et al (2011) on eight case-control studies and one observational study found a relative risk of 0.64 comparing the highest and lowest coffee consumption groups.

There are many examples that case-control studies more readily reveal associations than prospective studies do. One reason is that case-control studies are more likely to be encumbered with bias such as recall bias. Besides the Japanese study, we know of two prospective studies, both from Norway (Jacobsen *et al*, 1986; Stensvold and Jacobsen, 1994). None of these consistently supported an inverse association, but Stensvold and Jacobsen (1994) reported a borderline significant inverse association with cancer of the buccal cavity and pharynx in men.

Regarding the tendency for different findings in case-control and prospective studies, another example is the relation between coffee consumption and colorectal cancer. One meta-analysis of case-control studies suggested a favourable moderate effect of coffee consumption on colorectal cancer (Galeone *et al*, 2010b).

Another meta-analysis on prospective studies found no relationship (Je et al, 2009). On the other hand, there was a slight suggestion of an inverse association in some of the studies, and this suggestion was stronger in studies with shorter follow-up. The upshot might be reverse causation since people with disease symptoms might reduce their coffee consumption. We checked this possibility in our study population by estimating hazard ratios based on 5 years follow-up (77 cases). There was no tendency of lower hazard ratios (data not shown).

Our study is by far the largest prospective study as measured by the number at risk. Potential confounders have been taken into account and the follow-up is nearly complete using the National Cancer Registry and the Cause of Death Registry as end point registries. The Cancer Registry of Norway reports a completeness of 98.8% for the period 2001–2005 except for haematological malignancies and cancer of the central nervous system. For the period 2003–2007, 97.6% of the cancers in mouth and pharynx (ICD-10 C10-C14) and 95.0% of the oesophageal cancers (ICD-10 C15) were morphologically verified. (Cancer Registry of Norway, 2010).

#### Limitations

We have to keep in mind that this data set is from a systematic screening over a 15-year period with a primary focus on cardiovascular disease.

We have no information about what people added to the coffee, such as milk or sugar. These ingredients have not been linked to oral-oesophageal cancers, but milk might influence the temperature of the coffee that is consumed in a favourable way with regard to the risk of oesophageal cancer. However, the Expert Report Panel judged the evidence of high-temperature drinks as a cause of oesophageal cancer as limited (World Cancer Research Fund, 2007).

Another weakness is that we only have information on alcohol consumption in a subgroup and on fruit and vegetable consumption in an even smaller subgroup. These questions were introduced when the programme had been running for 9 and 12 years, respectively. The counties were visited every third year, when new cohorts of 40-42-year olds were invited. This means that the subgroups with information on alcohol and fruit/vegetables were born later and represent a minor selection of counties compared with the total study population, but there is no reason to believe that the distribution of alcohol dose and the prevalence of daily use of fruit or vegetables in the subgroups deviated from that in the total study population. Alcohol and fruit/vegetables have both been related to cancer risk; fruit and vegetables in a favourable way (La Vecchia et al, 1997), and alcohol in an unfavourable way (World Cancer research fund). Our data from the subgroups with fruit/vegetables and alcohol indicate that these variables were not important confounders in our study. Nevertheless, the fact remains

that we have not been able to adjust the entire study population for alcohol consumption and dietary intake of fruit and vegetables.

A proportion of smokers may have stopped smoking during follow-up. The official surveys show that the smoking prevalence in ages 15-74 years has declined from 35% in 1991 to 25% in 2006 (Statistics Norway, 2011). However, this would not influence the adjusted estimates of the coffee-cancer association unless smoking cessation depended on baseline coffee consumption or affected later coffee consumption.

As mentioned, we do not know what people put in their coffee. Other factors that may vary between studies are type of coffee (in Norway Coffee Arabica L), ways of preparing the coffee and size of cup. However, stratified analyses give no reason to believe that differences in the type of coffee or brewing methods can explain the conflicting results between our study and the majority of casecontrol studies. The power of our study was high to detect a hazard ratio of 0.8 between two adjacent coffee groups. But we cannot exclude a weak inverse relationship.

This study does not support an inverse relationship between coffee intake and cancers in the buccal cavity, pharynx and oesophagus.

#### Conflict of interest

The authors declare no conflict of interest.

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