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Dietary acrylamide intake and the risk of cancer among Finnish male smokers

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Abstract

Objective—To assess the association between dietary acrylamide intake and the risk of cancer among male smokers.

Methods—The study consisted of 27,111 male smokers, aged 50–69 years, without history of cancer. They were participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland. The men completed a validated dietary questionnaire and a questionnaire on general background characteristics (including smoking habits) at baseline. Incident cases of cancer were identified through the national Finnish Cancer Registry.

Results—During an average 10.2 year follow-up 1703 lung cancers, 799 prostate cancers, 365 urothelial cancers, 316 colorectal cancers, 224 stomach cancers, 192 pancreatic cancers, 184 renal cell cancers, and 175 lymphomas were diagnosed. Dietary acrylamide intake was positively associated with the risk of lung cancer; relative risk (RR) in the highest vs. the lowest quintile in the multivariate-adjusted model was 1.18 (95% confidence interval (CI) 1.01–1.38, p for trend 0.11). Other cancers were not associated with acrylamide intake.

Conclusions—High acrylamide intake is associated with increased risk of lung cancer but not with other cancers in male smokers.

Keywords

acrylamide intake; food; cancer; cohort studies

Introduction

Acrylamide is a substance formed when foods with high carbohydrate content are heated. Acrylamide is also formed in the pyrolysis of tobacco and acrylamide is present both in side stream and mainstream tobacco smoke [1]. High acrylamide content has been observed in foods like French fries, coffee, potato chips, crisp bread, and biscuits [2]. In addition, occupational exposure to acrylamide is also possible, but is more limited today [3] In a Swedish study, a major part of acrylamide was reported to be derived from tobacco smoke and the rest from food [4]. Both tobacco derived and dietary acrylamide were significantly associated with haemoglobin acrylamide adducts in the study.

Exposure to acrylamide is of concern because it is a genotoxic substance and has been observed to be carcinogenic in rodents [5]. The International Agency for Research on Cancer (IARC) has evaluated acrylamide as a probable carcinogen in humans (group 2A) [6]. A dose-response relationship has been reported between acrylamide exposure and the incidence of neoplasia in multiple organs both in mice and in rats, e.g. in skin, thyroid, mammary gland, central nervous system, uterus, and lung. Acrylamide itself is most probably not genotoxic, but its major metabolite, glycidamide, binds to DNA and results in the formation of DNA adducts. Acrylamide is metabolized to glycidamide by CYP2E1 [7]. In most of the epidemiologic studies acrylamide exposure has not been associated with cancer risk [8–22]. However, acrylamide exposure has been positively associated with the risk of renal cell cancer [12], endometrial and ovarian cancer [10, 22], and estrogen receptor positive breast cancer [19]. In addition, in one study, high acrylamide intake was associated with lower lung cancer risk among women [13].

We investigated the association between the intake of dietary acrylamide and the risk of several cancers in a cohort of male smokers.

Subjects and methods

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a double-blind, placebo-controlled, primary prevention trial undertaken to determine whether supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer in male smokers. The rationale, design, and methods of the study, as well as characteristics of the participants, have been described in detail elsewhere [23].

Participants of the ATBC study were recruited in 1985–1988 from the total male population aged 50–69 years in south-western Finland (n=290,406). To be eligible the subjects had to smoke at least five cigarettes per day at entry and give written informed consent. Exclusion criteria included a history of cancer or other serious disease limiting long-term participation; use of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses and treatment of anticoagulant agents.

Eligible men (n=29,133) were randomized into one of four supplementation regimens: alpha-tocopherol alone, beta-carotene alone, alpha-tocopherol and beta-carotene, or placebo. The trial ended on April 30, 1993, with ongoing follow-up through the Finnish Cancer Registry thereafter. The ATBC Study was approved by the institutional review boards of the National Public Health Institute of Finland and the US National Cancer Institute. Written informed consent was obtained from each participant before randomization.

Baseline measurements

At baseline (1985–1988) the men completed a questionnaire on general background characteristics and medical and smoking histories. Height and weight were measured. A chest x-ray was taken to exclude existing lung cancer.

Dietary assessment

Diet was assessed at baseline using a self-administered, modified diet history method [24]. The diet questionnaire included 276 food items and mixed dishes. It was used with a portion-size picture booklet of 122 photographs of foods, each with three to five different portion sizes. The subject was asked to report the frequency of consumption and the usual portion size of foods during the previous 12 months. Frequencies were reported as the number of times per month, week, or day. At the first baseline visit the questionnaire, along

with the picture booklet, was given to the subject to be completed at home. At the second baseline visit, 2 weeks later, the questionnaire was returned, reviewed, and completed together with a study nurse. The questionnaire was satisfactorily completed by 27,111 participants (93%).

To calculate intake of nutrient confounders (alcohol, energy adjusted fiber), food consumption data were computed into daily nutrient values based on the food composition database and related software at the National Public Health Institute (now National Institute for Health and Welfare).

Acrylamide levels in foods are mainly based on published Finnish data [2] and chemical analyses conducted particularly for the present study. In the study of Eerola and co-workers [2], a total of 201 food samples that included 30 different types of foods were analyzed. Acrylamide was measured in rye crisp breads, fresh rye breads, toasts, French fries, potato chips, potato-ham casseroles, fried bacons, meat balls, pizzas, chicken nuggets, minced meat patties, rye flour, oat flakes, biscuits, muesli, breakfast cereals, popcorn, coffee powder, coffee drink, instant coffee drink, tea drinks, chocolate drink, and cow milk[2]. The food samples included between 1 and 17 different brands of each type of food. In addition, some food items that could have been important sources of acrylamide in the ATBC Study were analyzed in this study. These include rye bread, beer, and Karelian pasty, which is a popular salty pasty having a rye crust. Samples were analysed according to Eerola and co-workers [2]. In brief, a homogenised sample was extracted with water in a horizontal shaker at room temperature protected from light. Before the extraction an internal standard (acrylamide-d3) was added. The extracts were frozen and subsequently centrifuged. The supernatant was purified by using solid-phase extraction (SPE). The SPE columns were preconditioned with methanol and water followed by the application of the sample into the column. The eluent was collected from SPE columns and filtered by using a centrifugal filter device. Acrylamide was determined by using LC-MS/MS (liquid chromatography, tandem mass spectrometry). The mobile phase consisted of methanol-water (5:95) using an isocratic elution. MS/MS was operated in the positive ion electrospray mode. Multiple Reaction Monitoring (MRM) technique was used for identification and quantification, in which protonated molecule was fragmented to the product ions with the following transitions: 72 → 55 m/z for acrylamide and 75 → 58 m/z acrylamide-d3, respectively. The acrylamide levels in the samples analysed for this study were (mean (min-max)): rye bread 51 µg/kg (<40–80 µg/kg), beer not detected and Karelian pasty 43 µg/kg. In addition to the analyses carried out in Finland, acrylamide levels from Swedish (Danish pastry, berry pie, muffin, pancake, pasta, vegetable hamburger) [25] and Dutch (white bread (non-toasted), doughnut, sausage, sponge cake, hamburger, fish finger, corn flakes) [26] analyses were used if applicable. All other foods were assumed not to contain acrylamide.

The dietary method was validated in a pilot study carried out among 190 men prior to the ATBC Study [24]. The men completed the questionnaire first and then kept food records for 24 days, spread over 6 months, as the reference method. They filled in the questionnaire again at the end of the pilot study. The Spearman correlations between the first and second questionnaires and the food records were 0.73 and 0.43, respectively for dietary acrylamide.

Cancer ascertainment

Incident cancer cases, diagnosed by April 1999, were identified through the Finnish Cancer Registry that provides nearly 100% case ascertainment [27]. The cancer diagnoses were confirmed through central review of all relevant hospital records by one or two study physicians.

Statistical analysis

Participants contributed follow-up time from the date of randomization until the first cancer, death, or 30th of April 1999. First cancer was defined based on ICD-9 codes 140–208 and 2337X excluding 173. Subject was defined as case if first cancer was the cancer type of interest and censored otherwise. If a subject had more than one cancer types as first cancer, all were considered as cases. Acrylamide and nutrient intakes were energy adjusted using Willett's residual method [28]. Men were grouped into quintiles of dietary acrylamide and nutrient intake based on the distribution in the entire cohort. Also other covariates than nutrients were grouped into quintiles, except supplementation group and education. Proportional hazards models were used to estimate relative risks (95% confidence intervals) of cancers associated with different intake levels of acrylamide. The relative risks were adjusted for age and trial supplementation group. The multivariable-adjusted model was constructed separately for each endpoint using stepwise regression. Covariates hypertension, education, total serum cholesterol, serum alpha-tocopherol, serum beta-carotene and serum retinol, the consumptions of fruits and berries, vegetables and red meat and the intakes of dairy fat, total fat, lycopene, total carbohydrates, energy and fiber were added one by one to the model which already included age, trial supplementation group, number of cigarettes smoked daily, years of smoking, physical activity, body mass index and alcohol intake. If the inclusion of a covariate changed the relative risk of the fifth quintile of acrylamide intake more than 5%, the covariate was included to the model. The multivariable-adjusted model was further adjusted for the consumptions of coffee, fried potatoes and rye bread. Tests for linearity of the trend were obtained from the Wald test by treating median values of each quintile as continuous variables in the proportional hazards model. Stratified analysis was performed in order to assess the possible effect modifications, and the significance of interactions was tested using the likelihood ratio test.

Results

Baseline characteristics by quintiles of energy-adjusted acrylamide are shown in Table 1. Men in 3rd–5th quintiles were slightly taller, consumed more fiber, coffee, rye bread and fried potatoes, and less alcohol than men in lower quintiles. The highest correlations between energy-adjusted acrylamide intake and dietary factors were between acrylamide intake and coffee ($r=0.63$), fried potatoes ($r=0.50$), fiber ($r=0.25$), rye bread ($r=0.23$), and alcohol intake ($r=-0.22$). Major sources of acrylamide intake were: coffee 15.2 $\mu\text{g/day}$ (40.4 %), fried potatoes 5.47 $\mu\text{g/day}$ (14.6 %), and rye bread 5.26 $\mu\text{g/day}$ (14.0 %).

During the 10.2 years of follow-up 1703 lung cancers, 799 prostate cancers, 365 urothelial cancers, 316 colorectal cancers, 224 stomach cancers, 192 pancreatic cancers, 184 renal cell cancers, and 175 lymphomas were diagnosed. Acrylamide intake was associated positively with the risk of lung cancer both in age- and supplementation-adjusted and in multivariate-adjusted models, relative risk (RR) 1.26 (95% confidence interval (CI) 1.09–1.47), p for trend=0.02 and RR 1.27 (95% CI 1.08–1.49), p for trend=0.02, respectively in the highest vs. lowest quintile (Table 2). The association of acrylamide intake and the risk of lung cancer weakened by further adjustment for sources of acrylamide: adjustment for coffee RR 1.12 (95% CI 0.92–1.36), p for trend=0.55, for fried potatoes RR 1.26 (95% CI 1.05–1.51), p for trend=0.05, and for rye bread RR 1.25 (95% CI 1.07–1.47), p for trend=0.02 in the highest vs. lowest quintile. There was a borderline significant positive association between coffee consumption and the risk of lung cancer when adjusted for age, supplementation group, number of cigarettes daily, physical activity, alcohol intake, and body mass index (RR of highest quintile vs. lowest 1.17 (95% CI 0.99–1.37), p for trend 0.03). Consumption of fried potatoes or rye bread were not associated with the risk of lung cancer.

The association between acrylamide intake and lung cancer was not modified by number of cigarettes smoked daily, alcohol intake or by body mass index. No association was observed between acrylamide intake and other cancers (Table 2). When analyses were repeated with exclusion of the cases that occurred during the first 2 years the results were unchanged.

Discussion

We observed a positive association between the dietary intake of acrylamide and the risk of lung cancer. Acrylamide intake was not associated with the risk of any other cancer.

Surprisingly, we found a positive association between acrylamide intake and the risk of cancer only for lung cancer. This is not consistent with the one published study that reported high acrylamide intake to be associated with lower lung cancer risk in women [14]. However, the authors interpreted the observation in a way that acrylamide may alter the hormonal balance, particularly because postmenopausal hormone treatment is in some studies associated with decreased risk of lung cancer. This mechanism of an estrogen effect is difficult to support in men because of much lower estrogen synthesis as compared with women. In fact, in never smoking men the risk of lung cancer in the second and third tertiles of intake was heightened compared to lowest tertile. However, because of the low number of lung cancer cases among never smokers, the confidence intervals were large. In conclusion, the role of hormone activity is an interesting issue in acrylamide related pathogenesis and particularly the association with lung cancer warrants further studies.

One reason for our observation that acrylamide intake was only associated with lung cancer risk could be that dietary intake is rather low compared to acrylamide exposure levels that have caused cancer in experimental animals [30]. Therefore, it is probable that the positive association between acrylamide intake and the risk of cancer can only be seen in studies and endpoints with high power; i.e., in the present study with over 1,700 lung cancers diagnosed. In addition, this study has the strength that since lung cancer was the primary endpoint in the ATBC study, a baseline chest X-ray was undertaken to exclude preexisting lung cancer. Therefore, for lung cancer the influence of preclinical disease could be excluded. To enhance the ascertainment of incident cases, a chest X-ray was obtained every 28 months and at each participant's exit from the trial.

The other cancer in which we saw an association - although not a statistically significant one - was renal cell cancer. This is in line with the study of Hogervorst and colleagues [9] in which risk of renal cell cancer was about 60% higher in highest quintile of intake compared to the lowest. In our study risk of renal cell cancer was heightened already in the second quintile of intake. The reason for this difference could be that in Dutch study acrylamide intake was lower than in our study. Therefore, the intake level (median 30.6 µg/day) in the second quintile corresponds the intake level seen in the fourth or fifth quintile in the Dutch study. Therefore, it could be hypothesized that both of these studies observed similar association in similar dose levels. The other reason why the association between acrylamide intake and risk of renal cell cancer was more pronounced in the Dutch study compared to our study, could be the fact that in the Dutch study the number of cases of renal cell cancer was 241 whereas in our study there were only 184 cases of renal cell cancer. Therefore, the statistical power was stronger in the Dutch study to observe the association than in ours.

On the other hand, most other studies have not found an association between acrylamide intake and the risk of cancer [8–22]. Apart from already discussed renal cell cancer and lung cancer, positive association between acrylamide intake and risk of cancer have been observed for endometrial and ovarian [10, 22] and for estrogen receptor positive breast cancer [19]. These findings support the hypothesis that hormonal factors are behind the

association between acrylamide intake and the risk of cancer. However, counterevidence for this hypothesis was observed in Italian case-control study for breast and ovarian cancers [9] in Swedish study on risk of epithelial ovarian cancer [15], and in two American studies on premenopausal breast cancer [19, 22]. In none of these studies acrylamide intake was associated with the risk of cancer. Therefore, more research – both epidemiologic and mechanistic – is needed to explore the hormonal activity and associations with hormone-dependent cancers of acrylamide. For other cancers examined in our study (cancers of prostate and stomach, lymphoma and colorectal and urothelial cancer) our study is in line with previous studies which have not observed an association between the risk and acrylamide intake [8, 9, 12, 15, 18, 27].

The biggest weakness is that since the dietary questionnaire was not designed to estimate the intake of acrylamide, the intake estimates could be inaccurate to some extent. In addition, we don't have any information of acrylamide content of foods in the 1980's, since acrylamide in Finnish foods were first analysed in 2005–2006. However, we have no reason to believe that acrylamide levels in foods would have been different in 1980's and 1990's. During the recent years efforts have been made to lower the acrylamide content of foods through “toolbox” approaches aiming for good manufacturing practices, but the results have been disappointing [31]. The other weakness common to all such studies that use ordinary food consumption data is that the large variation of acrylamide content in each food can not be taken into account. This can cause measurement error and weaken the possibility to observe an association between acrylamide intake and the risk of cancer.

The main sources of acrylamide in this study, coffee and rye bread, have also protective compounds (e.g. phenols) that could counteract the carcinogenic effect of acrylamide in these foods [32, 33]. On the other hand, it is possible that it is not acrylamide but some other carcinogenic substance in foods high in acrylamide that is responsible for the increased risk of lung cancer. One such candidate is, for example, furan which is found in high concentrations in coffee [34]. The role some other substance than acrylamide in coffee is supported by the facts that the association between acrylamide intake and lung cancer was disappeared by adding coffee to the model and that coffee itself was associated, although only borderline significantly, with the risk of lung cancer. Adding other sources of acrylamide to the model or modelling did not have similar effects. It is also possible that acrylamide intake is associated with some other foods containing either protective or carcinogenic compounds that are either positively or inversely associated with cancer risk and therefore are confounders. In this study adjusting for vegetable consumption strengthened the positive association between acrylamide intake and lung cancer. Vegetables contain a variety of bioactive compounds (e.g. carotenoids, flavonoids) that may confer protection against cancer, as has also previously been observed in this cohort [35]. In addition, it is possible that residual confounding caused by smoking related variables could bias the results.

Our results cannot be generalized to other populations e.g. non-smokers, since smoking is a very important acrylamide source. There could be additivity in the effects of smoke and diet derived acrylamide or the observed association could also be a result of interaction of acrylamide with other components of smoke. However, in the Dutch study there was no statistically significant interaction between smoking status and acrylamide intake in the risk of lung cancer [14].

In conclusion, acrylamide intake seems to be positively associated with the risk of lung cancer but not with other cancers in male smokers when adjusted for lifestyle related and other key confounders. Since the results of studies investigating the association between

acrylamide exposure and the risk of cancer have been contradictory, more studies are needed before drawing firm conclusions.

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Table 1
Baseline characteristics of study participants by energy-corrected acrylamide quintiles (medians or proportions)

Background characteristics	Quintile				
	Q1	Q2	Q3	Q4	Q5
Number of subjects	5419	5389	5445	5401	5457
Acrylamide intake (µg/day)	21.9	30.6	36.7	43.9	55.7
Age (years)	57.8	57.5	57.2	56.8	56.0
Smoking years	37	37	36	36	36
Number of cigarettes daily	20	20	20	20	20
Body mass index (kg/m ²)	26.0	25.9	25.9	26.1	26.0
Height (cm)	173	173	174	174	174
Physical activity, Moderate or Heavy (%)	54.7	58.3	60.4	60.8	58.2
Daily intake of:					
Energy (kJ)	10647	10929	11033	10928	10575
Alcohol (g)	18.2	12.3	10.7	9.2	7.7
Fiber (g)	21.3	24.0	25.1	26.2	26.9
Dairy fat (g)	61.1	62.5	61.7	60	56.2
Lycopene (µg)	868	899	891	895	829
Daily consumption of					
Coffee (g)	300	450	600	660	880
Rye bread (g)	60	80	100	105	105
Fried potatoes (g)	0	8.3	13.3	18.3	27.5
Vegetables (g)	247	267	279	291	306
					277

Table 2

Dietary intake of acrylamide and relative risks (95% confidence intervals) of cancer. Same data set is used both for age and supplementation group adjusted and multivariate-adjusted analyses

	Quintile of energy-adjusted intake					p for trend
	1	2	3	4	5	
Median acrylamide intake ($\mu\text{g/day}$)	21.9	30.6	36.7	43.9	55.7	
Lung cancer						
Number of cases	332	333	363	295	380	
Age-adjusted RR ^a	1.00	1.01 (0.87–1.18)	1.11 (0.95–1.29)	0.93 (0.80–1.1)	1.26 (1.09–1.47)	0.02
Multivariable-adjusted RR ^b	1.00	1.01 (0.86–1.18)	1.11 (0.95–1.29)	0.93 (0.79–1.1)	1.18 (1.01–1.38)	0.11
Prostate cancer						
Number of cases	163	153	167	163	153	
Age-adjusted RR ^a	1.00	0.94 (0.75–1.18)	1.04 (0.83–1.29)	1.05 (0.84–1.31)	1.04 (0.83–1.3)	0.49
Multivariable-adjusted RR ^b	1.00	0.95 (0.76–1.19)	1.03 (0.83–1.29)	1.06 (0.84–1.33)	1.05 (0.83–1.32)	0.43
Colorectal cancer						
Number of cases	73	64	60	62	57	
Age-adjusted RR ^a	1.00	0.88 (0.62–1.24)	0.82 (0.58–1.16)	0.87 (0.61–1.22)	0.82 (0.58–1.18)	0.3
Multivariable-adjusted RR ^b	1.00	0.93 (0.66–1.32)	0.89 (0.62–1.26)	0.95 (0.67–1.36)	0.93 (0.65–1.34)	0.75
Urothelial cancer						
Number of cases	75	70	83	60	77	
Age-adjusted RR ^a	1.00	0.94 (0.68–1.32)	1.12 (0.82–1.54)	0.84 (0.6–1.19)	1.14 (0.82–1.57)	0.67
Multivariable-adjusted RR ^c	1.00	0.91 (0.65–1.27)	1.06 (0.77–1.47)	0.78 (0.55–1.11)	0.99 (0.71–1.39)	0.71
Stomach cancer						
Number of cases	43	59	32	54	36	
Age-adjusted RR ^a	1.00	1.39 (0.93–2.07)	0.75 (0.47–1.19)	1.29 (0.86–1.95)	0.9 (0.57–1.41)	0.57
Multivariable-adjusted RR ^d	1.00	1.42 (0.94–2.13)	0.78 (0.49–1.26)	1.34 (0.88–2.05)	0.96 (0.6–1.53)	0.78

	Quintile of energy-adjusted intake					p for trend
	1	2	3	4	5	
Pancreatic cancer						
Number of cases	38	37	41	40	36	
Age-adjusted RR ^a	1.00	0.97 (0.61–1.55)	1.08 (0.69–1.69)	1.08 (0.69–1.7)	1 (0.63–1.6)	0.83
Multivariable-adjusted RR ^c	1.00	0.98 (0.61–1.56)	1.08 (0.69–1.71)	1.06 (0.66–1.69)	1 (0.62–1.62)	0.89
Renal cell cancer						
Number of cases	28	27	48	43	38	
Age-adjusted RR ^a	1.00	0.96 (0.56–1.65)	1.69 (1.05–2.73)	1.54 (0.95–2.51)	1.39 (0.84–2.29)	0.05
Multivariable-adjusted RR ^c	1.00	0.94 (0.55–1.62)	1.65 (1.02–2.67)	1.47 (0.89–2.41)	1.28 (0.76–2.15)	0.12
Lymphoma						
Number of cases	33	32	40	33	37	
Age-adjusted RR ^a	1.00	0.97 (0.59–1.59)	1.20 (0.75–1.92)	1.02 (0.62–1.67)	1.17 (0.72–1.89)	0.5
Multivariable-adjusted RR ^b	1.00	0.93 (0.56–1.53)	1.17 (0.73–1.88)	0.98 (0.59–1.61)	1.1 (0.67–1.8)	0.67

^a Adjusted for age and supplementation group.

^b Adjusted for age, supplementation group, number of cigarettes daily, years of smoking, physical activity, alcohol intake, and body mass index.

^c Adjusted for age, supplementation group, number of cigarettes daily, years of smoking, physical activity, alcohol intake, body mass index, and consumption of vegetables.

^d Adjusted for age, supplementation group, number of cigarettes daily, years of smoking, physical activity, alcohol intake, body mass index, and energy-adjusted fiber intake.