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Dietary Acrylamide and Human Cancer: A Systematic Review of Literature

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Abstract

Cancer remains the second leading cause of death in the United States, and the numbers of cases are expected to continue to rise worldwide. Cancer prevention strategies are crucial for reducing the cancer burden. The carcinogenic potential of dietary acrylamide exposure from cooked foods is unknown. Acrylamide is a by-product of the common Maillard reaction where reducing sugars (i.e., fructose and glucose) react with the amino acid, asparagine. Based on the evidence of acrylamide carcinogenicity in animals, the International Agency for Research on Cancer has classified acrylamide as a group 2A carcinogen for humans. Since the discovery of acrylamide in foods in 2002, a number of studies have explored its potential as a human carcinogen. This paper outlines a systematic review of dietary acrylamide and human cancer, acrylamide exposure and internal dose, exposure assessment methods in the epidemiologic studies, existing data gaps, and future directions. A majority of the studies reported no statistically significant association between dietary acrylamide intake and various cancers, and few studies reported increased risk for renal, endometrial, and ovarian cancers; however, the exposure assessment has been inadequate leading to potential misclassification or underestimation of exposure. Future studies with improved dietary acrylamide exposure assessment are encouraged.

Keywords

Dietary acrylamide; internal dose; exposure assessment; cancer; epidemiology

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Introduction

In 2002, the Swedish National Food Administration first reported the presence of acrylamide in foods (1). Acrylamide is a by-product of the cooking process and is formed when reducing sugars (glucose or fructose) react with the amino acid asparagine during the Maillard reaction (2;3), the reaction responsible for the browning of food during baking, frying, and roasting. The levels of acrylamide in cooked foods are thus influenced by factors such as the cooking temperature, length of cooking time, moisture content, and the amount of reducing sugar and asparagine in raw foods (4–6). In potatoes, the level can be affected by cultivar variety (7), fertilizer use (8), and storage temperature (9). For instance, the storage of potatoes at 2°C results in increased free sugar content that converts to higher acrylamide levels during cooking as compared with potatoes stored at 20°C (9;10). Variations of acrylamide content in various foods, and between batches of the same foods, have presented a challenge for estimating the actual intake by using the commonly used approach such as the food frequency questionnaire (FFQ). These variations also present a major challenge of accurately classifying individuals with low or high acrylamide intake.

Since the discovery of acrylamide in foods of everyday consumption (1), a number of epidemiological studies have evaluated its potential association with cancers of various organs such as reproductive organs (11–19), gastrointestinal tract (18;20–23), kidney (24–26), lung (27), and brain (28). Most epidemiological studies reviewed have assessed acrylamide intake by using the FFQ, whereas a few have also measured biomarkers (29;30). Exposure to dietary acrylamide depends on the amount of acrylamide present in food, the portion size consumed, and the frequency of consumption, as well as cooking and storage methods. Therefore, the variations in global dietary patterns result in different food items contributing most significantly to dietary acrylamide intake. Nonetheless, coffee, fried/baked potatoes, and bakery goods remain among the most common sources in all countries (31). The US Food and Drug Administration (FDA) database contains a comprehensive description of acrylamide content found in food items or in the total diet (32;33).

Acrylamide is a multi-organ carcinogen in both male and female rodent models. Acrylamide carcinogenicity has been well established in a number of animal models such as rat and mouse; however, the study doses used are 1,000–100,000 times higher than the usual amounts, on a weight basis, that humans are exposed to through dietary sources (31). Moreover, studies have also reported differences in the metabolism of acrylamide and a two- to four-fold lower internal exposure of its metabolite glycidamide in humans (34). Recently, a review by Hogervorst et al (35) compared epidemiological and experimental research, and Pelucchi et al (36) performed meta-analysis of 19 dietary, and 6 occupational studies of acrylamide exposure and cancer. We systematically reviewed evidence for dietary acrylamide exposure and internal dose, as well as, the 11 prospective, 10 case-cohort, 6 population-based case-control, and 3 hospital-based case-control original epidemiologic studies published to date that evaluated dietary acrylamide association with various types of cancers. Major scientific literature databases were searched for epidemiological studies on acrylamide, including PubMed and Google, as well as the Joint Institute for Food Safety and Applied Nutrition (JIFSAN), World Health Organization (WHO), and FDA websites. The literature search was focused on articles published between 2002 and March of 2013. A

combination of the following search terms was used: dietary acrylamide formation, food sources of acrylamide, acrylamide exposure, heat-formed compounds, cooking temperature, acrylamide metabolism, hemoglobin adducts, urinary metabolites, mercapturic acid, health effects, and cancer.

Acrylamide Exposure and Internal Dose

An individual's acrylamide exposure reflects the combined intake from diet, smoking, second-hand smoke, drinking water, occupational sources, toiletries and household items. Acrylamide absorption through dermal exposure is much lower because the skin provides a barrier that reduces acrylamide uptake (37). However, oral exposure is critical in determining the amount of acrylamide and its metabolites that circulate in the body. After oral ingestion in humans, acrylamide is rapidly absorbed and eliminated in the urine, with a reported half-life of 3.1–3.5 hours (38). Pathways of conjugation with glutathione play an important role in helping the body to excrete acrylamide as urinary metabolites (Figure 1). The acrylamide can also undergo epoxidation to form the genotoxic metabolite glycidamide through cytochrome P450 2E1 (CYP2E1) activity (39–41). Variation in exposure to glycidamide may result from polymorphisms in CYP2E1 that cause this enzyme to have different catalytic rates. In addition, compounds that can suppress CYP2E1 activity, such as allyl and diallyl sulfide, may suppress glycidamide formation in humans. Diallyl sulfide from garlic has been shown to inhibit CYP2E1 and suppress acrylamide metabolism to glycidamide in rat livers (42). Moreover, CYP2E1 knockout mice, compared with the wild type, showed a 95% reduction in acrylamide bioconversion to glycidamide (43). However, such effects in humans remain to be elucidated.

Both acrylamide and glycidamide bind to hemoglobin in red blood cells, and the determination of the resulting adducts provides an estimation of the internal dose that accounts for both absorption and metabolism of these compounds over the life of the red blood cells (120 days) (44). Smokers, on average, have three to five times higher hemoglobin adducts of acrylamide (HbAA) and glycidamide (HbGA) (45–47). Exposure to second-hand smoke also influences HbAA and HbGA levels (47). For an in-depth review of acrylamide exposure assessment and absorbed dose refer to Dybing et al (48).

Vesper et al (47) assessed the acrylamide and glycidamide exposure among general US population from the National Health and Nutrition Examination Survey 2003–2004. The levels of HbAA and HbGA ranged between 3–910 and 4–756 pmol/g hemoglobin, respectively. In addition to the wide variation in the adduct levels, data also suggested the presence of racial and age disparities. The highest levels were found in Mexican Americans and the lowest in non-Hispanic blacks. Surprisingly, children between the ages of 3–11 years had higher levels as compared with adults ≥ 60 years (47). Smokers had the highest levels for both HbAA and HbGA. In addition, participants with second-hand smoke exposure, compared with those with no smoke exposure, had higher HbAA and HbGA adducts. These results suggest that acrylamide exposure among nonsmokers may not only be through food consumption. The study by Vesper et al. estimated an average dietary acrylamide intake of 0.8 μg/kg/day in the nonsmoking US population (47). Children and adolescents have typically been reported to have higher exposure to dietary acrylamide,

which could be explained in part by their higher consumption of acrylamide-containing foods (such as potato chips, French fries, and cookies) and lower mean body weight compared with adults (48).

Svensson et al. conducted a study of dietary intake of acrylamide in Sweden in 2002. The authors used the 1997–1998 Swedish National Food Administration Food Survey consumption data (from a 7-day food record book from 200 subjects aged 18–74 years) and a dietary acrylamide analysis of 130 food samples from supermarkets (49). The average daily intake of acrylamide was 0.5 μg/kg body weight/day in the study population. However, the average dietary exposure in this study did not include acrylamide exposure from smoking; hence, the average intake may be underestimated for smokers and those individuals exposed to second-hand smoke. Similarly, dietary acrylamide intake in the Dutch population (aged 1–97 years) is estimated at 0.48 μg/kg body weight/day. Using the Dutch population data, acrylamide intake among children (aged 1–6 years) is estimated at 1.04 μg/kg body weight/day, representing twice as much acrylamide intake compared with the total population (50).

A pilot study of 11 pregnant women examined the trans-placental exposure of acrylamide to neonates. The levels of HbAA adducts in umbilical cord blood were approximately 50% of that of the mothers. Only one study participant was a smoker and the highest adduct levels were detected in the participant and her child (51). The ability of acrylamide to cross the placental barrier has raised concerns about its safety in infants and potential health effects. Studies from the Norwegian Mother and Child cohort (52), which recruited 100,000 pregnant women from 1999–2008, may provide such data on mothers and their children.

A number of epidemiologic studies have estimated acrylamide intake by using self-reported questionnaires and, occasionally, questionnaires administered by trained interviewers. It should be noted that such calculations, in the absence of measuring hemoglobin adduct biomarkers, will not reflect a biologically effective dose exposure. Batch-to-batch variation in the acrylamide content of foods, as well as reporting and recall biases may cause the estimate to be farther away from the true exposure level. Wilson et al (30) reported correlations of 0.26 (95% confidence interval (CI) 0.14–0.36, and 0.31 (95% CI 0.20–0.41) between acrylamide intake calculated by using FFQs and HbAA and HbGA adducts, respectively. Similarly, Kutting et al (53) reported that self-reported food intake is not useful for estimating dietary acrylamide exposure (53), Spearman correlation coefficients of 0.178 (95% CI 0.08–0.26), and 0.168 (95% CI 0.063–0.273) were observed for dietary acrylamide calculated from self-reported food intake and hemoglobin adducts among non-smokers men and women, respectively (53). More recently, Ferrari et al (54) estimated the exposure to dietary acrylamide using self-reported FFQ, 24-hr dietary recall, as well as the HbAA and HbGA adducts levels among 510 subjects (205 smokers and 250 non-smokers) from 9 European countries (European Prospective Investigation into Cancer and Nutrition cohort (55). The correlations between dietary measurements (FFQ and 24-hr recall) and the adduct levels were small 0.08, and 0.06, respectively. Similar correlations coefficients were observed for smokers (54). The important points to consider while evaluating acrylamide intake through FFQ data include: recall biases, exposures are estimated by capturing the previous year’s dietary intakes and variation in dietary patterns across different countries. In

addition, for a given cooked food item, acrylamide levels can be influenced by free sugars and asparagine composition of the raw food, variations in cooking temperatures, varying lengths of cooking time, and different cooking methods used. Estimation of exposure to acrylamide from cigarette smoking as well as from other potential sources could differ depending on how detail the questions are structured to capture such exposures.

Evidence from Cohort Studies

The literature search utilized in this paper resulted in a total ten cohort studies (Table 1) on dietary acrylamide intake and human cancer.

Cohort of Swedish Men

A prospective cohort study of Swedish men began in 1997, and 48,850 participants (aged 45–79 years) were recruited. The baseline dietary intake was measured using a 96-item self-administered FFQ (12). During the mean follow-up time of 9.1 years; there were 1,088 cases of localized prostate cancer and 951 cases of advanced prostate cancer. Information on the clinical stage and Gleason grade was available for the patients. The mean intake of dietary acrylamide estimated from the baseline FFQ was 36.1 ± 9.6 μg/day, and there was no statistically significant association between highest vs. lowest quintiles of dietary acrylamide exposure and prostate cancer (relative risk (RR) 0.88; 95% CI 0.70–1.09)(12). Later, using the same cohort data, Larsson et al (21) analyzed evaluated dietary acrylamide intake and colorectal cancer risk among 45,306 men (21), there were no statistically significant associations between dietary acrylamide intake and colorectal cancer (RR 0.95; 95% CI 0.74–1.20) (21). Given that cigarette smoke is an important source of acrylamide exposure, the authors further stratified participants according to smoking status, but this did not change the lack of associations between acrylamide and prostate or colorectal cancer (12;21). However, it is important to notice that for these analyses, acrylamide intake was assessed from the baseline FFQ only. The quality of these results is limited by the potential misclassifications resulting from any changes in acrylamide exposure over time, as well as lack of information on potentially new food items that might have contributed to acrylamide exposure in this population.

Cohorts of Swedish Women

Two breast cancer cohort studies: the Swedish Mammography Cohort and the Women's Lifestyle and Health Cohort from Sweden were included in this review. Larsson et al (13) analyzed the association between dietary acrylamide intake and breast cancer from the Swedish Mammography Cohort (13). Dietary acrylamide was estimated using FFQs among 36,664 women (13). The FFQs were administered at the baseline during 1987–1990, and then at follow-up in 1997 (13). However, the mean daily acrylamide exposure 24.6 ± 7.6 μg was estimated from the baseline questionnaire only (13). There were no statistically significant associations between acrylamide exposure and all invasive tumors (RR 0.91; 95% CI 0.80–1.02) (13), or hormone receptor specific tumors [estrogen receptor positive/ progesterone receptor positive (ER+PR+) RR 0.89; 95% CI 0.74–1.08, ER+/ progesterone receptor negative (PR-) RR 1.17; 95% CI 0.84–1.64, estrogen receptor negative (ER-)/PR- (RR 0.91; 95% CI 0.61–1.38)] (13); in addition, no significant effect modification were

observed by smoking status (13). The second study by Mucci et al (16), from the Women's Lifestyle and Health Cohort, was an 11-year follow-up study (1991–2002) of 43,404 women (16). Dietary acrylamide exposure, measured using a semi-quantitative questionnaire (16), showed a daily mean intake of 25.9 μg (16). There was no association between acrylamide exposure and breast cancer risk for the lowest vs. highest quintiles of dietary acrylamide intake (RR1.19; 95% CI 0.91–1.55) (16).

Recently, Larsson et al (14) reported lack of an association between long-term dietary acrylamide intake and ovarian cancer in a population of Swedish women. The study recruited 61,057 women, and measured dietary acrylamide intake at baseline (1987–1990) and again in 1997 with a follow-up questionnaire. The mean dietary acrylamide intake in this population was 24.6 ± 7.6 μg per day. After 17.5 years of follow-up (14), a total of 368 histologically confirmed cases of invasive epithelial ovarian cancer were identified (14). These cases were further categorized according to pathological subtypes (14). No association was observed between dietary acrylamide intake and ovarian cancer (RR 0.84; 95% CI 0.62–1.14) (14). There was a lack of smoking data at baseline (14), but the smoking data were collected on the follow-up questionnaire (14). The effect of smoking status on the association between acrylamide and cancer were evaluated in stratified analyses for smoking status (14). Furthermore, separate analyses stratified for alcohol intake, postmenopausal hormone therapy, and oral contraceptive usages were also performed (14). However, these stratified analyses did not change the lack of an association between acrylamide exposure and cancer (14)

Later, Larsson et al (15) used the same cohort to analyze the association between dietary acrylamide and endometrial cancer (15). Data were analyzed from 36,369 women, a total of 687 incident cases of endometrial adenocarcinoma occurred during the mean follow-up time of 17.7 years (15). The mean daily dietary acrylamide exposure was similar to that reported in the previous Ovarian cancer study by Larsson et al (14) (24.6 ± 7.6 μg). Subjects with hysterectomy or cancer diagnosis before the start of the study were excluded. The data stratification was similar to those previously described in the ovarian cancer study (14). The follow-up FFQs were analyzed for dietary acrylamide exposure and no associations were observed for endometrial cancer (RR 0.96; 95% CI 0.76–1.21) (15). Again, stratification by smoking status did not change this null association (15).

Nurses' Health Studies I and II

The Nurses' Health Study Cohort I started in 1976 and expanded to Nurses' Health Study II in 1989, explored lifestyle and health follow-up questionnaires administered every 6 months since the beginning of the study. A semi-quantitative FFQ first administered in 1991, with a follow-up every 4 years.

Wilson et al (19) analyzed dietary acrylamide intake and breast cancer risk among 90,628 premenopausal women (19). Dietary acrylamide intake was estimated from multiple follow-up FFQs from 1991, 1995, 1999, and 2003 (19). Women with a cancer diagnosis prior to 1991 and those with extreme energy intake (<800 or >4200 kcal/day) or postmenopausal status at baseline were excluded from the analysis (19). There were 1,179 invasive breast cancer cases documented during the 14-year follow-up period (19). Separate analyses were

performed according to smoking status and stratification of the study participants to a number of confounders. Similar to other prospective cohorts (13;16), this study did not reveal any increased risk of breast cancer associated with dietary acrylamide intake (RR 0.92; 95% CI 0.76–1.11) (19).

Wilson et al (56) analyzed dietary acrylamide intake and the risk of breast, endometrial, and ovarian cancers among US women from the Nurses' Health Study I cohort (56). There was lack of an association between dietary acrylamide exposure and overall breast cancer (RR 0.95; 95% CI 0.87–1.03), or hormone receptor specific cancer [ER+PR+ (RR 0.99; 95% CI 0.87–1.13), ER+PR (RR 1.04; 95% CI 0.80–1.34) (56), ER-PR+ (RR 1.09; 95% CI 0.63–1.87) (56), or ER-PR- (RR 0.88; 95% CI 0.70–1.11)] (56). The data showed an increased risk for endometrial cancer (RR 1.41; 95% CI 1.01–1.97) (56), but no associations were observed for overall ovarian cancer (RR 1.25; 95% CI 0.88–1.77)(56). There was a statistically significant increased risk for a serous subtype of ovarian cancer (RR 1.58; 95% CI 0.99–2.52) (56).

Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland

The ATBC study was a double-blind, placebo-controlled primary intervention study among Finnish smoker men between the ages 50 – 69 years that smoked least five cigarettes per day. The purpose of the study was to determine whether certain vitamin supplements would prevent lung cancer and other cancers in a group of 29,133 male smokers in Finland. At baseline, dietary data were collected using a comprehensive 276 food items FFQ along with a booklet of 122 pictures of portions sizes of various foods. Hirvonen et al. (57) estimated dietary acrylamide exposure from the baseline FFQ among 27,111 participants (57). The dietary acrylamide exposure was divided into quintiles (lowest quintile 21.9 μg/day, and highest quintile 55.7 μg/day). Dietary acrylamide exposure was associated with increased lung cancer for those in the highest compared to the lowest quintile (RR 1.18; 95% CI 1.01–1.38) (57). No associations between dietary acrylamide and cancer of the prostate, urothelial, pancreatic, stomach, renal cell, or lymphomas were observed (57). Given that the acrylamide exposure estimated from the baseline FFQ only, the dietary patterns as well as food levels of acrylamide may have changed over time (57). In addition, the ATBC trial was an intervention trial and was not designed to evaluate dietary acrylamide associations with cancer, also the fact that the similar interventions among smokers has previously been shown to increase lung cancer risk (58–60), and may have influenced the observed lung cancer associations in Hirvonen et al. (55) study.

The Health Professionals Follow-up Study

The Health Professionals Follow-up Study among US men began in 1986, and recruited 51,529 male health professionals between the ages of 40–75 years. The study administered first FFQ at the baseline in 1990 and a follow-up FFQ every 4 years. Subjects with missing dietary information, extremely high energy intakes, and those with cancer diagnosis within the first year of study initiation were excluded, and data from 47,896 subjects were included in the analyses (61). Dietary acrylamide exposure was estimated from the baseline as well as the follow-up FFQs. The mean acrylamide exposure values from baseline were assigned for the 1986–1990 follow-up, the mean values from the 1986 and 1990 FFQ were assigned for

the 1990–1994 follow-up, and so on for the cumulative long-term acrylamide exposure (61). From 1986–2006, a total of 5025 prostate cancer cases were diagnosed. The estimated mean dietary acrylamide exposure for the lowest vs. highest quintile was 10.1– 40.5 μg/day. There were no statistically significant associations observed between highest vs. lowest quintile of dietary acrylamide exposure and total prostate cancer (RR 1.02, 95% CI 0.93–1.13) (61). Further, no associations were observed for smokers (RR 1.01; 95% CI 0.85–1.19). In addition, dietary acrylamide was not associated with sub-types of stages of prostate cancer (61).

Evidence from Case-cohort Studies

We located a total of eight case-cohort studies from the Netherlands Cohort Study on Diet and Cancer, one case-cohort study from the UK Women's Cohort, and one case-cohort study from the Danish Diet, Cancer and Health Study (Table 2).

Netherlands Cohort Study on Diet and Cancer

The Netherlands Cohort Study on Diet and Cancer (NLCSDC) began in 1986 (62), and recruited 58,279 men and 62,573 women (N=120,852 participants) between the ages of 55–69 years (62). The baseline data on obesity, food habits, physical activity, smoking habits, occupational history, socioeconomic status, medical history, chronic drug use, and family history of cancer were collected using a self-administered questionnaire (62). A sub-cohort of 5,000 subjects was formed and followed to gather data on migration and vital statistics (62). The dietary intakes were assessed using a 175 items FFQ, and were analyzed from 3,500 subjects from the sub-cohort (62). To assess changes in eating habits, the investigators administered the questionnaires annually to a sub-sample of 250 subjects (62). However, no information about changes in dietary habits was reported in the case-cohort studies. It is unknown whether changes in dietary patterns were assessed for any potential changes in the acrylamide exposure during the follow-up period.

Pedersen et al (17) analyzed NLCSDC data for acrylamide intake and risk of postmenopausal breast cancer stratified by receptor status. The acrylamide exposure was estimated from the baseline FFQs (17). There were no statistically significant associations between dietary acrylamide exposure and total postmenopausal breast cancer (hazard ratio (HR) 1.15; 95% CI 0.86–1.53) (17), ER+ (HR 1.15; 95% CI 0.86–1.53) (17), PR+ (HR 1.47; 95% CI 0.86–2.51) (17), or ER+PR+ (HR 1.43; 95% CI 0.83–2.46), ER- (HR 0.95; 95% CI 0.52–1.72) (17), PR- (HR 0.84; 95% CI 0.63–1.56) (17), or ER-PR- (HR 0.90; 95% CI 0.48–1.68) breast cancer (17). Data on smoking status, years of smoking, and number of cigarettes smoked per day were also included in the models (17).

Hogervorst et al (20) analyzed a sub-cohort from NLCSDC for dietary acrylamide exposure and gastrointestinal cancer risk (20). No associations were observed for acrylamide exposure and colorectal (20), colonic (20), rectal (20), gastric (20), pancreatic (20), microscopically verified pancreatic (20), or esophageal cancers (20), or esophageal adenocarcinoma or esophageal squamous cell carcinoma (Figures 2 a–b) (20). The mean acrylamide exposure among the sub-cohort was 21.7 ± 12.1 μg (0.17–0.47 μg/kg body weight/day) (20), and is lower than the average daily intake reported among the US non-smoking population (0.8

μg/kg body weight/day) (47). Hogervorst et al evaluated the associations between dietary acrylamide exposure and the subsequent risk of endometrial, ovarian, and breast cancers in 2007 (11); and risk of renal cell bladder, and prostate cancers in 2008 (24). Because cigarette smoke is an important source for acrylamide exposure, data on smoking status (both past and current), duration of smoking, and number of cigarettes smoked per day were included in the models (11;24). In addition, separate analyses were performed for a subgroup of never-smokers (11). The analysis included 221 endometrial, 195 ovarian, and 1,350 breast cancer cases (11). Highest versus lowest quintiles of dietary acrylamide exposure was significantly associated with increased ovarian cancer risk (HR 1.78; 95% CI 1.10–2.88) (11), and the association among never-smokers was also statistically significant (HR 2.22; 95% CI 1.20–4.08) (11). In addition, increased risk for endometrial cancer was also observed among a sub-group of never-smokers (HR 1.99; 95% CI 1.12–3.52) (11).

Nevertheless, dietary acrylamide exposure (highest versus lowest quintiles) was significantly associated with renal cell cancer (HR 1.59; 95% CI 1.09–2.30) (24), but not in never-smokers (24). The renal cell cancer association was significant in a model in which acrylamide exposure was used as a continuous variable for men and women, both combined and separately (24). This is the first study to report an increased risk of dietary acrylamide and renal cell cancer (24). Previously, studies by Mucci et al (22;25) and Pelucchi et al (26) did not observe such associations (Figure 3a).

Dietary acrylamide exposure was not associated with breast, prostate, bladder, or endometrial cancers (11;24). Hogervorst et al speculated that acrylamide might be responsible for hormonally driven cancers (27). However, the lack of associations in breast cancer, the most prevalent type of cancer among women, and prostate cancer among men raises doubt for this theory (Figure 4 a–c).

Smokers have been previously shown to have nearly five times more HbAA adducts as compared to non-smokers (31). The important question to address would be the challenges of separating the effects of smoking from dietary exposures and the lack of such biomarkers that can distinguish acrylamide from dietary vs. smoking exposure remains an area for further research and exploration.

Hogervorst et al (28) analyzed NLCSDC data to determine the associations between dietary acrylamide exposure and risk of brain cancer. The authors reported a total of 259 cases of primary brain cancer (28), with 205 being microscopically identifiable after 16.3 years of follow-up (28). Dietary acrylamide exposure was 21.8 ± 12.1 and 22.1 ± 12.9 (mean ± SD) μg/day among sub-cohort participants and cases, respectively (28). Dietary acrylamide analyzed as continuous, or tertiles, or quintiles was not associated with brain cancer (28). After exclusions for cancer diagnosis at baseline, a total of 216 cases were included in the analyses. Dietary acrylamide exposure was not associated with total brain cancer, histological subtypes of astrocytic glioma, or high-grade astrocytic glioma (28). In addition, a subgroup analysis among nonsmokers revealed the lack of an association (28)

In 2009, Schouten et al (63) analyzed the NLCSDC sub-cohort data of the 2,022 participants for evaluating associations between dietary acrylamide exposure and risk of head-neck and

thyroid cancer (63). Mean dietary acrylamide intake estimated from baseline FFQ among sub-cohort was 22.5±12.2μg/day. There were no significant associations between dietary acrylamide and overall head and neck or thyroid cancers (HR 0.74; 95% CI 0.4–1.15 among men (63), and HR 1.01; 95% CI 0.53–1.93 among women) (63). However, increased risk for oral cavity was observed for a sub-group of non-smoker women (n = 12) (HR 1.28; 95% CI 1.01–1.62 per 10 μg intake/day) (63).

Interestingly, a statistically significant decreased risk for head and neck cancer was observed among a sub-group of non-smoker men (n = 63) in the highest tertile of acrylamide exposure (HR 0.45; 95% CI 0.21–0.94) (63) (Figure 3.b). The authors reported these results as a possible chance finding because of small number of non-smoker cases (63). Future prospective studies with substantial number of non-smoker cases are needed to understand the influence of gender, and smoking status, on such associations.

Recently, Bongers et al (64) analyzed the associations between dietary acrylamide exposure and risk of lymphatic malignancies from the NLCSDC cohort. The baseline FFQ data was analyzed for estimating the mean dietary acrylamide exposure, and was 23 ± 12 μg/day among the sub-cohort, and ranged between 21± 11 μg/day to 26 ± 16 μg/day among the cases (64). There were 1233 microscopically confirmed lymphatic malignancies had occurred. Dietary acrylamide was not associated with diffuse large cell lymphoma. Dietary acrylamide exposure modeled as continuous variable, there were increased risk for multiple myeloma (HR 1.14; 95% CI 1.01–1.27) and follicular lymphoma (HR 1.28; 95% CI 1.38–2.85) among men per 10 μg acrylamide exposure per day (64). In addition, among non-smoking men there were significant interactions observed for increased associations between dietary acrylamide and multiple myeloma risk among men with highest alcohol intake (HR 2.28; 95% CI 1.28–4.06) (64). Among women, there were no statistically significant associations observed between dietary acrylamide exposure and lymphatic malignancies. Interesting, for dietary acrylamide as a continuous variable, a decreased risk for chronic lymphocytic leukemia was observed for both men and women (64).

Given that the baseline FFQ were analyzed to estimate the dietary acrylamide exposure, and the question of whether it would be the most relevant exposure after 11–13 years of follow-up remains unanswered. It is possible that dietary changes were not same across the cohort members and any potential changes in dietary intakes that may have led to changes to acrylamide exposure might not have been accurately captured. Some subjects in the sub-cohort analyses might have been potentially misclassified. Therefore, the results obtained from the above reported cohort studies should be interpreted with caution.

Case-cohort study from UK Women's Cohort

UK Women's Cohort is a large prospective study of 35,372 women with detailed baseline validated FFQ that comprised 217 food items (65). A total of 1084 breast cancer incidences had occurred during the median follow-up time of 11 years. Recently, Burley et al (66) analyzed the associations between dietary acrylamide exposure and breast cancer within this cohort (66). Overall, dietary acrylamide exposure (highest vs. lowest quintile) was not associated with breast cancer risk (OR 1.16; 95% CI 0.88–1.52) (66), which is in agreement with other prospective cohort (13;16;19;56), and case-cohort (11;17) studies that have

reported no associations for dietary acrylamide and increased risk of breast cancer. Stratified analysis by menopausal status revealed no significant associations for postmenopausal women (OR 0.97; 95% CI 0.68–1.39)(66), or premenopausal women (OR 1.47; 95% CI 0.96–2.27) (66). However, a significant increased risk for increasing acrylamide exposure per 10 μg/day among premenopausal women was observed (OR 1.18; 95% CI 1.05–1.34) (66). Further sub-group analyses among never-smokers showed no association between dietary acrylamide and overall breast cancer or by menopausal status (66).

Evidence from Nested case-control studies

Olesen et al (29) analyzed the association between HbAA adducts and postmenopausal breast cancer among 374 breast cancer cases and matched 374 controls (29) from the Danish Diet, Cancer and Health Cohort. The prospective cohort was designed to study etiologic role of diet on cancer risk among women ages between 50–64 years from Denmark. At the baseline lifestyle and dietary data were collected using questionnaires, and blood samples were collected (67). In the nested-case control study, tobacco smoke was the major source for acrylamide exposure, and smokers had elevated levels of HbAA (3.8 times higher) and HbGA (2.8 times higher) adduct compared to non-smokers (29). Overall, the incidence rate ratio for associations between the adducts levels and breast cancer was not statistically significant (IRR 1.5; 95% CI 0.8–3.0) (29). In addition, in a separate analyses of never smokers (64 cases and 64 controls), no significant associations were observed for HbAA adduct levels and total breast cancer (IRR 2.7; 95% CI 0.3–24) (29). In the fully adjusted model, receptor specific analyses revealed significant increased risk for ER+ breast cancer among women with highest adduct levels as compared to the lowest adduct levels(IRR 2.7; 95% CI 1.1–6.6) (29). Future studies with follow-up blood samples drawn at multiple time-points to allow analyses for any seasonal variations, changes in the diet, and lifestyle factors that could potentially influence adduct levels are needed.

Recently, Xie et al (68), analyzed the association between dietary acrylamide exposure measured as HbAA and HbGA and ovarian cancer risk among 263 cases and matched 526 controls from the Nurses' Health Study and Nurses' Health Study II. The median acrylamide and glycidamide (total acrylamide) adducts among cases and control was 112.6 and 113.9 pmol/g hemoglobin, respectively. There were no statistically significant associations for ovarian cancer when compared to women with total acrylamide adducts < 99 pmol/g hemoglobin to those with > 99-134.1 pmol/g hemoglobin (RR 0.83; 95% CI 0.56–1.24) or with those total acrylamide adducts levels ≥ 134.1 pmol/g hemoglobin (RR 0.79; 95% CI 0.50–1.24) (68). In addition, adduct levels were analyzed separately. No associations were observed for glycidmide adducts (p trend = 0.19), but a borderline significant inverse association was observed for acrylamide adducts (p trend = 0.05) (68).

Evidence from Population-Based Case-Control Studies

From our literature search, we located three population-based case-control studies on acrylamide and cancer (Table 3). In a population-based Swedish case-control study, Mucci et al (22) included 591 large bowel, 263 kidney, 133 bladder cancer cases, and 538 controls that were both age and gender matched (22). The study was a secondary analysis from a

parent population-based case-control study of heterocyclic amines and cancer (69). Dietary data were collected by using a semi-quantitative FFQ that comprised a total of 188 food items. The main focus of the questionnaire was to capture foods rich in heterocyclic amines; for example, 69 meat dishes were included, along with pictures that showed the browning of cooked food at different temperatures prepared by different cooking methods (frying, roasting, or broiling) (70). There were no associations between dietary acrylamide exposure and risk of large bowel (OR 0.6; 95% CI 0.4–1.0) (22), kidney (OR 0.8; 95% CI 0.5–1.5) (22), or bladder cancer (OR 0.8; 95% CI 0.4–1.7) (22). Given that the study was a secondary data analyses from the heterocyclic amines and cancer study, it is possible that foods that would account for most of the acrylamide load for this population were not included in the questionnaire. Hagmar (71) published a brief commentary about the results of the large bowel, kidney, and bladder cancer study by Mucci et al (22), and urged readers to view the null results along with possible weaknesses of the case-control study design and possible exposure misclassification (71).

Mucci et al (25) analyzed the data from the Diet and Renal Cell Cancer Population-Based Case-Control Study (72), to evaluate the association between acrylamide exposure and renal cell cancer risk (25). Trained interviewers assessed the dietary acrylamide exposure among 379 cases and 353 controls using a structured questionnaire, along with information on 11 food items with potentially higher acrylamide content (25). The odds ratio for comparing highest vs. lowest quartiles of dietary acrylamide exposure was not statistically significant for renal cell cancer risk (OR 1.1; 95% CI 0.7–1.8) (25).

Wilson et al (30) recruited cases of prostate cancer from the Cancer of the Prostate in Sweden study (73), to evaluate acrylamide intake and prostate cancer risk by measuring HbAA levels as a biomarker of exposure in addition to questionnaire-measured exposure (30). The dietary questionnaire included 261 food items (30). Detailed information on the tumor subtype, node, and prostate-specific antigen at diagnosis was obtained from the Prostate Cancer Registries (30). The final analysis included 1,489 cases and 1,111 controls, and the mean acrylamide exposure among cases and controls were 43.8 and 44.5 μg/day, respectively (30). Acrylamide exposure measured by FFQs or HbAA levels was not associated with overall or specific subtypes of prostate cancer (30). The acrylamide exposures measured by FFQ was only moderately associated with the HbAA adduct (among controls r = 0.35; 95% CI 0.21–0.45, and among cases r = 0.15; 95% CI 0.00–0.30) (30), which questions the usefulness of FFQ-based acrylamide exposure estimations (30).

Lin et al (74) analyzed data from the Symptomatic Gastroesophageal Reflux as a Risk Factor for Esophageal Adenocarcinoma (75), a population-based case-control study from Sweden to evaluate the associations between dietary acrylamide exposure and esophageal cancer risk among 618 cases and 820 controls (74). Data on dietary habits from the previous 20 years were collected using FFQs, and acrylamide exposure was assessed by the consumption of nine food items: French fries, fried potatoes, baked potatoes, bread (soft, coarse, and crisp), biscuits, cookies, and coffee. Sub-group analyses were performed for overweight and obese subjects (74). Dietary acrylamide exposure was significantly associated with an increased risk for overall esophageal cancers (OR 1.23; 95% CI 1.02–

1.75) (74), and the risk estimates increased among obese and overweight subjects (OR 1.88; 95% CI 1.06–3.34) (74).

Evidence from Hospital-Based Case-Control Studies

Three hospital-based case-control studies from Europe were identified (Table 4). Pelucchi et al (76) obtained data from six different hospital-based case-control studies on diet and cancer involving oral cavity and pharyngeal (77), esophageal (78), laryngeal (79), large bowel (80), ovarian (81), and breast (82) cancers from the Southern Europe region in an attempt to explore potential associations between fried potato consumption and human cancer (76). Dietary data were collected using the same questionnaire and demographic information across these studies, and data on smoking and alcohol consumption were also collected (76). The combined analysis of all of these studies did not show any significant association between fried/baked potatoes intake and cancers of the oral cavity and pharyngeal OR 1.1; 95% CI 0.9–1.4 (76), esophageal OR 1.0; 95% CI 0.7–1.5 (76), laryngeal OR 1.1; 95% CI 0.8–1.5 (76), colon OR 0.8; 95% CI 0.7–1.0 (76), ovarian OR 1.1; 95% CI 0.9–1.3 (76), or breast OR 0.9; 95% CI 0.8–1.1 (76). An inverse association was observed between fried potato intake and large bowel cancer OR 0.8; 95% CI 0.7–1.0(76), and the authors reported that this finding was likely due to chance alone (76). Data were adjusted for smoking status. From 1992–2004, Pelucchi et al. conducted a similar hospital-based study of dietary acrylamide and renal cell cancer in four Italian regions among 767 histologically confirmed renal cancer cases and 1574 controls (26). Dietary acrylamide exposures were estimated by interview based78-item FFQ, which included commonly consumed food items with higher acrylamide contents such as baked potatoes and other bakery products. Similar to the previous results (25), no association was observed between highest vs. lowest quartile of dietary acrylamide exposure and renal cell cancer (OR 1.20, 95%CI 0.88–1.63) (26).

Pelucchi et al (83) evaluated the associations between dietary acrylamide exposure and pancreatic cancer risk in a hospital based case-control study among 326 cases and 652 age and sex matched controls in northern Italy. The acrylamide exposure estimated from the 78-item FFQ and was 33.52 ± 17.42 μg/day among cases, and 32.20 ± 19.80 μg/day among controls. There were no associations observed between dietary acrylamide exposure (highest vs. lowest quintile) and pancreatic cancer (OR 1.49; 95% CI 0.83–2.70) (83). In addition, there were no statistically significant associations when dietary acrylamide exposure was modeled as continuous variable (OR 1.01; 95% CI 0.92–1.10) (83).

Data Gaps

Dietary patterns and different food sources of acrylamide contribute to varying dietary acrylamide exposure among different populations. Large variations have been reported in acrylamide content among different brands of similar food items, and such data is not being collected on the FFQ. Although, FFQs are a useful tool for assessing usual dietary pattern they were not designed for capturing chemical exposures. Information such as recipe information, browning of food, length of cooking, micronutrient composition of the raw food, storage of food, and so on is not being collected but is highly important for assessing

acrylamide exposures. The measurement errors resulting from above discussed factors have potential for misclassification for ranking individuals for high vs. low acrylamide exposure. The subsequent lack of reproducibility of epidemiological results points toward the utmost need for developing better methods to capture true intake, which would include absorption and metabolism assessments and would be capable of separating dietary exposure from other sources. The studies that estimated acrylamide using FFQ as well as acrylamide adducts, reported a lack of strong correlation between FFQ and HbAA, suggesting that these measurements represent exposures over the different time interval lengths. The HbAA measures the exposure from last 120 days, and even by assuming that the FFQ is adequately capturing long term dietary acrylamide exposures, the correlation could be influenced by seasonality, recent exposures etc. For chronic disease end-points such as cancer, the goal is to estimate long-term exposure as compared to recent ones. So, one could potentially estimate the HbAA pattern by measuring repeated HbAA adducts over long time will be highly useful (one time point just gives us a snap-shot, not the pattern).

In the absence of food-specific biomarkers, controlled feeding studies among healthy volunteers to evaluate the changes in the HbAA adduct levels by changing the dietary acrylamide intake doses are lacking. Such studies would provide the evidence about the maximal reduction of acrylamide that could be achieved by reducing the food related acrylamide intake and would also provide evidence of the proportion of acrylamide exposure from other environmental sources.

Foods that are sources of acrylamide also contain a range of nutrients and most of these foods are high-energy sources, resulting in a high correlation between energy, nutrients, and acrylamide. High-energy intake itself is associated with obesity and the increased the risk of several cancers, as well as exposure to acrylamide. Most of the studies included in this review used several statistical approaches to reduce the effect of energy on the association between acrylamide and cancer. Future studies that compare people with balanced diet vs. more western type diet may provide additional insight into associations between dietary acrylamide and cancer. Because smoking is an established source of acrylamide exposure, the majority of the reviewed studies adjusted for smoking status and included separate models for never-smokers. Future studies of dietary acrylamide that accounts for second-hand smoke exposure and with large sample size of never smokers are needed.

Although a number of studies have reported disparity in acrylamide intake, with children being at the highest exposure level, none of the studies to date has evaluated childhood exposure to acrylamide as a potential risk factor for cancer later in life. It is unknown if the magnitude of associations would be different for populations who are generally considered vulnerable such as older adults, and populations who are at higher risk for cancer due to weak immune response and other underlying diseases.

Conclusions and Future Directions

In the reviewed epidemiologic studies, the dietary acrylamide exposure assessment has been inadequate leading to potential misclassification. In addition, the case-control studies have reported nearly same magnitude of dietary acrylamide exposures among both cases and

controls. For disease end-point such as cancer, the exposure assessment methods that could capture the long-term exposures are highly recommended. However, majority of the reviewed epidemiologic studies have rather estimated one-time point exposures from the baseline FFQs with the huge assumption that the dietary acrylamide content as well as the individual exposures over time remained constant. This is especially worrisome since a number of new food items are introduced in the market each year. In addition, food consumption patterns can be influenced by factors such as seasonality, prices, sales, as well as social factors such as holidays etc. resulting in potential changes in dietary acrylamide exposure.

The future studies with improved dietary acrylamide exposure assessment by including longitudinal HbAA adducts every three months, along with improved tools of dietary assessment are highly encouraged (Figure 5). Until we have the improved exposure assessment methods incorporated, the epidemiologic studies assessing relationship between dietary acrylamide and cancer will not have any meaningful interpretations.

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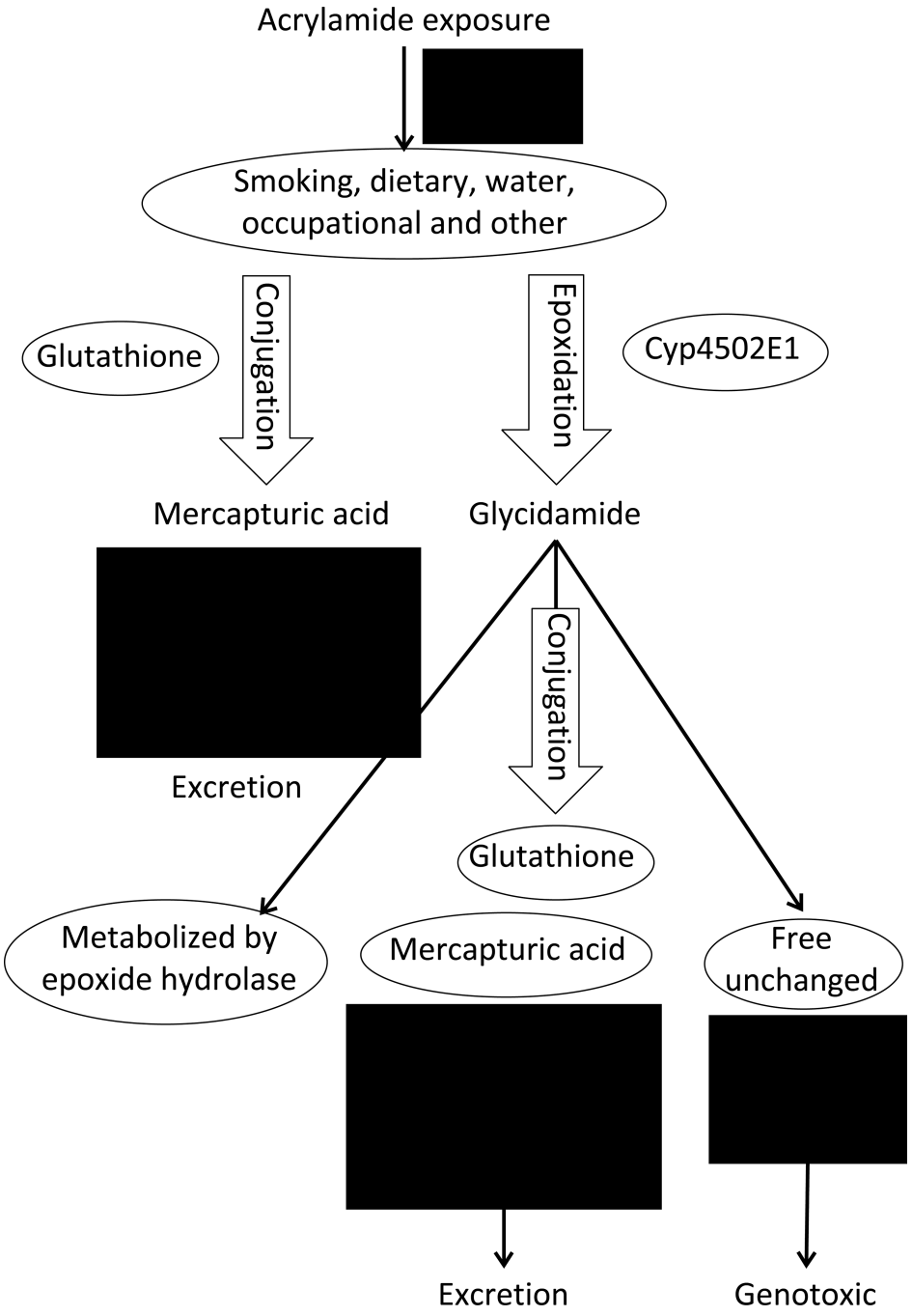
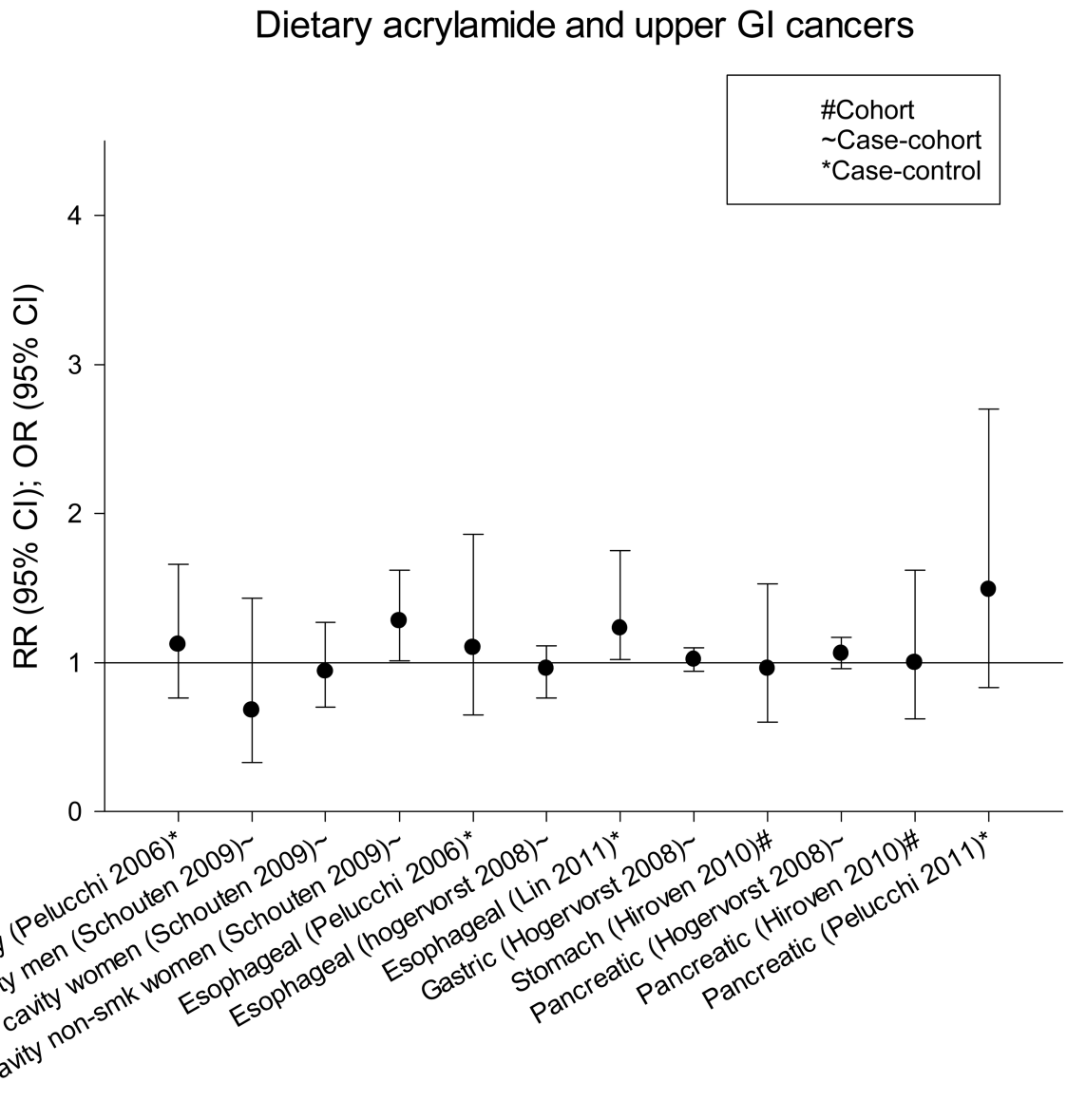


Figure 1.
The metabolism of acrylamide

a



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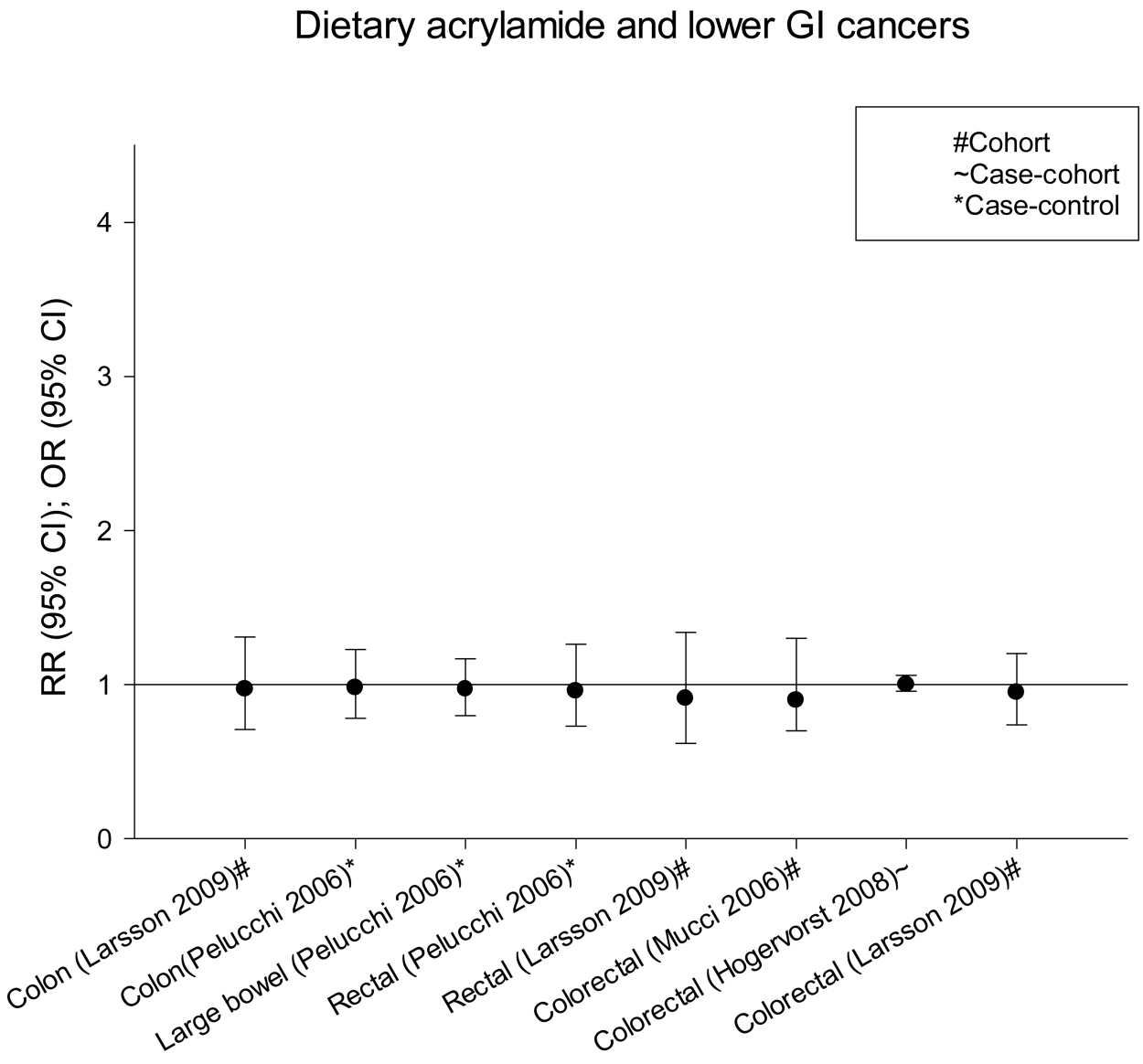
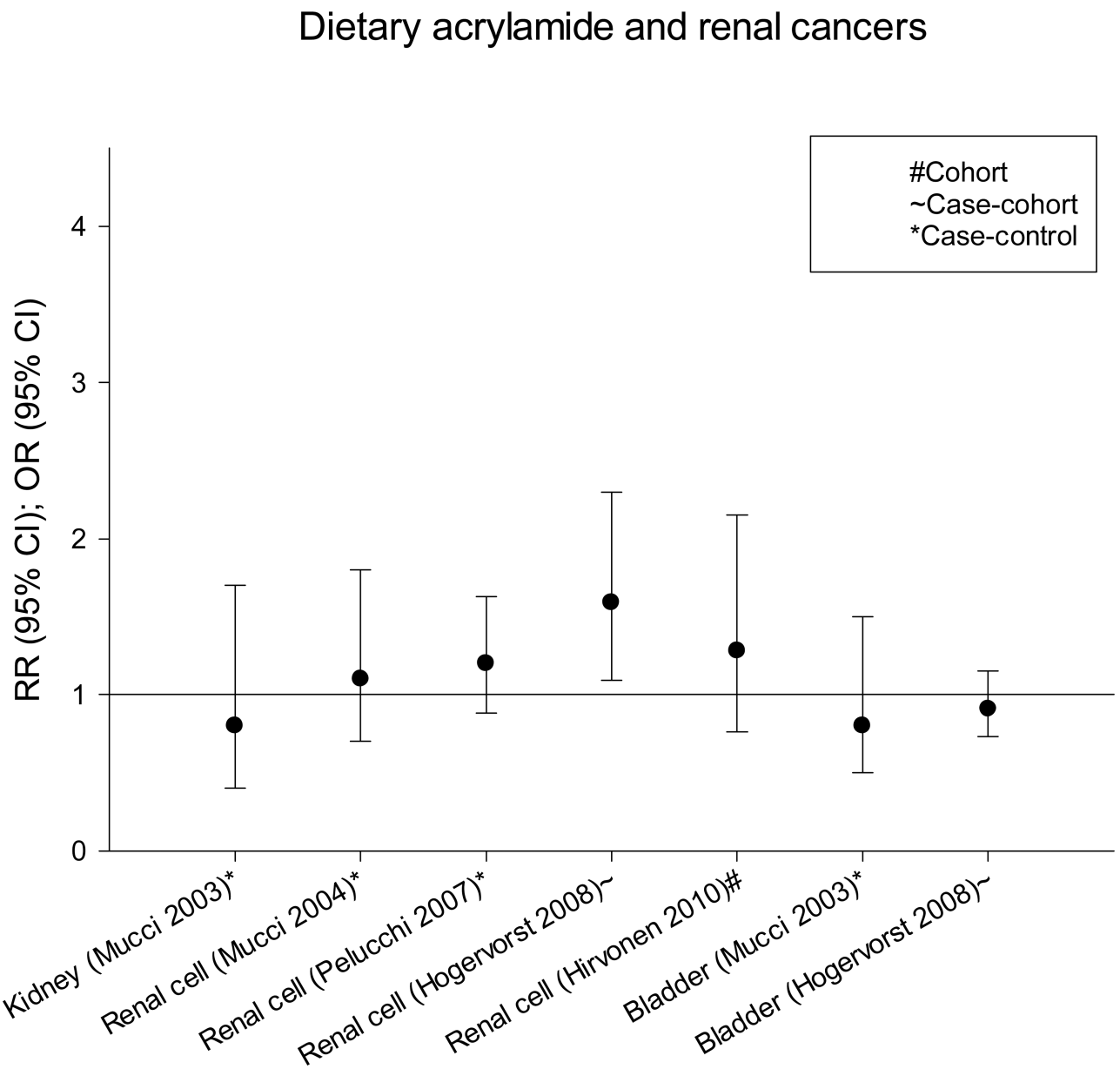


Figure 2.

a Dietary acrylamide intake and the risk of upper gastrointestinal cancers from the epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk.

b Dietary acrylamide intake and the risk of lower gastrointestinal cancers from the epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk.

a



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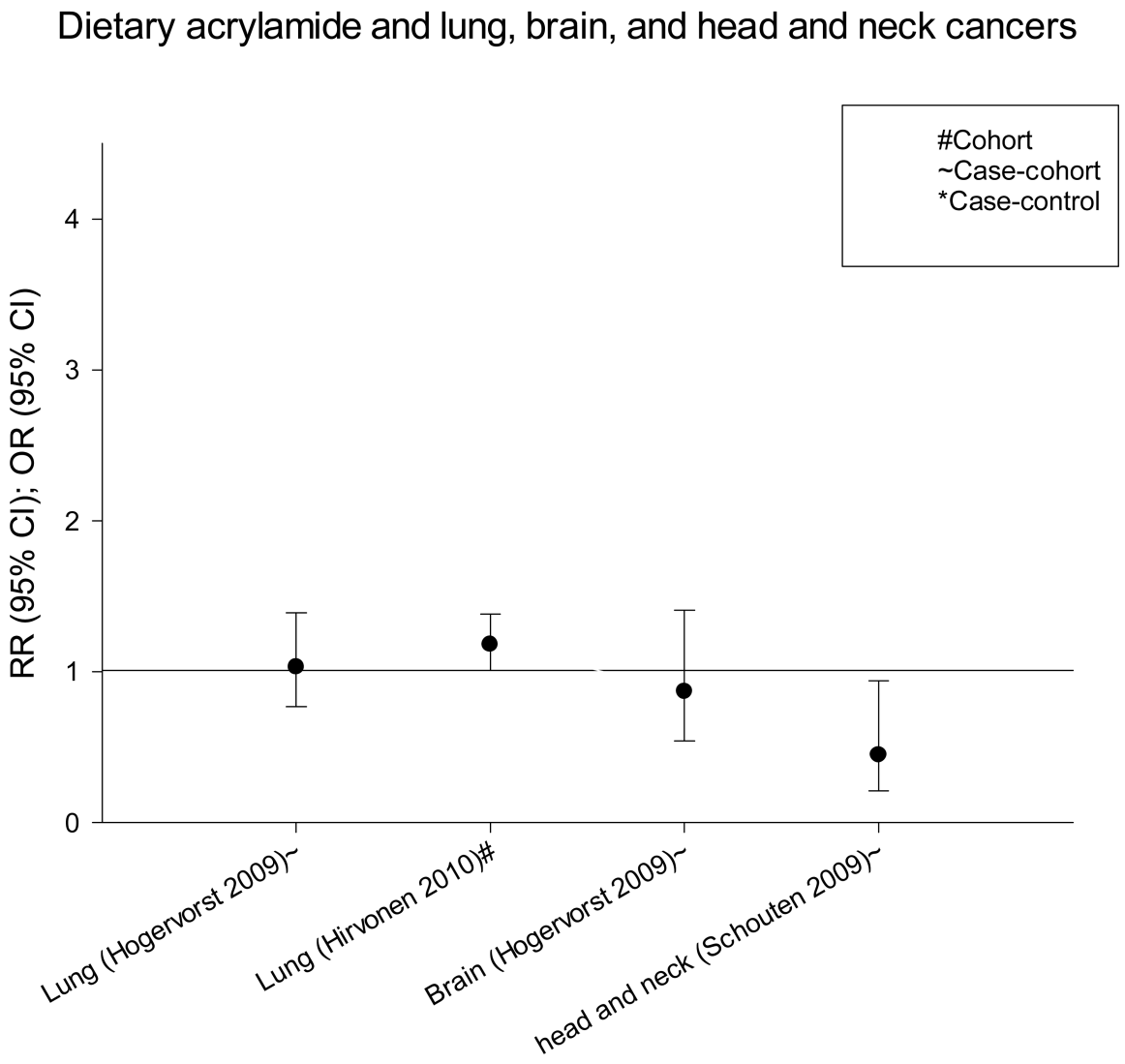
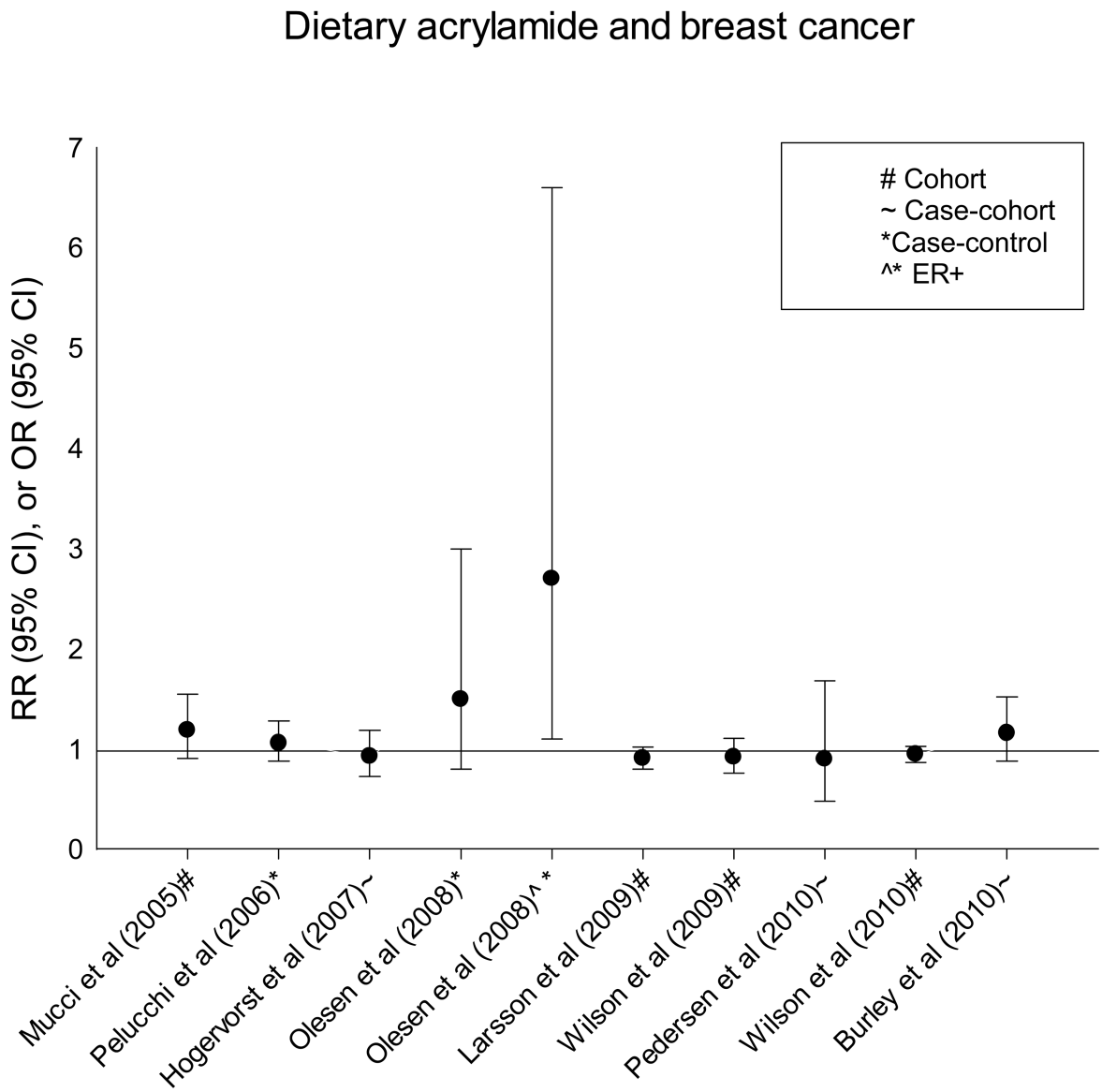


Figure 3.

a Dietary acrylamide intake and the risk of renal cancers from the reviewed epidemiology studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk.

b. Dietary acrylamide intake and the risk of brain, lung, head and neck cancers from the reviewed epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk.

a



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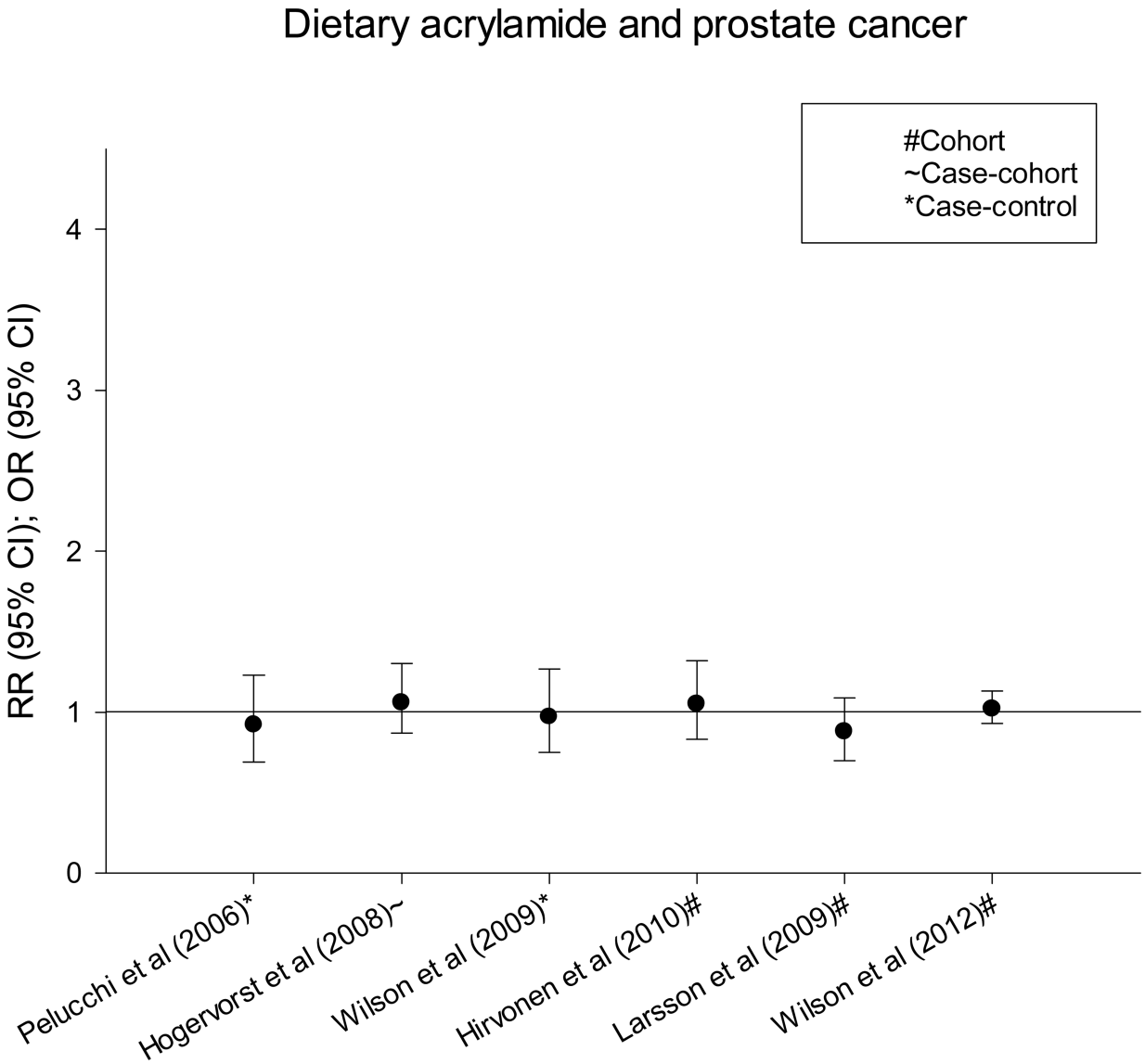

c

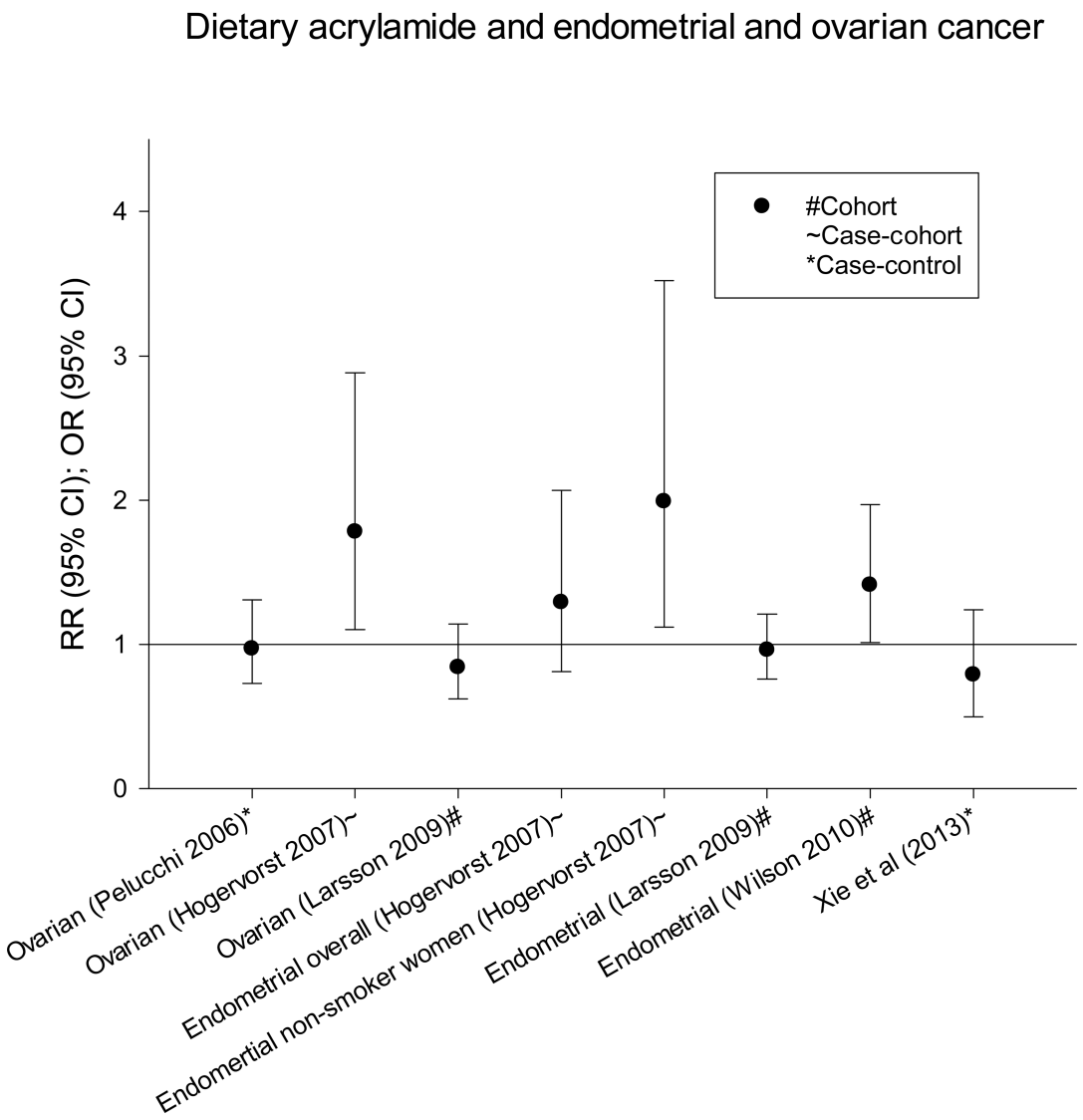

Figure 4.

a Associations between dietary acrylamide intake and the risk of breast cancer the epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk. b Associations between dietary acrylamide intake and the risk of prostate cancer from the epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk. c Associations between dietary acrylamide intake and the risk of endometrial and ovarian cancer from the epidemiological studies. CI indicates confidence interval; OR, odds ratio; RR, relative risk.

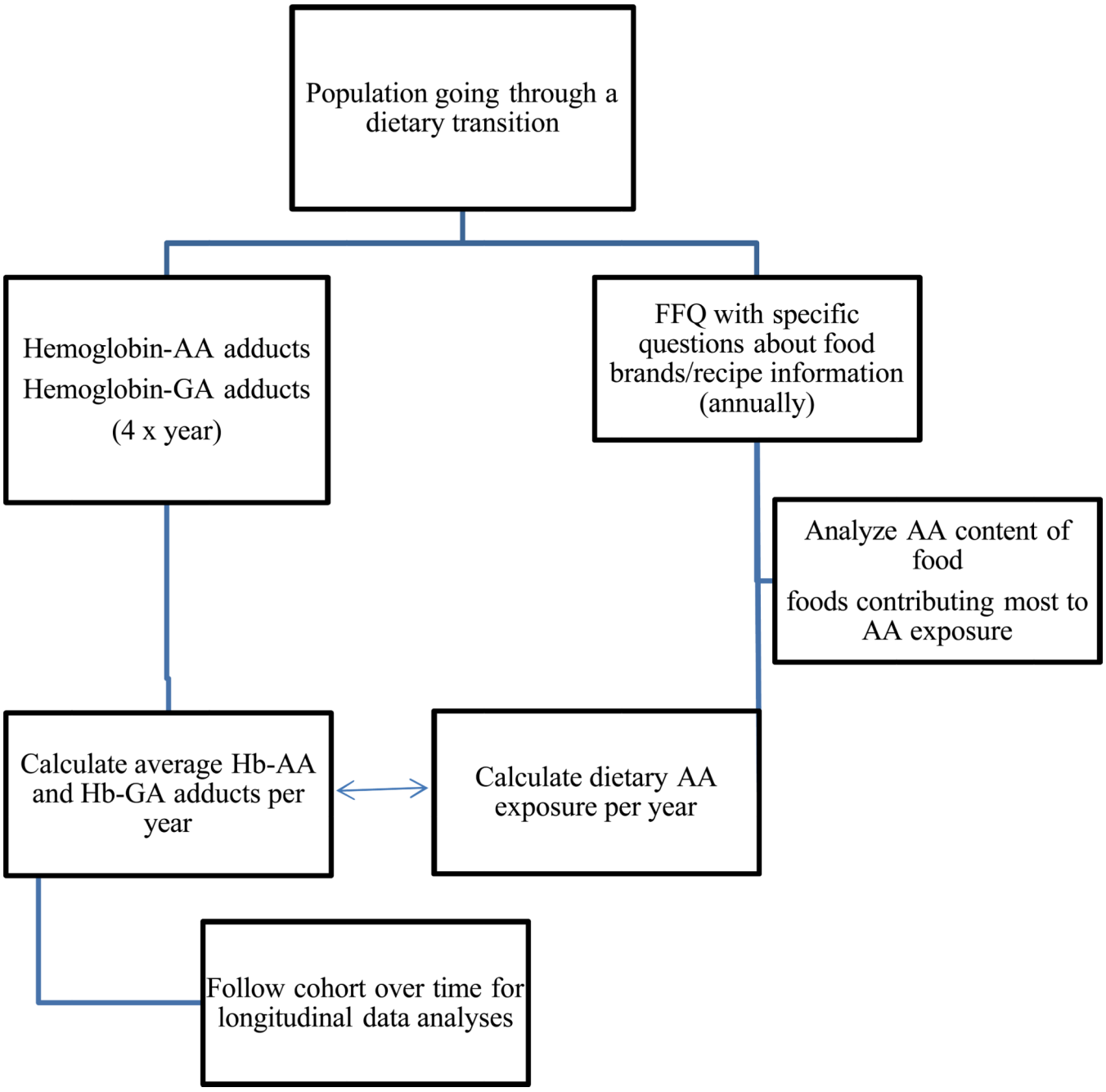

Figure 5.
Future study overview

Table 1

Prospective cohort studies of dietary acrylamide intake and cancer

Reference	Study cohort (cohort sample size)	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake	Relative risk (95% CI)	Conclusions
Mucci et al. (2005) (16)	Cohort of Swedish women (43,404)	Breast cancer	667	FFQ at baseline with questions about acrylamide-containing foods	25.9 μg/day	1.19 (0.91–1.55)	No association
Mucci et al. (2006) (23)	Swedish Mammography cohort (61,467)	Total colorectal cancer	741	Baseline FFQ	24.6 μg/day	0.9 (0.7–1.3)	No association
		Colon cancer	504			0.9 (0.6–1.4)	
		Rectal cancer	237			1.0 (0.6–1.8)	
Larsson et al. (2009) (12)	Cohort of Swedish men (45,306)	Total prostate cancer	2,696	96-item dietary FFQ at baseline	36.1 ± 9.6 μg/day	0.88 (0.70–1.09)	No association
		Localized prostate cancer	1,088			1.07 (0.87–1.32)	
		Advanced prostate cancer	951			0.98 (0.78–1.22)	
Larsson et al. (2009) (21)	Cohort of Swedish men (45,306)	Total colorectal cancer	676	96-item dietary FFQ at baseline	36.1 ± 9.6 μg/day	0.95 (0.74–1.20)	No association
		Colon cancer	410			0.97 (0.71–1.31)	
		Rectal cancer	266			0.91 (0.62–1.34)	
Larsson et al. (2009) (13)	Cohort of Swedish women (61,433 at baseline; 36,664 at 9.4 years' follow-up)	All invasive breast tumors	2,952	FFQ at baseline	24.6 ± 7.6 μg/day at baseline	0.91 (0.80–1.02)	No association between baseline dietary acrylamide intake and overall invasive or receptor-specific breast cancer
		ER+PR+ tumors	1,286			0.89 (0.74–1.08)	
		ER+PR- tumors	417			1.17 (0.84–1.64)	
		ER-PR- tumors	266			0.91 (0.61–1.38)	
		ER-PR+	93			—	
		9.4 years' follow-up		Follow-up FFQ	Not reported		No association between acrylamide and breast cancer after follow-up information on smoking status
		All invasive breast tumors	1,008			0.90 (0.71–1.14)	
		ER+PR+ tumors	562			0.81 (0.59–1.12)	
		ER+PR- tumors	244			0.87 (0.53–1.42)	

Reference	Study cohort (cohort sample size)	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake	Relative risk (95% CI)	Conclusions
		ER-PR- tumors	110			0.98 (0.48–2.02)	
		ER-PR+	9			—	
Larsson et al. (2009) (14)	Cohort of Swedish women (61,057)	Total ovarian Cancer	368	Baseline 67-item FFQ	24.6 ± 7.6 μg/day	0.84 (0.62–1.14)	No association between dietary acrylamide intake and total ovarian cancer or serous subtype
				Follow-up 96- item FFQ			
		Subtypes					
		Serous	182			1.01 (0.65–1.56)	
		Endometrioid	60			—	
		Mucinous	25			—	
		Clear cell	9			—	
		Other	92			—	
Larsson et al. (2009) (15)	Cohort of Swedish women (61,226)	Endometrial	687	Baseline 67-item FFQ	24.6 ± 7.6 μg/day	0.96 (0.76–1.21)	No association
				Follow-up 96-item FFQ			
Wilson et al. (2009) (19)	Nurses' Health Study (90,628)	Premenopausal invasive breast cancer	1,179	Semi-quantitative FFQ at baseline and follow-up every 4 years	Lowest quintile: 10.8 μg/day	0.92 (0.76–1.11)	Dietary acrylamide not associated with premenopausal breast cancer
					Highest quintile: 37.8 μg/day		
Wilson et al. (2010) (55)	Nurses' Health Study (88,672)	Total breast	6,301	Semi-quantitative FFQ at baseline and follow-up every 4 years	Lowest quintile: 9 μg/day	0.95 (0.87–1.03)	No association with overall or hormone receptor specific breast cancer.
		ER+/PR+	2805			0.99 (0.87–1.13)	
		ER+/PR-	737			1.04 (0.80–1.34)	
		ER-/PR+	138			1.09 (0.63–1.87)	
		ER-/PR-	839			0.88 (0.70–1.11)	
		Endometrial	484		Highest quintile: 26 μg/day	1.41 (1.01–1.97)	**Increased risk for endometrial cancer**.
		Epithelial ovarian	416			1.25 (0.88–1.77)	No association with ovarian cancer.
Hirvonen et al. (2010) (56)	The Alpha Tocopherol, Beta-Carotene Cancer Prevention Study (27,111)	Lung	1,703	FFQ with 276 –items at baseline with picture booklet for three to five different portion sizes	Lowest quintile: 21.9 μg/day	1.18 (1.01–1.38)	**Increased risk for lung cancer**
		Prostate	799			1.05 (0.83–1.32)	
		Urothelial	365			0.99 (0.71–1.39)	
		Colorectal	316			0.93 (0.65–1.34)	

Reference	Study cohort (cohort sample size)	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake	Relative risk (95% CI)	Conclusions
		Stomach	224		Highest quintile: 55.7 μg/day	0.96 (0.60–1.53)	
		Pancreatic	192			1.00 (0.62–1.62)	
		Renal cell	184			1.28 (0.76–2.15)	
		Lymphomas	175			1.10 (0.67–1.80)	
Wilson et al (2012) (60)	The Health Professionals Follow-up Study	All prostate cancer cases	5,025	Cumulative average intake estimated from semi-quantitative FFQ at the baseline and 4 follow-up FFQs administered once every 4 years	Lowest quintile: 12 μg/day Highest quintile: 35 μg/day	1.02 (0.92–1.13)	No association with overall or sub-types of prostate cancer
		Lethal cases	642			0.98 (0.75–1.27)	
		Advanced cases	896			0.98 (0.79–1.23)	
		Localized cases	3,221			1.09 (0.96–1.23)	

CI, confidence interval; ER-, estrogen receptor negative; ER+, estrogen receptor positive; FFQ, food frequency questionnaire; PR-, progesterone receptor negative; PR+, progesterone receptor positive; RR, relative risk; Bolding indicates significant increased risk; —, no RR reported due to insufficient number of cases.

Table 2

Case-cohort studies of dietary acrylamide intake and cancer

Reference (parent cohort)	Sample size of sub-cohort	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake (μg/day)	Hazard ratio (95% CI)	Conclusions
Hogervorst et al. (2007)(11) (The Netherlands Cohort)	15,836 person-years	Endometrial	327	Self-administered FFQ at baseline	21.0 ± 11.9	1.29 (0.81–2.07)	Increased risk among nonsmokers
		Ovarian	300			**1.78 (1.10–2.88)**	**Significant increased risk**
		Breast cancer	1,835			0.93 (0.73–1.19)	No association
Hogervorst et al. (2008)(20) (The Netherlands Cohort)	4,438	Colorectal	2,190	Self-administered FFQ at baseline	21.8 ± 12.1	1.00 (0.96–1.06)	No association between dietary acrylamide intake and increased cancer risk
		Gastric	563			1.02 (0.94–1.10)	
		Pancreatic	349			1.06 (0.96–1.17)	
		Esophageal	216			0.96 (0.76–1.11)	
Hogervorst et al. (2008)(24) (The Netherlands Cohort)	2,191 men and 2,247 women	Renal cell	339	Self-administered FFQ at baseline	21.8 ± 12.0	**1.59 (1.09–2.30)**	**Significant increased risk**
		Bladder	1,210			0.91 (0.73–1.15)	No association
		Prostate	2,246			1.06 (0.87–1.30)	No association
Pedersen et al. (2010)(17) (The Netherlands Cohort)	22,879	Postmenopausal breast cancer (total)	1,690	Self-administered FFQ at the baseline	Median 18.3 (14.6)	1.15 (0.86–1.53)	No association between dietary acrylamide intake and overall or receptor-specific breast cancer
		ER+	586			1.31 (0.81–1.97)	
		PR+	300			1.47 (0.86–2.51)	
		ER+PR+	291			1.43 (0.83–2.46)	
		ER-	150			0.95 (0.52–1.72)	
		PR-	160			0.84 (0.63–1.56)	
		ER-PR-	80			0.90 (0.48–1.68)	
Hogervorst et al. (2009)(27) (The Netherlands Cohort)	2,191 men	Overall lung cancer		Self-Administered FFQ at baseline		1.03 (0.77–1.39)	Acrylamide intake not associated with overall lung cancer or its sub-types
		Squamous cell carcinoma	871			1.18 (0.80–1.74)	
		Large cell lung carcinoma	275			1.08 (0.65–1.79)	

Reference (parent cohort)	Sample size of sub-cohort	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake (μg/day)	Hazard ratio (95% CI)	Conclusions
		Small cell lung carcinoma	359			1.23 (0.74–2.06)	
		Adenocarcinoma	426			0.85 (0.53–1.36)	
	2,247 women	Overall lung cancer				0.45 (0.27–0.76)	Statistically significant inverse association between acrylamide and overall lung cancer, and adenocarcinoma
		Squamous cell carcinoma	83			0.56 (0.27–1.16)	
		Large cell lung carcinoma	52			—	
		Small cell lung carcinoma	63			—	
		Adenocarcinoma	102			0.40 (0.21–0.78)	
Hogervorst et al. (2009)(28) (The Netherlands Cohort)	4,438	Total brain cancer	216	Self-administered FFQ at baseline	Sub-cohort 21.8 ± 12.1 Cases 22.1 ± 12.9	0.87 (0.54–1.41)	No association
		Astrocytic glioma	151		21.7 ± 12.2	0.78 (0.43–1.42)	
		High-grade astrocytic glioma	132		21.3 ± 12.0	0.66 (0.33–1.31)	
Schouten et al. (2009)(62) (The Netherlands Cohort)	2,202 men and 2,089 women			Self-administered FFQ at baseline	Sub-cohort 22.5 ± 12.2 ♂ 21.1 ± 11.9 ♀		No association with overall head and neck, but decreased risk in non-smoker men.
		Head and neck cancer	284 ♂ total 63♂ non-smoker 73 ♀		Cases 21.5 ± 13.0 ♂ 19.4 ± 10.3 ♀	0.74 (0.4–1.15)♂ 0.45 (0.21–0.94) non-smoker♂ 1.01 (0.53–1.93)♀	
		Oral cavity cancer	61♂ 40♀ total 12♀ non-smoker		18.8 ± 10.3♂ 18.8 ± 10.0♀	0.68 (0.33–1.43)♂ 0.94 (0.70–1.27)♀ overall 1.28 (1.01–1.62) non-smoker ♀	**Increased risk for oral cavity cancer in non-smoker women**
		Oro-and hypopharynx	61♂ 22♀		18.3 ± 10.7♂ 20.7 ± 11.9♀	0.50 (0.24 –1.04)♂ 0.94 (0.61–1.43)♀	
		Larynx cancer	170♂ 10♀		23.3 ± 14.1♂ 21.0 ± 7.7♀	0.95 (0.55–1.65)♂ —	

Reference (parent cohort)	Sample size of sub-cohort	Type and clinical stage of cancer	Number of cases	Acrylamide exposure measured	Mean dietary acrylamide intake (μg/day)	Hazard ratio (95% CI)	Conclusions
		Thyroid cancer	19♂ 47♀		22.1 ± 12.7♂ 21.6 ± 10.2♀	— 1.05 (0.86–1.28)♀	
Bongers et al. (2012) (63) (The Netherlands Cohort)	2191 men 2247 women			Self-administered FFQ at baseline	Sub-cohort: 23 ± 12 ♂ 21 ± 12♀		
		Multiple myeloma	172 ♂ 161♀		25 ± 13 ♂ 21 ± 13 ♀	1.14 (1.01–1.27) ♂ 0.92 (0.77–1.11) ♀	Increased risk of multiple myeloma among men
		Diffuse large cell lymphoma	165♂ 104♀		23 ±13 ♂ 21 ± 11 ♀	1.04 (0.91–1.20) ♂ 1.02 (0.85–1.24) ♀	No association for diffuse large cell lymphoma
		Chronic lymphocytic leukemia	139♂ 68♀		21 ± 11 ♂ 20 ± 11 ♀	0.88 (0.74–1.04) ♂ 0.83 (0.64–1.09) ♀	No associations for chronic lymphocytic leukemia
Burley et al. (2010) (65) (The UK Women's Cohort)	35,372 women	Total breast cancer	1084	FFQ with 217 food items at baseline	Median 15μg/day (10 μg/day–21μg/day)	1.16 (0.88–1.52)	No association for highest vs. lowest quintile of dietary acrylamide and breast cancer.
		Premenopausal breast cancer				1.47 (0.96–2.27)	
		Postmenopausal breast cancer				0.97 (0.68–1.39)	

CI, confidence interval; ER-, estrogen receptor negative; ER+, estrogen receptor positive; FFQ, food frequency questionnaire; PR-, progesterone receptor negative; PR+, progesterone receptor positive; HbAA, hemoglobin adducts of acrylamide; HbGA, Hemoglobin adducts of glycidamide; RR, relative risk. Bolding indicates significant increased risk; —, no hazard ratio reported due to insufficient number of cases; IRR, Incidence rate ratios.

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Table 3

Population-based case-control studies of acrylamide intake and cancer

Reference	Type and clinical stage of cancer	Sample size	Acrylamide exposure measured	Mean dietary acrylamide intake	Odds ratio (95% CI)	Conclusions
Mucci et al. (2003)(22)		538 controls	Semi-quantitative FFQ	2 7.5 ± 0.6 μg/day		No association
	Large bowel	591 cases		28.6 ± 0.6 μg/day	0.6 (0.4–1.0)	
	Bladder	263 cases		29.4 ± 0.9 μg/day	0.8 (0.5–1.5)	
	Kidney	133 cases		28.4 ± 1.2 μg/day	0.8 (0.4–1.7)	
Mucci et al. (2004)(25)	Renal cell cancer	353 controls	Interview-based structured questionnaire	27.6 ± 0.6 μg/day	1.1 (0.7–1.8)	No association
		379 cases		27.6 ± 0.7 μg/day		
Wilson et al. (2009)(30)	Prostate cancer	1,111 controls	261-item FFQ	44.5 μg/day	0.97 (0.75–1.27)	No association
		1,489 cases		43.8 μg/day		
		Blood biomarker	Hemoglobin-acrylamide adducts		0.93 (0.47–1.85)	
		161 controls				
		170 cases				

CI, confidence interval; FFQ, food frequency questionnaire.

Table 4

Hospital-based case-control studies of acrylamide intake and cancer

Reference	Type and clinical stage of cancer	Sample size (controls / cases)	Acrylamide exposure measured	Mean dietary acrylamide intake	Odds ratio (95% CI)	Conclusions
Pelucchi et al. (2006)(18)			78-item FFQ	Controls: 0.33–0.40 μg/kg/day		No associations
	Oral cavity/pharyngeal	1,172 / 749		0.40 μg/kg/day	1.12 (0.76–1.66)	
	Esophageal	1,066 / 395		0.36 μg/kg/day	1.10 (0.65–1.86)	
	Laryngeal	1,297 / 527		0.40 μg/kg/day	1.23 (0.80–1.90)	
	Large bowel	4,765 / 2,280		0.40 μg/kg/day	0.97 (0.80–1.18)	
	Colon	4,765 / 1,394		0.40 μg/kg/day	0.98 (0.78–1.23)	
	Rectal	4,765 / 886		0.40 μg/kg/day	0.96 (0.73–1.26)	
	Breast	3,122 / 2,900		0.38 μg/kg/day	1.06 (0.88–1.28)	
	Ovarian	2,411 / 1,031		0.37 μg/kg/day	0.97 (0.73–1.31)	
	Prostate	1,451 / 1,294		0.33 μg/kg/day	0.92 (0.69–1.23)	
Pelucchi et al. (2007)(26)	Renal cell cancer	1,534 / 767	78-item FFQ	37 μg/day	1.20 (0.88–1.63)	No association
Pelucchi et al. (2011)(82)	Pancreatic cancer	652 controls (348 ♂ 304 ♀)	78-item FFQ	32.19 6 ± 19.80 μg/day	1.49 (95% CI 0.83–2.70) highest vs. lowest quintile	No association
		326 cases (174 ♂ 152 ♀)		33.51 6 ± 17.42 μ/day		

CI, confidence interval; FFQ, food frequency questionnaire