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The association between high oral intake of acrylamide and risk of breast cancer: An updated systematic review and meta-analysis

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ABSTRACT

Background: The consumption of acrylamide through different types of food products can be correlated with cancer risk. In this study, the correlation between high oral intake of acrylamide and breast cancer risk was assessed with the aid of meta-analysis.

Scope and approach: Some of the databases such as Web of Science, Scopus, PubMed, and Embase were screened to up to September 2019 in order to retrieve the related articles. Therefore, ten articles with 57 studies (data-reports) were included in the current meta-analysis. Also, the relative risks (RRs) of breast cancer for high vs low intake acrylamide were calculated by a fixed-effects model (FEM). Also, the publication bias was assessed using Begg and Egger tests.

Key findings and conclusions: The pooled relative risk (RRs) of breast cancer was significance (RR = 0.95; 95%CI: 0.92–0.97) with low heterogeneity (I2: 0.0%, P-value: 0.994). Significant RRs in all women subgroup was observed as a marginally significant (0.95, 95%CI: 0.92–0.98), however, RRs was not significant in never-smoking women subgroup (0.93, 95%CI: 0.86–1.01). Additionally, no significant RRs were found in all hormone receptors. Moreover, no significant difference among RRs in body mass index (BMI) status subgroups (BMI < 12 kg/m^2 (0.93; 95%CI: 0.83–1.02) and BMI ≥ 12 kg/m^2 (0.97; 95%CI: 0.91–1.03) and coffee consumption (0.96; 95%CI: 0.84–1.09)) were noted. The high intake acrylamide can reduces the risk of breast cancer as marginal significantly. Therefore, in order to assess the related mechanisms, further studies are recommended.

1. Introduction

Acrylamide with high mobility in the groundwater and soil is a colorless, odorless, biodegradable and low molecular weight crystalline compound with a melting point of 84.5 °C (Riboldi, Vinhas, & Moreira, 2014) which is soluble in water, ethanol acetone and several organic solvents (Riboldi et al., 2014). Acrylamide is a water-soluble substance that is easily absorbed and transported to various organs like mammary glands (Thonning Olesen et al., 2008). Bioavailability is defined as part of the oral intake dose that reaches the circulation systemic (Kocadağlı

Abbreviations: Alternate Healthy Eating Index, AHEI; Confidence intervals, CIs; fixed-effects model, FEM; Body mass index, BMI; Relative Risk, RR; Healthy Eating Index, HEI; Hazard risk, HR; Diet Quality Index-Revised, DQI-R; Odds Ratio, OR; Recommended Food Score, RFS; Alternate Mediterranean Diet Score, aMed

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& Gökmen, 2015). Previous investigations demonstrated that intake acrylamide via oral can result in further rapid absorption in both humans and rodents (Kadry, Friedman, & Abdel-Rahman, 1999; Kocadağlı & Gökmen, 2015; Miller, Carter, & Sipes, 1982).

Human exposure to acrylamide can occur through different sources such as industrial chemicals, smoking, and the ingestion of heated food products (Urban, Kavvadias, Riedel, Scherer, & Tricker, 2006). While the main pathway of acrylamide formation in carbohydrate-rich foods such as breakfast cereal, potato crisps, French fries, toast, cookies, tahdig, and coffee is due to Maillard reaction during frying, roasting, cooking, toasting and baking at the high temperature (> 120 °C) (Maier et al., 2012; Mottram, Wedzicha, & Dodson, 2002; Rannou, Laroque, Renault, Prost, & Sérot, 2016; Shahrbabki et al., 2018). Acrylamide is classified as a "probable human carcinogen" compound (class 2A carcinogenic) (IARC, 2014) and/or "reasonably anticipated to be a human carcinogen" (NTP, 2014) which can cause different types of cancers (IARC, 2014; Wang, Feng, Guo, Shuang, & Choi, 2013). In this regard, several animal studies demonstrated that high intake dose of acrylamide (higher than average acrylamide intake daily by a human) can cause cancer in mammary glands of female rats, testicular cancer in male rats, and cancer tumors in the uterus and clitoral gland, central nervous system, thyroid gland and oral tissues (M. A. Friedman, Dulak, & Stedham, 1995; Riboldi et al., 2014) by endocrine and genotoxicity mechanisms (Besaratinia & Pfeifer, 2003; M.; Friedman, 2003; J. G. Hogervorst, P. A. van den Brandt, R. W. Godschalk, F.-J. van Schooten, & L. J.; Schouten, 2019; Rice, 2005; Spivey, 2010). Moreover, a strong association between acrylamide intake and emersion of mammary glands tumor in female rats was observed (M. A. Friedman et al., 1995; Johnson et al., 1986). In terms of humans, a significant, positive association between high intake of acrylamide and ovarian besides endometrial cancers risks were demonstrated by several studies (Janneke G Hogervorst, Leo J Schouten, Erik J Konings, R Alexandra Goldbohm, & Piet A van den Brandt, 2007). Although a possible association between acrylamide and biomarkers of breast cancers in postmenopausal women was documented (Pedersen et al., 2010), no significant evidence regarding the association of dietary intake acrylamide and breast cancer risk was reported (Janneke G Hogervorst, Schouten, Konings, Goldbohm, & van den Brandt, 2007a, 2007b; Larsson, Åkesson, & Wolk, 2008; Mucci et al., 2005; Pelucchi et al., 2006; Wilson et al., 2009).

However, the association high oral intake of acrylamide and different types of cancer risk was meta-analyzed previously, no significant association in the all-women subgroups and most cancers was declared (RR = 0.96, 95%C I: 0.90–1.01) (Pelucchi, Bosetti, Galeone, & La Vecchia, 2015b). Since there have been several studies in recent years that were not included in the previous meta-analysis; hence, conducting a new meta-analysis was crucial.

Therefore, the current study aimed to the analysis of the studies published up to September 2019 based on defined subgroups, such as study design (cohort and case-control), smoking status (Smoker and never-smoker women subgroups and never-smoking women subgroups), hormone receptor status (positive and negative estrogen), body mass index (BMI) status and coffee consumption status.

2. Strategy of search

2.1. The protocol and search strategy

All relevant studies were systematically reviewed based on the Cochrane protocol in agreement with the PRISMA guideline(Moher et al., 2015). In this regard, some international databases such as the Scopus, PubMed, Web of Sciences, and Embase databases were screened to collect the related studies from inception to 1 September 2019. Keywords and MeSH terms of "Glycidamide "OR "Acrylamide" AND "Cancer" OR "Breast cancer" AND "Food "OR" Foods "OR" dietary "OR" Diet" AND "Relative risk" OR "risk ratio" were used. Terms of "AND/OR" also were applied to increase search sensitivity. Moreover, the study designs of the cohort and case-control were included in the current study.

The title and abstract of studies were reviewed and suitable articles were downloaded for review of the full text. The references of articles also were screened to retrieve more articles based on similar conducted systematic review studies (Atamaleki et al., 2019; Khaneghah et al., 2019; Khaneghah, Fakhri, Raeisi, Armoon, & Sant'Ana, 2018; Mousavi Khaneghah, Fakhri, Gahruie, Niakousari, & Sant'Ana, 2019; Mousavi Khaneghah, Kamani, et al., 2019).

2.2. Eligibility inclusion and exclusion criteria

An article was included when it met the following inclusion criteria: (1) published the article in the English language, and (2) present relative risk (RR) including Hazard risk (HR) and/or odds ratio (OR) of breast cancer due to high vs low dietary intake of acrylamide. Genetic and animal studies, books, theses, and review articles, due to lack of peer review as well as original articles with other languages, were excluded to avoid any mistake during translation. Studies that not separated the types of cancers due to high vs low intake of acrylamide were also excluded (Rahmani, Alipour, et al., 2018; Rahmani, Miri, et al., 2018).

2.3. Data collection, synthesis, and extraction

The extracted data can be summarized as the study design (cohort and case-control) such as relative risk (RRs) of breast cancer in the subgroups including all women, never smoker women, hormone receptor status (estrogen positive, estrogen negative and etc.), coffee consumption habitat, body mass index (BMI) status and RR following 95% confidence interval (CIs) that multivariable-adjusted.

2.4. Meta-analysis of data

Heterogeneity was determined among studies via and I^2 index and Cochrane Q statistics based on the P-value. If I^2 index is ≤ 50% and > 50%, the heterogeneity is low and high, respectively (Higgins & Thompson, 2002). In the current study, the I^2 index was lower than 50%, therefore, then the fixed-effect model (FEM) was used while the RR > 1 shows an increasing effect of the high intake of acrylamide on RRs of breast cancer risk. Begg and Egger's tests were used to determine the bias of publication (Egger, Smith, Schneider, & Minder, 1997). A meta-analysis of RR of breast cancer was performed by STATA 14.0 (Statistical Software, College Station, TX, USA). Statistical significance was assumed with a P-value < 0.05.

3. Major findings

3.1. Selection of process of studies

In the identification step, 393 articles out of 471 retrieved articles in databases were excluded due to duplication by the aid of EndNote X7® software (Thomson Reuters, Canada). In the screening step, according to title and abstract, 67 articles were excluded due to (1) no original data including workshop, review articles, and book (2) studies that not separate types of cancers and (3) presenting of the intake acrylamide except oral intake. In the eligibility phase, 10 articles with 59 studies (data-reports) were included in the meta-analysis (Fig. 1 and Table 1s).

3.2. Association breast cancer with intake acrylamide

In this study review, the high oral intake of acrylamide with breast cancer risk, considering the most important behavioral factors of dietary intake, coffee consumption, smoking practice, and dependent factors of hormone receptors, and BMI status was assessed.

RRs of breast cancer in the high vs low dietary intake of acrylamide

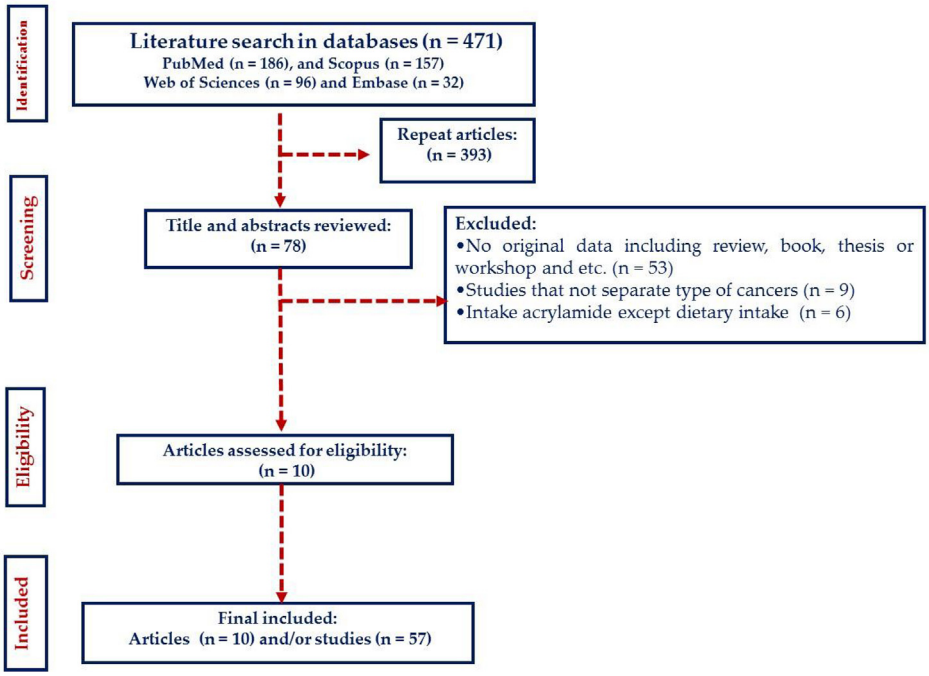

Fig. 1. Searching of articles in databases and including and excluding process.

in the cohort and case-control studies were 0.94, 95%CI (0.91–0.97) and 1.06, 95%CI (0.86–1.26), respectively (Fig. 2). The overall, high oral intake of acrylamide decreased RRs of breast cancer as marginal significant (RR = 0.95; 95%CI: 0.92–0.97) (Fig. 2).

Smoke contains acrylamide compounds (J. G. Hogervorst, van den Brandt, Godschalk, van Schooten, & Schouten, 2019), therefore, meta-analysis RRs of breast cancer in women based on smoke status showed some interesting results. A significant RRs in all women (smoker and non-smoker) subgroup was observed as marginal significant (0.95, 95%CI: 0.92–0.98), however, RRs were not significant in never-smoking women subgroup (0.93, 95%CI: 0.86–1.01) (Fig. 3). Tobacco is an important source of acrylamide exposure. However, smoking can also contribute to the dietary acrylamide effect through the releasing of additional chemicals with antiestrogenic effects (Janneke G. Hogervorst, Leo J. Schouten, Erik J. Konings, R. Alexandra Goldbohm, & Piet A. van den Brandt, 2007; Thonning Olesen et al., 2008). Epoxide hydrolase inducing also can be released by the smoking which enhances glycidamide metabolism and consequently less remaining glycidamide to damage DNA (Hogervorst et al., 2007a, 2007b; Schettgen et al., 2004).

In general, an accurate estimation of dietary acrylamide intake seems to be very difficult as food type, preparation conditions, cooking method, and storage condition are varied (Gökmen, 2015; Pelucchi, Bosetti, Galeone, & La Vecchia, 2015a; Riboldi et al., 2014; Rydberg et al., 2005). In this regard, it was demonstrated that the high level of acrylamide in Dutch spiced cake is attributed to the presence of a high level of reducing sugar (Hogervorst et al., 2007a, 2007b). Moreover, time and temperature of storage can influence the acrylamide formation in foods like potatoes (Wilson et al., 2009). Whilst some studies have been conducted considering the carcinogenicity risk (breast cancer) of dietary acrylamide (Tareke, Rydberg, Karlsson, Eriksson, & Törnqvist, 2002) regarding the (V. J. Burley et al., 2010; Hogervorst et al., 2007a, 2007b; Kotemori et al., 2018b; Pelucchi et al., 2015a), insignificant and contradictory results were reported (Burley et al., 2010; Larsson et al., 2008). According to our findings, high oral intake acrylamide decreased RRs of breast cancer as marginal significant, while in another meta-analysis, no association was observed between high vs low intake of acrylamide and breast cancer risk(Pelucchi et al., 2015a). While no significant association between breast cancer's risks with intake dietary acrylamide among the all defined subgroups was obvious.

Scientific advances have also accompanied the food industry over time, leading to new technologies that ultimately affect the acrylamide formation during food production procedures (Hogervorst et al., 2007a, 2007b). For example, a significant reduction in acrylamide formation was obtained as a result of the incorporation of bamboo leaves into potato crisps and French fries before frying (Zhang, Chen, Zhang, Wu, & Zhang, 2007). Since the animal studies based dose-response experiments have demonstrated a strong association between dietary acrylamide and cancer in some organs especially mammary glands (M. A. Friedman et al., 1995; Johnson et al., 1986; Larsson et al., 2008), the reducing effect of food ingredients on acrylamide metabolism is also possible. In this context, the protective role of catechin and neem leaves due to their antioxidant and anti-inflammatory activities on acrylamide toxicity in rats was demonstrated (Mansour, Ibrahim, El-Kholy, & El-Madawy, 2008). Also, the protective effects of virgin olive oil against nephrotoxicity related to acrylamide were declared (Ghorbel et al., 2017).

Hormones in the human body can be involved in oxidative stress, therefore, investigating regarding the RRs of breast cancer in hormone receptor of women was essential(Yasuda, Sakakibara, & Shimoi, 2017). No significant RRs for breast cancer risk due to high oral intake acrylamide in the all hormone receptor subgroups including ES positive and PR positive status (RR = 0.91; 95%CI: 0.82–1.00); ES positive status (RR = 1.03; 95%CI: 0.93–1.12); ES negative and PR negative status (RR = 0.88; 95%CI: 0.73–1.02); PR positive status (RR = 1.08; 95%CI: 0.80–1.35); ES negative status (RR = 0.88; 95%CI: 0.59–1.16); PR negative status (RR = 0.88; 95%CI: 0.59–1.16); ES negative and PR positive status (RR = 1.09; 95%CI: 0.47–1.71); ES positive and PR negative status (RR = 1.12; 95%CI: 0.27–1.97) was observed (Fig. 4). Since the interaction of hormones with each other is very complex, it was difficult to interpret these results, hence further studies is recommended (Hackney, 2016).

Since BMI is one of the effective variables on the incidence of cancers in human (Iyengar et al., 2019); the RRs of breast cancer due to high oral intake acrylamide in the BMI subgroups was investigated. BMI

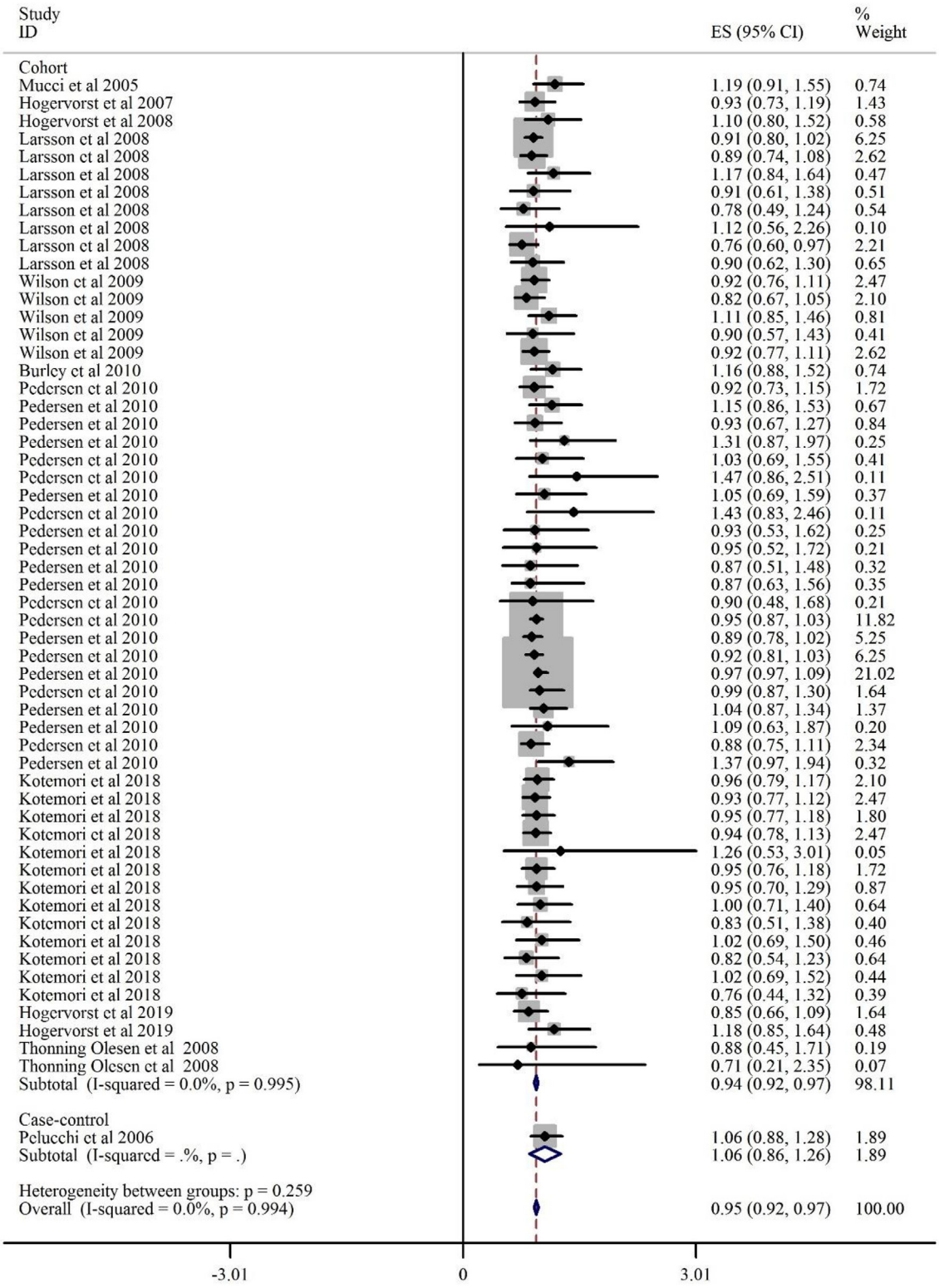

Fig. 2. The meta-analysis association between acrylamide intake and breast cancer risk based on study design subgroups.

even can influence the hormonal balance as the level of circulating ES in obese women is higher then thin women (Olsen et al., 2012). Additionally, no significance RRs of breast cancer risk with high oral intake acrylamide in the BMI lower than 12 kg/m^2 (RR = 0.93; 95%CI: 0.83–1.02) and BMI equal and higher than 12 kg/m^2 (RR = 0.97; 95%CI: 0.91–1.03) was observed (Fig. 5). Considering some diet quality indices, like Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI), Diet Quality Index-Revised (DQI-R), Recommended Food Score (RFS), and the Alternate Mediterranean Diet Score (aMed), a lower risk of ER − breast cancer was associated with those individuals who were scored as high (Fung et al., 2006). Herein, no significant association between RRs of breast cancer with high vs low intake acrylamide based on BMI subgroups was noted (Fig. 5).

Coffee is one of the main sources of acrylamide intake (Schouten,

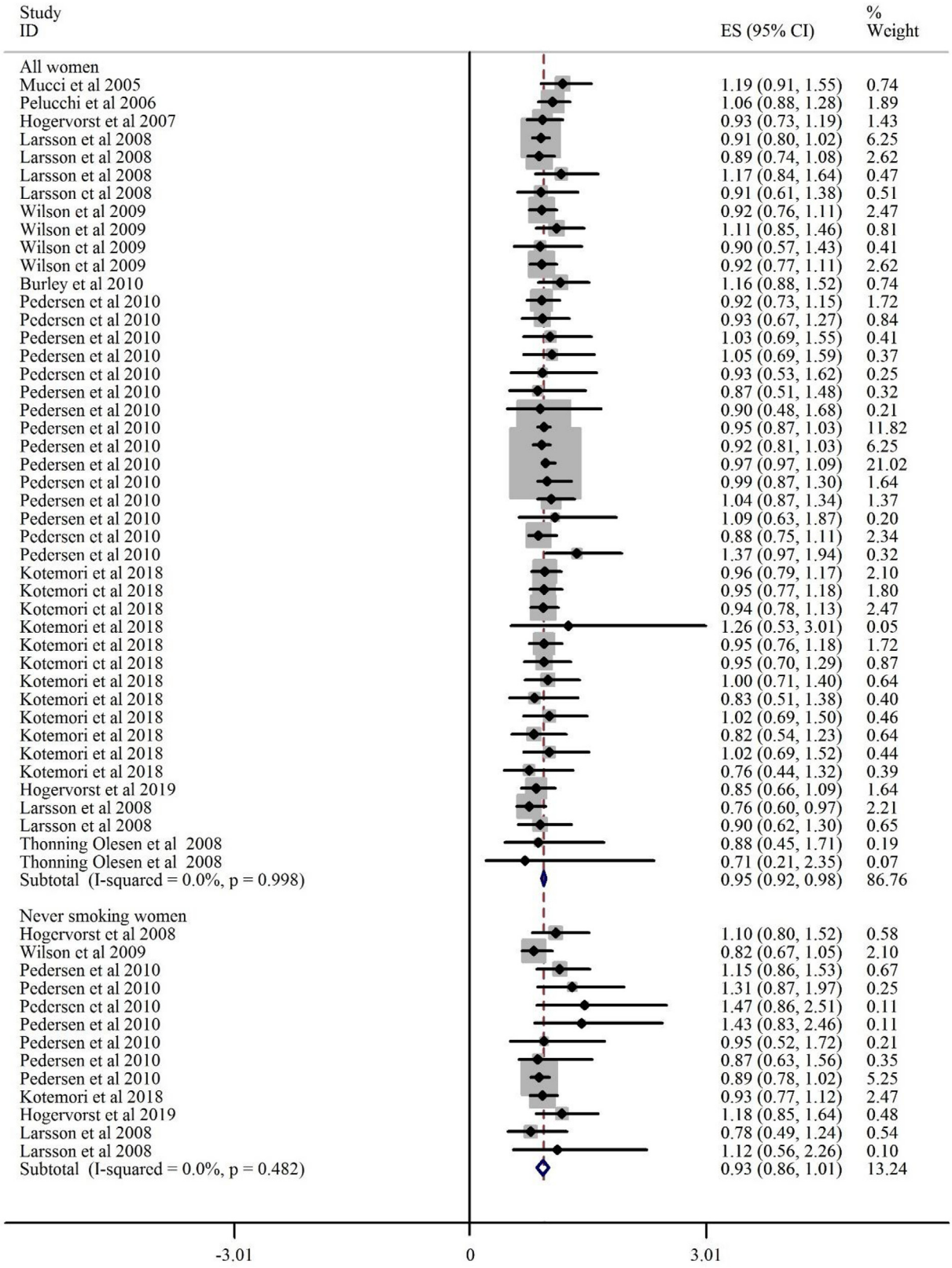

Fig. 3. The meta-analysis association between acrylamide intake and breast cancer risk.

Tappi, & Romani, 2020). In this regard, the RRs of breast cancer with different coffee consumption amounts was assessed. According to findings, no significant RRs of breast cancer with high oral intake acrylamide in the high amount of coffee consumption (1 and more cup/week) was observed (RR = 0.96; 95%CI: 0.84–1.09) (Fig. 6). With respect to the antioxidant properties of coffee (V. J. Burley et al., 2010; Natella, Nardini, Giannetti, Dattilo, & Scaccini, 2002), and in concordance with processes described above, coffee is likely able to overcome the toxicity of acrylamide while no significant association between RRs of breast cancer with high intake acrylamide due to coffee

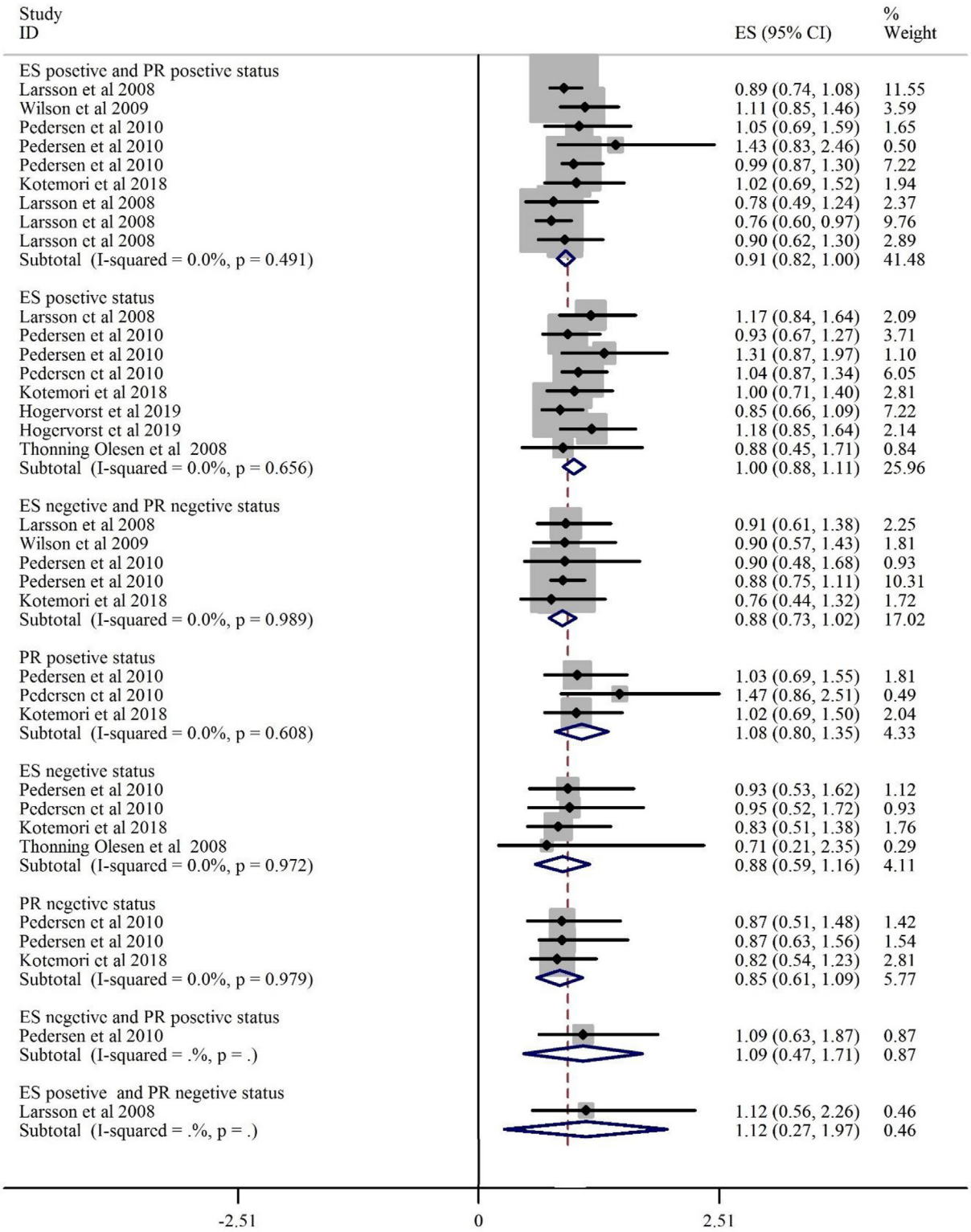

Fig. 4. The meta-analysis association between acrylamide intake and breast cancer risk based on hormone receptor status subgroups.

consumption was noted (Fig. 6). Therefore, a variation of acrylamide levels in foods, and the effectiveness of interfering agents on acrylamide metabolism are likely the most important reasons for explaining the conflicting results in reviewed articles.

According to Begg's (p-value = 0.15) and Egger's (p-value = 0.34) no significant publication bias among included studies was reported (Fig. 1s).

In an overview, probable causes for decrease relative risk of breast cancer due to high intake acrylamide were including (1) Many studies estimated acrylamide in a limited number of foods (J. G. F. Hogervorst, P. A. van den Brandt, R. W. L. Godschalk, F.-J. van Schooten, & L. J. Schouten, 2019; Pelucchi et al., 2006); (2) The antioxidant effect of other foods such as coffee has not been studied(Burley et al., 2010; Natella et al., 2002); (3) Acrylamide exposure may occur during a long time, while many studies considered acrylamide exposure at a specific, relatively short time. For instance, the acrylamide exposure through

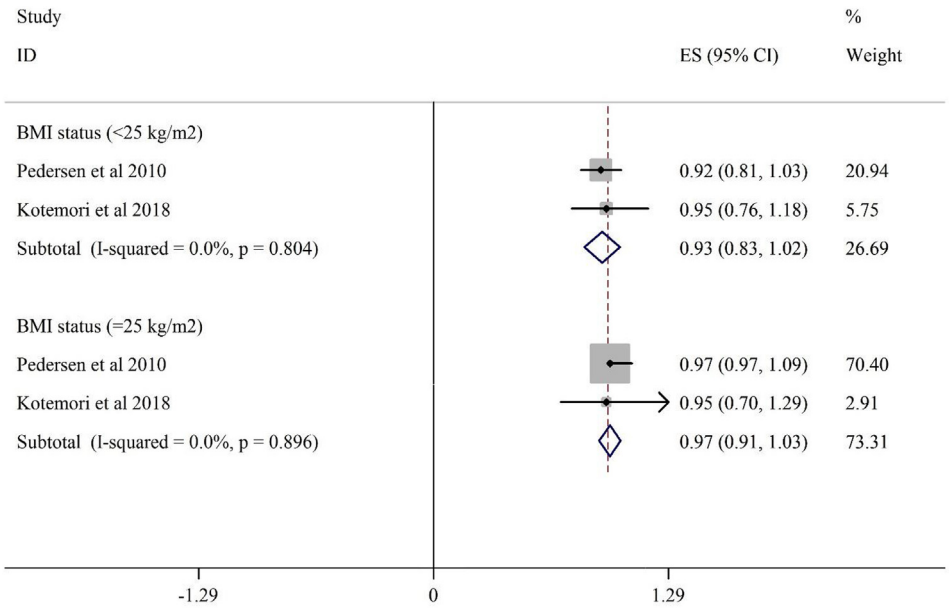

Fig. 5. The meta-analysis association between acrylamide intake and breast cancer risk based on BMI status subgroups.

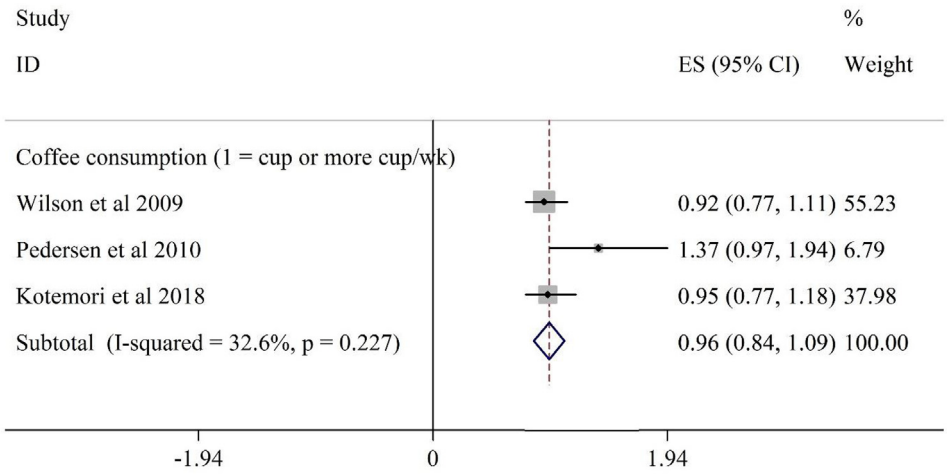

Fig. 6. The meta-analysis association between acrylamide intake and breast cancer risk based on coffee consumption status subgroups.

AA-Hb and GA-Hb is recognizable after 4 months, while it is recommended that the time of acrylamide exposure be considered based on breast cancer mortality (Olsen et al., 2012). Additionally, Kipnis et al. proposed that dietary data for validation of food frequency questionnaires (FFQs) must be recorded in multiple days (Kipnis et al., 2001). However, applying of a wide database included 42 food contained acrylamide type(Wilson et al., 2009), and following up the analysis results for 13.3 years (Hogervorst et al., 2019); (4) Drinking water, as one of the most important components of human nutrition with acrylamide contamination (Gökmen, 2015; Hogervorst et al., 2007a, 2007b; Larsson et al., 2008), is an obvious example related to mentioned problems that directly and/or indirectly is consumed by every people; (5) Problems is attributed to study method components such as reliability (acrylamide level variation), data collection and statistical methods in studies (Hogervorst et al., 2019; Pelucchi et al., 2006). The FFQ is able to evaluate the rank order of acrylamide intake by peoples. Moreover, in some studies, data was collected once, while some factors like BMI are changing during the time, so, it is better to data be collected from elderly peoples, due to their diet stability (Hogervorst et al., 2019); (6) Another possible cause for the insignificant risk of breast cancer in defined subgroups with high acrylamide intake may be the difference in the pattern of consumption foods in different age groups as well as different countries (Larsson et al., 2008), which can markedly affect the exposure levels to food contaminants. Or even, it can be said that these interests are different around the world due to differences in food consumption patterns (Kotemori et al., 2018b; Wilson et al., 2009). Hogervorst et al. (2007a, 2007b) expressed that young people have more interest in the consumption of potato crisps and French fries (Hogervorst et al., 2007a, 2007b).

4. Conclusions

In this work, the association between oral intake of acrylamide with breast cancer risk based on some subgroups such as coffee consumption, smoking practice, hormone receptors, and BMI status was meta-analyzed. The high oral intake acrylamide in all women (smoker and non-smoker women) reduced the risk of breast cancer as marginal significantly, however, no significant reduction in risk in the non-smokers' subgroup was noted. Also, the association of breast cancer risk with hormone receptor, BMI and coffee consumption subgroups was not significant. The results showed that high oral intake of acrylamide can decrease RRs of breast cancer as marginal significant; which reinforces

the need for further studies. Although acrylamide consumption did not increase the risk of breast cancer, more epidemiological studies in the future could result in a reliable conclusion about the association between breast cancer risk and oral acrylamide intake.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tifs.2020.04.006.

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