Dietary Heterocyclic Amine Intake and Colorectal Adenoma Risk: A Systematic Review and Meta-analysis

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Abstract: BACKGROUND Heterocyclic amines (HCA) are potent carcinogenic substances formed in meat. Because of their mutagenic activity, they may increase the risk of colorectal adenomas, which are the precursors of colorectal cancer, one of the most prevalent cancers worldwide. The aim of this meta-analysis was to synthesize the knowledge about the intake of HCAs and its associations with CRA. METHODS We conducted a systematic search in PubMed and EMBASE. We used odds ratios (OR); or relative risks, RR) from every reported intake and compared the highest versus lowest level of dietary HCAs. In addition, we assessed a dose-response relationship. RESULTS Twelve studies on HCA intake and risk of CRA were included in our analysis. We observed a statistically significant association when comparing top versus bottom intake category of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine [PhIP; OR = 1.20; 95% confidence interval (CI) = 1.12-1.29], 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx; OR = 1.20; 95% CI = 1.08-1.34), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx; OR = 1.16; 95% CI = 1.05-1.27), benzo(a)pyrene (BaP; OR = 1.15; 95% CI = 1.04-1.27), and mutagenicity index (OR = 1.22; 95% CI = 1.06-1.41). Furthermore, we observed a significant dose-response effect for PhIP, MeIQx, and mutagenicity index. CONCLUSIONS This meta-analysis suggests that there is a positive association of HCAs, BaP, mutagenicity index with risk of CRA. In addition, our dose-response analyses showed an increased risk of CRA for PhIP, MeIQx, and mutagenicity index. IMPACT This study provides evidence for a positive association between the dietary intake of meat mutagens and CRA risk.

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Dietary Heterocyclic Amine Intake and Colorectal Adenoma Risk: A Systematic Review and Meta-Analysis

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Running title: HCA and colorectal adenoma risk: a meta-analysis

Abbreviations:

BaP, benzo(a)pyrene

CI, confidence interval

CRA, colorectal adenoma

CRC, colorectal cancer

DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline

HCA, heterocyclic aromatic amines

MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline

OR, odds ratio

PAH, polycyclic aromatic hydrocarbons

PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine

RR, rate ratio

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Conflicts of Interest. None

Abstract:

Background: Heterocyclic amines (HCAs) are potent carcinogenic substances formed in meat. Due to their mutagenic activity, they may increase the risk of colorectal adenomas (CRA), which are precursors of colorectal cancer (CRC), one of the most prevalent cancers worldwide. The aim of this meta-analysis was to synthesize the knowledge about the intake of HCAs and its associations with CRA.

Methods: We conducted a systematic search in PubMed and EMBASE. We used odds ratio (OR) (or relative risks, RR) from every reported intake and compared the highest versus lowest level of dietary HCAs. In addition, we assessed a dose-response relationship.

Results: Twelve studies on HCA intake and risk of CRA were included in our analysis. We observed a significant association when comparing top versus bottom intake category of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (OR= 1.20, 95% CI=1.12 to 1.29), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) (OR=1.20; 95% CI=1.08 to 1.34), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) (OR=1.16; 95% CI=1.05 to 1.27), benzo(a)pyrene (BaP) (OR=1.15; 95% CI=1.04 to 1.27) and mutagenicity index (OR=1.22;95% CI=1.06 to 1.41). Furthermore, we observed a significant dose-response effect for PhIP, MeIQx and mutagenicity index.

Conclusion: This meta-analysis suggests that there is a positive association of HCAs, BaP, mutagenicity index with risk of CRA. Additionally, our dose-response analyses showed an increased risk for CRA in the case of PhIP, MeIQx and mutagenicity index.

Impact: This study provides evidence for a positive association between the dietary intake of meat mutagens and CRA risk.

Keywords: colorectal adenomas, heterocyclic amines (HCAs), diet, meta-analysis, review

Introduction

In 2017, about 135,430 new cases of colorectal cancer (CRC) will be diagnosed in the United States and 50,260 persons will die from the disease [1]. In 2012, the International Agency for Research on Cancer (IARC) estimated that CRC was the third most common cancer worldwide in men and the second in women [2]. About 95% of CRCs emanate from benign, neoplastic adenomatous polyps (adenomas) [3], which are found in up to 40% of a population by the age of 60 [4]. More than 50% of CRCs occur in developed countries, being Oceania and Europe the ones with the highest incidence [5]. Common risk factors are age, race, family history of CRC and lifestyle, including sedentarism, smoking and Western dietary patterns [1, 6]. Meat consumption, especially red and processed meat, has been identified as an important dietary risk factor for CRC and colorectal adenomas (CRA) [7, 8]. Based on the results of several epidemiological studies, in October 2015, the IARC evaluated the association between red, processed meat and cancer and classified the consumption of red meat as probably carcinogenic to humans (Group 2A) with limited evidence and the consumption of processed meat as carcinogenic to humans (Group 1) with sufficient evidence [9]. After the decision of the IARC, more epidemiological studies and reviews have addressed this issue [8, 10]. Recently, Domingo *et al.* have reviewed the latest evidence, supporting the classification of red and processed meat as carcinogenic [11].

Several mechanisms have been suggested to explain the association between red and processed meat with CRC. Possible factors that may increase the carcinogenic process are cooking products found in meat such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAH) [12]. Other compounds are nitrates and nitrites, which are characteristic of processed meat and that have been classified as a “probable human carcinogens (Group 2A)” by the IARC [13] and heme iron, which is abundant in red meat.

HCAs arise during the thermal processing of meat, fish and poultry at temperatures over 150 degrees Celsius. Their formation depends on the type of meat and cooking method, and their amount increases with the duration and temperature of cooking [14]. Although more than 20 HCAs have been identified [14], the three most abundant carcinogenic HCAs formed in meats are 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) [15]. They are considered as potent carcinogenic substances, therefore, in 1993 PhIP, MeIQ and MeIQx were classified as "possible human carcinogens" (Group 2B) by the IARC [16]. Similarly, one of the PAHs, BaP, was also part of the list of carcinogens provided by the IARC. BaP was classified as "carcinogenic to humans" (Group 1) in 2012 [17].

The purpose of this systematic review was to investigate the association of HCA and BaP intake with CRA risk. Additionally, we aimed to examine whether the association between these compounds and colorectal adenoma risk differed by adenoma site and sex.

Materials and Methods

Data sources and search strategy

To identify eligible studies on the association of HCAs with CRA, a systematic literature search was conducted by two independent authors (VM, PC). Any disagreement was resolved after discussion with a third reviewer (SR). We searched in PubMed and EMBASE through March 2017 with no limitations on year or language of publication. The following search terms were used: ("colorectal adenoma" OR "colorectal polyps") AND ("heterocyclic amines" OR "PhIP" OR "MeIQx" OR "DiMeIQx" OR "polycyclic aromatic hydrocarbons" OR "meat"). Additionally, the reference lists of already identified articles were examined for other eligible studies based on the above-mentioned key words. Relevant studies were imported to EndNote (X7) to search for duplicates.

We carried out this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [18].

Study selection

Studies were included in the systematic review if they 1) were cohort, case-control or cross-sectional studies in humans; 2) investigated the association between HCAs and B(a)P intake and colorectal adenoma risk, 3) reported relative risk estimates (odds ratio [OR] or risk ratios [RR]) with 95% confidence intervals (CI) and if 4) the quantity of each single compound was stated.

We selected the most recent publications that included the largest number of cases, excluding overlapping studies. We further excluded studies if they focused on adenoma recurrence or only examined genetics.

Data extraction

We reviewed the eligible studies and carried out the extraction of data. The following information were abstracted: first author's last name, year of publication, country, study design, study size, number of cases and controls, sex, age, year diet was assessed, diet-assessment method, follow-up time, HCAs, BaP, or total mutagenicity index, adenoma outcome, statistical adjustments for confounders, mutagen doses comparisons, and the OR/RR estimates with 95% CI for the highest versus lowest level of intake for each mutagen. Multivariable adjusted analyses were extracted in preference over crude measures.

Quality assessment

To assess the methodological quality of the studies, we used the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies [19]. Each study was awarded a maximum of 9 points based on selection of controls, comparability and exposure in case of case-control studies, and outcome, in the case of cohort studies. The complete assessment is presented in supplementary tables 1 (cohort studies) and 2 (case-control studies).

Statistical analysis

We conducted meta-analyses utilizing OR (or RR) from every reported intake and we compared the highest versus lowest level of dietary mutagens. Primary meta-analyses models evaluate colorectal adenoma and the mutagen exposures. Forest plots were generated for the primary meta-analyses stratified by study type (i.e., cohort vs. case-control and cross-sectional studies). Further meta-analyses were performed stratified by adenoma site (colon and rectum) and sex to examine potential associations.

We assessed dose-response relationships between HCAs and colorectal adenoma following the method of Greenland and Longnecker [20]. The method requires the number of cases and controls per exposure level (therefore, we could not include all studies; we excluded 3 studies [24 ,25 ,26]), the ORs with CI and the mean or median for each category. In a sensitivity analysis, we also excluded the study by Gunter et al. [27] because the maximum values in the top category were several times higher than the top intake in all other studies. We used cubic splines with the knots for quantiles 0.25, 0.5 and 0.75 to assess the association between the mutagen exposure and CRA.

To evaluate heterogeneity of included studies, Cochran's Q test and I^2statistic were used. Publication bias was assessed with Egger's test by creating funnel plots [21]. All analyses were conducted using the statistical program STATA software version 13.1 (College Station, Texas) and R version 3.3.2.

Results

Figure 1 shows our search results: Until March 23, 2017 334 publications from PubMed and 139 from EMBASE were found. After screening, we included 12 publications (3 cohort [22-24], 8 case-control [25-32] and 1 cross-sectional [33] studies; in the following, study [33] will also be considered a case-control study) that examined the association of dietary mutagen

exposures (PhIP, MeIQx, DiMeIQx, total HCAs, BaP and mutagenicity index) with CRA in the systematic literature search. We excluded 6 studies because they overlapped with other publications [34, 35, 36, 37, 38, 39] or only explored adenoma recurrence [40].

Among eligible articles, 9 studies examined men and women [23-28, 30, 31, 33], 1 study that examined men and women only separately [32], 1 male cohort [22], and 1 female case-control study [29]. Most of the studies were from the United States [22, 24-31], one was from Canada [33], another one from Japan [32], and one was conducted in Europe [23]. A total of 76,657 participants including 9,995 colorectal adenoma cases were evaluated in this meta-analysis. Table 1 shows descriptive study characteristics of the studies; supplementary table 3 provides details on HCA assessment.

PhIP

Eleven studies on PhIP intake and CRA were included in the meta-analysis [22-25, 27-33]. Overall, dietary PhIP intake was related to increased risk of CRA (OR= 1.20, 95% CI= 1.12 to 1.29 comparing top versus bottom intake category). No significant heterogeneity between studies was observed; Figure 2A shows that results were similar in case-control and cohort studies. Figure 3A reveals a positive the dose-response association between PhIP intake and CRA. For 40 ng /day, the OR was 1.14 (95% CI=1.02 to 1.29) and the p value was 0.0160. Supplementary figure 1 shows that excluding Gunter et al. [27] from the dose-response analysis changed the dose-response curve, but not the interpretation of our results (for 40 ng/day: OR = 1.16, 95% CI=1.02 to 1.32; p value 0.0016). We performed sub-analyses by sex and site of adenoma (colon, rectum) [24, 27] and observed a significant association for colon adenoma, but not for rectal adenoma; results by sex were not statistically significant (Table 2). Figure 4A shows no indication of publication bias was observed from the funnel plot.

MeIQx

Eleven studies evaluated the association between MeIQx intake and CRA [22-25, 27-33] and were included in this meta-analysis. The meta-analysis resulted in a statistically significant

association (OR=1.20, 95% CI=1.06 to 1.34, top versus bottom category) with no evidence of heterogeneity between studies as shown in Figure 2B. However, results of case-control studies were stronger than those of cohort studies. Table 2 revealed a statistically significant association between MeIQx intake and risk of adenomas in women. Figure 3B indicated a positive dose-response relationship between MeIQx and CRA. For 50 ng/day, the OR was 1.25 (95% CI= 1.09 to 1.43) with a p value of 0.002 (excluding [27]: OR 1.28 [95% CI= 1.10 to 1.48]; p-value = 0.0016; supplementary figure 1). Figure 4B gives no indication of publication bias.

DiMeIQx

Ten studies provided results for DiMeIQx intake and CRA [22-25, 27-32] and were included in the meta-analysis. We found a significant association between DiMeIQx intake and CRA (OR=1.16, 95% CI=1.05 to 1.28). Figure 2C does not indicate any heterogeneity between studies, but the association was stronger in case-control than in cohort studies. Table 2 shows no indication of an association between DiMeIQx and rectal adenoma; associations for colon adenomas and by sex were positive, but not statistically significant. In Figure 3C, no evidence of a dose-response relationship was observed for incremental intake levels of DiMeIQx. Figure 4C does not provide any evidence of publication bias.

BaP

Six studies described the association of BaP intake and CRA [24, 26-29, 31] and were included in the meta-analysis. Figure 2D shows a positive association between BaP intake and CRA (OR=1.15, 95% CI=1.04 to 1.27, top versus bottom category). Only one cohort study reported on the association between BaP and CRA. Table 2 provides no evidence of heterogeneity between studies. Figure 3D shows no statistically significant relationship in the dose-response analysis. Figure 4D shows the funnel plot for BaP intake and CRA indicating no publication bias.

Mutagenicity index

Seven studies were identified that included data on meat-derived mutagenicity index and CRA [22, 24, 25, 27, 29, 31, 32]. Figure 2E shows the meta-analysis of studies between mutagenicity

index and CRA with a positive association (OR=1.22 95% CI=1.06 to 1.42, top versus bottom category) and no statistically significant study heterogeneity (p=0.076). Only two cohort studies examined the association between mutagenicity index and CRA and their summary result was weaker than the association observed in case-control studies. No statistically significant associations were observed in the sub-analyses by adenoma site or sex (Table 2). Figure 3E shows a positive dose-response association between mutagenicity index and CRA. For 7000 revertants/day the OR was 1.26 (95% CI= 1.02 to 1.55) with a p value of 0.0003. Figure 4E shows the funnel plot for mutagenicity index with an indication of publication bias.

Discussion

The relationship between dietary HCAs, BaP, mutagenicity index and CRA has been a topic of debate for several years. In this meta-analysis, we examined the association of HCAs, BaP and mutagenicity index with CRA risk. When comparing the highest versus the lowest intake of PhIP, MeIQx, DiMeIQx, BaP and mutagenicity index, we found a statistically significant positive association with CRA for all exposures. In addition, we observed a significant dose-response effect in the case of PhIP, MeIQx and mutagenicity index. Only few cohort studies examined these associations and, besides PhIP, the results were weaker than in case-control studies. CRA is a precursor of CRC and its evolution to carcinoma occurs through the chromosomal or the microsatellite instability pathway. Genes affected by mutations can lead to most cancers [41], including CRC. The mutagenicity of HCAs and BaP has been demonstrated in animal studies [42]. One of the potential mechanisms that could explain this is the formation of DNA adducts [43(3)], which increases with the intake of dietary HCAs and BaP [44(4)]. Despite the knowledge of these mechanisms, the association between HCA and BaP intake and risk of CRC is less consistent than the association with CRA (see [45]). Also, although there is limited and inconsistent evidence, epidemiological studies have also reported an association between HCAs and breast [46, 47, 48], bladder [49] and prostate cancer [50, 51]. In fact, in order to

damage DNA, these carcinogenic compounds need to be bioactivated by cytochrome P450 1A2 and then by N-acetyltransferase-2. It has been observed that the population is not equally affected by the activity of these enzymes [37], and several studies [32, 33, 35-39] have investigated the role of genetics, HCAs and CRA risk. For instance, Voutsinas et al. observed an increased risk of CRA when the intake of HCAs was combined with a rapid NAT2 phenotype [37]. However, the association between NAT2 acetylation genotype and CRA was not supported by the investigation of Budhathoki et al. [32]. Additionally, Barbir et al. [38] found that HCA intake was positively associated with CRA risk independently of the phenotypes involved in the metabolism of HCA.

It is well known that diet plays an important role in the process of colorectal carcinogenesis because the colon is exposed to several carcinogens, such as HCAs or BaP, resulting in a malignant transformation of the colonocytes [52]. Besides carcinogenic compounds found in meat, there are some other foods with anticarcinogenic properties that may be protective. For instance, Platt et al. evaluated the role of fruits and vegetables against the genotoxicity of HCAs, reporting positive effects [53]. Furthermore, Rohrmann et al. examined the intake of flavonoids, which are mainly found in fruits and vegetables, and observed a positive association of PhIP intake with adenoma risk in participants with a low flavonol intake [23]. In addition, Puangsombat et al. investigated the inhibitory activity of Asian spices and their results suggest that the addition of these spices can be relevant to decrease the levels of HCAs in beef [54]. Another factor that can influence the carcinogenicity of HCAs is the gut microbiota. Recently, experimental studies have shown how microbes can reduce the toxicity of HCAs in the gut [55].

Due to the low number of data available, we could only stratify the analysis by sex and adenoma site, without the possibility to analyze data from the different countries. The results of the sub-analysis were, with two exceptions, not statistically significant. However, it should be taken into account that the number of studies for site and sex were limited.

Strengths and limitations

Previously, a meta-analysis by Chiavarini et al. [56] examined the association between HCA intake and risk of CRA and CRC. However, they did not fully exclude overlapping publications (for example, Rohrmann et al. [23] and Barbir et al. [38] were both included although they analysed largely overlapping data; for details see Supplementary Table 4). Nevertheless, our results and those by Chiavarini are very similar although we included fewer studies.

There are some challenges to evaluate exposures such as HCAs or BaP in epidemiological studies. First, it is well known that dietary questionnaires in general are a source of information bias. Second, the intake of HCAs is difficult to assess since their formation in meat changes according to the type of meat, cooking method, duration and temperature. Most studies used the Computarized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) to generate the intake estimates of HCAs. Biomarkers reflect exposure in the human body, which are considered more accurate measures than self-reported dietary questionnaires. Budhathoki et al. compared the intake of HCAs estimated from an FFQ against HCA levels measured in human hair [31]. In their validation study, Spearman rank correlation coefficients between HCA from the FFQ and in hair ranged between 0.32 and 0.55 [57].

We did not generally observe large heterogeneity between the studies included in our analysis besides our sub-analysis of mutagenicity index and rectal adenomas. In addition, in most cases, we did not observe indications for publication bias. However, we plotted funnel plots even in cases with less than ten studies and, thus, their power may be too low.

Only three of the studies were cohort studies; most of the studies are of case-control design, which are prone to recall bias.

Some studies [22, 27] found differences by adenoma size, which we could not examine because the number of studies was limited. For instance, Rohrmann et al. observed that PhIP intake was associated with a higher risk of small adenomas, but not large one [22]. On the

contrary, Gunter et al. reported a positive association of BaP intake and risk of large (>1 cm), but not small adenomas [27].

Last, but not least, it is currently unclear if the association between HCA and BaP intake that has been observed in several studies is a causal association. Although the carcinogenicity of HCA and PAH has been proven in animal studies, it is disputable whether the intake in humans is sufficient to cause cancer. Rohrmann et al. have shown that the positive association between PhIP intake and CRA risk remained statistically significant, which was also true after mutually adjusting for other HCA [23]. On the other hand, Le et al. observed a positive association between PhIP intake from red meat and risk of proximal colon cancer but not PhIP from white meat [45]. This could indicate that the association between PhIP intake (or HCA intake in general) and cancer risk is not causal and that other mutagenic compounds, which arise from cooking of red meat, may be a risk factor for cancer. MDM, in contrast, integrates mutagenic activity of different compounds in cooked meats such as HCA or BaP, but also yet unidentified compounds.

Conclusion

In conclusion, this meta-analysis suggests a potential association of HCAs, BaP, mutagenicity index with the risk of CRA, which is supported by dose-response relationships for PhIP, MeIQx and meat mutagenicity. Further studies are needed to analyse whether these associations have equal effects depending on sex, size and site of adenoma, which should be prospective in design to minimize biases common in case-control studies. In addition, the question whether HCA, PAHs or other yet unidentified components in red and processed meat are responsible for the observed associations need to be addressed.

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Figure legends

Figure 1: Flow diagram of systematic literature search on meat mutagens and CRA risk. Describes the search strategy to examine the association between meat mutagens and the risk of colorectal adenomas (CRA)

Figure 2: Meta-analyses of the associations between meat mutagens and CRA risk by study type. Shows forest plots of the association between intake of PhIP (A), MeIQx (B), DiMeIQx (C), BaP (D), and mutagenicity index (E) with CRA

Figure 3: Non-linear dose-response analyses of meat mutagens and CRA risk. Shows dose-response relationships between intake of PhIP (A), MeIQx (B), DiMeIQx (C), BaP (D), and mutagenicity index (E) with CRA

Figure 4: Funnel plots of the analyses of meat mutagens and CRA risk. Shows funnel plots of the association between intake of PhIP (A), MeIQx (B), DiMeIQx (C), BaP (D), and mutagenicity index (E) with CRA to examine potential publication bias.

Table 1 Characteristics of studies of HCAs, mutagenicity and adenoma

Author, year	Country	Study design	Participants (cases) and setting	Age range (mean)	Year diet assessed	Follow up, years	HCAs and total mutagenicity analysed	Adenoma outcome	Statistical adjustments
Wu et al, 2006	HPFS (US)	Cohort	14,032 (581) Men only	40-75	1996 and 2002		PhIP MelQx DiMelQx Meat-derived mutagenicity	Distal colon adenoma	Age, family history of colorectal cancer, reason for endoscopy, negative endoscopy before 1996, physical activity, smoking status, race, aspirin use, total energy intake, calcium and folate intake
Rohrmann et al, 2009	EPIC (Europe)	Cohort	3,699 (516)	35-65	1994-1998	5.4 ± 2.4 cases 7.8 ± 1.7 controls	DiMelQx MelQx PhIP	Colorectal adenoma	Energy intake without energy from alcohol, ethanol intake, milk and milk product consumption, fiber consumption, BMI, family history of colorectal cancer, physical activity, intake of nonsteroidal anti-inflammatory drugs, smoking, pack-years of smoking, education, age and sex
Ferruci et al, 2012	PLCO (US)	Cohort	17,072 (1,008)	55-74	1993-2001	3-5 years	DiMelQx MelQx PhIP BP Mutagenic activity	Any distal adenoma, descending/ sigmoid colon adenoma, rectal adenoma	Age at baseline, study centre, gender, ethnicity, education, family history of colorectal cancer, NSAIDS use, physical activity, smoking status, alcohol intake, dietary calcium, supplemental calcium, dietary fibre, total energy intake
Sinha et al, 2001	US	Case-control	146 cases 228 controls	58 (46,70) median cases 57 (46,71) median controls	1994-1996		DiMelQx (without results) MelQx PhIP Mutagenic activity	Colorectal adenoma	Age, gender, total caloric intake, fiber intake, reason for screening, physical activity level, pack-years of cigarette smoking, use of NSAIDs, and white meat

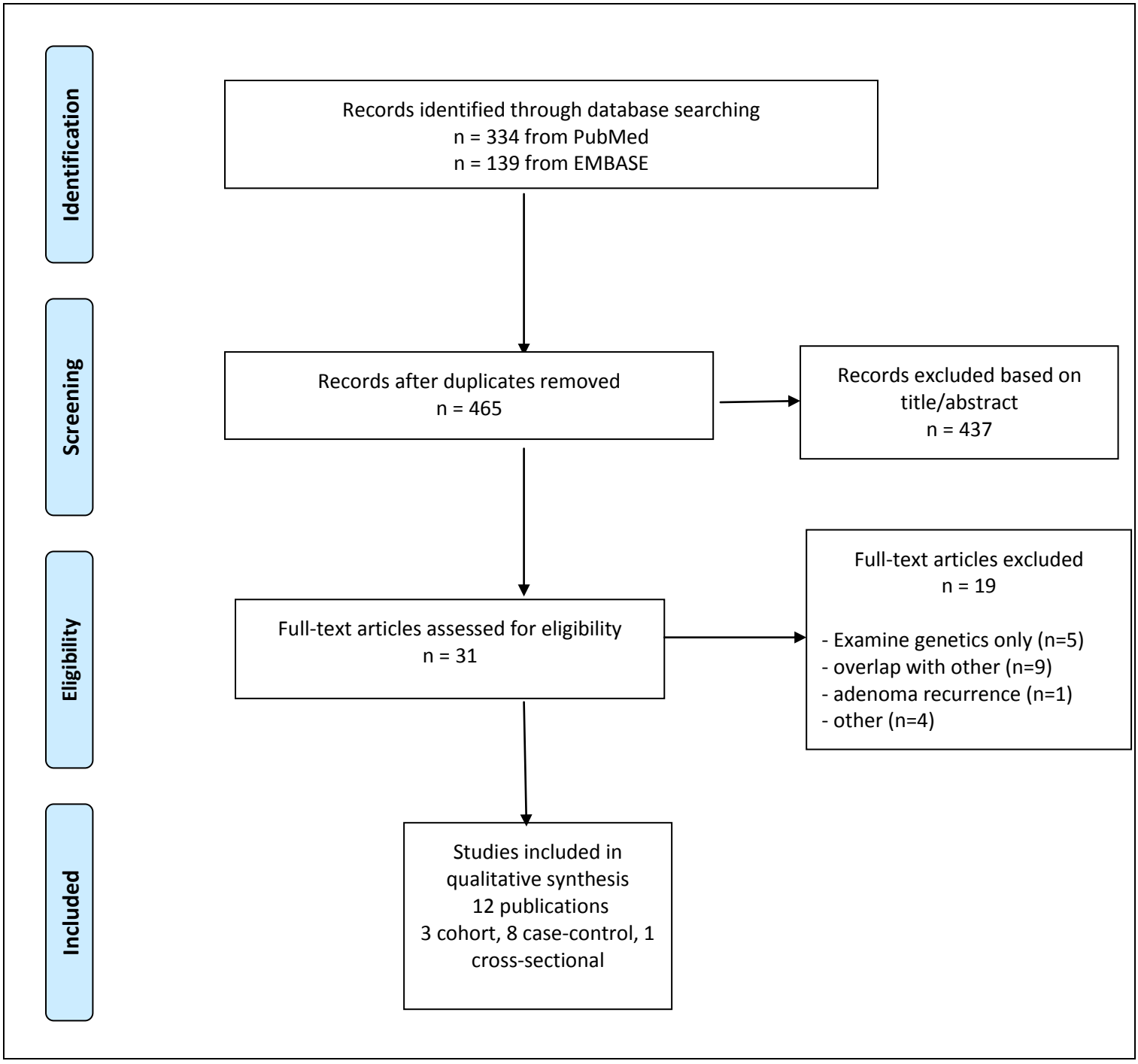
Sinha et al, 2005	US	Case-control	146 cases 228 controls	58 median cases 59 median controls	1994-1996	BP	Colorectal adenoma	Age, gender, total caloric intake, fiber intake, reason for screening, physical activity level, pack-years of cigarette smoking, use of NSAIDs
Sinha et al, 2005	PLCO (US)	Case-control	3,696 cases 34,817 controls	55-74	1993-2001	Mutagenicity, DiMelQx MelQx PhIP BP	All adenomas, stage (nonadvanced, advanced); site (colon, rectum); number of adenomas (single, multiple)	Age, gender, screening center, energy intake, ethnicity, educational attaintment, tobacco use, alcohol use, use of aspirin and ibuprofen separately, vigorous physical activity, total folate intake, calcium intake and dietary fiber intake
Gunter et al, 2005	California	Case-control	261 cases 304 controls	50-74	1991-1993 sigmoidoscopy 1995-1998 diet cooking module	BP DiMelQx MelQx PhIP	Total adenomas Large (>1 cm) adenomas	Age, gender, energy, center, fruit and vegetable intake, smoking status and BMI
Ferruci et al, 2009	CONCeRN study (US)	Case-control	158 cases 649 controls (Women only)	60.2 ± 9.0 (mean cases) 57.2 ± 7.6 (mean controls)	2000 - 2002	DIMelQx MelQx PhIP BP Mutagenic activity	Adenoma	Age, education, race, smoking status, physical activity, BMI, study center, current HRT use, family history of colorectal polyps or cancer, regular NSAID use, alcohol intake, fiber, dietary calcium, calcium from supplements, total caloric intake

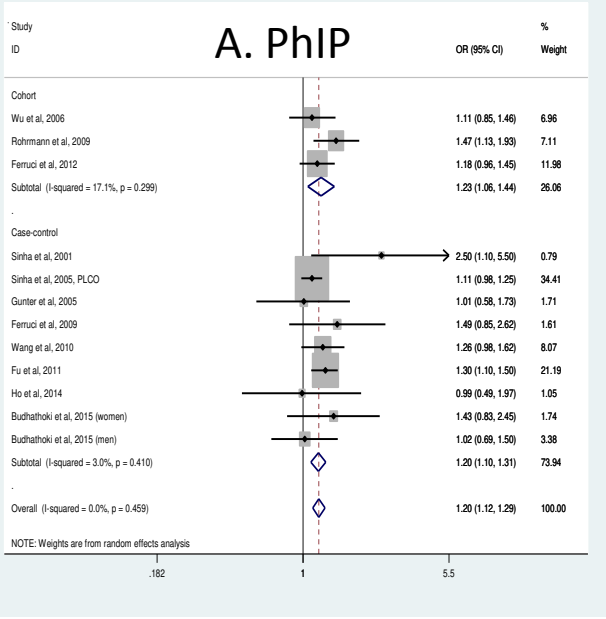
Wang et al, 2010	PLCO (US) and Kaiser Permanente Hawaii's Gastroenterology Screening Clinic and Gastroenterology Department Hawaii	Case-control	914 cases 1185 controls	61 (55,68) mean cases 62 (56,68) mean controls	1996-2000 1995-2007 2002-2007	PhIP MelQx DiMelQx Total HAAs	Colorectal adenoma	Age, sex, ethnicity, daily energy intake, lifetime hours of recreational physical activity and additionally for recruitment site and examination procedure, BMI, pack-years of smoking, alcohol intake, folate intake in the adenoma study and BMI 5 years before diagnosis, ever use of aspirin, years of schooling, daily intake of calcium
Fu et al, 2011	TCPS (US)	Case-control	1,881 cases 3,764 controls	40-75	2003-2010	DiMelQx MelQx PhIP BP Mutageneity index	Adenomas, HPP	Age, sex, race, study sites, educational attainment, indications for colonoscopy, smoking, alcohol consumption, BMI, physical activity, regular NSAIDs use, total energy intake, and recruitment before or after colonoscopy
Ho et al, 2014	Canada	Case-control	336 participants	40-65	2009-2012	DiMelQx MelQx PhIP Meat mutagenicity	Colorectal adenoma	Sex, smoking status, fruit and vegetable intake, dietary fiber intake and biomarker levels of albumin and folate
Budhathoki et al, 2015	Japan	Case-control	738 cases (men n= 498) (women n= 240) 697 controls (men n=453) (women n=244)	50-79 (men) 40-79 (women)	2004-2005	PhIP MelQx MelQ Total HCA	Colorectal adenoma	Age, screening period, smoking, alcohol consumption, body mass index, physical activity, family history of colorectal cancer, and NSAID use. Further adjusted in females: age at menarche, menopausal status, and current use of hormones

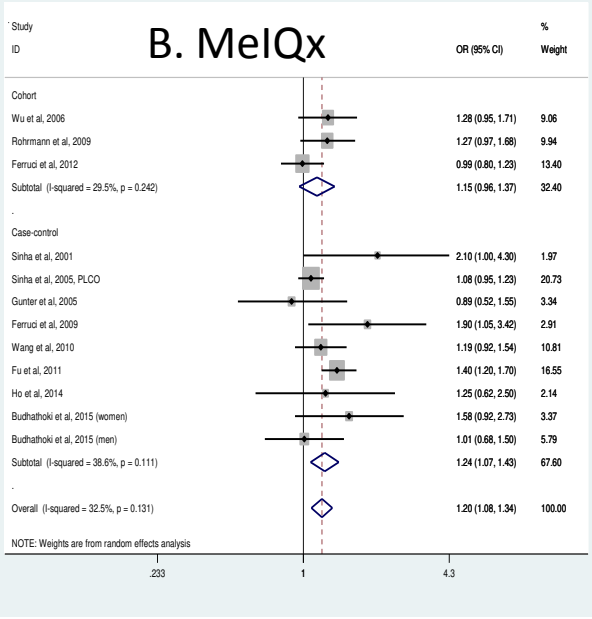
HPFS, Health Professionals Follow-up Study; EPIC European Prospective Investigation into Cancer and Nutrition; PLCO, Prostate, Lung, Colorectal, Ovarian Screening Trial; CONCeRN, Colorectal Neoplasia screening with Colonoscopy in asymptomatic women at Regional Navy/army medical centers; TCPS, Tennessee Colorectal Polyp Study; BMI, Body mass index; NSAIDs non-steroidal anti-inflammatory drugs; HPP, hyperplastic polyp

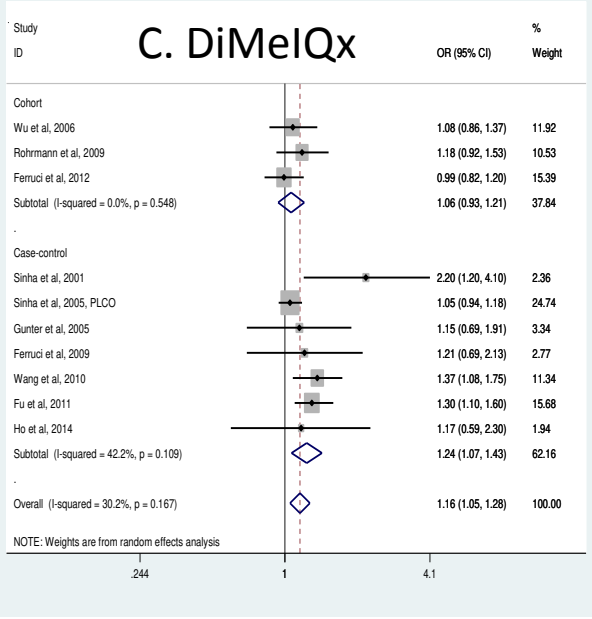
Table 2. Associations between meat mutagens and CRA by sex and site

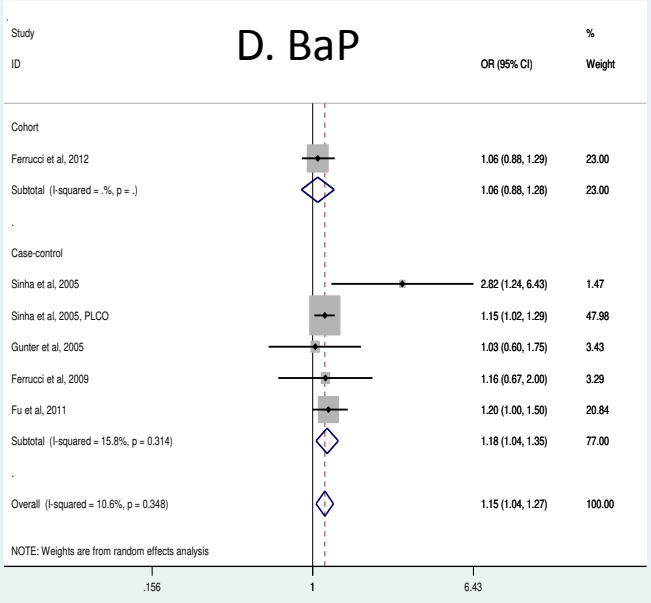
Mutagen	Number of studies	Results [OR (95% CI)]	Test of heterogeneity *p*
PhIP			
male	3	1.11 (0.89, 1.38)	0.453
female	3	1.18 (0.71, 1.96)	0.157
colon	4	1.18 (1.04, 1.33)	0.317
rectum	3	1.23 (0.86, 1.76)	0.086
MelQx			
male	3	1.20 (0.95, 1.51)	0.510
female	3	1.58 (1.09, 2.30)	0.498
colon	3	1.14 (0.99, 1.31)	0.293
rectum	2	0.90 (0.65, 1.26)	0.174
DiMelQx			
male	2	1.09 (0.87, 1.36)	0.827
female	2	1.09 (0.67, 1.77)	0.731
colon	3	1.04 (0.91, 1.19)	0.229
rectum	2	0.99 (0.74, 1.34)	0.177
B(a)P			
male			
female			
colon	2	1.06 (0.83, 1.35)	0.062
rectum	2	1.27 (0.94, 1.72)	0.168
Mutagenicity index			
male	2	1.46 (0.87, 2.47)	0.241
female	2	1.13 (0.43, 2.92)	0.096
colon	3	1.12 (0.97, 1.29)	0.261
rectum	2	1.18 (0.71, 1.96)	0.042

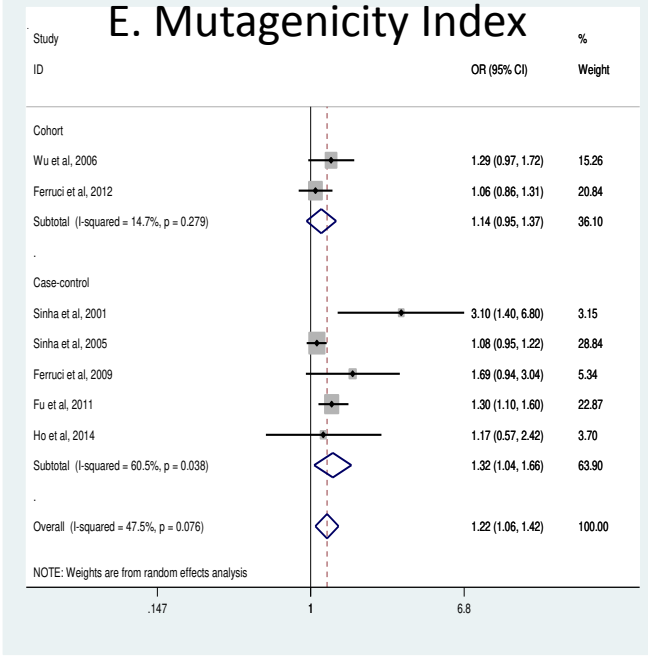

Identification
Screening
Eligibility
Included
Records identified through database searching
n = 334 from PubMed
n = 139 from EMBASE
Records after duplicates removed
n = 465
Records excluded based on title/abstract
n = 437
Full-text articles assessed for eligibility
n = 31
Full-text articles excluded
n = 19
- Examine genetics only (n=5)
- overlap with other (n=9)
- adenoma recurrence (n=1)
- other (n=4)
Studies included in qualitative synthesis
12 publications
3 cohort, 8 case-control, 1 cross-sectional

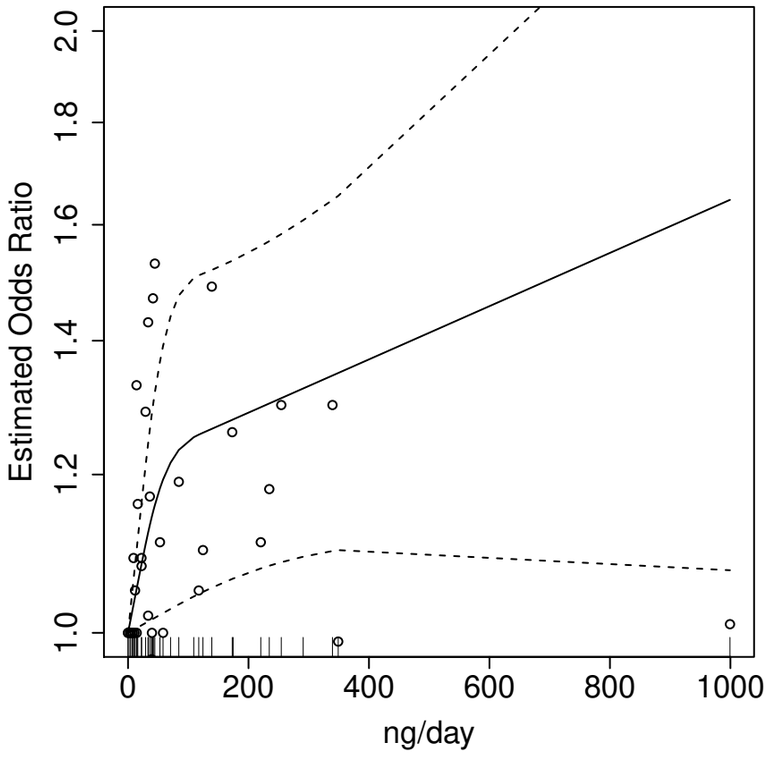

A. PhIP
Study
ID
OR (95% CI)
%
Weight
Cohort
Wu et al, 2006 1.11 (0.85, 1.46) 6.96
Rohrmann et al, 2009 1.47 (1.13, 1.93) 7.11
Ferruci et al, 2012 1.18 (0.96, 1.45) 11.98
Subtotal (I-squared = 17.1%, p = 0.299) 1.23 (1.06, 1.44) 26.06
Case-control
Sinha et al, 2001 2.50 (1.10, 5.50) 0.79
Sinha et al, 2005, PLCO 1.11 (0.98, 1.25) 34.41
Gunter et al, 2005 1.01 (0.58, 1.73) 1.71
Ferruci et al, 2009 1.49 (0.85, 2.62) 1.61
Wang et al, 2010 1.26 (0.98, 1.62) 8.07
Fu et al, 2011 1.30 (1.10, 1.50) 21.19
Ho et al, 2014 0.99 (0.49, 1.97) 1.05
Budhathoki et al, 2015 (women) 1.43 (0.83, 2.45) 1.74
Budhathoki et al, 2015 (men) 1.02 (0.69, 1.50) 3.38
Subtotal (I-squared = 3.0%, p = 0.410) 1.20 (1.10, 1.31) 73.94
Overall (I-squared = 0.0%, p = 0.459) 1.20 (1.12, 1.29) 100.00
NOTE: Weights are from random effects analysis
.182
1
5.5

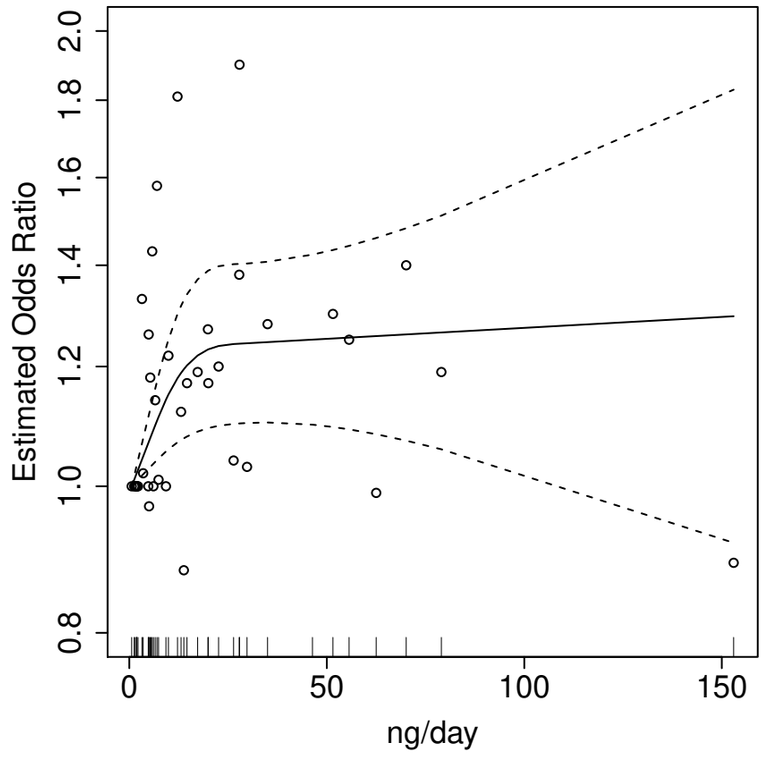

B. MeIQx
Study
ID
OR (95% CI)
%
Weight
Cohort
Wu et al, 2006 1.28 (0.95, 1.71) 9.06
Rohrmann et al, 2009 1.27 (0.97, 1.68) 9.94
Ferruci et al, 2012 0.99 (0.80, 1.23) 13.40
Subtotal (I-squared = 29.5%, p = 0.242) 1.15 (0.96, 1.37) 32.40
Case-control
Sinha et al, 2001 2.10 (1.00, 4.30) 1.97
Sinha et al, 2005, PLCO 1.08 (0.95, 1.23) 20.73
Gunter et al, 2005 0.89 (0.52, 1.55) 3.34
Ferruci et al, 2009 1.90 (1.05, 3.42) 2.91
Wang et al, 2010 1.19 (0.92, 1.54) 10.81
Fu et al, 2011 1.40 (1.20, 1.70) 16.55
Ho et al, 2014 1.25 (0.62, 2.50) 2.14
Budhathoki et al, 2015 (women) 1.58 (0.92, 2.73) 3.37
Budhathoki et al, 2015 (men) 1.01 (0.68, 1.50) 5.79
Subtotal (I-squared = 38.6%, p = 0.111) 1.24 (1.07, 1.43) 67.60
Overall (I-squared = 32.5%, p = 0.131) 1.20 (1.08, 1.34) 100.00
NOTE: Weights are from random effects analysis
.233
1
4.3

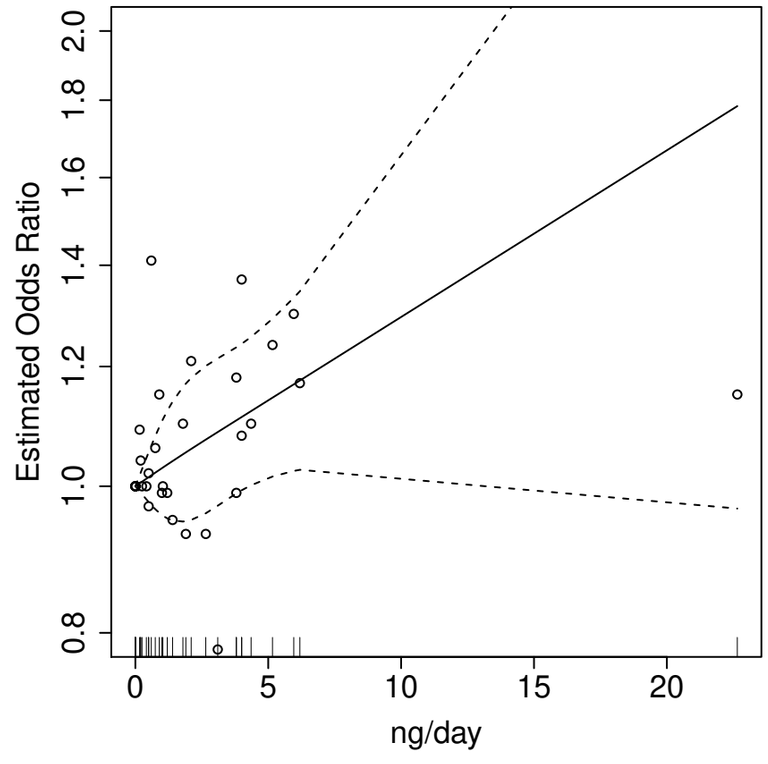

C. DiMeIQx
Study
ID
OR (95% CI)
%
Weight
Cohort
Wu et al, 2006 1.08 (0.86, 1.37) 11.92
Rohrmann et al, 2009 1.18 (0.92, 1.53) 10.53
Ferruci et al, 2012 0.99 (0.82, 1.20) 15.39
Subtotal (I-squared = 0.0%, p = 0.548) 1.06 (0.93, 1.21) 37.84
Case-control
Sinha et al, 2001 2.20 (1.20, 4.10) 2.36
Sinha et al, 2005, PLCO 1.05 (0.94, 1.18) 24.74
Gunter et al, 2005 1.15 (0.69, 1.91) 3.34
Ferruci et al, 2009 1.21 (0.69, 2.13) 2.77
Wang et al, 2010 1.37 (1.08, 1.75) 11.34
Fu et al, 2011 1.30 (1.10, 1.60) 15.68
Ho et al, 2014 1.17 (0.59, 2.30) 1.94
Subtotal (I-squared = 42.2%, p = 0.109) 1.24 (1.07, 1.43) 62.16
Overall (I-squared = 30.2%, p = 0.167) 1.16 (1.05, 1.28) 100.00
NOTE: Weights are from random effects analysis
.244
1
4.1

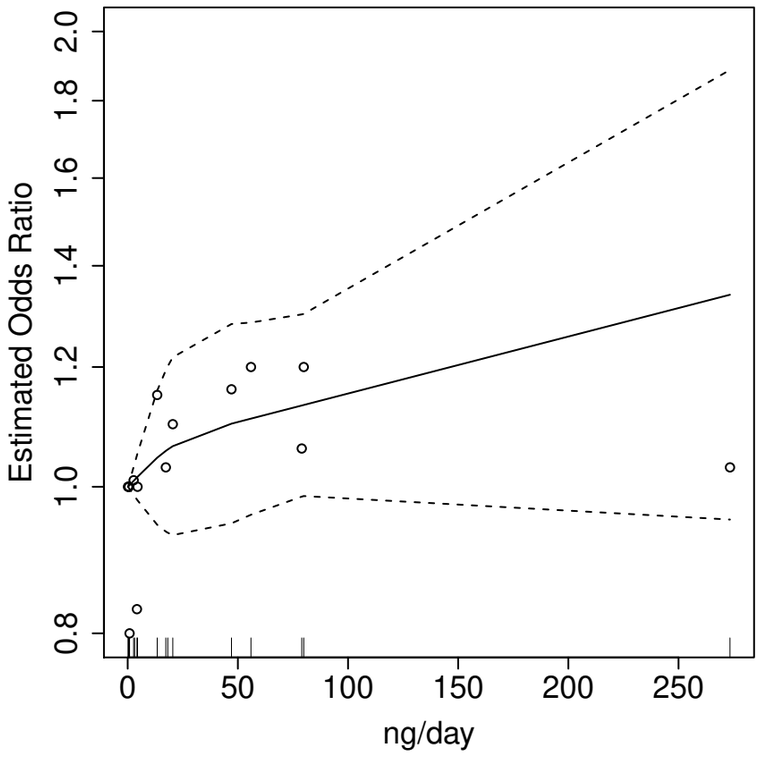

D. BaP
Study
ID
OR (95% CI)
%
Weight
Cohort
Ferrucci et al, 2012 1.06 (0.88, 1.29) 23.00
Subtotal (I-squared = .%, p = .) 1.06 (0.88, 1.28) 23.00
Case-control
Sinha et al, 2005 2.82 (1.24, 6.43) 1.47
Sinha et al, 2005, PLCO 1.15 (1.02, 1.29) 47.98
Gunter et al, 2005 1.03 (0.60, 1.75) 3.43
Ferrucci et al, 2009 1.16 (0.67, 2.00) 3.29
Fu et al, 2011 1.20 (1.00, 1.50) 20.84
Subtotal (I-squared = 15.8%, p = 0.314) 1.18 (1.04, 1.35) 77.00
Overall (I-squared = 10.6%, p = 0.348) 1.15 (1.04, 1.27) 100.00
NOTE: Weights are from random effects analysis
.156
1
6.43

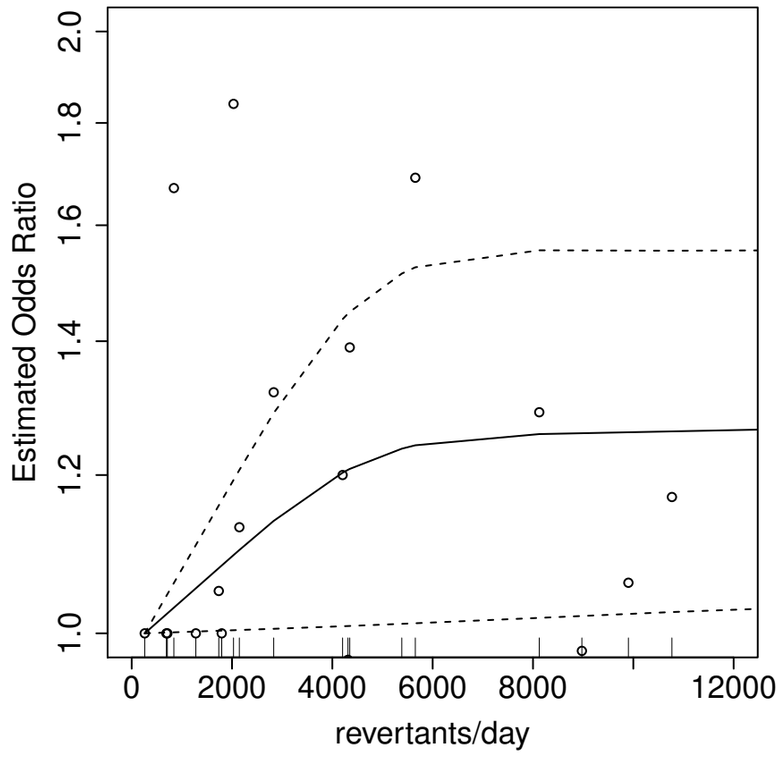

E. Mutagenicity Index
Study
ID
OR (95% CI)
%
Weight
Cohort
Wu et al, 2006 1.29 (0.97, 1.72) 15.26
Ferruci et al, 2012 1.06 (0.86, 1.31) 20.84
Subtotal (I-squared = 14.7%, p = 0.279) 1.14 (0.95, 1.37) 36.10
Case-control
Sinha et al, 2001 3.10 (1.40, 6.80) 3.15
Sinha et al, 2005 1.08 (0.95, 1.22) 28.84
Ferruci et al, 2009 1.69 (0.94, 3.04) 5.34
Fu et al, 2011 1.30 (1.10, 1.60) 22.87
Ho et al, 2014 1.17 (0.57, 2.42) 3.70
Subtotal (I-squared = 60.5%, p = 0.038) 1.32 (1.04, 1.66) 63.90
Overall (I-squared = 47.5%, p = 0.076) 1.22 (1.06, 1.42) 100.00
NOTE: Weights are from random effects analysis
.147
1
6.8

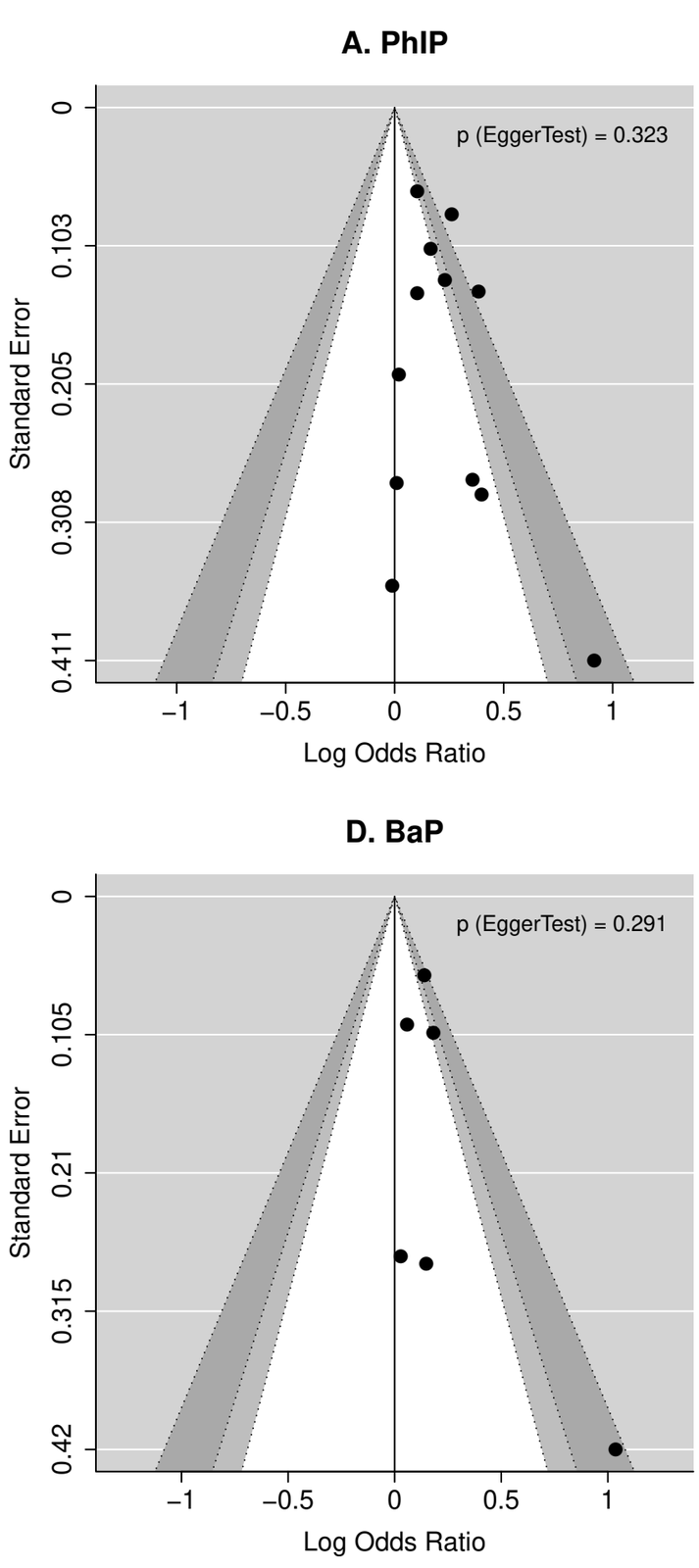

A. PhIP
Estimated Odds Ratio
1.0
1.2
1.4
1.6
1.8
2.0
0
200
400
600
800
1000
ng/day


B. MeIQx
Estimated Odds Ratio
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0
50
100
150
ng/day


C. DiMeIQx
Estimated Odds Ratio
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0
5
10
15
20
ng/day


D. BaP
Estimated Odds Ratio
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0
50
100
150
200
250
ng/day


E. Mutagenicity Index
Estimated Odds Ratio
1.0
1.2
1.4
1.6
1.8
2.0
0
2000
4000
6000
8000
12000
revertants/day


A. PhIP
p (EggerTest) = 0.323
Standard Error
0
0.103
0.205
0.308
0.411
−1
−0.5
0
0.5
1
Log Odds Ratio
B. MeIQx
p (EggerTest) = 0.200
Standard Error
0
0.093
0.186
0.279
0.372
Log Odds Ratio
C. DiMeIQx
p (EggerTest) = 0.106
Standard Error
0
0.087
0.174
0.26
0.347
Log Odds Ratio
D. BaP
p (EggerTest) = 0.291
Standard Error
0
0.105
0.21
0.315
0.42
Log Odds Ratio
E. Mutagenicity Index
p (EggerTest) = 0.014
Standard Error
0
0.101
0.202
0.302
0.403
Log Odds Ratio
0.01 < p < 0.05
0.05 < p < 0.10
p > 0.10