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Original Article

Light Alcohol Drinking and Risk of Cancer: A Meta-analysis of Cohort Studies

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Running title: Light alcohol drinking and cancer

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Abstract

Purpose

To determine whether light alcohol drinking increases the risk of cancer by using a meta-analysis of cohort studies because the newly revised 2015 European Code against Cancer 4th edition on alcohol and cancer was based on critical flaws in the interpretation and citation of the previous meta-analyses.

Materials and Methods

PubMed and EMBASE were searched in April, 2016. Two authors independently reviewed and selected cohort studies on the association between very light (≤0.5 drink/day), light (≤1 drink/day), or moderate drinking (1-2 drinks/day) and the risk of cancer incidence and mortality. A pooled relative risk with its 95% confidence interval was calculated by a random-effects meta-analysis. Main outcome measures were cancer incidence and mortality.

Results

A total of 60 cohort studies from 135 articles were included in the final analysis. Very light drinking or light drinking was not associated with the incidence of most cancers except for female breast cancer in women and male colorectal cancer. Conversely, light drinking was associated with a decreased incidence of both female and male lung cancer significantly and both female and male thyroid cancer marginally significantly. Moderate drinking significantly increased the incidence of male colorectal cancer and female breast cancer, whereas it decreased the incidence of both female and male hematologic malignancy.

Conclusion

We found that very light or light alcohol drinking was not associated with the risk of most of the common cancers except for the mild increase in the incidence of breast cancer in women and colorectal cancer in men.

Key words Alcohols, Neoplasms, Cohort studies, Meta-analysis

Introduction

Alcohol is classified as Group 1 carcinogen by the International Agency for Research on Cancer (IARC), which category is used when there is sufficient evidence of carcinogenicity in humans [1]. However, it was usually excessive alcohol drinking that was condemned for causing cancer, and light or moderate alcohol consumption has been conceived as acceptable or even encouraged because of its known benefits in preventing cardiovascular diseases. Previously in 2003, the third edition of European Code against Cancer (ECAC) recommended that “If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman." [2,3]. In 2015, the IARC published an article involving the newly revised ECAC 4th edition on alcohol drinking and cancer, which recommends “If you drink alcohol of any type, limit your drinking. Not drinking is better for cancer prevention." [4].

Since the publication of the ECAC 4th edition, however, Prof. Myung, the corresponding author of this paper claimed in the letter to the editor that the new ECAC on alcohol should be corrected because there were considerable critical flaws in the interpretation and citation of the existing observational epidemiological studies and meta-analyses on the association between light alcohol drinking (≤1 drink/day or 12.5g/day) and the risk of cancer [5]. He criticized that the authors of the ECAC 4th edition did not consider the difference in findings between case-control studies and cohort studies: there was no significant association between light alcohol drinking and the risk of oropharyngeal cancer and colon cancer in the meta-analysis of cohort studies, whereas light alcohol drinking increased the risk of oropharyngeal cancer and colorectal cancer in the meta-analysis of case-control studies. Moreover, they incorrectly used the data for ‘moderate drinking (2-3 drinks/day)’ or just ‘drinking’ instead of ‘light drinking’ in some analyses. Prof. Myung also published another letter to the editor [6]

criticizing erroneous conclusions about the association between light alcohol drinking and the risk of cancer in Bagnardi *et al*'s meta-analysis [7], which concluded that light alcohol drinking increased the risk of cancer of oropharynx, oesophagus, and female breast and consequently contributed to the newly revised ECAC. Similarly, he pointed out that in Bagnardi *et al*'s meta-analysis, except for female breast cancer, the meta-analysis of cohort studies did not show any significant association between light alcohol drinking and the risk of cancer of oropharynx, larynx, oesophagus, colorectum, and liver, whereas the meta-analysis of case-control studies showed a significant positive association between light drinking and cancer of oropharynx and oesophagus [6]. In summary, regarding the association between light alcohol drinking and the risk of cancer, the previous meta-analysis and the new ECAC 4th edition led to erroneous conclusions and incorrect recommendations due to the wrong interpretation and citations of the existing observational epidemiological studies.

Thus, we performed a comprehensive meta-analysis of cohort studies on this topic in order to investigate whether or not very light or light alcohol drinking as well as moderate alcohol drinking increased the risk of cancer.

Methods

Search strategy

We searched PubMed and EMBASE in March 31, 2016 using keywords "alcohol consumption," "alcohol intake," "cancer," and "cohort study." We also reviewed the bibliographies of relevant articles to find additional studies.

Selection criteria

We included prospective or retrospective cohort studies reporting a multivariate adjusted

relative risk (RR) with its 95% confidence interval (CI) for the association between light alcohol drinking (≤1 drink/day) and/or moderate alcohol drinking (1-2 drinks/day) and the risk of cancer. The current analysis involved general healthy populations. Thus, we excluded studies involving patients with underlying cancer and populations at high risk for a specific cancer such as patients with liver cirrhosis or hepatitis B virus carriers at high risk for liver cancer and those with Barrett's esophagus at high risk for esophageal cancer. Also, we excluded 1) studies that adjusted for only age and/or sex in the multivariate analysis, 2) studies that used 0-2 drink/day as criteria for light alcohol drinking instead of 1-2drinks/day, and 3) studies that used 0.5 drink/day or more as a reference value.

Selection of relevant studies

Two authors (YJ Choi and JH Lee) of the current study independently selected relevant studies in the first screening process. Any disagreements were solved by discussion and in consult with a third author (SK Myung). If data were duplicated or shared in more than one article, we included the more comprehensive or more recently published article for the analysis.

Main analysis and subgroup analysis

We investigated the risk of each type of cancer in both incidence and mortality according to different levels of alcohol drinking: very light drinking (≤0.5 drink/day), light drinking (≤1 drink/day), and moderate drinking (1-2 drinks/day). In general, one drink of alcohol corresponds to one unit of alcohol (12.5g) which is contained in one glass of beer (355mL), one glass of wine, and a single shot of hard liquor. However, since a number of studies used up to 15 g/day as 1 drink/day, we accepted up to 15 g as 1 drink of alcohol. 7 drinks/week,

105 g/week, 30 drinks/month, and 15 ounce/month were considered equivalent to 1 drink/day or light drinking. Likewise, 3.5 drink/week, 52.5 g/week, 15 drinks/month, and 7.5 ounce/month were considered as 0.5 drink/day or very light drinking. Also, 15-30 g/day, 7-14 drinks/week, 105-210 g/week, 30-60 drinks/month, and 15-30 ounce/month were categorized to 1 to 2 drinks/day or moderate drinking. We chose the upper limit of the range of drinking to categorize levels of drinking: 5-15g/day of drinking was considered as light drinking; if the upper limit exceeded 15g/day, then it was categorized as moderate drinking. We performed the subgroup meta-analysis by type of cancer and gender.

Assessment of methodological quality of included studies

The methodological quality of the included studies was based on the Newcastle-Ottawa Scale (NOS) [8] (Supplementary S3 and S4). This scale has a star system (range, 0-9 stars) for the assessment. Standard criteria for high quality have not been established. Regarding outcome assessment, a star was given for a follow-up period of ≥5 years and a follow-up rate of ≥90%.

Statistical analysis

We used the adjusted RR with its 95% CI in order to compute a pooled RR with its 95% CI. Heterogeneity was assessed by Higgins I^2, which is the percentage of total variation across the studies as follows:

$$I^2 = 100\% \times (Q-df)/Q$$

where df refers to degrees of freedom, and Q refers to Cochran's heterogeneity statistics [9]. An I^2 value lies between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). In general, an I^2 greater than 50% is considered to have substantial heterogeneity. We used a

random-effects model meta-analysis based on the DerSimonian and Laird method because most cohort studies were conducted in the different populations [10, 11]. A STATA version 13.1 software (StataCorp LP, College Station, TX, USA) was used for statistical analysis.

Results

Selection of relevant studies

Figure 1 shows a flow diagram of how we selected relevant studies. We identified a total of 4721 articles consisting of 3264 articles from PubMed and 1457 articles from EMBASE. We excluded 787 duplicate articles and 3503 articles that did not meet the selection criteria after reviewing 3934 articles based on titles and abstracts. After reviewing the full text of the remaining 431 articles along with additional 65 articles newly located from relevant bibliographies, 361 articles were excluded because of studies sharing an identical population (n = 27), insufficient data (n = 94), studies with no available data for outcome measures (n = 53), review or meta-analysis (n = 18), case-studies or other study designs (n = 23), and no relevant studies (n = 146). From a total of 135 articles, 60 cohort studies were included in the final analysis (References of 135 articles are presented in eReferences available on-line).

Characteristics of studies included in the final analysis

All the 60 cohort studies included in the final analysis involved a total of 9,428,076 participants (5,478,133 women and 3,949,943 men). As an outcome measure, all studies reported cancer incidence, and 14 studies reported cancer mortality. The number of studies according to cancer organ site were as follows (incidence, mortality): oral cavity and oropharynx (n = 5, n = 2), oesophagus (squamous cell carcinoma) (n = 2), oesophagus (adenocarcinoma) and cardia (n = 3), stomach (n = 9, n = 2), colorectum (n = 16, n = 5), liver (n =

2, n = 2), pancreas (n = 5, n = 4), lung cancer (n = 10, n = 5), female breast (n = 27, n = 7), endometrium (n = 9), ovary (n = 5), prostate (n = 14, n = 4), kidney (n = 7, n = 1), bladder (n = 4), hematologic malignancies (n = 8, n = 2), and skin (malignant melanoma) (n = 3) (Table 1). Studies were conducted in North America (n = 30, n = 10), Europe (n = 21), and Asia (n = 9, n = 4) (Table 1). General characteristics of the studies included in the final analysis by cancer incidence and mortality are presented in supplementary S1 and S2 Tables available on-line.

Methodological quality of studies

Supplementary S3 and S4 Tables shows the methodological quality of the studies included in the analysis. The range of scores was 5 to 9 for cancer incidence and 6-8 for cancer mortality. The mean score was 6.8 for cancer incidence studies (n = 121) and 6.9 for cancer mortality studies (n = 14).

Very light alcohol drinking and the risk of cancer

Incidence

Table 2 shows the associations between cancer incidence and very light, light, and moderate alcohol drinking. Overall very light drinking (≤0.5 drink/day) was not associated with the incidence of most cancers. However, very light drinking was significantly associated with a decreased incidence of both female and male lung cancer (RR, 0.89; 95% CI, 0.84-0.93; I^2 = 3%; n = 3), female lung cancer (RR, 0.82; 95% CI, 0.70-0.95; I^2 = 12.9%; n = 2), whereas it increased the incidence of female breast cancer (RR, 1.04; 95% CI, 1.01-1.07; I^2 = 3.7%; n = 20). There was no significant association between very light drinking and the incidence of head and neck cancer, oesophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, endometrial cancer, ovary cancer, prostate cancer, kidney cancer, bladder cancer,

thyroid cancer, and hematologic malignancy.

Mortality

Table 3 shows the associations between cancer mortality and very light, light, and moderate alcohol drinking. Very light drinking reduced the mortality of both female and male lung cancer (RR, 0.81; 95% CI, 0.69-0.94; I^2 = 0.0%; n = 2), female lung cancer (RR, 0.70; 95% CI, 0.56-0.89; n = 1) and female breast cancer (RR, 0.79; 95% CI, 0.64-0.97; I^2 = 0.0%; n = 2). There was no significant association between very light drinking and the mortality of colorectal cancer, gall bladder cancer, prostate cancer, and hematologic malignancy.

Light alcohol drinking and the risk of cancer

Incidence

As shown in Table 2, similar to the findings of very light alcohol drinking, overall light drinking (≤1 drink/day) was not associated with the incidence of most cancers. However, light drinking was significantly associated with a decreased incidence of both female and male lung cancer (RR, 0.91; 95% CI, 0.90-0.94; I^2 = 0.0%; n = 10), male lung cancer (RR, 0.91; 95% CI, 0.90-0.95; I^2 = 0.0%; n = 3), and female lung cancer (RR, 0.90; 95% CI, 0.87-0.94; I^2 = 0.0%; n = 4), whereas it increased the incidence of female breast cancer (RR, 1.09; 95% CI, 1.06-1.12; I^2 = 32.8%; n = 25; Figure 2), both female and male colorectal cancer (RR, 1.04; 95% CI, 1.04-1.06; I^2 = 0.0; n = 14), male colorectal cancer (RR, 1.06; 95% CI, 1.01-1.11; I^2 = 0.0%; n = 6; Figure 3), and both female and male malignant melanoma (RR, 1.44; 95% CI, 1.18-1.76; I^2 = 0.0%; n = 3). In the subgroup meta-analysis by type of male colorectal cancer, light drinking was not associated with the incidence of either colon cancer (RR, 1.02; 95% CI, 0.87-1.21; I^2 = 0.0%; n = 5) or rectal cancer (RR, 1.07; 95% CI, 0.69-1.64; I^2 = 0.0%; n = 3).

Also, light drinking was marginally associated with a decreased incidence of both female and male thyroid cancer (RR, 0.89; 95% CI, 0.79-1.00; I^2 = 0.0%; n = 6). There was no significant association between light drinking and the incidence of oropharyngeal cancer, head and neck cancer, oesophageal cancer, stomach cancer, liver cancer, pancreatic cancer, endometrial cancer, ovary cancer, prostate cancer, kidney cancer, bladder cancer, and hematologic malignancy.

Mortality

As shown in Table 3, light drinking reduced the mortality of female stomach cancer (RR, 0.65; 95% CI, 0.44-0.98; n = 1) and male lung cancer (RR, 0.79; 95% CI, 0.70-0.87; I^2 = 0.0%; n = 5). There was no significant association between light drinking and the mortality of oropharyngeal cancer, oesophageal cancer, larynx cancer, colorectal cancer, liver cancer, female gall bladder cancer, pancreatic cancer, breast cancer, cervical cancer, prostate cancer, and hematologic malignancy.

Moderate alcohol drinking and the risk of cancer

Incidence

As shown in Table 2, moderate drinking (1-2 drinks/day) increased the incidence of both female and male oropharyngeal cancer (RR, 1.12; 95% CI, 1.01-1.24; I^2 = 19.5%; n = 3), female oropharyngeal cancer (RR, 1.18; 95% CI, 1.05-1.33; I^2 = 0.0%; n = 3), female larynx cancer (RR, 1.74; 95% CI, 1.25-2.41; n = 1), both female and male squamous cell oesophageal cancer (RR, 1.98; 95% CI, 1.25-3.14; I^2 = 0.0%; n = 2), both female and male colorectal cancer (RR, 1.10; 95% CI, 1.03-1.19; I^2 = 10.6%; n = 6), male colorectal cancer (RR, 1.19; 95% CI, 1.06-1.35; I^2 = 10.6%; n = 6), female breast cancer (RR, 1.13; 95% CI,

1.11-1.15; I^2 = 0%; n = 15), and both female and male malignant melanoma (RR, 1.77; 95% CI, 1.35-2.33; I^2 = 0.0%; n = 2). Also, it was marginally significantly associated with an increased incidence of female and male liver cancer (RR, 1.26; 95% CI, 1.00-1.58; I^2 = 0.0%; n = 2). On the contrary, moderate drinking reduced the incidence of both female and male kidney cancer (RR, 0.93; 95% CI, 0.86-1.00; I^2 = 0.0%; n = 3), female kidney cancer (RR, 0.93; 95% CI, 0.80-0.94; n = 1), both female and male thyroid cancer (RR, 0.68; 95% CI, 0.56-0.84; I^2 = 0.0%; n = 3), female thyroid cancer (RR, 0.67; 95% CI, 0.53-0.85; I^2 = 0.0%; n = 2), and both female and male hematologic malignancy (RR, 0.89; 95% CI, 0.81-0.99; I^2 = 52.3%; n = 6). There was no significant association between moderate drinking and the incidence of head and neck cancer, adenomatous oesophageal cancer and cardia, stomach cancer, pancreatic cancer, lung cancer, endometrial cancer, ovary cancer, prostate cancer, and bladder cancer.

Mortality

As shown in Table 3, overall moderate drinking was not associated with the mortality of most cancers. However, it increased the mortality of female colorectal cancer (RR, 2.51; 95% CI, 1.31- 4.82; n = 1) and female breast cancer (RR, 1.04; 95% CI, 1.01- 1.07; I^2 = 0.0%; n = 2), while it reduced the mortality of male kidney cancer (RR, 0.46; 95% CI, 0.23- 0.93; n = 1).

Discussion

Principal findings

In the current large scale meta-analysis of cohort studies, we found that compared with non

or occasional alcohol drinking, very light (≤0.5 drink/day) or light (≤1 drink/day did not increase the incidence of most cancers except for female breast cancer and male colorectal cancer by up to 9% and 6%, respectively. Conversely, light drinking was associated with a decreased incidence of both female and male lung cancer significantly and both female and male thyroid cancer marginally significantly. In the meantime, moderate drinking, i.e., 1 to 2 drink/day significantly increased the incidence of two types of cancer, male colorectal cancer and female breast cancer, whereas it decreased the incidence of both female and male hematologic malignancy. Also, there is a limitation to draw definite conclusions on the associations between very light or light drinking and the risk of several types of cancer such as lung cancer, malignant melanoma, and rectal cancer in incidence along with those associations in mortality and the associations between moderate drinking and the risk of most cancers except for male colorectal cancer, female breast cancer, and hematologic malignancy in both incidence and mortality because of a paucity of the included studies.

Comparison with previous findings

Our conclusion on the association between light drinking and the risk of cancer are inconsistent with those from a previous large scale meta-analysis of observational epidemiological studies. Bagnardi *et al*'s meta-analysis of 222 articles which included case-control studies and cohort studies published before December 2010 concluded that light drinking (1 drink/day) increased the risk of cancer of oral cavity, pharynx, oesophagus, and female breast [6]. As mentioned before in the introduction section, however, they did not consider the difference in findings between case-control studies and cohort studies and drew a wrong conclusion based on the findings from combining the results of both case-control studies and cohort studies. As Prof. Myung pointed out in his letter, except for breast cancer,

the subgroup meta-analysis of cohort studies which generally provide a higher level of evidence than case-control studies did not show any significant association between light alcohol drinking and the risk of cancers of oral cavity, pharynx, and oesophagus although light drinking was significantly associated with the increased risk of these cancers in the subgroup meta-analysis of case-control studies. Therefore, Bagnardi *et al*'s meta-analysis should have concluded that overall light drinking was not associated with the risk of cancer, although it increased the risk of female breast cancer slightly.

After the publication of Bagnardi *et al*'s meta-analysis, the 2015 newly revised ECAC 4th edition changed its recommendation on drinking from 'Moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman' to 'Not drinking is better for cancer prevention' based on the similar conclusions to those from Bagnardi *et al*. The ECAC 4th edition also did not consider the difference in findings between case-control studies and cohort studies and moreover wrongly used data for moderate drinking or just drinking instead of light drinking for the meta-analysis.

Meaning and implications of the current findings for policy makers and clinicians

In our study, except for only two types of cancer, female breast cancer and male colorectal cancer, very light or light drinking was not associated with the risk of most cancers. Although the incidence of malignant melanoma was increased with light drinking, it remains inconclusive due to a small number of included studies. As for female breast cancer, its incidence was increased at even the level of very light drinking (≤0.5 drink/day), which can be interpreted that there is no safe level for alcohol drinking regarding female breast cancer. Also, light drinking (≤1 drink/day) was associated with the increased incidence of male colorectal cancer. However, except for these two types of cancer, there was no sufficient

evidence to support that very light or light drinking up to 1 drink /day increases the risk of most of cancers. On the contrary, light drinking significantly decreased the incidence of both female and male lung cancer significantly and thyroid cancer marginally significantly. Thus, our findings imply that very light or light drinking has both benefits and harms in cancer prevention according to type of cancer.

Possible mechanisms for the main findings

The possible mechanisms on the association between alcohol consumption and the risk of breast cancer include the effect of alcohol on estrogen levels and estrogen receptor (ER) in mammary epithelial cells, the carcinogenic effect of ethanol metabolites, the effect of ethanol on epigenetic regulation of gene expression in the breast [12]. As for colon cancer, potential mechanisms to be examined in human-based studies are acetaldehyde production in the colon, cell proliferation due to ethanol or acetaldehyde exposure, and alterations in DNA repair mechanisms[13]. However, it still remains unclear why even very light or light drinking levels increase the incidence of female breast cancer and male colorectal cancer unlike the remaining common cancers.

In the meantime, very light or light drinking was associated with the decreased incidence of lung cancer significantly and thyroid cancer marginally significantly. It has been suggested that the protective effect of low or moderate alcohol consumption on lung cancer is attributable to its anti-inflammatory effects through lower plasma concentration of several systemic biomarkers of inflammation compared with no consumption [14], antioxidant effects in tumor promotion and progression [15], and anti-carcinogenic effects through induction of protective enzymes such as carcinogen detoxification enzymes [16,17]. However, it remains unclear why these effects would be specific for lung cancer. Also, the possible biological

mechanisms on the inverse association between alcohol consumption and the risk of thyroid cancer are the protective effect on developing thyroid cancer by decreased levels of thyroid-stimulating hormone and the direct toxic effect on thyroid cells and consequently reduction of thyroid volume [18].

Strengths of the current meta-analysis

This is the first meta-analysis of cohort studies that comprehensively investigated the association between very light and light alcohol drinking and the risk of a variety of cancers. Our study has its originality in that for the first time, we claim that overall light alcohol drinking is not associated with the risk of most of the common cancers except for female breast cancer and male colorectal cancer. Our findings refute the newly revised ECAC 4th edition on alcohol drinking and cancer and those from Bagnardi *et al*'s meta-analysis.

Limitations

There are several limitations in our study. First, except for breast cancer, colorectal cancer, and lung cancer, due to a paucity of data on very light or light drinking for most cancers, we were unable to clearly evaluate the associations between very light or light drinking and most cancers. Thus, further studies are necessary to confirm these associations. Second, there might be possible interactions between drinking and other factors such as smoking on the development of breast cancer and colorectal cancer. Although all the included cohort studies adjusted various factors in each multivariable analysis, those factors varied across studies. For example, however, because most studies included the important factors affecting the development of breast cancer such as age, smoking, age at menopause, age at first birth, family history of breast cancer, hormone replacement therapy, and oral contraceptives, the

effect of other unknown confounding factors would be minimal. Last, the generalization of our findings is limited because a small number of cohort studies among Asian populations were included in our analysis. More cohort studies are required to investigate that our findings can be applied to Asian populations.

Our meta-analysis of cohort studies found that compared with non or occasional alcohol drinking, very light or light drinking was not associated with the risk of most cancers except for female breast cancer and male colorectal cancer with a small increase in incidence. Although the IARC re-published 'the ECAC 4th edition: Alcohol drinking and cancer' in December 2016 [19] with a few corrections of data cited on the association between light alcohol drinking and cancer risk, they still did not consider the difference in findings between case-control studies and cohort studies and stick to the previously revised recommendation. Therefore, we suggest that the revision of the current ECAC 4th edition on alcohol drinking and cancer should be seriously considered from "If you drink alcohol of any type, limit your drinking. Not drinking is better for cancer prevention" to "If you drink alcohol of any type, limit your drinking. Not drinking is better in order to prevent breast cancer in women and colorectal cancer in men."

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Fig. 1. Flow diagram of identification of relevant studies

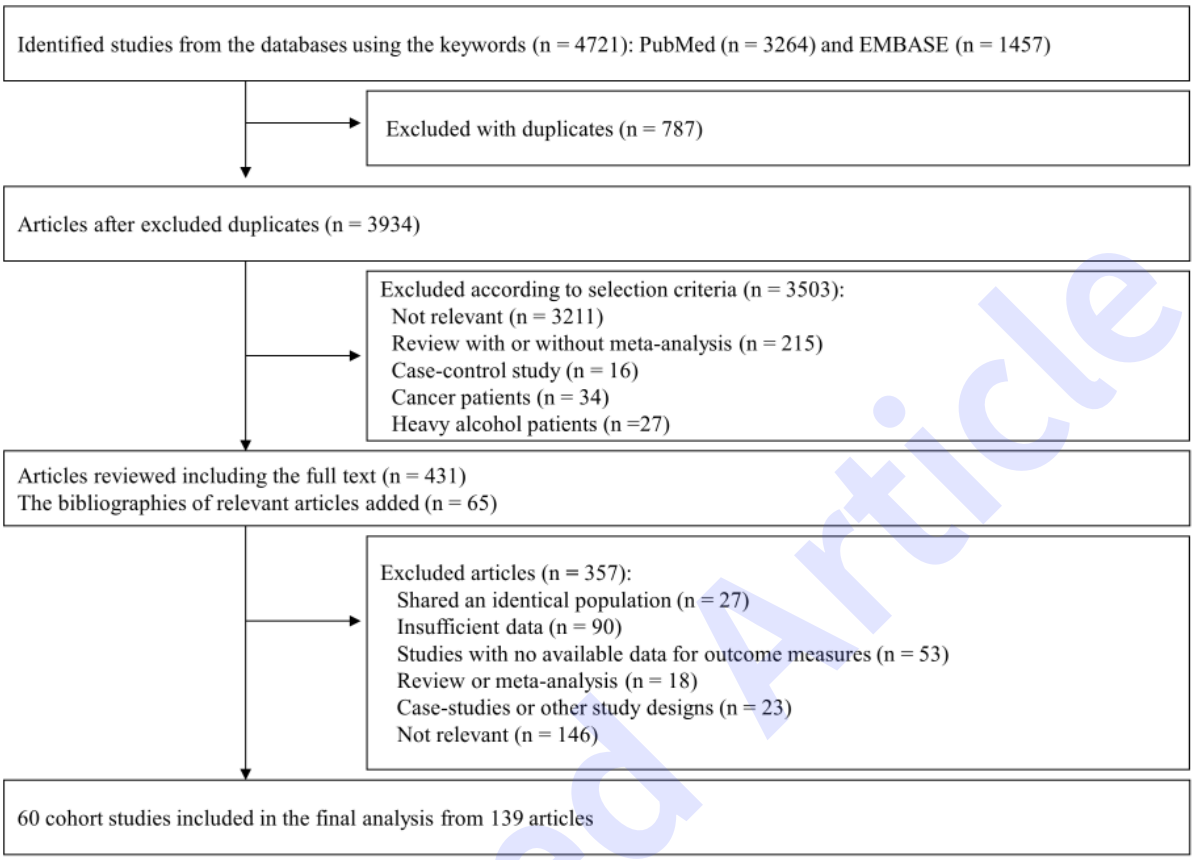

Fig. 2. Association between light alcohol drinking (≤1drink/day) and the risk of female breast cancer in a random-effects meta-analysis

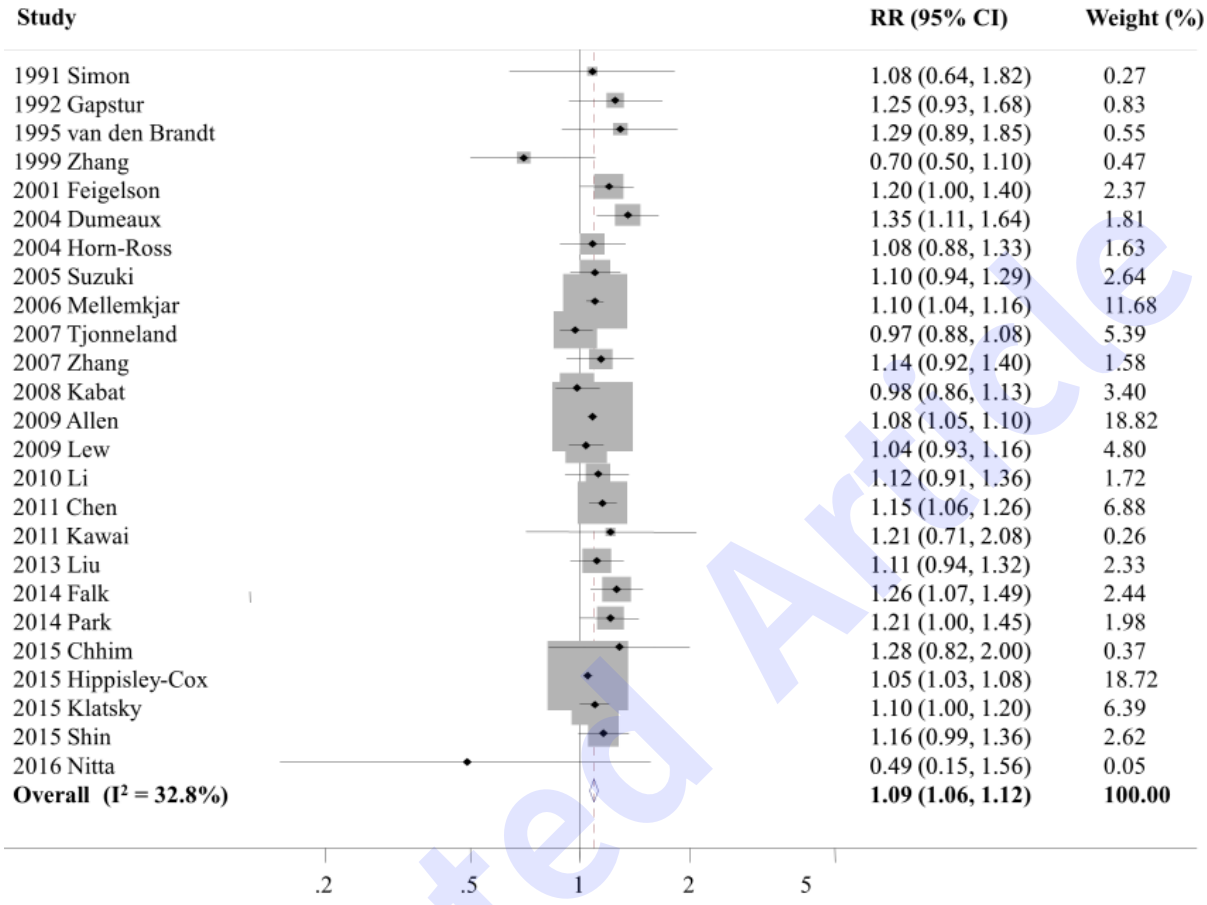

Fig. 3. Association between light alcohol drinking (≤1drink/day) and the risk of male colorectal cancer in a random-effects meta-analysis

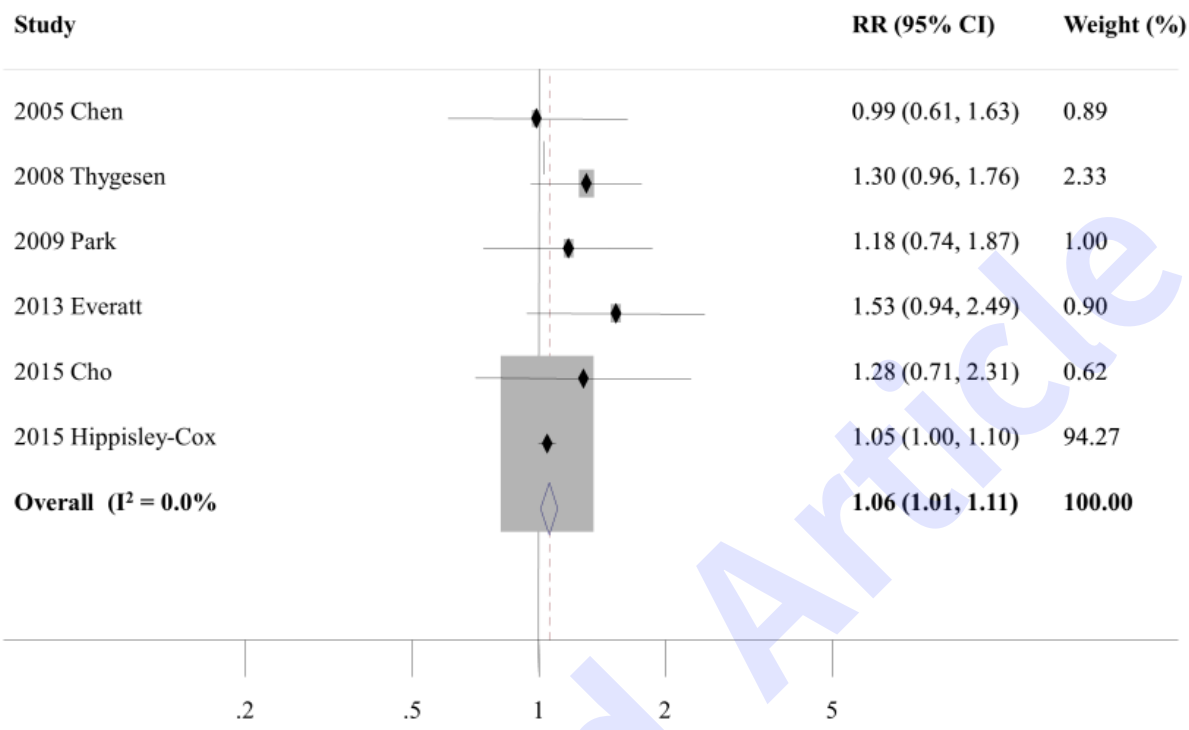

Table 1. Number of articles and studies by organ site and country among 135 articles and 60 cohort studies

Category	Site of cancer	Incidence		Mortality	
		Number of articles	Number of studies	Number of articles	Number of studies
Upper digestive tract	Oral & Pharynx	5	5	2	2
	Oesophagus (SCC)	2	2	5	4
	Oesophagus (ADC) & Cardia	3	3		
	Head and Neck	2	2	NA	NA
Gastrointestinal tract	Stomach (Non-cardia)	11	9	2	2
	Colorectum	16	16	6	5
	Colon	10	10		
	Rectum	9	9		
Hepatobiliary system	Liver	2	2	2	2
	Pancreas	5	5	4	4
	Gall Bladder	NA	NA	1	1
Respiratory tract	Lung	10	10	6	5
	Larynx	1	1	1	1
Women's cancer	Breast (Female)	34	27	7	7
	Endometrium	9	9	NA	NA
	Ovary	5	5	NA	NA
	Cervix/Uterus	2	2	1	1
Men's cancer	Prostate	15	14	4	4
Urological system	Kidney	7	7	1	1

	Bladder	4	4	NA	NA
Others	Thyroid	6	6	NA	NA
	Hematologic Malignancy	8	8	2	2
	Malignant Melanoma	3	3	NA	NA
Category	**Country**	**Incidence**		**Mortality**	
		Number of articles	**Number of studies**	**Number of articles**	**Number of studies**
Asia	China	3	2	NA	NA
	Japan	5	4	2	2
	Korea	3	2	1	1
	Singapore	3	1	NA	NA
	Honk Kong	NA	NA	1	1
North America	US	70	28	9	9
	Canada	4	2	1	1
Europe	UK	5	5	NA	NA
	Sweden	6	3	NA	NA
	Norway	1	1	NA	NA
	Netherland	10	3	NA	NA
	Lithuania	2	2	NA	NA
	France	2	2	NA	NA
	Finland	1	1	NA	NA
	European countries	1	1	NA	NA
	Denmark	5	3	NA	NA

Table 2. Association between very light, light, and moderate alcohol drinking and cancer incidence

Site Of Cancer	Total No. of Study	Population	Very light drinking (≤0·5 drink/day)			Light drinking (≤1 drink/day)			Moderate drinking (1-2 drink/day)		
			No. of Study	RR (95% CI)	I^2 (%)	No. of Study	RR (95% CI)	I^2 (%)	No. of Study	RR (95% CI)	I^2 (%)
Head & Neck	2	Women/Men	1	1·11 (0·75–1·65)	NA	2	1·00 (0·75–1·33)	0·0	2	1·18 (0·67–2·07)	63·8
Oral & Pharynx	5	Women/Men	0	NA	NA	4	0·96 (0·84–1·11)	68·9	3	1·12 (1·01–1·24)	19·5
		Women	0	NA	NA	3	0·95 (0·75–1·19)	77·6	3	1·18 (1·05–1·33)	0·0
		Men	0	NA	NA	1	0·89 (0·79–1·00)	NA	2	1·04 (0·93–1·17)	0·0
Larynx	1	Women/Men	0	NA	NA	0	NA	NA	0	NA	NA
		Women	0	NA	NA	1	1·13 (0·75–1·70)	NA	1	1·74 (1·25–2·41)	NA
		Men	0	NA	NA	0	NA	NA	0	NA	NA
Ooesophagus (Squamous cell carcinoma)	2	Women/Men	1	0·85 (0·42–1·73)	NA	2	1·45 (0·90–2·33)	0·0	2	1·98 (1·25–3·14)	0·0
		Women	0	NA	NA	0	NA	NA	0	NA	NA
		Men	0	NA	NA	1	1·22 (0·62–2·44)	NA	1	1·87 (0·99–3·53)	NA
Ooesophagus (adenocarcinoma)&Cardia	3	Women/Men	1	1·17 (0·69–1·98)	NA	3	0·83 (0·52–1·33)	44·5	3	0·81 (0·56–1·17)	0·0
		Women	0	NA	NA	0	NA	NA	0	NA	NA

		Men	0	NA	NA	0	NA	NA	0	NA	NA
Stomach, Non-Cardia	11	Women/Men	3	1·00 (0·78–1·30)	0·0	7	1·00 (0·95–1·07)	0·0	6	0·91 (0·78–1·06)	0·0
		Women	1	1·11 (0·71–1·73)	NA	0	NA	NA	0	NA	NA
		Men	2	1·04 (0·66–1·64)	0·0	2	1·01 (0·92–1·11)	0·0	2	0·91 (0·68–1·20)	0·0
Colorectum	16	Women/Men	6	1·10 (0·94–1·28)	39·7	14	1·04 (1·01–1·06)	0·0	10	1·10 (1·03–1·19)	41·0
		Women	2	0·92 (0·78–1·08)	0·0	7	1·02 (0·98–1·06)	0·0	5	1·04 (0·95–1·13)	4·4
		Men	3	1·31 (0·92–1·86)	47·3	6	1·06 (1·01–1·11)	0·0	6	1·19 (1·06–1·35)	10·6
Colon	10	Women/Men	2	0·91 (0·55–1·49)	79·4	11	0·99 (0·93–1·05)	1·4	6	1·01 (0·88–1·15)	43·3
		Women	0	NA	NA	5	1·12 (0·90–1·40)	60·4	5	1·03 (0·91–1·17)	28·4
		Men	1	1·42 (0·83–2·45)	NA	5	1·02 (0·87–1·21)	0·0	5	1·08 (0·89–1·31)	0·0
Rectum	9	Women/Men	2	1·47 (0·95–2·29)	0·0	10	1·04 (0·96–1·12)	0·5	7	1·03 (0·94–1·12)	0·0
		Women	0	NA	NA	4	1·02 (0·93–1·11)	0·0	3	0·99 (0·90–1·09)	0·0
		Men	0	NA	NA	3	1·07 (0·69–1·64)	0·0	2	1·35 (0·77–2·35)	0·0
Liver	2	Women/Men	0	NA	NA	2	0·95 (0·76–1·20)	0·0	2	1·26 (1·00–1·58)	0·0
		Women	0	NA	NA	1	0·94 (0·72–1·21)	NA	1	1·20 (0·93–1·55)	NA
		Men	0	NA	NA	0	NA	NA	0	NA	NA
Pancreas	5	Women/Men	4	1·06 (0·87–1·30)	0·0	3	1·02 (0·83–1·26)	6·3	3	1·03 (0·86–1·23)	0·0
		Women	0	NA	NA	0	NA	NA	1	1·01 (0·53–1·91)	NA
		Men	2	1·25 (0·90–1·74)	0·0	1	1·39 (0·75–2·56)	NA	1	1·24 (0·66–2·32)	NA

Lung	10	Women/Men	3	0·89 (0·84–0·93)	6·9	10	0·91 (0·90–0·94)	0·0	8	0·98 (0·91–1·07)	50·0
		Women	2	0·82 (0·70–0·95)	12·9	4	0·90 (0·87–0·94)	0·0	4	1·05 (0·99–1·11)	0·0
		Men	1	0·86 (0·71–1·03)	NA	3	0·91 (0·90–0·95)	0·0	4	0·98 (0·82–1·16)	52·1
Breast (Female)	34	Women	20	1·04 (1·01–1·07)	3·7	25	1·09 (1·06–1·12)	32·8	15	1·13 (1·11–1·15)	0·0
Endometrium	9	Women	6	0·95 (0·80–1·12)	52·1	7	0·98 (0·93–1·03)	0·0	4	0·93 (0·84–1·04)	6·8
Ovary	5	Women	2	1·00 (0·82–1·22)	0·0	5	1·02 (0·88–1·20)	52·4	4	1·20 (0·92–1·56)	66·6
Cervix & Uterus	2	Women	NA	NA	NA	2	1·02 (0·88–1·19)	0·0	2	0·99 (0·83–1·17)	0·0
Prostate	15	Men	3	1·16 (0·94–1·44)	0·0	13	1·04 (0·97–1·11)	50·0	3	1·04 (0·96–1·11)	0·0
Kidney	7	Women/Men	2	0·73 (0·50–1·08)	0·0	7	0·90 (0·81–1·00)	0·0	3	0·93 (0·86–1·00)	0·0
		Women	1	0·75 (0·45–1·29)	NA	2	0·79 (0·41–1·50)	66·9	1	0·93 (0·80–0·94)	NA
		Men	NA	NA	NA	3	0·90 (0·78–1·03)	0·0	1	0·94 (0·64–1·03)	NA
Bladder	4	Women/Men	2	1·22 (0·82–1·82)	27·5	5	1·09 (0·97–1·23)	0·0	4	1·06 (0·77–1·47)	64·2
		Women	0	NA	NA	1	1·05 (0·92–1·21)	NA	1	0·91 (0·77–1·07)	NA
		Men	0	NA	NA	1	1·31 (0·80–2·13)	NA	0	NA	NA
Thyroid	6	Women/Men	1	1·01 (0·76–1·36)	NA	6	0·89 (0·79–1·00)	0·0	3	0·68 (0·56–0·84)	0·0
		Women	0	NA	NA	5	0·89 (0·78–1·01)	0·0	2	0·67 (0·53–0·85)	0·0
		Men	0	NA	NA	1	0·62 (0·25–1·54)	NA	1	0·69 (0·40–1·20)	NA
Hematologic Malignancy	8	Women/Men	3	1·05 (0·87–1·26)	15·1	6	0·98 (0·91–1·05)	41·4	6	0·89 (0·81–0·99)	52·3

		Women	1	1·16 (0·88–1·54)	NA	4	0·99 (0·93–1·06)	0·0	3	0·91 (0·81–1·02)	0·0
		Men	0	NA	NA	2	0·98 (0·81–1·19)	54·2	2	0·90 (0·78–1·04)	0·0
Malignant Melanoma	3	Women/Men	0	NA	NA	3	1·44 (1·18–1·76)	0·0	2	1·77 (1·35–2·33)	0·0
		Women	0	NA	NA	2	1·32 (0·97–1·79)	0·0	1	1·70 (0·90–3·10)	NA
		Men	0	NA	NA	0	NA	NA	1	0·90 (0·20–3·00)	NA

RR, relative risk; CI, confidence interval; NA, not applicable.

Table 3. Association betweenvery light, light, and moderate alcohol drinking and cancer mortality

Site of cancer	Total no· of Study	population	Very light drinking (≤0·5 drink/day)			Light drinking (≤1 drink/day)			Moderate drinking (1-2 drink/day)		
			No. of Study	RR (95% CI)	I^2 (%)	No. of Study	RR(95% CI)	I^2 (%)	No. of Study	RR(95% CI)	I^2 (%)
Oral & Pharynx	2	women/men	0	NA	NA	0	NA	NA	0	NA	NA
		women	0	NA	NA	0	NA	NA	0	NA	NA
		men	0	NA	NA	2	0·71 (0·24–2·16)	72·0	1	0·75 (0·27–2·06)	NA
Ooesophagus	4	women/men	0	NA	NA	0	NA	NA	0	NA	NA
		women	0	NA	NA	0	NA	NA	0	NA	NA
		men	0	NA	NA	4	1·17 (0·98–1·39)	0·0	2	1·46 (0·93–2·16)	0·0
Larynx	1	women/men	0	NA	NA	0	NA	NA	0	NA	NA
		women	0	NA	NA	0	NA	NA	0	NA	NA
		men	0	NA	NA	1	1·31 (0·60–2·85)	NA	1	0·87 (0·32–2·35)	NA
Stomach	2	women/men	0	NA	NA	3	0·81 (0·58–1·12)	49·5	2	1·11 (0·79–1·56)	43·6
		women	0	NA	NA	1	0·65 (0·44–0·98)	NA	1	1·48 (0·85–2·57)	NA
		men	0	NA	NA	2	0·95 (0·83–1·10)	0·0	1	1·00 (0·85–1·18)	NA
Colorectum	6	women/men	2	0·88 (0·70–1·12)	0·0	6	0·97 (0·83–1·14)	32·6	2	1·55 (0·67–3·58)	82·4
		women	1	0·74 (0·53–1·03)	NA	4	0·79 (0·58–1·06)	26·3	1	2·51 (1·31–4·82)	NA
		men	2	1·06 (0·72–1·55)	0·0	5	1·11 (0·95–1·28)	0·0	1	1·06 (0·80–1·40)	NA
Liver	2	women/men	0	NA	NA	2	0·92 (0·81–1·04)	0·0	2	1·00 (0·88–1·14)	37·7
		women	0	NA	NA	2	0·78 (0·48–1·25)	0·0	1	1·80 (0·90–1·10)	NA
		men	0	NA	NA	2	0·93 (0·81–1·06)	0·0	2	0·98 (0·91–1·07)	0·0
Gall Bladder	1	women/men	0	NA	NA	0	NA	NA	0	NA	NA
		women	1	1·49 (0·59–3·74)	NA	1	1·14 (0·28–4·70)	NA	0	NA	NA

		men	0	NA	NA	0	NA	NA	0	NA	NA
Pancreas	4	women/men	0	NA	NA	4	0·93 (0·78–1·11)	22·0	1	0·95 (0·72–1·27)	0·0
		women	0	NA	NA	1	0·66 (0·35–1·23)	NA	1	0·50 (0·12–2·05)	NA
		men	1	0·52 (0·23–1·15)	NA	3	1·01 (0·55–1·85)	55·8	1	0·98 (0·73–1·31)	NA
Lung	5	women/men	2	0·81 (0·69–0·94)	0·0	6	0·90 (0·79–1·04)	49·3	0	NA	NA
		women	1	0·70 (0·56–0·89)	NA	3	1·03 (0·80–1·31)	43·1	1	0·94 (0·45–1·94)	NA
		men	2	0·84 (0·68–1·03)	0·0	5	0·79 (0·70–0·87)	0·0	1	0·78 (0·68–0·90)	NA
Breast	7	women	2	0·79 (0·64–0·97)	0·0	6	1·06 (0·97–1·16)	31·5	2	1·04 (1·01–1·07)	0·0
Cervix/Uterus	1	women	0	NA	NA	1	1·09 (0·50–2·35)	NA	1	1·10 (0·25–4·79)	NA
Prostate	4	men	2	0·92 (0·68–1·25)	0·0	1	1·14 (0·85–1·52)	0·0	1	1·75 (0·72–4·22)	NA
Kidney	1	women/men	0	NA	NA	0	NA	NA	0	NA	NA
		women	0	NA	NA	0	NA	NA	0	NA	NA
		men	0	NA	NA	1	0·63 (0·35–1·12)	NA	1	0·46 (0·23–0·93)	NA
Hematologic Malignancy	2	women/men	0	NA	NA	2	1·24 (0·40–3·86)	55·6	1	1·00 (0·63–1·60)	NA
		women	0	NA	NA	1	3·26 (0·79–13·48)	NA	0	NA	NA
		men	1	0·87 (0·49–1·53)	NA	3	0·80 (0·54–1·18)	1·9	1	1·00 (0·63–1·60)	NA

RR, relative risk; CI, confidence interval; NA, not applicable.

Supplementary Material

S1Table. General characteristics of the studies included in the final analysis - cancer incidence

Study	Country	Cohort	Enroll year	Population	Cancer type	Alcohol consumption amount (baseline)	RR (95% CI)
Oral cavity and pharyngeal cancer							
2007 Freedman[1]	US	NIH-AARP Diet and Health Study	1995-2000	men (492960 men/women)	oral cavity	0 drinks/day	1.43 (1.03 - 2.00)
						<1 drink/day	1.0
						1-3 drinks/day	1.22 (0.85 - 1.76)
				women		0 drinks/day	1.24 (0.74 - 2.10)
						<1 drink/day	1.0
						1-3 drinks/day	1.74 (0.95 - 3.20)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Oral cavity & pharyngeal cancer	Nondrinkers	1.18 (1.02 to 1.36)
						3 to 6 drinks/wk	1.13 (0.97 to 1.32)
						7 to 14 drinks/wk	1.13 (0.96 to 1.34)
2010 Shanmugham[3]	US	Nurses' Health Study	1980–2006	87621 Women (30–55yrs)	Oral cancer	0	1.00
						0.1 to 14.9 g/day	0.59 (0.39 to 0.87)
2015 Hippisley–Cox[4]	UK	Primary care patients from open cohort study using Qresearch database (EMIS computer system)	1998–2013	Women	Oral cancer	Nondrinkers	1.0
						<1 unit/day	1.03 (0.91 to 1.16)
						1–2 units/day	1.18 (0.99 to 1.40)
				Men	Oral cancer	Nondrinkers	1.0
						<1 unit/day	0.89 (0.79 to 1.00)
						1–2 units/day	1.02 (0.90 to 1.15)
2007 Friborg[5]	Singapore	Singapore Chinese Health Study	1993–2005	61320 Women/Men(45–74yrs) (34028 Women, 27292 Men)	Nasopharyngeal carcinoma	Nondrinkers	1.00
						1 to 7 drinks/wk	0.9 (0.6 to 1.4)
					Oropharyngeal carcinoma	Nondrinkers	1.00
						1 to 7 drinks/wk	1.4 (0.8 to 2.7)

Laryngeal cancer							
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Laryngeal cancer	Nondrinkers	1.09 (0.79 to 1.52)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.13 (0.75 to 1.70)
						7 to 14 drinks/wk	1.74 (1.25 to 2.41)
Head and neck cancer							
2013 Hashibe[6]	US	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort(PLCO)	1992–2001	101182 Women/Men(55–74yrs)	Head and neck cancer	Nondrinkers	1.00
						>0 to <1 drink/day	0.87 (0.58 to 1.29)
						1 to 1.9 drink/day	0.85 (0.49 to 1.49)
2014 Maasland[7]	Netherlands	Netherlands Cohort Study	1986–2003	120852 Women/Men	Head and neck cancer	Abstainers	1.00
						>0 to <5 g/day	1.11 (0.75 to 1.65)
						5 to <15 g/day	1.15 (0.77 to 1.71)
						15 to <30 g/day	1.52 (1.02 to 2.27)
Esophageal cancer (squamous cell carcinoma)							
2008 Fan[8]	China	Shanghai Cohort Study	1986–2006	18244 Men	Esophageal cancer	Nondrinkers	1.00
						>0 to <1 drink/day	1.22 (0.62 to 2.44)
						1 to <2 drinks/day	1.87 (0.99 to 3.53)
2010 Steevens[9]	Netherland	Netherlands Cohort Study	1986–2002	120852 Women/Men	Esophageal cancer	Abstainers	1
						>0 to <5 g/day	1.85 (0.42 to 1.73)
						5 to <15 g/day	1.65 (0.85 to 3.17)
						15 to <30 g/day	2.11 (1.08 to 4.14)
Esophageal and gastric cardia adenocarcinoma							
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Esophageal ADC	Nondrinkers	1.28 (1.01 to 1.63)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.25 (0.96 to 1.62)

						7 to 14 drinks/wk	0.77 (0.53 to 1.13)
2010 Steevens[9]	Netherland	Netherlands Cohort Study	1986–2002	120852 Women/Men	Esophageal ADC	Abstainers	1.00
						>0 to <5 g/day	1.17 (0.69 to 1.98)
						5 to <15 g/day	0.91 (0.51 to 1.60)
						15 to <30 g/day	1.01 (0.56 to 1.82)
					Gastric cardia ADC	Abstainers	1.00
						>0 to <5 g/day	0.75 (0.44 to 1.30)
						5 to <15 g/day	1.11 (0.68 to 1.82)
						15 to <30 g/day	0.92 (0.54 to 1.57)
2014 Yates[10]	UK	EPIC–Norfolk Study	1993–2008	24068 Women/Men	Esophageal ADC	No alcohol	1.00
						>0 to <7 units/wk	1.34 (0.63 to 2.88)
						7 to <14 units/wk	0.73 (0.28 to 1.86)
						14 to <21 units/wk	0.47 (0.12 to 1.79)
Gastric cancer							
1995 Nomura[11]	Japan	American Men of Japanese ancestry residing in Hawaiian island	1965–1990	7972 Men	Gastric cancer	Nondrinkers	1.0
						<5 oz/month	0.9 (0.6 to 1.3)
						5–14 oz/month	1.1 (0.8 to 1.6)
1998 Galanis[12]	US	Japanese residents of Hawaii	1975–1994	11907 Women/Men (6297 Women, 5610 Men)	Gastric cancer	Nondrinkers	1.00
						1–2 drinks/day	0.50 (0.2 to 1.1)
2005 Barstad[13]	Denmark	Copenhagen Center for Prospective Population Studies (Copenhagen City Heart Study, Copenhagen Male Study, Copenhagen County Center for Preventive Medicine)	1964–1997	28463 Women/Men	Gastric cancer	<1 drink/wk	1.00
				13227 Women		1–6 drinks/wk	1.47 (0.93 to 2.02)
				15236 Men		7–13 drinks/wk	0.95 (0.32 to 1.58)

2007 Larsson[14]	Sweden	Swedish Mammography Cohort	1987–2005	61433 Women	Gastric cancer	Nondrinkers	1.00
						0.1 to 19.9 g/wk	0.85 (0.58 to 1.25)
						20.0 to 39.9 g/wk	1.18 (0.73 to 1.91)
2007 Sung[15]	Korea	National Health Insurance Corporation Study	1996–2002	669570 Men	Gastric cancer	0	1.0
						1 to 14.9 g/day	1.0 (0.9 to 1.1)
						15.0 to 24.9 g/day	1.1 (1.0 to 1.3)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Gastric cancer	Nondrinkers	1.27 (1.12 to 1.44)
						3 to 6 drinks/wk	1.06 (0.91 to 1.22)
						7 to 14 drinks/wk	0.79 (0.65 to 0.95)
2010 Moy[16]	China	Shanghai Cohort Study	1986–2005	18244 Men	Gastric cancer	Nondrinkers	1.00
						>0 to <20 g/day	0.88 (0.67 to 1.16)
2010 Steevens[9]	Netherland	Netherlands Cohort Study	1986–2002	120852 Women/Men	Gastric non–cardia ADC	Abstainers	1.00
						>0 to <5 g/day	0.92 (0.69 to 1.23)
						5 to <15 g/day	1.07 (0.80 to 1.43)
						15 to <30 g/day	0.77 (0.55 to 1.08)
2012 Everatt[17]	Lithuania	Kaunas Rotterdam Intervention Study (KRIS), Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)	1972–2008	7150 Men (40–59yrs)	Gastric cancer	0.1 to 9.9 g/wk	1.00
						10.0 to 24.9 g/wk	1.04 (0.66 to 1.64)
						25.0 to 99.9 g/wk	1.44 (0.91 to 2.29)
2015 Eom[18]	Korea	Korean National Health Insurance Corporation data	1998–2007	2291132 Women/Men	Gastric cancer	0	1
						1–14.9 g/day	0.98 (0.89 to 1.06)
						>15 g/day	1.16 (0.99 to 1.36)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser	1978–2012	124193 Women/Men	Gastric cancer	Never drinkers	1.0
						<1 drink/day	0.9 (0.7 to 1.2)

		Permanente)				1 to 2 drinks/day	0.8 (0.6 to 1.4)
Colorectal cancer							
2002 Flood[20]	US	Breast Cancer Detection Demonstration Project (BCDDP)	1987–1995	45264 Women	Colorectal cancer	0	1.00
						0.01 to 0.50 servings/day	0.92 (0.73 to 1.16)
						0.51 to 1.00 servings/day	1.00 (0.74 to 1.35)
						1.01 to 2.00 servings/day	0.94 (0.62 to 1.42)
2003 Otani[21]	Japan	Japan Public Health Center–based prospective study (cohort I)	1990–1999	90004 Women/Men	Colorectal cancer	Never drinkers, ex–drinkers	1.0
						occasional drinkers	0.8 (0.4 to 1.4)
						regular drinkers (1–149 g/wk)	0.9 (0.6 to 1.4)
2004 Sanjoaquin[22]	UK	Oxford Vegetarian Study	1980–1999	10998 Women/Men (6836 Women, 4162 Men)	Colorectal cancer	<1 drink/wk	1.00
						1–7 drinks/wk	1.53 (0.94 to 2.49)
2005 Chen[23]	China	Population of Jiashan County	1989–2001	64100 Women/Men	Colorectal cancer	Nondrinkers	1
						occasional (<7drinks/wk)	1.13 (0.79 to 1.64)
						daily (≥7drinks/wk)	1.11 (0.74 to 1.67)
				33148 Women		Nondrinkers	1
						occasional (<7drinks/wk)	1.33 (0.78 to 2.26)
						daily (≥7drinks/wk)	1.06 (0.33 to 3.48)
				30952 Men		Nondrinkers	1
						occasional (<7drinks/wk)	0.99 (0.61 to 1.63)
						daily (≥7drinks/wk)	1.03 (0.65 to 1.64)
2007 Tsong[24]	Singapore	Singapore Chinese Health Study	1993–1998	63257 Women/Men	Colorectal cancer	Nondrinkers	1.00
						<7 drinks/wk	0.96 (0.72 to 1.25)
2008 Bongaerts[25]	Netherlands	Netherlands Cohort Study	1986–1999	120852 Women/Men	Colorectal cancer	Abstainers	1.00

				(62573 Women, 58279 Men, 55–69 yrs)		0 to <5.0 g/day	1.06 (0.91 to 1.23)
						5.0 to 15.0 g/day	0.97 (0.82 to 1.14)
						15.0 to <30.0 g/day	1.00 (0.83 to 1.20)
				62573 Women		Abstainers	1.00
						0 to <30.0 g/day	0.91 (0.74 to 1.12)
				58279 Men		Abstainers	1.00
						0 to <30.0 g/day	1.16 (0.91 to 1.48)
2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980–2000	49654 Women	Colorectal cancer	Never	1.00
						>0 to <5g/day	0.92 (0.73 to 1.14)
						5 to <10 g/day	0.93 (0.71 to 1.22)
						10 to <20 g/day	1.04 (0.79 to 1.36)
						20 to <30 g/day	1.13 (0.77 to 1.64)
2008 Thygesen[27]	US	Health Professional Follow–up Study	1986–2002	47432 Men	Colorectal cancer	Nondrinkers	1
						0.1 to 5 g/day	1.05 (0.79 to 1.40)
						5.1 to 10 g/day	1.30 (0.96 to 1.76)
						10.1 to 20 g/day	1.38 (1.04 to 1.83)
						20.1 to 30 g/day	1.43 (0.99 to 2.07)
2008 Toriola[28]	Finland	Kuopio Ischemic Heart Study (KIHD)	1984–2005	2682 Men	Colorectal cancer	0 to 3.2 g/wk	1
						3.3 to 17.2 g/wk	2.4 (0.9 to 6.8)
						17.3 to 48.8 g/wk	2.5 (0.9 to 7.2)
						48.9 to 115.2 g/wk	2.2 (0.8 to 6.4)
2009 Park[29]	UK	UK Norfolk arm of EPIC study	1995–2003	25639 Women/Men (40–79yrs)	Colorectal cancer	Nondrinkers	1.00
						>0–<7drinks/wk	0.91 (0.69 to 1.21)
						7 to <14 drinks/wk	0.74 (0.52 to 1.07)
				14032 Women		>0–<7drinks/wk	0.79 (0.55 to 1.14)

						7 to <14 drinks/wk	0.60 (0.34 to 1.05)
				11607 Men		>0–<7drinks/wk	1.18 (0.74 to 1.87)
						7 to <14 drinks/wk	0.97 (0.57 to 1.64)
2011 Razzak[30]	US	Iowa Women's Health Study	1986–2004	38001 Women	Colorectal cancer	Nondrinkers	1.00
						>0 to ≤1.8 g/day	1.04 (0.88 to 1.24)
						1.80 to ≤3.4 g/day	0.92 (0.74 to 1.15)
						3.4 to ≤11 g/day	1.10 (0.91 to 1.33)
2013 Everatt[31]	Lithuania	Kaunas Rotterdam Intervention Study (KRIS), Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)	1978–2008	7150 Men	Colorectal cancer	Nondrinker	1.24 (0.72 to 2.16)
						0.1 to 10 g/wk	1.00
						10.1 to 40.0 g/wk	1.46 (1.01 to 2.11)
						40.1 to 70.0 g/wk	0.81 (0.41 to 1.60)
						70.1 to 140.0 g/wk	1.32 (0.83 to 2.09)
2014 Nishihara[32]	US	Nurses' Health Study, Health Professionals Follow–up Study	1976–2008	173230 Women/Men (121701 Women, 51529 Men)	Colorectal cancer	0	1.00
						1 to 14 g/day	1.13 (0.97 to 1.32)
2015 Cho[33]	Korea	Korean Multi–center Cancer Cohort	1993–2005	18707 Women/Men	Colorectal cancer	Never drinkers	1.0
				Women		<10 g/day	0.82 (0.41 to 1.63)
						10–29 g/day	0.95 (0.23 to 3.87)
				Men		<10 g/day	1.28 (0.71 to 2.31)
						10–29 g/day	1.77 (0.96 to 3.26)
						Never drinkers	1.0
2015 Hippisley–Cox[4]	UK	Primary care patients from open cohort study using Qresearch database (EMIS computer system)	1998–2013	4960000 Women/Men	Colorectal cancer	Nondrinkers	1.0
				Women		<1 unit/day	1.02 (0.98 to 1.06)
						1–2 units/day	1.05 (1.00 to 1.11)

				Men		<1 unit/day	1.05 (1.00 to 1.10)
						1–2 units/day	1.14 (1.08 to 1.20)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Colorectal cancer	Never drinkers	1.00
						<1 drink/day	1.1 (1.0 to 1.3)
						1 to 2 drinks/day	1.2 (1.0 to 1.4)
Colon cancer							
1988 Klatsky[34]	US	Members of Kaiser Permanente Medical Care Program in Northern California	1978–1984	106203 Women/Men	Colon cancer	None	1.0
						>0 –<1 drinks/day	1.16 (0.75 to 1.79)
						1 to 2 drinks/day	1.59 (0.95 to 2.64)
				Women		>0 –<1 drinks/day	1.29 (0.77 to 2.17)
						1 to 2 drinks/day	1.80 (0.92 to 3.52)
				Men		>0 –<1 drinks/day	0.89 (0.41 to 1.98)
						1 to 2 drinks/day	1.15 (0.50 to 2.64)
1990 Stemmermann[35]	US	American Men of Japanese ancestry residing in Hawaiian island (Oahu)	1965–1989	8006 Men	Colon cancer	0	1.0
						>0 to <5 oz/month	0.68 (0.45 to 1.05)
						5 to 14 oz/month	0.96 (0.63 to 1.47)
						15 to 39 oz/month	1.16 (0.78 to 1.72)
1994 Goldbohm[36]	Netherland	from 204 municipal population registries throughout the country	1986–1989	120852 Women/Men (62573 Women , 58279 Men, 55–69yrs)	Colon cancer	Abstainers	1.0
						0.1 to 4.9 g/day	0.7 (0.5 to 1.0)
						5.0 to 14.9 g/day	0.6 (0.4 to 0.9)
						15.0– 29.9 g/day	0.9 (0.5 to 1.6)
1995 Giovannucci[37]	US	Male health professionals	1986–1992	47931 Men (40–75yrs)	Colon cancer	0 to 0.25 drinks/day	1.0
						0.26 to 0.50 drinks/day	1.42 (0.83 to 2.45)

						0.51 to 1.0 drink/day	1.67 (1.03 to 2.69)
						1.1 to 2.0 drinks/day	1.68 (1.03 to 2.74)
2003 Pederson[38]	Denmark	Copenhagen Center for Prospective Population Studies (Copenhagen City Heart Study, Copenhagen Male Study, Copenhagen County Center for Preventive Medicine)	-1999, median 14.7yrs	29132 Women/Men (23–95yrs)	Colon cancer	<1 drink/wk	1.00
						1 to 6 drinks/wk	1.0 (0.8 to 1.3)
						7 to 13 drinks/wk	0.9 (0.7 to 1.2)
2004 Su[39]	US	National Health and Nutrition Examination Survey (NHANES I)	1982–1993	10220 Women/Men (55970 Women, 50040 Men)	Colon cancer	0	1.00
						<1 drink/day	1.08 (0.65 to 1.79)
2004 Wei[40]	US	Nurses' Health Study, Health Professionals Follow–up Study	NHS 1980–2000, HPFS 1986–2000	134365 Women/Men		<10 g/day	0.97 (0.82 to 1.14)
						10–19 g/day	1.04 (0.85 to 1.26)
				87733 Women		0	1.00
						<10 g/day	0.97 (0.81 to 1.17)
						10–19 g/day	0.99 (0.78 to 1.27)
				46632 Men		0	1.00
						<10 g/day	1.08 (0.75 to 1.55)
						10–19 g/day	1.27 (0.86 to 1.86)
2005 Chen[23]	China	Population of Jiashan County	1989–2001	64100 Women/Men	Colon cancer	Nondrinkers	1.00
						occasional (<7drinks/wk)	1.06 (0.61 to 1.83)
				33148 Women		Nondrinkers	1.00
						occasional (<7drinks/wk)	1.23 (0.52 to 2.91)
				30952 Men		Nondrinkers	1.00
						occasional (<7drinks/wk)	0.87 (0.44 to 1.74)

2007 Tsong[24]	Singapore	Singapore Chinese Health Study	1993–1998	63257 Women/Men	Colon cancer	Nondrinkers	1.00
						<7 drinks/wk	0.96 (0.72 to 1.25)
2008 Bongaerts[25]	Netherlands	Netherlands Cohort Study	1986–1999	120852 Women/Men (55–69yrs)	Colon cancer	Abstainers	1.00
						0 to <5.0 g/day	1.03 (0.87 to 1.22)
						5.0 to 15.0 g/day	0.93 (0.78 to 1.13)
						15.0 to <30 g/day	0.93 (0.75 to 1.14)
				62573 Women		0 to <30.0 g/day	0.91 (0.72 to 1.15)
				58279 Men		0 to <30.0 g/day	1.00 (0.75 to 1.34)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Colon cancer	Nondrinkers	1.00 (0.94 to 1.07)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	0.99 (0.93 to 1.06)
						7 to 14 drinks/wk	1.02 (0.95 to 1.09)
2009 Park[29]	UK	UK Norfolk arm of EPIC study	1995–2003	25639 Women/Men (40–79yrs)	Colon cancer	Nondrinkers	1.00
						>0–<7drinks/wk	0.93 (0.66 to 1.31)
						7 to <14 drinks/wk	0.64 (0.41 to 1.01)
				Women		>0–<7drinks/wk	0.85 (0.54 to 1.33)
						7 to <14 drinks/wk	0.59 (0.29 to 1.17)
				Men		>0–<7drinks/wk	1.10 (0.63 to 1.90)
						7 to <14 drinks/wk	0.75 (0.39 to 1.43)
2012 Cho[41]	US	Health Professional Follow–up Study, Nurses' Health Study	1980–2006	135151 Women/Men		None	1.00
						0.1 to <5 g/day	1.16 (0.87 to 1.54)
						5.0 to <10 g/day	1.08 (0.91 to 1.28)
						10 to <15 g/day	1.26 (0.96 to 1.66)
						15 to < 30 g/day	1.11 (0.92 to 1.33)

				87861 Women		None	1.00
						15 to < 30 g/day	1.11 (0.85 to 1.45)
						0.1 to <5 g/day	1.32 (1.12 to 1.56)
						5.0 to <10 g/day	1.09 (0.87 to 1.36)
						10 to <15 g/day	1.43 (1.13 to 1.82)
						15 to < 30 g/day	1.11 (0.86 to 1.43)
				47290 Men	Colon cancer	None	1.00
						0.1 to <5 g/day	0.99 (0.78. to 1.25)
						5.0 to <10 g/day	1.07 (0.82 to 1.39)
						10 to <15 g/day	1.08 (0.82 to 1.44)
Rectal cancer							
1988 Klatsky[34]	US	Members of Kaiser Permanente Medical Care Program in Northern California	1978–1984	106203 Women/Men	Rectal cancer	None	1.0
						>0 –<1 drinks/day	1.42 (0.57 to 3.55)
						1 to 2 drinks/day	2.28 (0.83 to 6.26)
1990 Stemmermann[35]	US	American Men of Japanese ancestry residing in Hawaiian island (Oahu)	1965–1989	8006 Men	Rectal cancer	0	1.0
						>0 to <5 oz/month	0.86 (0.45 to 1.62)
						5 to 14 oz/month	1.69 (0.96 to 2.99)
						15 to 39 oz/month	1.45 (0.80 to 2.61)
1994 Goldbohm[36]	Netherland	204 municipal population registries throughout the country	1986–1989	120852 Women/Men (55–69yrs)	Rectal cancer	Abstainers	1.0
						0.1 to 4.9 g/day	1.2 (0.6 to 2.4)
						5.0 to 14.9 g/day	0.8 (0.4 to 1.6)
						15.0– 29.9 g/day	1.5 (0.7 to 3.2)
2003 Pederson[38]	Denmark	Copenhagen Center for Prospective Population	(~1999, median	29132 Women/Men(2	Rectal cancer	<1 drink/wk	1.00
						1 to 6 drinks/wk	1.5 (0.9 to 2.3)

		Studies (Copenhagen City Heart Study, Copenhagen Male Study, Copenhagen County Center for Preventive Medicine)	14.7yrs)	3–95yrs)		7 to 13 drinks/wk	1.5 (0.9 to 2.5)
2004 Wei[40]	US	Nurses' Health Study (NHS), Health Professionals Follow–up Study (HPFS)	NHS 1980–2000, HPFS 1986–2000	134,365 Women/Men	Rectal cancer	0	1.00
						<10 g/day	1.04 (0.77 to 1.40)
						10–19 g/day	1.07 (0.75 to 1.55)
				87733 Women		0	1.00
						<10 g/day	1.12 (0.80 to 1.58)
						10–19 g/day	0.96 (0.60 to 1.54)
				46632 Men		0	1.00
						<10 g/day	0.93 (0.47 to 1.82)
						10–19 g/day	1.31 (0.66 to 2.62)
2005 Chen[23]	China	Population of Jiashan County	1989–2001	64100 Women/Men	Rectal cancer	Nondrinkers	1.00
						occasional (<7drinks/wk)	1.20 (0.73 to 1.98)
				33148 Women		Nondrinkers	1.00
						occasional (<7drinks/wk)	1.38 (0.70 to 2.71)
				30952 Men		Nondrinkers	1.00
						occasional (<7drinks/wk)	1.15 (0.56 to 2.35)
2007 Tsong[24]	Singapore	Singapore Chinese Health Study	1993–1998	63257 Women/Men	Rectal cancer	Nondrinkers	1.00
						<7 drinks/wk	1.22 (0.17 to 2.35)
2008 Bongaerts[25]	Netherlands	Netherlands Cohort Study	1986–1999	120852 Women/Men (55–69yrs)	Rectal cancer	Abstainers	1.00
						0 to <5.0 g/day	1.10 (0.83 to 1.45)
						5.0 to 15.0 g/day	1.00 (0.74 to 1.34)
						15.0 to <30 g/day	1.04 (0.75 to 1.44)

				58279 Men		Abstainers	1.00
						0 to <30.0 g/day	1.23 (0.80 to 1.89)
				62573 Women		Abstainers	1.00
						0 to <30.0 g/day	0.90 (0.58 to 1.40)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Rectal cancer	Nondrinkers	0.94 (0.86 to 1.03)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.01 (0.92 to 1.11)
						7 to 14 drinks/wk	1.0 (0.97 to 1.18)
2009 Park[29]	UK	UK Norfolk arm of EPIC study	1995–2003	25639 Women/Men (40–79yrs)	Rectal cancer	Nondrinkers	1.00
						>0 to <7drinks/wk	0.87 (0.52 to 1.46)
						7 to <14 drinks/wk	0.96 (0.52 to 1.77)
				Men		Nondrinkers	1.00
						>0 to <7drinks/wk	1.2 (0.50 to 2.97)
						7 to <14 drinks/wk	1.42 (0.55 to 3.65)
				Women		Nondrinkers	1.00
						>0 to <7drinks/wk	0.73 (0.38 to 1.41)
						7 to <14 drinks/wk	0.68 (0.27 to 1.74)
Liver cancer							
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Liver cancer	Nondrinkers	1.41 (1.16 to 1.72)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	0.94 (0.72 to 1.21)
						7 to 14 drinks/wk	1.20 (0.93 to 1.55)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Liver cancer	Never drinkers	1.00
						<1 drink/day	1.0 (0.6 to 1.5)
						1 to 2 drinks/day	1.5 (0.9 to 2.5)

Pancreatic cancer							
2001 Michaud[42]	US	Nurses' Health Study	1980–1996	88799 Women (30–55yrs)	Pancreatic cancer	0	1.0
						0.1 to 1.4 g/day	0.72 (0.41 to 1.30)
						1.5 to 4.9 g/day	1.07 (0.68 to 1.67)
						5.0 to 29.9 g/day	0.93 (0.61 to 1.42)
		Health Professionals Follow–up Study	1986–1994	47794 Men (40–75yrs)		0	1.0
						0.1 to 1.4 g/day	1.01 (0.36 to 2.83)
						1.5 to 4.9 g/day	1.44 (0.67 to 3.12)
						5.0 to 29.9 g/day	1.23 (0.59 to 2.53)
		Pooled		136593 Women/Men		0	1.0
						0.1 to 1.4 g/day	0.78 (0.47 to 1.30)
						1.5 to 4.9 g/day	1.15 (0.78 to 1.69)
						5.0 to 29.9 g/day	1.00 (0.69 to 1.44)
2001 Stolzenberg–Solomon[43]	US	Alpha–Tocopherol Beta–Carotene Cancer Prevention Study cohort	1985–1997	27101 Men	Pancreatic cancer	None	1.0
						>0 to 5.3 g/day	1.39 (0.75 to 2.56)
						>5.3 to 13.4 g/day	1.39 (0.75 to 2.56)
						>13.4 to 27.7 g/day	1.24 (0.66 to 2.32)
2002 Isaksson[44]	Sweden	Swedish Twin Registry	1969–1997	21884 Women/Men	Pancreatic cancer	None	1.00
						1 to 209 g/month	0.89 (0.61 to 1.30)
2009 Heinen[45]	Netherlands	Netherlands Cohort Study	1986	120852 Women/Men	Pancreatic cancer	Abstainers	1.00
						0.1 to <5 g/day	1.03 (0.74 to 1.42)
						5 to <15 g/day	1.12 (0.79 to 1.57)
						15 to <30 g/day	0.86 (0.58 to 1.28)
2015 Klatsky[19]	US	Multiethnic Northern	1978–2012	124193	Pancreatic	Never drinkers	1.00

		California population (Kaiser Permanente)		Women/Men	cancer	<1 drink/day	0.9 (0.7 to 1.2)
						1 to 2 drinks/day	1.1 (0.8 to 1.5)
Lung cancer							
1990 Stemmermann[35]	US	American Men of Japanese ancestry residing in Hawaiian island (Oahu)	1965–1989	8006 Men	Lung cancer	0	1.0
						>0 to <5 oz/month	0.75 (0.48 to 1.17)
						5 to 14 oz/month	0.93 (0.59 to 1.47)
						15 to 39 oz/month	1.43 (0.99 to 2.06)
1999 Prescott[46]	Denmark	Copenhagen City Heart Study	1976–1992	13053 Women	Lung cancer	0 to <1 drinks/wk	1.0
						1 to 6 drinks/wk	0.89 (0.64 to 1.25)
						7 to 13 drinks/wk	1.00 (0.64 to 1.56)
				15107 Men		0 to <1 drinks/wk	1.0
						1 to 6 drinks/wk	0.85 (0.60 to 1.22)
						7 to 13 drinks/wk	1.01 (0.72 to 1.42)
2002 Djousse[47]	US	Framingham Study cohort, offspring cohort	1948, 1971	9238 Women/Men	Lung cancer	0	1.0
				5126 Women		0.1 to 12 g/day	1.2 (0.7 to 2.1)
				4112 Men		12.1 to 24 g/day	1.1 (0.6 to 2.1)
2005 Freudenheim[48]	US	Pooled cohort(CNBSS, IWHS, NCS, NYSC, NHS)		262432 Women	Lung cancer	None	1.00
						>0 to <5 g/day	0.78 (0.67 to 0.91)
						5 to <15 g/day	0.81 (0.68 to 0.97)
						15 to <30 g/day	0.92 (0.74 to 1.13)
		Pooled cohort(ATBC, HPFU, NLCS, NYSC)		137335 Men	Lung cancer	None	1.00
						>0 to <5 g/day	0.86 (0.71 to 1.03)
						5 to <15 g/day	1.0 (0.84 to 1.20)
						15 to <30 g/day	0.83 (0.62 to 1.10)

2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980–2000	49654 Women	Lung cancer	Never	1.00
						>0 to <5g/day	0.94 (0.69 to 1.27)
						5 to <10 g/day	0.77 (0.52 to 1.13)
						10 to <20 g/day	0.76 (0.53 to 1.11)
						20 to <30 g/day	0.81 (0.49 to 1.34)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Lung cancer	Nondrinkers	1.17 (1.12 to 1.23)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	0.91 (0.85 to 0.97)
						7 to 14 drinks/wk	1.06 (1.00 to 1.13)
2011 Chao[49]	US	VITAL Study	2000–2007	66186 Women/Men	Lung cancer	Nondrinkers	1.00
						>0 to <1 drink/day	1.00 (0.82 to 1.22)
				Women		>0 to <1 drink/day	0.94 (0.64 to 1.39)
				Men		>0 to <1 drink/day	0.84 (0.62 to 1.15)
2015 Hippisley–Cox[4]	UK	primary care patients from open cohort study using Qresearch database (EMIS computer system)	1998–2013	Men	Lung cancer	Non-drinkers	1.00
						<1 unit/day	0.91 (0.87 to 0.95)
						1–2 units/day	0.92 (0.87 to 0.97)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Lung cancer	Never drinkers	1.00
						<1 drink/day	1.0 (0.9 to 1.2)
						1 to 2 drinks/day	1.0 (0.8 to 1.2)
2016 Troche[50]	US	NIH–AARP Diet and Health Study	1995–2006	492902 Women/Men (198656 Women, 294246 Men)	Lung cancer	None	1.0
						0.01–0.49 drinks/day	0.92 (0.87 to 0.97)
						0.5–0.99 drinks/day	0.89 (0.82 to 0.96)
Breast cancer							
1989	US	Framingham Heart Study	1948	2636 Women	Breast cancer	None	1.0

Schaatzkin[51]			(32yrs)	(32–64yrs)		0.1 to 1.4 g/day	1.0 (0.6 to 1.5)
						1.5 to 4.9 g/day	0.7 (0.4 to 1.1)
1991 Simon[52]	US	Tecumseh Community Health Study (TCHS)	1959–1960 (28yrs)	1954 Women	Breast cancer	Never	1.0
						>0 to <1 drink/day	1.08 (0.64 to 1.82)
						1 to <2 drinks/day	1.23 (0.49 to 3.10)
1992 Gapstur[53]	US	Iowa Women's Health Study	1986–1989	41837 Women	Breast cancer	0	1.0
						>0 to <1.5 g/day	1.18 (0.86 to 1.61)
						1.5 to 4.9 g/day	1.20 (0.93 to 1.56)
						5.0 to 14.9 g/day	1.25 (0.93 to 1.68)
1995 van den Brandt[54]	Netherland	Netherlands Cohort Study	1986–1989 (3.3yrs)	62573 Women (55–69yrs)	Breast cancer	Nondrinkers	1.00
						>0 to <5 g/da	1.30 (0.96 to 1.75)
						5 to 14 g/day	1.29 (0.89 to 1.85)
						15 to 29 g/day	1.28 (0.81 to 2.03)
1999 Garland[55]	US	Nurses' Health Study II	1989 (6yrs)	116671 Women (25–42yrs)	Breast cancer	Nondrinker	1.00
						>0 to 1.5 g/day	0.96 (0.72 to 1.28)
						>1.5 to 5 g/day	0.78 (0.59 to 1.62)
						>5 to 10 g/day	1.01 (0.72 to 1.41)
						>10 to 20 g/day	1.12 (0.77 to 1.63)
1999 Zhang[56]	US	Framingham Original Cohort & Offspring Cohort	1948–1993, 1971–1993	5048 Women	Breast cancer	Nondrinker	1.00
						0.1 to <5.0 g/day	0.80 (0.60 to 1.10)
						5.0 to <15 g/day	0.70 (0.50 to 1.10)
2000 Rohan[57]	Canada	Canadian National Breast Screening Study (NBSS)	1980–1993	56837 Women (40–59yrs)	Breast cancer	0	1.0
						>0 to 10 g/day	1.01 (0.84 to 1.22)
						>10 to 20 g/day	1.16 (0.91 to 1.47)

						>20 to 30 g/day	1.27 (0.91 to 1.78)
2001 Feigelson[58]	US	American Cancer society Cancer Prevention Study II Nutrition Cohort (CPS–II Nutrition Cohort)	1982–1996	242010 Women	Breast cancer	None	1.0
						<0.25 drinks/day	1.1 (0.88 to 1.3)
						0.26 to <1 drink/day	1.2 (1.0 to 1.4)
						1 to <2 drinks/day	1.3 (1.1 to 1.6)
2002 Chen[59]	US	Nurses' Health Study	1980–1994	44186 Women	Breast cancer (invasive tumors)	None	1.00
						0.1 to 4.9 g/day	1.07 (0.95 to 1.20)
						5.0 to 9.9 g/day	0.99 (0.83 to 1.18)
						10 to 19.9 g/day	1.22 (1.06 to 1.42)
2002 Horn–Ross[60]	US	California Teachers Study cohort	1995–1998	111526 Women	Breast cancer	Nondrinkers	1.0
						<5 g/day	0.9 (0.7 to 1.2)
						5 to 9 g/day	0.9 (0.7 to 1.2)
						10 to 14 g/day	1.2 (0.9 to 1.6)
						15 to 19 g/day	1.0 (0.8 to 1.4)
2003 Feigelson[61]	US	American Cancer society Cancer Prevention Study II Nutrition Cohort (CPS–II Nutrition Cohort)	1992–1998	66561 Women	Breast cancer	None	1.00
						0.1 to <5 g/day	1.00 (0.88 to 1.15)
						5 to <10 g/day	0.94 (0.77 to 1.16)
						10 to <15 g/day	1.18 (0.96 to 1.46)
2004 Dumeaux[62]	Norway	Norwegian Women and Cancer Study	1991–2001	86948 Women (30–70yrs)	Breast cancer	None	1.00
						0.1 to 4.9 g/day	1.24 (1.06 to 1.44)
						5.0 to 9.9 g/day	1.35 (1.11 to 1.64)
2004 Horn–Ross[63]	US	California Teachers Study cohort	1995–2001	103460 Women (postmenopausal)	Breast cancer	Nondrinkers	1.00
						<5 g/day	1.03 (0.86 to 1.24)
						5–9 g/day	1.04 (0.86 to 1.27)
						10–14 g/day	1.08 (0.88 to 1.33)

2004 Sellers[64]	US	Iowa Women's Health Study	1986–1999	33552 Women (55–69yrs)	Breast cancer	0	1.00
						>0 to 4 g/day	1.07 (0.95 to 1.21)
2005 Suzuki[65]	Sweden	Swedish Mammography Cohort	1987–2004	51847 Women	Breast cancer (invasive tumors)	Nondrinkers	1.00
						>0 to <3.4 g/day	1.08 (0.94 to 1.25)
						3.4 to 9.9 g/day	1.10 (0.94 to 1.29)
2006 Mellemkjar[66]	Denmark	Danish Prospective Cohort Study	1993–2002	23788 Women	Breast cancer	Abstainers	0.94 (0.56 to 1.58)
						>0 to 12 g/day	1.10 (1.04 to 1.16)
2006 Stolzenberg–Solomon[67]	US	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial	1993–2001	25400 Women (55–74yrs)	Breast cancer	0 to 0.01 g/day	1.00
						>0.01 to 0.43 g/day	1.21 (0.94 to 1.57)
						>0.43 to 1.39 g/day	1.18 (0.92 to 1.51)
						>1.39 to 7.62 g/day	0.94 (0.72 to 1.22)
2007 Tjonneland[68]	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC)	-1999/2004 (6.4yrs)	274688 Women	Breast cancer (invasive tumors)	Abstainers	1.01 (0.91 to 1.13)
						>0 to 1.5 g/day	1.00
						>1.5 to 4.7 g/day	0.98 (0.89 to 1.09)
						>4.7 to 10 g/day	0.97 (0.88 to 1.08)
						>10 to 19 g/day	1.07 (0.96 to 1.19)
2007 Zhang[69]	US	Women's Health Study (US female health professionals)	1992–2004	38454 Women	Breast cancer (invasive and in situ tumors)	None	1.00
						0.1 to 4.9 g/day	1.02 (0.90 to 1.15)
						5.0 –9.9 g/day	1.13 (0.95 to 1.34)
						10.0 to 14.9 g/day	1.14 (0.92 to 1.40)
						15.0 to 29.9 g/day	1.16 (0.92 to 1.40)
					Breast cancer (invasive tumors)	None	1.00
						0.1 to 4.9 g/day	1.00 (0.88 to 1.15)
						5.0 –9.9 g/day	1.03 (0.84 to 1.25)
						10.0 to 14.9 g/day	1.16 (0.92 to 1.47)

						15.0 to 29.9 g/day	1.19 (0.93 to 1.53)
2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980–2000	49654 Women	Breast cancer	never	1.00
						>0 to <5g/day	1.00 (0.90 to 1.12)
						5 to <10 g/day	0.98 (0.86 to 1.13)
						10 to <20 g/day	1.07 (0.93 to 1.23)
						20 to <30 g/day	1.08 (0.89 to 1.32)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Breast cancer	Nondrinkers	1.00 (0.97 to 1.03)
						3 to 6 drinks/wk	1.08 (1.05 to 1.10)
						7 to 14 drinks/wk	1.13 (1.10 to 1.16)
2009 Lew[70]	US	NIH–AARP Diet and Health Study	1995–2003	184418 Women	Breast cancer	0	1.00
						>0 to 5 g/day	1.04 (0.97 to 1.10)
						>5 to 10 g/day	1.04 (0.93 to 1.16)
						>10–20 g/day	1.13 (1.02 to 1.25)
2010 Li[71]	US	Women's Health Initiative to observational study (WHI–OS)	1993–2005	87724 Women	Breast cancer	Nondrinkers	1.00
						>0 to <0.5 drinks/wk	1.02 (0.87 to 1.18)
						0.5 to 0.9 drinks/wk	1.05 (0.85 to 1.28)
						1.0 to 3.9 drinks/wk	1.10 (0.94 to 1.30)
						4.0 to 6.9 drinks/wk	1.12 (0.91 to 1.36)
						7.0 to 13.9 drinks/wk	1.27 (1.05 to 1.53)
2011 Chen[72]	US	Nurses' Health Study	1980–2008	105986 Women (30–55yrs)	Breast cancer (invasive tumors)	Nondrinkers	1.00
						0.1 to 4.9 g/day	1.07 (1.00 to 1.14)
						5 to 9.9 g/day	1.15 (1.06 to 1.26)
2011 Kawai[73]	Japan	The Miyagi Cohort Study	1990–2003	19227 Women	Breast cancer	Never	1.00
						< 5.0 g/day	1.02 (0.72 to 1.46)
						5 to <15 g/day	1.21 (0.71 to 2.08)

2013 Liu[74]	US	Nurses' Health Study II	1989–2009	91005 Women (25–44yrs)	Breast cancer	0	1.00
						0.1 to 4.9 g/day	1.08 (0.94 to 1.23)
						5.0 to 14.9 g/day	1.11 (0.94 to 1.32)
2014 Falk[75]	US	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort	1993–2009	54562 Women (55–74yrs)	Breast cancer	Never	1.00
						<0.5 drink/wk	1.15 (0.97 to 1.36)
						0.5 to <1 drink/wk	1.25 (1.03 to 1.53)
						1 to <7 drinks/wk	1.26 (1.07 to 1.49)
2014 Park[76]	US	Multiethnic Cohort in California and Hawaii	1993–2007 (mean12.4yrs)	85089 Women	Breast cancer	0	1.00
						0.1 to 4.9 g/day	0.98 (0.91 to 1.07)
						5 to 9.9 g/day	1.23 (1.06 to 1.42)
						10 to 14.9 g/day	1.21 (1.00 to 1.45)
2015 Chhim[77]	France	SU.VI.MAX	1994–2007	3771 Women	Breast cancer	0 to <3 g/day	1.00
						3 to 12 g/day	1.28 (0.82 to 2.00)
2015 Fagherazzi[78]	France	French E3N–EPIC cohort	1993–2008	66481 Women	Breast cancer	None	1.00
						10 to 20 g/day	1.02 (0.97 to 1.07)
2015 Hippisley–Cox[4]	UK	primary care patients from open cohort study using Qresearch database (EMIS computer system)	1998–2013	Women	Breast cancer	Non-drinkers	1.00
						<1 unit/day	1.05 (1.03 to 1.08)
						1–2 units/day	1.11 (1.07 to 1.15)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Breast cancer	Never drinkers	1.00
						<1 drink/day	1.1 (1.0 to 1.2)
						1 to 2 drinks/day	1.2 (1.1 to 1.4)
2015 Shin[79]	Sweden	Swedish Women's Lifestyle and Health study	1991–2009	45233 Women	Breast cancer	0	1.00
						0.1 to 5 g/day	1.03 (0.89 to 1.20)
						5.1 to 15 g/day	1.16 (0.99 to 1.36)
2016 Nitta[80]	Japan	Japan Collaborative Cohort	1988–2009	38610 Women	Breast cancer	0	1.00

		Study (JACC)				0.1 to 4.9 g/day	1.25 (0.64 to 2.41)
						5.0 to 14.9 g/day	0.49 (0.15 to 1.56)
Endometrial cancer							
1993 Gapstur[81]	US	Iowa Women's Health Study	1986–1990	25170 Women	Endometrial cancer	0	1.0
						>0 to <4.0 g/day	0.7 (0.5 to 1.1)
1999 Terry[82]	Sweden	Swedish Twin Registry	1967–1992	11659 Women	Endometrial cancer	None	1.0
						Up to 2 drinks/wk	1.7 (1.03 to 2.82)
						2 to 4 drinks/wk	1.2 (0.6 to 2.4)
2007 Loerbroks[83]	Netherland	Netherlands Cohort Study	1986–1997 (11.3yrs)	62573 Women (55–69yrs)	Endometrial cancer	No	1.00
						0.1 to 4 g/day	1.09 (0.78 to 1.52)
						5 to 14 g/day	0.95 (0.62 to 1.45)
						15 to 29 g/day	0.94 (0.52 to 1.69)
2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980–2000	49654 Women	Endometrial cancer	Never	1.00
						>0 to <5g/day	1.15 (0.88 to 1.51)
						5 to <10 g/day	1.00 (0.71 to 1.41)
						10 to <20 g/day	1.21 (0.86 to 1.68)
						20 to <30 g/day	1.34 (0.85 to 2.12)
2008 Setiawan[84]	US	Multiethnic Cohort Study in California and Hawaii	1993–2002 (ave8.3yrs)	41574 Women	Endometrial cancer	Nondrinkers	1
						<1 drink/day	1.01 (0.77 to 1.33)
						1 to <2 drinks/day	1.09 (0.62 to 1.93)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Endometrial cancer	Nondrinkers	1.06 (1.00 to 1.12)
						3 to 6 drinks/wk	0.99 (0.92 to 1.05)
						7 to 14 drinks/wk	0.90 (0.83 to 0.97)
2009 Friberg[85]	Sweden	Swedish Mammography	1987–1997	61226 Women	Endometrial	Nondrinkers	1.00

		Cohort			cancer	>0 to <3.4 g/day	1.01 (0.85 to 1.20)
						3.4 to 9.9 g/day	0.95 (0.75 to 1.19)
2011 Yang[86]	US	NIH–AARP Diet and Health study	1995–2006	114414 Women	Endometrial cancer	Nondrinkers	1.00
						>0 to <12 g/day	0.97 (0.87 to 1.09)
2014 Je[87]	US	Nurses' Health Study	1980–2010	68067 Women (34–59yrs)	Endometrial cancer	Nondrinkers	1.00
						0.1 to 4.9 g/day	0.78 (0.66 to 0.94)
						5 to 14.9 g/day	0.88 (0.71 to 1.09)
						15 to 29.9 g/day	0.83 (0.61 to 1.14)
Ovarian cancer							
2007 Chang[88]	US	California Teachers Study cohort	1995–2003	90371 Women	Ovarian cancer	None	1.00
						>0 to <10.0 g/day	1.04 (0.76 to 1.42)
						10.0 to <20.0 g/day	1.47 (1.06 to 2.03)
2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980–2000	49654 Women	Ovarian cancer	Never	1.00
						>0 to <5g/day	0.90 (0.63 to 1.29)
						5 to <10 g/day	1.33 (0.89 to 1.96)
						10 to <20 g/day	0.85 (0.54 to 1.32)
						20 to <30 g/day	1.50 (0.88 to 2.56)
2008 Tworoger[89]	US	Nurses' Health Study (NHS)	1976–2004	110454 Women	Ovarian cancer (epithelial)	<0.1 g/day	1.00
						0.1 to 4.9 g/day	1.05 (0.83 to 1.33)
						5.0 to 14.9 g/day	0.99 (0.75 to 1.30)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Ovarian cancer	Nondrinkers	0.94 (0.88 to 1.01)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	0.89 (0.83 to 0.95)
						7 to 14 drinks/wk	0.97 (0.90 to 1.05)
2015 Klatsky[19]	US	Multiethnic Northern	1978–2012	124193	Ovarian cancer	Never drinkers	1.0

		California population (Kaiser Permanente)		Women/Men		<1 drink/day	1.2 (0.9 to 1.6)
						1 to 2 drinks/day	1.2 (0.8 to 1.8)
Cervix and uterus cancer							
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Cervix cancer	Nondrinkers	1.31 (1.10 to 1.55)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.04 (0.86 to 1.27)
						7 to 14 drinks/wk	0.98 (0.79 to 1.22)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Cervix cancer	Never drinkers	1.00
						<1 drink/day	1.0 (0.8 to 1.3)
						1 to 2 drinks/day	1.0 (0.8 to 1.4)
Prostate cancer							
1990 Stemmermann[35]	US	American Men of Japanese ancestry residing in Hawaiian island (Oahu)	1965–1989	8006 Men	Prostate cancer	0	1.00
						>0 to <5 oz/month	0.87 (0.61 to 1.25)
						5 to 14 oz/month	0.86 (0.57 to 1.29)
						15 to 39 oz/month	1.02 (0.69 to 1.52)
1999 Breslow[90]	US	National Health and Nutrition Examination Survey (NHANES I)	1971–1992	5766 Men	Prostate cancer	Nondrinkers	1.00
						>0 to 1 drinks/wk	0.97 (0.67 to 1.41)
						2 to 7 drinks/wk	0.88 (0.64 to 1.21)
						8 to 14 drinks/wk	0.96 (0.61 to 1.50)
1999 Parker[91]	US	NCI's SEER program	1980-1995	1177 men	prostate cancer	none	1.0
						<22 g/week	1.3 (0.7 - 2.5)
						23-92 g/week	2.4 (1.3 - 4.2)
1999 Schuurman[92]	Netherland	Netherlands Cohort Study	1986 (6.3yrs)	58279 Men (aged55–69)	Prostate cancer	Nondrinkers	1.0
						0.1 to 4 g/day	1.1 (0.8 to 1.5)

						5 to 14 g/day	0.9 (0.7 to 1.3)
						15 to 29 g/day	1.1 (0.8 to 1.4)
2000 Ellison[93]	Canada	Nutrition Canada Survey (NCS)	1970–1993	3400 Men (50–84yrs)	Prostate cancer	0	1.00
						>0 to 9.9 mL/day	0.96 (0.63 to 1.47)
						10.0 to 24.9 mL/day	0.85 (0.50 to 1.45)
2001 Sesso[94]	US	Harvard alumni	1988–1993	7612 Men (mean 66yrs)	Prostate cancer	almost never	1.00
						1 drink/month to <3 drink/wk	1.33 (0.88 to 2.01)
						3 drinks/wk to <1 drink/day	1.65 (1.12 to 2.44)
2002 Albertsen[95]	Denmark	Copenhagen Center for Prospective Population Studies (Copenhagen City Heart Study, Copenhagen Male Study, Copenhagen County Center for Preventive Medicine)	1976–1994(mean 12.3yrs)	12989 Men (20–98yrs)	Prostate cancer	<1 drink/wk	1.00
						1 to 6 drinks/wk	0.90 (0.61 to 1.34)
						7 to 13 drinks/wk	0.86 (0.57 to 1.29)
						14 to 20 drink/wk	0.91 (0.58 to 1.44)
2004 Platz[96]	US	Health Professionals Follow–up Study	1986–1998	47843 Men (40–75yrs)	Prostate cancer	0	1.00
						0.1 to 4.9 g/day	0.99 (0.87 to 1.11)
						5.0 to 14.9 g/day	1.05 (0.94 to 1.18)
						15.0 to 29.9 g/day	1.13 (0.98 to 1.31)
2006 Weinsterin[97]	US	Alpha–Tocopherol Beta–Carotene Cancer Prevention Study cohort	1985–2002	29133 Men	Prostate cancer	Nondrinkers	1
						≤3.7 g/day	0.98 (0.8 to 1.2)
						>3 to ≤10 g/day	0.96 (0.78 to 1.17)
						>10 to ≤18.7 g/day	1.03 (0.84 to 1.26)
						>18.7 to ≤32.2 g/day	0.90 (0.83 to 1.11)
2006 Velicer[98]	US	VITAL Study	2000–2004	34565 Men	Prostate cancer	None or <1 drink/mo	1
						<1/mo to <4drinks/mo	1.26 (1.05 to 1.5)

						5 drinks/mo to 2/day	1.20 (0.99 to 1.46)
2007 Sutcliffe[99]	US	Health Professionals Follow–up Study (HPFS)	1986–2002	45433 Men	Prostate cancer	No alcohol consumption	1.00
						0.01 to 1.31 g/day	0.90 (0.74 to 1.09)
						1.32 to 2.41 g/day	1.02 (0.85 to 1.22)
						2.42 to 7.03 g/day	1.12 (0.97 to 1.29)
						7.04 to 16.4 g/day	1.16 (1.01 to 1.32)
2009 Gong[100]	US	Prostate Cancer Prevention Trial		2129 Men	Prostate cancer	No alcohol consumption	1.00
						>0 to < 3g/day	0.97 (0.85 to 1.11)
						3 to <15 g/day	0.98 (0.85 to 1.12)
						15 to <30 g/day	1.05 (0.89 to 1.23)
2010 Chao[101]	US	California Men's Health Study (CMHS)	2002–2007	65972 Men	Prostate cancer	Nondrinker	1.0
						<1 drink/day	0.98 (0.86 to 1.11)
						1 to <3 drinks/day	0.98 (0.84 to 1.15)
2010 Watters[102]	US	NIH–AARP Diet and Health Study	1995–2005	294707 Men (50–71yrs)	Prostate cancer	Nondrinkers	1.00
						>0 to <1 drinks/day	1.06 (1.01 to 1.10)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Prostate cancer	Never drinkers	1.00
						<1 drink/day	1.1 (0.9 to 1.2)
						1 to 2 drinks/day	1.1 (1.0 to 1.3)
Renal cell carcinoma							
2005 Mahabir[103]	US	Alpha–Tocopherol BetaCarotene (ATBC) Cancer Prevention STudy	1985–1999	27111 Men	Renal cell carcinoma	0 to 2.5 g/day	1.00
						2.6 to 11.0 g/day	0.91 (0.62 to 1.33)
						11.1 to 25.6 g/day	0.94 (0.64 to 1.38)
2007 Setiawan[104]	US	Hawaii–Los Angeles Multiethnic Cohort	1993–2002 (8.3yrs)	85964 Women	Renal cell carcinoma	None	1.00
						>0 to <4.2 g/day	0.75 (0.45 to 1.24)
				75162 Men		None	1.00
						>0 to <14.5 g/day	0.84 (0.61 to 1.15)

2008 Schouten[105]	Netherlands	NLCS on Diet and Cancer	1986–1997	5044 Women/Men (2415 Women, 2629 Men)	Renal cell carcinoma	No alcohol intake	1.00
						0.1 to 4.9 g/day	0.71 (0.50 to 1.00)
						5.0 to 14.9 g/day	0.66 (0.46 to 0.94)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Renal cell carcinoma	Nondrinkers	1.12 (1.00 to 1.26)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.01 (0.89 to 1.14)
						7 to 14 drinks/wk	0.93 (0.80 to 1.07)
2012 Macleod[106]	US	VITAL study	2000–2009	77260 Women/Men (50–76yrs)	Renal cell carcinoma	Nondrinkers	1.00
						1 drink/day	0.94 (0.71 to 1.26)
						2 drinks/day	0.76 (0.47 to 1.20)
2015 Karami[107]	US	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)	1993–2001	107998 Women/Men	Renal cell carcinoma	None	1
						>0 to 1.75 g/day	0.98 (0.75 to 1.29)
						>1.75 to 9.75 g/day	0.77 (0.58 to 1.02)
				Women		None	1
						>0 to 1.75 g/day	0.86 (0.58 to 1.28)
						>1.75 to 9.75 g/day	0.51 (0.30 to 0.88)
				Men		None	1
						>0 to 1.75 g/day	1.09 (0.76 to 1.58)
						>1.75 to 9.75 g/day	0.93 (0.66 to 1.31)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Renal cell carcinoma	Never drinkers	1.00
						<1 drink/day	1.0 (0.7 to 1.4)
						1 to 2 drinks/day	0.9 (0.6 to 1.4)
Bladder cancer							
1993 Chyou[108]	Japan	American Men of Japanese ancestry residing in Hawaiian island	1965~	7995 Men	Bladder cancer	0	1.0
						<15 g/day	1.31 (0.8 to 2.13)

2001 Zeegers[109]	Netherland	Netherlands Cohort Study	1986–1992	62573 Women	Bladder cancer	No alcohol	1.0
						<5 g/day	0.97 (0.56 to 1.69)
				58279 Men		No alcohol	1.0
						<5 g/day	1.49 (1.00 to 2.21)
						5–<15 g/day	1.52 (1.04 to 2.21)
						15–<30 g/day	1.16 (0.78 to 1.71)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Bladder cancer	Nondrinkers	1.06 (0.94 to 1.21)
						3 to 6 drinks/wk	1.05 (0.92 to 1.21)
						7 to 14 drinks/wk	0.91 (0.77 to 1.07)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Bladder cancer	Never drinkers	1.00
						<1 drink/day	1.2 (0.9 to 2.6)
						1 to 2 drinks/day	1.3 (0.9 to 1.7)
Thyroid cancer							
2005 Navarro Silvera[110]	Canada	Canadian National Breast Screening Study (NBSS)	~2000	89835 Women	Thyroid cancer	None	1.0
						1 to 3 g/day	1.17 (0.68 to 2.01)
						3 to 10 g/day	0.67 (0.36 to 1.22)
2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Thyroid cancer	Nondrinkers	1.10 (0.91 to 1.33)
						3 to 6 drinks/wk	0.90 (0.74 to 1.10)
						7 to 14 drinks/wk	0.70 (0.55 to 0.91)
2009 Meinhold[111]	US	NIH–AARP Diet and Health Study	1995–1996 (7.5yrs, median)	490159 Women/Men (50–71yrs)	Thyroid cancer	Nondrinkers	1.00
						>0 to <1 drink/wk	0.87 (0.66 to 1.13)
						1 to 6 drinks/wk	0.87 (0.66 to 1.16)
						1 to 2 drinks/day	0.67 (0.44 to 1.00)
				198058 Women		Nondrinkers	1.00
						>0 to <1 drink/wk	0.81 (0.58 to 1.14)

						1 to 6 drinks/wk	0.84 (0.57 to 1.24)
						1 to 2 drinks/day	0.55 (0.31 to 0.95)
				292101 Men		Nondrinkers	1.00
						>0 to <1 drink/wk	0.97 (0.62 to 1.51)
						1 to 6 drinks/wk	0.90 (0.59 to 1.38)
						1 to 2 drinks/day	0.69 (0.40 to 1.20)
2010 Meinhold[112]	US	US Radiologic Technologists Study	1983–2006	69506 Women	Thyroid cancer	Nondrinker	1.0
						<1 drink/wk	0.86 (0.62 to 1.20)
						1–6 drinks/wk	0.86 (0.60 to 1.23)
				21207 Men		Nondrinker	1.0
						<1 drink/wk	1.03 (0.45 to 2.38)
						1–6 drinks/wk	0.62 (0.25 to 1.54)
2012 Kabat[113]	US	Women's Health Initiative	1993–2002	159340 Women (50–79yrs)	Thyroid cancer	Nondrinkers	1.00
						>0 to <1 drink/wk	0.93 (0.69 to 1.25)
						1 to <7 drinks/wk	0.95 (0.72 to 1.25)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Thyroid cancer	Never drinkers	1.00
						<1 drink/day	1.0 (0.6 to 1.6)
						1 to 2 drinks/day	0.6 (0.3 to 1.1)
						1 to <4 g/day	1.01 (0.76 to 1.36)
Hematologic malignancy							
1999 Chiu[114]	US	Iowa Women's Health Study	1987–1992	41837 Women	Hematologic malignancy (NHL)	Nondrinkers	1.0
						≤3.4 g/day	0.78 (0.51 to 1.21)
2007 Lim[115]	US	NIH–AARP Diet and Health Study	1995–2000	465858 Women/Men	Hematologic malignancy (Hodgkin's lymphoma)	None	1.00
						0.1 to 1.9 drinks/wk	0.73 (0.39 to 1.36)
						2 to 7 drinks/wk	not shown
						7.1 to 14 drinks/wk	0.76 (0.37 to 1.58)

2009 Allen[2]	UK	Million Women Study	1996–2001	1280296 Women	Hematologic malignancy (Non–Hodgikin's Lymphoma)	Nondrinkers	1.03 (0.95 to 1.12)
						1 to 2 drinks/wk	1.00
						3 to 6 drinks/wk	1.02 (0.94 to 1.11)
						7 to 14 drinks/wk	0.86 (0.78 to 0.96)
						3 to 6 drinks/wk	0.93 (0.81 to 1.07)
2009 Klatsky[116]	US	members of comprehensive pre–paid health care programme in SF Bay area	1978–2006 (16.9yrs)	126293 Women/Men (mean41.0yrs)	Hematologic malignancy	never to <1 drink/month	1.00
						>0 to <1 drink/day	1.0 (0.90 to 1.20)
						1 to 2 drinks/day	0.9 (0.70 to 1.00)
				70598 Women		never to <1 drink/month	1.00
						>0 to <1 drink/day	0.9 (0.8 to 1.2)
						1 to 2 drinks/day	0.9 (0.7 to 1.2)
				55695 Men		never to <1 drink/month	1.00
						>0 to <1 drink/day	1.1 (0.9 to 1.4)
						1 to 2 drinks/day	0.9 (0.7 to 1.1)
2010 Chang[117]	US	California Teachers Study	1995–2007	102721 Women	Hematologic malignancy (B–cell NHL)	Nondrinkers	1.00
						0.1 to <5 g/day	1.16 (0.88 to 1.54)
						5 –< 10g/day	0.98 (0.73 to 1.31)
					Hematologic malignancy (multiple myeloma)	Nondrinkers	1.00
						0.1 to <10 g/day	0.65 (0.39 to 1.09)
2010 Troy[118]	US	PLCO Cancer Screening Trial	1993–2006	142982 Women/Men (55–74yrs)	Hematologic malignancy (NHL)	0 to <1 drink/wk	1.00
						1 to 3 drinks/wk	1.08 (0.85 to 1.37)
						4 to 13 drinks/wk	0.88 (0.68 to 1.14)
2012 Gapstur[119]	US	Cancer Prevention Study II Nutrition cohort	1992–2007	143124 Women/Men (50–74yrs)	Hematologic malignancy (NHL)	Nondrinkers	1.00
						>0 to <1 drink/day	0.93 (0.83 to 1.03)
						1 to 2 drinks/day	0.91 (0.78 to 1.06)
				74,785 Women		Nondrinkers	1.00

						>0 to <1 drink/day	0.95 (0.81 to 1.10)
						1 to 2 drinks/day	0.87 (0.67 to 1.14)
				68,339 Men		Nondrinkers	1.00
						>0 to <1 drink/day	0.90 (0.78 to 1.05)
						1 to 2 drinks/day	0.90 (0.75 to 1.09)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Hematologic cancer	Never drinkers	1.0
						<1 drink/day	1.1 (0.9 to 1.2)
						1 to 2 drinks/day	1.0 (0.8 to 1.2)
Malignant melanoma							
2003 Freedman[120]	US	US Radiologic Technologists (USRT) Study	1983–1998	68588 Women/Men	Melanoma	Never	1.0
						<1 to 6 drinks/wk	1.2 (0.8 to 1.8)
						7 to 14 drinks/wk	1.4 (0.8 to 2.5)
				54045 Women		Never	1.0
						<1 to 6 drinks/wk	1.2 (0.7 to 1.9)
						7 to 14 drinks/wk	1.7 (0.9 to 3.1)
				14543 Men		Never	1.0
						<1 to 6 drinks/wk	1.5 (0.7 to 3.4)
						7 to 14 drinks/wk	0.9 (0.2 to 3.0)
2014 Kubo[121]	US	Women's Health Initiative to observational study (WHI–OS)	1993–2010	59575 Women	Melanoma	Nondrinkers	1.00
						<1 drink/wk	1.10 (0.74 to 1.66)
						1 to <7 drinks/wk	1.40 (0.95 to 2.06)
					Non–melanoma	Nondrinkers	1.00
						<1 drink/wk	1.08 (0.98 to 1.20)
						1 to <7 drinks/wk	1.15 (1.05 to 1.27)
2015 Klatsky[19]	US	Multiethnic Northern California population (Kaiser Permanente)	1978–2012	124193 Women/Men	Melanoma	Never drinkers	1.0
						<1 drink/day	1.6 (1.2 to 2.1)
						1 to 2 drinks/day	1.9 (1.4 to 2.6)

S2 Table. General characteristics of the studies included in the final analysis to cancer mortality

Study	Country	Cohort	Enroll year	Population	Cancer type	Alcohol consumption amount (baseline)	RR (95% CI)
Oral cavity, pharyngeal cancer mortality							
1988 Garfinkel[122]	US	American Cancer Society's study	1959–1972	581321 Women	Oral cavity cancer mortality	None	1.00
						1 drink/day	0.40 (0.17 to 0.95)
						2 drinks/day	1.02 (0.54 to 1.94)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Lip, oral cavity cancer mortality	Nondrinker	1
						1.0 to 14.9 g/day	1.7 (0.94 to 3.05)
						15.0 to 29.9 g/day	0.82 (0.38 to 1.80)
Esophageal cancer mortality							
1988 Garfinkel[122]	US	American Cancer Society's study	1959–1972	581321 Women	Esophageal cancer mortality	None	1.00
						1 drink/day	1.37 (0.81 to 2.30)
						2 drinks/day	1.61 (0.94 to 2.77)
1990 Boffetta[124]	US	American Cancer Society	1959–1972	276802 Men	Esophageal cancer mortality	Nondrinkers	1.00
						1 drink/day	1.37 (0.81 to 2.30)
						2 drinks/day	1.61 (0.94 to 2.77)
2005 Sakata[125]	Japan	JACC Study	1988–1994	46465 Men	Esophageal cancer mortality	Nondrinkers	1
						<1.0 units/day	1.47 (0.28 to 7.68)
						1.0–1.9 units/day	1.58 (0.65 to 3.86)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Esophageal cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	1.23 (0.82 to 1.85)
						15.0 to 29.9 g/day	1.43 (0.92 to 2.22)
2013 Shen[126]	Hong Kong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men	Esophageal cancer mortality	Never	1
						Social (<1/wk)	0.95 * 0.88 to 1.03)
						Wkly social (<10g/day)	1.12 (0.91 to 1.38)
						Moderate(≤30g/day for	1.11 (0.98 to 1.27)

						Men, ≤20g/day for Women)	
				44140 Women		Never	1
						Social (<1/wk)	2.20 (0.96 to 5.06)
						Wkly social (<10g/day)	NA
						Moderate(≤30g/day for Men, ≤20g/day for Women)	2.62 (0.35 to 19.60)
				22680 Men		Never	1
						Social (<1/wk)	1.00 (0.47 to 2.14)
						Wkly social (<10g/day)	0.80 (0.11 to 6.01)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	2.94 (1.42 to 6.07)
Stomach cancer mortality							
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Stomach cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.65 (0.44 to 0.98)
						15.0 to 29.9 g/day	1.48 (0.85 to 2.57)
				919199 Men		Nondrinkers	1
						1.0 to 14.9 g/day	0.96 (0.83 to 1.11)
						15.0 to 29.9 g/day	1.00 (0.85 to 1.18)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men(22680 Men, 44140 Women)	Stomach cancer mortality	Never	1
						Social (<1/wk)	0.73 (0.50 to 1.05)
						Wkly social (<10g/day)	0.55 (0.17 to 1.73)
						Moderate (≤30g/day for Men, ≤20g/day for Women)	1.18 (0.71 to 1.95)
				44140 Women		Never	1
						Social (<1/wk)	0.96 (0.50 to 1.85)
						Wkly social (<10g/day)	NA

						Moderate (≤30g/day for Men, ≤20g/day for Women)	NA
				22680 Men		Never	1
						Social (<1/wk)	0.64 (0.41 to 1.00)
						Wkly social (<10g/day)	0.61 (0.19 to 1.94)
						Moderate (≤30g/day for Men, ≤20g/day for Women)	1.21 (0.72 to 2.04)
Colorectal cancer mortality							
1997 Camargo[127]	US	Physicians' Health Study	1981–1993	22071 Men	Colorectal cancer mortality	0	1
						1 to 6 drinks/wk	0.98 (0.56 to 1.72)
1997 Thun[128]	US	Cancer Prevention Study II	1982–1991	230552 Women	Colorectal cancer mortality	0	1
						less than daily	0.8 (0.7 to 1.0)
				226871 Men		0	1
						less than daily	1.0 (0.9 to 1.3)
						1 drink/day	1.0 (0.8 to 1.3)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Colorectal cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.99 (0.62 to 1.59)
						15.0 to 29.9 g/day	2.51 (1.31 to 4.82)
				919199 Men		Nondrinkers	1
						1.0 to 14.9 g/day	1.14 (0.90 to 1.45)
						15.0 to 29.9 g/day	1.06 (0.80 to 1.40)
2011 Breslow[129]	US	National Health Interview Survey	1988–2006	323354 Women/Men	Colorectal cancer mortality	Never drinker	1
						Light (≤3 drinks/wk)	0.86 (0.67 to 1.10)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	1.04 (0.78 to 1.39)
				184764		Never drinker	1

				Women		Light (≤3 drinks/wk)	0.74 (0.53 to 1.03)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	0.99 (0.59 to 1.68)
				138590 Men		Never drinker	1
						Light (≤3 drinks/wk)	1.05 (0.66 to 1.67)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	1.22 (0.78 to 1.91)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men (22680 Men, 44140 Women)	Colorectal cancer mortality	Never	1
						Social (<1/wk)	0.96 (0.78 to 1.18)
						Wkly social (<10g/day)	1.24 (0.75 to 2.06)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.79 (0.54 to 1.16)
				44140 Women		Never	1
						Social (<1/wk)	0.98 (0.71 to 1.35)
						Wkly social (<10g/day)	0.61 (0.15 to 2.47)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.46 (0.11 to 1.83)
				22680 Men		Never	1
						Social (<1/wk)	0.98 (0.76 to 1.28)
						Wkly social (<10g/day)	1.51 (0.87 to 2.61)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.88 (0.59 to 1.33)
2000 Gaziano[130]	US	Physicians' Health Study	1982–1990	89299 Men	Colon cancer mortality	Never	1.0
						1–3 drinks/mo	1.28 (0.61 to 2.69)
						1 drinks/wk	0.88 (0.40 to 1.93)
						2–4 drinks/wk	1.08 (0.55 to 2.11)

						5–6 drinks/wk	0.84 (0.36 to 1.97)
						1 drink/day	1.21 (0.66 to 2.20)
Liver cancer mortality							
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Liver cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.74 (0.44 to 1.22)
						15.0 to 29.9 g/day	1.80 (0.90 to 3.57)
				919199 Men		Nondrinkers	1
						1.0 to 14.9 g/day	0.92 (0.80 to 1.05)
						15.0 to 29.9 g/day	0.95 (0.82 to 1.11)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men(22680 Men, 44140 Women)	Liver cancer mortality	Never	1
						Social (<1/wk)	0.81 (0.62 to 1.06)
						Wkly social (<10g/day)	1.15 (0.63 to 2.12)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	1.16 (0.79 to 1.71)
				44140 Women		Never	1
						Social (<1/wk)	0.70 (0.42 to 1.17)
						Wkly social (<10g/day)	1.11 (0.28 to 4.54)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.83 (0.20 to 3.34)
				22680 Men		Never	1
						Social (<1/wk)	0.86 (0.62 to 1.19)
						Wkly social (<10g/day)	1.17 (0.59 to 2.32)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	1.24 (0.82 to 1.88)
Pancreatic cancer mortality							
2000 Gaziano[130]	US	Physicians' Health Study	1982–1990	89299 Men	Pancreatic	Never	1

					cancer mortality	1–3 drinks/mo	0.89 (0.40 to 1.97)
						1 drinks/wk	0.50 (0.20 to 1.25)
						2–4 drinks/wk	0.52 (0.23 to 1.15)
						5–6 drinks/wk	0.72 (0.30 to 1.72)
						1 drink/day	0.79 (0.42 to 1.49)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Pancreatic cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.66 (0.35 to 1.23)
						15.0 to 29.9 g/day	0.50 (0.12 to 2.05)
				919199 Men		Nondrinkers	1
						1.0 to 14.9 g/day	0.81 (0.61 to 1.06)
						15.0 to 29.9 g/day	0.98 (0.73 to 1.31)
2011 Gapstur[131]	US	Cancer Prevention Study II	1982–2006	1030467 Women/Men	Pancreatic cancer mortality	Nondrinkers	1
						1 drink/day	1.03 (0.91 to 1.16)
						2 drinks/day	1.04 (0.92 to 1.18)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men (22680 Men, 44140 Women)	Pancreatic cancer mortality	Never	1
						Social (<1/wk)	1.15 (0.77 to 1.71)
						Wkly social (<10g/day)	1.49 (0.54 to 4.08)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.54 (0.20 to 1.48)
				44140 Women		Never	1
						Social (<1/wk)	0.75 (0.38 to 1.48)
						Wkly social (<10g/day)	NA
						Moderate(≤30g/day for Men, ≤20g/day for Women)	NA
				22680 Men		Never	1
						Social (<1/wk)	1.59 (0.93 to 2.73)

						Wkly social (<10g/day)	2.58 (0.90 to 7.39)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.74 (0.26 to 2.09)
GB cancer mortality							
2008 Yagyu[132]	Japan	Japan Collaborative Cohort Study	1988–2003	113496 Women/Men	GB cancer mortality	None	1
				Women		0 to 5.9 g/day	1.49 (0.59 to 3.74)
						6.0 to 11.9 g/day	1.14 (0.28 to 4.70)
						12.0 to 23.9 g/day	no mortality
				Men		None	1
						0 to 23.9 g/day	0.90 (0.25 to 3.20)
						24.0 to 47.9 g/day	1.60 (0.58 to 4.44)
						48.0 to 71.9 g/day	2.13 (0.74 to 6.15)
Lung cancer mortality							
1997 Camargo[127]	US	Physicians' Health Study	1981–1993	22071 Men	Lung cancer mortality	< 1drink/wk	1
						1 to 6 drinks/wk	1.06 (0.56 to 2.00)
2000 Gaziano[130]	US	Physicians' Health Study	1982–1990	89299 Men	Lung cancer mortality	Never	1.0
						1–3 drinks/mo	0.50 (0.25– 1.01)
						1 drinks/wk	0.63 (0.34 to 1.16)
						2–4 drinks/wk	0.97 (0.60 to 1.57)
						5–6 drinks/wk	0.85 (0.48 to 1.52)
						1 drink/day	0.89 (0.58 to 1.36)
2009 Thun[133]	US	Cancer Prevention Study II	1982–2006	150247 Women	Lung cancer mortality	<1 drink/d	1.14 (0.95 to 1.35)
						1 drink/day	1.04 (0.76 to 1.43)
				72969 Men		Nondrinkers	1
						<1 drink/d	0.99 (0.78 to 1.26)
						1 drink/day	1.04 (0.71 to 1.53)

						2–3 drinks/d	0.99 (0.75 to 1.31)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Lung cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	1.29 (0.91 to 1.83)
						15.0 to 29.9 g/day	0.94 (0.45 to 1.94)
				919199 Men		Nondrinkers	1
						1.0 to 14.9 g/day	0.75 (0.66 to 0.85)
						15.0 to 29.9 g/day	0.78 (0.68 to 0.90)
2011 Breslow[129]	US	National Health Interview Survey	1988–2006	323354 Women/Men	Lung cancer mortality	Never drinker	1
						Light (≤3 drinks/wk)	0.79 (0.67– 0.92)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	0.85 (0.72 to 1.01)
				184764 Women		Never drinker	1
						Light (≤3 drinks/wk)	0.70 (0.56 to 0.89)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	0.83 (0.61 to 1.12)
				138590 Men		Never drinker	1
						Light (≤3 drinks/wk)	0.81 (0.64 to 1.02)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	0.85 (0.67 to 1.07)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men(22680 Men, 44140 Women)	Lung cancer mortality	Never	1
						Social (<1/wk)	0.85 (0.74 to 0.98)
						Wkly social (<10g/day)	0.83 (0.57 to 1.21)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.93 (0.75 to 1.16)
				44140 Women		Never	1
						Social (<1/wk)	0.91 (0.73 to 1.14)

						Wkly social (<10g/day)	NA
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.98 (0.55 to 1.75)
				22680 Men		Never	1
						Social (<1/wk)	0.82 (0.68 to 0.98)
						Wkly social (<10g/day)	0.69 (0.43 to 1.10)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.92 (0.73 to 1.16)
Breast cancer mortality							
1988 Garfinkel[122]	US	American Cancer Society's study	1959–1972	581321 Women	Breast cancer mortality	None	1
						occasional	0.96 (0.82 to 1.13)
						1 drink/day	1.18 (1.03 to 1.36)
						2 drinks/day	1.06 (0.86 to 1.30)
1995 Fuchs[134]	US	Nurses' Health Study	1980–1992	85709 Women	Breast cancer mortality	0	1
						0.1 to 1.4 g/day	0.67 (0.45 to 1.01)
						1.5 to 4.9 g/day	0.85 (0.61 to 1.16)
						5.0 to 14.9 g/day	0.96 (0.71 to 1.32)
1997 Thun[128]	US	Cancer Prevention Study II	1982–1991	230552 Women	Breast cancer mortality	0	1
						less than daily	1.1 (0.9 to 1.3)
						1 drink/day	1.2 (1.0 to 1.6)
2000 Jain[135]	Canada	National Breast Screening Study (NBSS)	1980–1993	58926 Women	Breast cancer mortality	0	1
						>0 to ≤10 g/day	1.01 (0.99 to 1.03)
						>10 to ≤20 g/day	1.04 (1.01 to 1.07)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Breast cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.82 (0.42 to 1.62)
						15.0 to 29.9 g/day	1.33 (0.46 to 3.86)
2011 Breslow[129]	US	National Health Interview	1988–2006	184764	Breast cancer	Never drinker	1

		Survey		Women	mortality	Light (≤3 drinks/wk)	0.75 (0.57 to 0.98)
						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	1.02 (0.66 to 1.57)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	44140 Women	Breast cancer mortality	Never	1
						Social (<1/wk)	0.87 (0.45 to 1.67)
						Wkly social (<10g/day)	NA
						Moderate(≤30g/day for Men, ≤20g/day for Women)	NA
Uterine cancer mortality							
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	422194 Women	Uterine cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	1.09 (0.50 to 2.35)
						15.0 to 29.9 g/day	1.10 (0.25 to 4.79)
Prostate cancer mortality							
1997 Camargo[127]	US	Physicians' Health Study	1981–1993	22071 Men	Prostate cancer mortality	0	1
						1 to 6 drinks/wk	0.88 (0.49 to 1.60)
						1 drink/day	0.6 (0.4 to 0.8)
2000 Gaziano[130]	US	Physicians' Health Study	1982–1990	89299 Men	Prostate cancer mortality	Never	1
						1–3 drinks/mo	0.56 (0.21 to 1.50)
						1 drinks/wk	0.09 (0.01 to 0.71)
						2–4 drinks/wk	0.86 (0.42 to 1.78)
						5–6 drinks/wk	0.69 (0.27 to 1.76)
						1 drink/day	1.01 (0.55 to 1.85)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Prostate cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	1.32 (0.59 to 3.00)
						15.0 to 29.9 g/day	1.75 (0.72 to 4.22)
2011 Breslow[129]	US	National Health Interview Survey	1988–2006	138590 Men	Prostate cancer mortality	Never drinker	1
						Light (≤3 drinks/wk)	0.93 (0.66 to 1.30)

						Moderate (>3–7 drinks/wk for Women, >3–14 drinks/wk for Men)	1.22 (0.86 to 1.72)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	22680 Men	Prostate cancer mortality	Never	1
						Social (<1/wk)	0.92 (0.61 to 1.39)
						Wkly social (<10g/day)	0.83 (0.26 to 2.64)
						Moderate(≤30g/day for Men, ≤20g/day for Women)	0.87 (0.46 to 1.63)
Kidney cancer mortality							
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Kidney cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.63 (0.35 to 1.12)
						15.0 to 29.9 g/day	0.46 (0.23 to 0.93)
Hematologic malignancy mortality							
2000 Gaziano[130]	US	Physicians' Health Study	1982–1990	89299 Men	Hematologic malignancy mortality	Never	1.0
						1–3 drinks/mo	1.09 (0.59 to 2.04)
						1 drinks/wk	1.08 (0.60 to 1.96)
						2–4 drinks/wk	0.87 (0.49 to 1.53)
						5–6 drinks/wk	0.70 (0.33 to 1.45)
						1 drink/day	0.67 (0.38 to 1.15)
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Hematologic malignancy (leukemia) mortality	Nondrinkers	1
						1.0 to 14.9 g/day	0.76 (0.48 to 1.20)
						15.0 to 29.9 g/day	1.00 (0.63 to 1.6)
2013 Shen[126]	HongKong	18 Elderly Health Centers of the Hong Kong Government Department of Health	1998–2012	66820 Women/Men (22680 Men, 44140 Women)	Hematologic malignancy (leukemia) mortality	Never	1
						Social (<1/wk)	1.14 (0.68 to 1.94)
						Wkly social (<10g/day)	2.45 (0.88 to 6.82)
						Moderate (≤30g/day for Men, ≤20g/day for Women)	1.70 (0.76 to 3.84)

				44140 Women		Never	1
						Social (<1/wk)	0.95 (0.43 to 2.07)
						Wkly social (<10g/day)	3.26 (0.79 to 13.48)
						Moderate (≤30g/day for Men, ≤20g/day for Women)	NA
				22680 Men		Never	1
						Social (<1/wk)	1.51 (0.70 to 3.26)
						Wkly social (<10g/day)	2.25 (0.51 to 9.91)
						Moderate (≤30g/day for Men, ≤20g/day for Women)	2.45 (1.00 to 6.00)
Laryngeal cancer mortality							
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000–2005	919199 Men	Laryngeal cancer mortality	Nondrinkers	1
						1.0 to 14.9 g/day	1.31 (0.60 to 2.85)
						15.0 to 29.9 g/day	0.87 (0.32 to 2.35)

S3 Table. Methodological quality of studies in the final analysis based on the Newcastle-Ottawa Scale - incidence

Study	Country	Cohort	Follow-up period	S1	S2	S3	S4	C	O1	O2	O3	Total score
1988 Klatsky[34]	US	members of Kaiser Permanente Medical Care Program in Northern California	1978-1984	1	1	0	0	2	1	1	0	6
1989 Schaatzkin[51]	US	Framingham Heart Study	1948-1980	1	1	1	1	2	1	1	1	9
1990 Stemmermann[35]	US	American men of Japanese ancestry residing in Hawaiian island (Oahu)	1965-1989	1	1	0	0	2	1	1	0	6
1991 Simon[52]	US	Tecumseh Community Health Study (TCHS)	1959-1960	1	1	1	0	2	1	1	0	7
1992 Gapstur[53]	US	Iowa Women's Health Study	1986-1989	1	1	0	1	2	1	0	0	6
1993 Chyou[108]	Japan	American men of Japanese ancestry residing in Hawaiian island	1965-1991	1	1	1	1	2	1	1	1	9
1993 Gapstur[81]	US	Iowa Women's Health Study	1986-1990	1	1	0	1	2	1	0	0	6
1994 Goldbohm[36]	Netherland	from 204 municipal population registries throughout the country	1986-1989	1	1	0	1	2	1	0	0	6
1995 Giovannucci[37]	US	male health professionals	1986-1992	0	1	0	1	2	1	1	1	7
1995 Nomura[11]	Japan	American men of Japanese ancestry residing in Hawaiian island	1965-1990	1	1	1	1	2	1	1	1	9
1995 van den Brandt[54]	Netherland	Netherlands Cohort Study	1986-1989	1	1	0	1	2	1	0	0	6
1998 Galanis[12]	US	Japanese residents of Hawaii	1975-1994	1	1	1	1	2	1	1	0	8
1999 Breslow[90]	US	National Health and Nutrition Examination Survey (NHANES I)	1971-1992	1	1	1	1	2	1	1	0	8

1999 Chiu[114]	US	Iowa Women's Health Study	1987-1992	1	1	0	1	2	1	1	0	7
1999 Garland[55]	US	Nurses' Health Study II	1989-1995	0	1	0	1	2	1	1	0	6
1999 Parker[91]	US	NCI's SEER program -> IOWA Cancer Registry	1980-1995	1	1	0	0	2	1	1	1	7
1999 Prescott[46]	Denmark	Copenhagen City Heart Study	196401992	1	1	0	0	2	1	1	1	7
1999 Schuurman[92]	Netherland	Netherlands Cohort Study	1986-1992	1	1	0	1	2	1	1	1	8
1999 Terry[82]	Sweden	Swedish Twin Registry	1967-1992	0	1	1	1	2	1	1	0	7
1999 Zhang[56]	US	Framingham Original Cohort & Offspring Cohort	1948-1993, 1971-1993	1	1	0	0	2	1	1	0	6
2000 Ellison[93]	Canada	Nutrition Canada Survey (NCS)	1970-1993	1	1	1	2	2	1	0	0	8
2000 Rohan[57]	Canada	Canadian National Breast Screening Study (NBSS)	1980-1993	1	1	0	0	2	1	1	0	6
2001 Feigelson[58]	US	American Cancer society Cancer Prevention Study II Nutrition Cohort (CPS-II Nutrition Cohort)	1982-1996	1	1	0	1	2	1	1	0	7
2001 Michaud[42]	US	Nurses' Health Study	1980-1996	0	1	0	1	2	1	1	1	7
2001 Sesso[94]	US	Harvard alumni	1988-1993	0	1	0	1	2	0	1	1	6
2001 Stolzenberg-Solomon[43]	US	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort	1985-1997	0	1	0	1	2	1	1	0	6
2001 Zeegers[109]	Netherland	Netherlands Cohort Study	1986-1992	1	1	0	1	2	1	1	0	7
2002 Albertsen[95]	Denmark	Copenhagen Centre for Prospective Population Studies	1976-1994	1	1	0	0	2	1	1	1	7
2002 Chen[59]	US	Nurses' Health Study	1980-1994	0	1	0	1	2	1	1	0	6
2002 Djousse[47]	US	Framingham Study cohort, offspring cohort	1948, 1971	1	1	0	0	2	1	1	0	6

2002 Flood[20]	US	Breast Cancer Detection Demonstration Project (BCDDP)	1987-1995	1	1	0	1	2	1	1	1	8
2002 Horn-Ross[60]	US	California Teachers Study cohort	1995-1998	0	1	0	1	2	1	0	1	6
2002 Isaksson[44]	Sweden	Swedish Twin Registry	1969-1997	0	1	0	0	2	1	1	0	5
2003 Feigelson[61]	US	American Cancer society Cancer Prevention Study II Nutrition Cohort (CPS-II Nutrition Cohort)	1992-1998	1	1	0	1	2	1	1	0	7
2003 Freedman[120]	US	US Raiologic Technologists (USRT) Study	1983-1998	0	1	0	0	2	1	1	0	5
2003 Otani[21]	Japan	Japan Public Health Center-based prospective study(cohort I)	1990-1999	1	1	0	1	2	1	1	1	8
2003 Pederson[38]	Denmark	Copenhagen Centre for Prospective Population Studies	1970-1999	1	1	0	0	2	1	1	1	7
2004 Dumeaux[62]	Norway	Norwegian Women and Cancer Study	1991-2001	1	1	0	1	2	1	1	0	7
2004 Horn-Ross[63]	US	California Teachers Study cohort	1995-2001	0	1	0	1	2	1	1	0	6
2004 Platz[96]	US	Health Professionals Follow-up Study	1986-1998	0	1	0	1	2	1	1	1	7
2004 Sanjoaquin[22]	UK	Oxford Vegetarian Study	1980-1999	0	1	0	1	2	1	1	0	6
2004 Sellers[64]	US	Iowa Women's Health Study	1986-1999	1	1	0	1	2	1	1	0	7
2004 Su[39]	US	National Health and Nutrition Examination Survey (NHANES I)	1982-1993	1	1	0	1	2	1	1	0	7
2004 Wei[40]	US	Nurses' Health Study, Health Professionals Follow-up Study	NHS 1980-2000, HPFS 1986-2000	0	1	0	1	2	1	1	0	6
2005 Barstad[13]	Denmark	Copenhagen Centre for Prospective Population Studies	1964-1992	1	1	0	0	2	1	1	1	7

2005 Chen[23]	China	population of Jiashan County	1989-2001	1	1	0	1	2	1	1	0	7
2005 Freudenheim[48]	US	pooled cohort(ATBC, HPFU, NLCS, NYSC)	Various	1	1	0	0	2	1	1	0	6
2005 Mahabir[103]	US	Alpha-Tocopherol BetaCarotene (ATBC) Cancer Prevention STudy	1985-1999	0	1	0	1	2	1	1	0	6
2005 Navarro Silvera[110]	Canada	Canadian National Breast Screening Study (NBSS)	1982-2000	1	1	0	0	2	1	1	0	6
2005 Suzuki[65]	Sweden	Swedish Mammography Cohort	1987-2004	1	1	0	1	2	1	1	0	7
2006 Mellemkjar[66]	Denmark	Danish Prospective Cohort Study	1993-2002	1	1	0	1	2	1	1	0	7
2006 Stolzenberg-Solomon[67]	US	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial	1993-2001	1	1	0	1	2	1	1	0	7
2006 Velicer[98]	US	VITAL Study	2000-2004	1	1	0	1	2	1	0	0	6
2006 Weinsterin[97]	US	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort	1985-2002	0	1	0	1	2	1	1	0	6
2007 Chang[88]	US	California Teachers Study cohort	1995-2003	0	1	0	1	2	1	1	0	6
2007 Freedman[1]	US	NIH-AARP Diet and Health Study	1995-2000	1	1	0	1	2	1	1	0	7
2007 Friborg[5]	Singapore	Singapore Chinese Health Study	1993-2005	1	1	1	1	2	1	1	0	8
2007 Larsson[14]	Sweden	Swedish Mammography Cohort	1987-2005	1	1	0	0	2	1	1	0	6
2007 Lim[115]	US	NIH-AARP Diet and Health Study	1995-2000	1	1	0	1	2	1	0	1	7
2007 Loerbroks[83]	Netherland	Netherlands Cohort Study	1986-1997	1	1	0	1	2	1	1	1	8
2007 Setiawan[104]	US	Hawaii-Los Angeles Multiethnic Cohort	1993-2002	1	1	0	1	2	1	1	1	8
2007 Sung[15]	Korea	National Health Insurance Corporation Study	1996-2002	1	1	0	0	2	1	1	0	6

2007 Sutcliffe[99]	US	Health Professionals Follow-up Study (HPFS)	1986-2002	0	1	0	1	2	1	1	1	7
2007 Tjonneland[68]	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC)	Various	1	1	0	0	2	1	1	0	6
2007 Tsong[24]	Singapore	Singapore Chinese Health Study	1993-1998	1	1	1	1	2	1	1	0	8
2007 Zhang[69]	US	Women's Health Study (US female health professionals)	1992-2004	0	1	0	1	2	1	1	1	7
2008 Bongaerts[25]	Netherlands	Netherlands Cohort Study	1986-1999	1	1	0	1	2	1	1	0	7
2008 Fan[8]	China	Shanghai Cohort Study	1986-2006	1	1	1	1	2	1	1	1	9
2008 Kabat[26]	Canada	Canadian National Breast Screening Study	1980-2000	1	1	0	1	2	1	1	0	7
2008 Schouten[105]	Netherlands	NLCS on Diet and Cancer	1986-1997	1	1	0	1	2	1	1	1	8
2008 Setiawan[84]	US	Multiethnic Cohort Study in California and Hawaii	1993-2002	1	1	0	1	2	1	1	0	7
2008 Thygesen[27]	US	Health Professional Follow-up Study	1986-2002	1	1	0	0	2	1	1	0	6
2008 Toriola[28]	Finland	Kuopio Ischemic Heart Study (KIHD)	1984-2005	1	1	0	1	2	1	1	1	8
2008 Tworoger[89]	US	Nurses' Health Study (NHS)	1976-2004	0	1	0	1	2	1	1	1	7
2009 Allen[2]	UK	Million Women Study	1996-2001	1	1	0	0	2	1	1	0	6
2009 Friberg[85]	Sweden	Swedish Mammography Cohort	1987-1997	1	1	0	0	2	1	1	1	7
2009 Gong[100]	US	Prostate Cancer Prevention Trial	1996-1993	0	1	0	1	2	1	1	0	6
2009 Heinen[45]	Netherlands	Netherlands Cohort Study	1986-1999	1	1	0	1	2	1	1	0	7
2009 Klatsky[116]	US	members of comprehensive pre-paid health care programme in SF Bay area	1978-2006	1	1	0	1	2	1	1	0	7
2009 Lew[70]	US	NIH-AARP Diet and Health Study	1995-2003	1	1	0	1	2	1	1	0	7
2009 Meinhold[111]	US	NIH-AARP Diet and Health Study	1995-1996	1	1	0	1	2	1	1	0	7

2009 Park[29]	UK	UK Norfolk arm of EPIC study	1995-2003	1	1	0	1	2	1	1	0	7
2010 Chang[117]	US	California Teachers Study	1995-2007	0	1	0	1	2	1	1	0	6
2010 Chao[101]	US	California Men's Health Study (CMHS)	2002-2007	1	1	0	1	2	1	1	0	7
2010 Li[71]	US	Women's Health Initiative - observational study (WHI-OS)	1993-2005	1	1	0	1	2	1	1	0	7
2010 Meinhold[112]	US	US Radiologic Technologists Study	1983-2006	1	1	0	1	2	1	1	0	7
2010 Moy[16]	China	Shanghai Cohort Study	1986-2005	1	1	1	1	2	1	1	1	9
2010 Shanmugham[3]	US	Nurses' Health Study	1980-2006	0	1	0	1	2	1	1	1	7
2010 Steevens[9]	Netherland	Netherlands Cohort Study	1986-2002	1	1	0	1	2	1	1	1	8
2010 Troy[118]	US	PLCO Cancer Screening Trial	1993-2006	1	1	0	1	2	1	1	0	7
2010 Watters[102]	US	NIH-AARP Diet and Health Study	1995-2005	1	1	0	1	2	1	1	0	7
2011 Chao[49]	US	VITAL Study	2000-2007	1	1	0	1	2	1	1	0	7
2011 Chen[72]	US	Nurses' Health Study	1980-2008	0	1	0	1	2	1	1	1	7
2011 Kawai[73]	Japan	The Miyagi Cohort Study	1990-2003	1	1	0	1	2	1	1	1	8
2011 Razzak[30]	US	Iowa Women's Health Study	1986-2004	1	1	0	1	2	1	1	0	7
2011 Yang[86]	US	NIH-AARP Diet and Health study	1995-2006	1	1	0	1	2	1	1	0	7
2012 Cho[41]	US	Health Professional Follow-up Study, Nurses' Health Study	1980-2006	0	1	0	1	2	1	1	1	7
2012 Everatt[17]	Lithuania	KRIS, MIHDP	1972-2008	1	1	1	1	2	1	1	0	8
2012 Gapstur[119]	US	Cancer Prevention Study II Nutrition cohort	1992-2007	1	1	0	1	2	1	1	0	7
2012 Kabat[113]	US	Women's Health Initiative	1993-2002	1	1	0	1	2	1	1	1	8
2012 Macleod[106]	US	VITAL study	2000-2009	1	1	0	1	2	1	1	0	7

2013 Everatt[31]	Lithuania	Kaunas Rotterdam Intervention Study (KRIS), Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)	1978-2008	1	1	0	1	2	1	1	0	7
2013 Hashibe[6]	US	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort(PLCO)	1992-2001	1	1	0	1	2	1	1	0	7
2013 Liu[74]	US	Nurses' Health Study II	1989-2009	0	1	0	1	2	1	1	0	6
2014 Falk[75]	US	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort	1993-2009	1	1	0	1	2	1	1	0	7
2014 Je[87]	US	Nurses' Health Study	1980-2010	0	1	0	1	2	1	1	0	6
2014 Kubo[121]	US	Women's Health Initiative - observational study (WHI-OS)	1993-2010	1	1	0	1	2	1	1	0	7
2014 Maasland[7]	Netherlands	Netherlands Cohort Study	1986-2003	1	1	0	1	2	1	1	1	8
2014 Nishihara[32]	US	Nurses' Health Study, Health Professionals Follow-up Study	1976-2008	0	1	0	1	2	1	1	0	6
2014 Park[76]	US	Multiethnic Cohort in California and Hawaii	1993-2007	1	1	0	1	2	1	1	0	7
2014 Yates[10]	UK	EPIC-Norfolk Study	1993-2008	1	1	0	1	2	1	1	1	8
2015 Chhim[77]	France	SU.VI.MAX	1994-2007	0	1	0	1	2	1	1	0	6
2015 Cho[33]	Korea	Korean Multi-center Cancer Cohort	1993-2005	1	1	1	1	2	1	1	0	8
2015 Eom[18]	Korea	Korean National Health Insurance Corporation data	1998-2007	1	1	0	1	2	1	1	0	7
2015 Fagherazzi[78]	France	French E3N-EPIC cohort	1993-2008	1	1	0	1	2	1	1	0	7
2015 Hippisley-Cox[4]	UK	primary care patients from open cohort study using Qresearch database (EMIS computer system)	1998-2013	1	1	1	1	2	1	1	0	8

2015 Karami[107]	US	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)	1993-2001	1	1	0	1	2	1	1	0	7
2015 Klatsky[19]	US	multiethnic Northern California population (Kaiser Permanente)	1978-2012	1	1	0	0	2	1	1	0	6
2015 Shin[79]	Sweden	Swedish Women's Lifestyle and Health study	1991-2009	1	1	0	1	2	1	1	0	7
2016 Nitta[80]	Japan	Japan Collaborative Cohort Study (JACC)	1988-2009	1	1	0	1	2	1	1	0	7
2016 Troche[50]	US	NIH-AARP Diet and Health Study	1995-2006	1	1	0	1	2	1	1	0	7

S, selection; C, comparability; O, Outcome. Refer to the following link for more information: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

S4Table. Methodological quality of studies in the final analysis based on the Newcastle-Ottawa Scale – mortality

Study	Country	Cohort	Follow-up period	S1	S2	S3	S4	C	O1	O2	O3	Total
1988 Garfinkel[122]	US	American Cancer Society's study	1959-1972	1	1	0	0	2	1	1	1	7
1990 Boffetta[124]	US	American Cancer Society	1959-1972	1	1	0	0	2	1	1	1	7
1995 Fuchs[134]	US	Nurses' Health Study	1980-1992	0	1	0	1	2	1	1	0	6
1997 Camargo[127]	US	Physicians' Health Study	1981-1993	0	1	0	1	2	1	1	0	6
1997 Thun[128]	US	Cancer Prevention Study II	1982-1991	1	1	0	1	2	1	1	1	8
2000 Gaziano[130]	US	Physicians' Health Study	1982-1990	0	1	0	1	2	1	1	0	6
2000 Jain[135]	Canada	National Breast Screening Study (NBSS)	1980-1993	1	1	0	1	2	1	1	0	7
2005 Sakata[125]	Japan	JACC Study	1988-1994	1	1	0	1	2	1	1	0	7
2008 Yagyu[132]	Japan	Japan Collaborative Cohort Study	1988-2003	1	1	0	1	2	1	1	0	7
2009 Thun[133]	US	Cancer Prevention Study II	1982-2006	1	1	0	1	2	1	1	0	7
2010 Kim[123]	Korea	Korea National Health Insurance Corporation	2000-2005	1	1	0	1	2	1	1	0	7

2011 Breslow[129]	US	National Health Interview Survey	1988-2006	1	1	1	0	2	1	1	0	7
2011 Gapstur[131]	US	Cancer Prevention Study II	1982-2006	1	1	0	1	2	1	1	1	8
2013 Shen[126]	HongKong	18 Elderly Health Centres of the Hong Kong Government Department of Health	1998-2012	1	1	1	0	2	1	1	0	7

S, selection; C, comparability; O, Outcome. Refer to the following link for more information: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

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