Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Hamid Jalalian Javadpour

The Role of Ginseng in Cancer Prevention:

A systematic review and meta-analysis of observational studies and randomized controlled trials

Master's thesis in Pharmacy
Supervisor: Abhijit Sen
Co-supervisor: Dagfinn Aune
April 2022

NTNU
Norwegian University of Science and Technology

Hamid Jalalian Javadpour

The Role of Ginseng in Cancer Prevention:

A systematic review and meta-analysis of observational studies and randomized controlled trials

Master's thesis in Pharmacy
Supervisor: Abhijit Sen
Co-supervisor: Dagfinn Aune
April 2022

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

Table of Contents

List of figures

List of tables

List of abbreviations

ACF	Aberrant crypt foci
CI	Confidence interval
Cyclin kinase D1	A protein involves in the cell cycle
Cyclin dependent kinase (Cdk) inhibitor $p21^{WAF1/CIP1}$	An antiestrogen-regulated inhibitor of Cdk4 in human breast cancer cells.
Cdk6	Cyclin Dependent Kinase 6
DEN	Dietyl-nitrosamine
DNA	Deoxyribonucleic acid
HR	Hazard ratio
HRT	Hormone replacement therapy
CRC	Colorectal cancer
COX-2	Cyclooxygenase-2 inhibitor enzyme
LNCaP cell line	Prostate adenocarcinoma cell line
MGC-803 cell	Gastric cancer cell line
MCF-7 cell	Breast cancer cell line
iNOS	Inducible nitric oxide synthase
NF-*k*B	Nuclear factor kappa-light-chain-enhancer of activated B cells
OR	Odds ratio
PARP	Poly (ADP-ribose) polymerase
PCNA	Proliferating cell nuclear antigen
P21	A protein involves in the G cell cycle
P27	A key regulator of cell proliferation
PC3 xenograft tumors	PC3 cell line contains prostate
tumorsRb2/p130	Tumor suppressor gene
RR	Relative risk
RCT	Randomized controlled trial
RNA	Ribonucleic acid
Rg-3	Ginsenoside
Rh	Ginsenoside
4-XL-PPD	A novel ginsenoside
25-OH-PPD	25-hydroxyprotopanaxadiol

Preface

This master thesis has been conducted at Norwegian University of Science and Technology (NTNU), Department of Public Health and Nursing in Trondheim.

I gratefully acknowledge Dr. Abhijit Sen at NTNU and Dr. Dagfinn Aune at Imperial College London in the UK for their great supervision and motivation throughout my master thesis.

Summary

Background: Ginseng has traditionally been used as a strengthening tonic to increase energy, lower blood sugar and improve overall health. Some studies, have suggested that ginseng may reduce the risk of developing certain cancers, however, the available evidence is not entirely consistent. The aim of this project was to conduct a systematic review and meta-analysis of observational studies (case-control, cohort) and experimental studies (randomized controlled trials) to address the impact of ginseng on cancer risk.

Methods: PubMed and Embase databases were searched for relevant articles up to March 30th, 2022. Summary relative risks (RRs) and 95% confidence intervals (CIs) were estimated to assess the association between ginseng use and cancer incidence using random effects models.

Results: Eight publications (7 studies) with 4954 cancer cases and 235264 participants were included in the analyses. The summary of RR was 0.49 (95% CI: 0.43-0.55, I^2=0%, n=3) for total cancer, 0.54 (95% CI: 0.27, 1.06, I^2=85.3%, n=4) for stomach cancer, 0.63 (95% CI: 0.35, 1.14, I^2=49.9%, n=3) for colorectal cancer, 0.63 (95% CI: 0.38, 1.05, I^2=33.9%, n=3) for liver cancer, 0.56 (95% CI: 0.33, 0.96, I^2=73.1%, n=4) for lung cancer and 0.69 (95% CI: 0.55, 0.87, I^2=0.0%, n=2) for breast cancer. The summary RR per 12 times/year was 0.47 (95% CI: 0.42-0.54, I^2=0%, n=2) for the dose-response analysis of frequency of ginseng use and total cancer risk. There was some indication of a nonlinear association between frequency of ginseng use and total cancer risk, although the test for nonlinearity was only borderline significant (p=0.07), and there was a 62% reduction in risk at a frequency of 12 times/year compared to no intake, but no further reduction in risk at intakes up to 15 times/year.

Conclusion: These results suggest that use of ginseng is associated with a statistically significant 51% reduction in risk of total cancer, a 44% reduction in risk of lung cancer, and 31% reduction in breast cancer risk and non-significant 37-46% reductions in risk of stomach, colorectal, and liver cancer. However, further cohort studies and randomized trials are needed before firm conclusions can be made.

Sammendrag

Bakgrunn: Ginseng har tradisjonelt blitt brukt for å få mer energi, redusere blodsukkeret og styrke helsen generelt. Noen studier har vist at ginseng kan redusere risikoen for å utvikle enkelte kreftformer, men de tilgjengelige funnene er ikke helt konsistente. Målet med dette prosjektet var derfor å gjennomføre en systematisk litteraturgjennomgang og meta-analyse av observasjonsstudier (kasus-kontroll-og kohort studier) og eksperimentelle studier (randomiserte kontrollerte studier) for å undersøke effekten av ginseng på kreftrisiko.

Metode: PubMed og Embase databaser ble søkt for relevante artikler frem til 30 mars, 2022. Samlede relativ risiko (RR) estimater og 95% konfidensintervall (KI) ble estimert for å studere sammenhengen mellom bruk av ginseng kreftinsidens ved å bruke en «random-effects model».

Resultat: Åtte publikasjoner (7 studier) med 4954 krefttilfeller og 235264 deltakere ble inkludert i analysene. Samlet RR var 0.49 (95% KI: 0.43-0.55, I^2=0 %, n=3) for total kreft, 0.54 (95% KI: 0.27, 1.06, I^2=85.3%, n=4) for magesekkreft, 0.63 (95% KI: 0.35, 1.14, I^2=49.9%, n=3) for kolorektal kreft, 0.63 (95% KI: 0.38, 1.05, I^2=33.9%, n=3) for leverkreft, 0.56 (95% KI: 0.33, 0.96, I^2=73.1 %, n=4) for lungekreft og 0.69 (95% KI: 0.55, 0.87, I^2=0.0 %, n=2) for brystkreft. Samlet RR per 12 ganger i året var 0.47 (95% KI: 0.42-0.54, I^2=0 %, n=2) for dose-responsanalysen av frekvensen av ginsengbruk og total kreftrisiko. Det var en viss indikasjon for en ikke-lineær sammenheng mellom frekvens av ginseng bruk og total kreftrisiko, selv om testen for ikke-linearitet var marginalt signifikant (p=0.07), og det var en 62% reduksjon i risiko med en frekvens på 12 ganger i året sammenlignet med intet inntak, men ingen ytterligere reduksjon i risiko ved inntak opptil 15 ganger i året.

Konklusjon: Disse resultatene tyder på at bruk av ginseng er assosiert med en statistisk signifikant 51% reduksjon i risiko for total kreft, en 44% reduksjon i risiko for lungekreft og 31% reduksjon i brystkreft risiko og ikke-signifikant 37-46% reduksjoner i risiko for magesekkreft, kolorektal kreft og leverkreft. Imidlertid, trengs det flere kohort-studier og randomiserte kontrollerte studier før klare konkusjoner kan trekkes.

1. Introduction

1.1. Cancer prevalence, incidence and mortality

Cancer is a major cause of morbidity and the second leading cause of death globally with 19.3 million incident cases and 10 million deaths observed in 2020 (Sung et al., 2021). The prevalence of cancer is estimated to increase by approximately 38% by 2040 due to improved life expectancy, increases in population size, and changes in risk factors, including more obesity, less physical activity, unhealthy dietary changes as well as a higher alcohol consumption and tobacco smoking in certain countries (Ferlay et al., 2019; Ilbawi, 2020; NIPH, 2018). The most common cancer globally in 2020 was breast cancer with an estimated 2.26 million cancer cases, while lung cancer accounted for 2.2 million cases, prostate cancer accounted for 1.4 million cases, colorectal cancer accounted for 1.82 million cases, stomach cancer accounted for 1.09 million cases, and liver cancer accounted for 0.9 million cases (Ferlay et al., 2019; Sung et al., 2021). There are both differences and similarities in cancer incidence by sex globally. While prostate cancer was the most frequently diagnosed cancer among men in 112 countries, followed by lung cancer in 36 countries, and colorectal cancer and liver cancer each in 11 countries in 2020, breast cancer was the most commonly diagnosed cancer and the leading cause of cancer death in women, followed by colorectal and lung for incidence, and mortality (Sung et al., 2021).

The large variation in the rates of cancer across globe, and the observation that the incidence of several cancers has changed substantially over time suggests that modifiable risk factors play an important role in cancer etiology (GLOBOCAN, 2021; Liu et al., 2020). Asian countries have lower rates of colorectal, breast, lung, prostate cancers, but higher rates of esophageal, stomach and liver cancer, than European countries and North America (GLOBOCAN, 2021; Liu et al., 2020). Secular trend studies from Japan and China have suggested substantial increases in the risk of colorectal, breast, lung and prostate cancers over time, concurrent with changes in diet and lifestyles. However, reductions in the rates of esophageal and stomach cancer have been observed over time (GLOBOCAN, 2021; Liu et al., 2020). These studies suggested that the importance of modifiable risk factors, and hence prevention strategies in reducing cancer incidence and death.

1.2. Risk factors for cancer

Tobacco smoking, exposure to UV sunlight, carcinogenic asbestos substances, excess alcohol intake, low physical activity, obesity, inadequate intake of fiber-rich foods, whole grains and fruits and vegetables, high consumption of red and processed meat and salted foods, and hormone replacement therapy (HRT) are some of the known risk factors associated with various cancer types (Lizama et al., 2020).

Physical activity has a beneficial effect on cancer risk by reductions in circulating oestrogen levels, insulin resistance and inflammation, and these mechanisms are linked to cancer development in various anatomical sites in case of increased levels (WCRF, 2018). For example, physical activity improves insulin sensitivity and reduces fasting insulin and oestrogen levels which may associated with reduction in the risk of breast cancer. Also, physical activity and not being obese may reduce the risk of stomach, breast, endometrial, kidney, bladder, colon and esophageal cancers (WCRF, 2018).

Smoking tobacco can cause cancers of the mouth and throat, laryngeal, esophageal, stomach, kidney, pancreas, liver, bladder, cervix, colon and rectum, and leukaemia (CDC, 2016). Lung cancer is one of the major cancer related deaths among men and women, with smoking as the main risk factor (OECD, 2019). The role of tobacco smoking in the development of lung cancer is due to presence of several carcinogen compounds in tobacco smoke. The major concerns are the tobacco-specific N-nitrosamines formed by nitrosation of nicotine, specially 4-(methylnitrosamino)-1(3-pyridyl)-1-butanone during tobacco processing and smoking and induction of lung cancer. Carcinogenesis compounds from tobacco may damage to DNA structure through their metabolites, and formation of free radical damage (Bade & Dela Cruz, 2020).

Alcohol consumption is associated with various cancer types like larynx, stomach, head and neck, mouth and pharynx (NIH, 2021a). Increased alcohol consumption may lead to various cancer types by diverse mechanisms including production of genotoxic and carcinogenic metabolites like acetaldehyde which can be carcinogenic to cells like colonocytes due to conversion of ethanol to acetaldehyde by colonic bacteria (WCRF, 2018). Alcohol drinks may also induce oxidative stress through increase production of reactive oxygen species damage DNA, trigger inflammation which recognized as a hallmark and linked to various

cancer types including gastric cancer, colon cancer and even pathogenesis of ovarian cancer (WCRF, 2018). Furthermore, excess alcohol consumption may reduce apoptosis and involve in folate deficiency which might to contribute to genome instability (WCRF, 2018).

Obesity is also major risk factor for cancer development via inflammatory mediators, and cause of metabolic and endocrine abnormalities, that lead to promotion of cell growth and trigger anti-apoptotic effects (WCRF, 2018). This may result that cancer cells do not self-destruct even in case of severe DNA damage in cells. Obesity is related to different cancer types including gastric cancer, breast cancer, endometrial cancer, kidney cancer, bladder cancer, colorectal cancer, and esophageal cancer, liver cancer, multiple myeloma, pancreatic cancer (NIH, 2021b).

Being physically active, consuming wholegrains and foods containing dietary fibre, use of dairy products, and limiting consumption of red or processed meat as well as taking calcium supplements are related to reduced risk of colorectal cancer (WCRF, 2018). There is also strong evidence that being obese and consuming alcoholic drinks increases risk for the mouth, pharynx, larynx and liver cancers (Pelucchi et al., 2006; WCRF, 2018).

Diet plays an important role in gastric cancer prevention and management. Increasing evidence from epidemiological studies indicated that natural dietary products including fruits, vegetables, spices, soy, cereals and edible fungi have anti-cancer activity (Mao et al., 2020). On the other hand, a study from Asia suggested that consumption of food preserved by salting such as meat, fish, vegetables and general salt processed foods are associated with stomach cancer. Also, consumption of foods contaminated with aflatoxins is associated with liver cancer risk (WCRF, 2018).

In addition to these established risk factors for cancer, it has been speculated that certain characteristics of Asian populations, such as high consumption of soy foods, use of curcumin, as well as use of ginseng could reduce cancer risk, however, current data on these factors is limited (GLOBOCAN, 2021; Liu et al., 2020).

1.3. Treatment of cancer

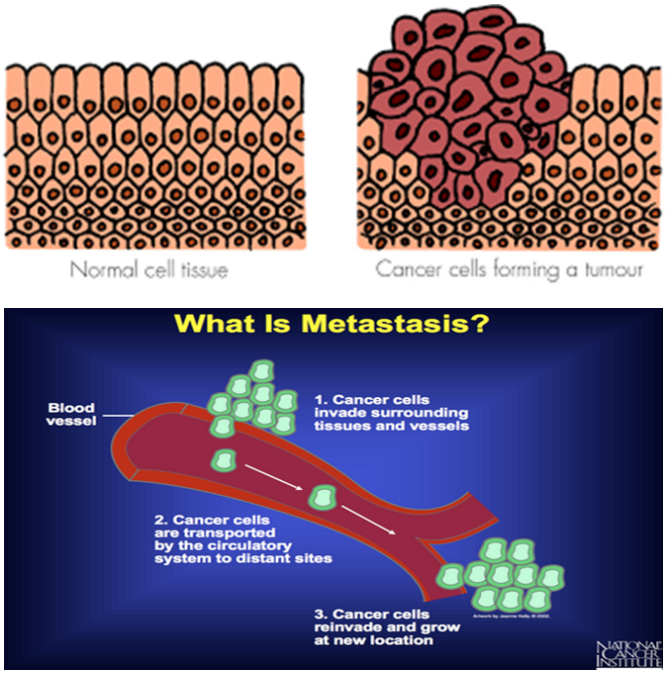
Currently, the treatment of cancer types is based on chemotherapeutic agents, radiotherapy, surgical removal and lately gene therapy, immune therapy or even stem-cell therapy (Jenq & van den Brink, 2010; Lo et al., 2012; Yun, 2001). Despite the comprehensive and innovative treatment available, there are still many patients who do not show adequate response to such therapies. On the other hand, many cancer patients who have experienced side effects such as fatigue, vomiting nausea generally have a reduced quality of life following such therapies both in an early and late lifetime (Lo et al., 2012; Yun, 2001).
Importantly, the overall survival prognosis differs from one cancer type to another, despite today's enabling cancer therapies, showing the necessity of supplementary treatment to improve and to prolong a patient´s survival rate after diagnosis (Park et al., 2020; Zhang et al., 2017).

Herbs used in traditional Chinese medicine such as *Oldenlandia diffusa, Astragalus membranaceus, Ganoderma lucidum, Curcuma longa* (turmeric) have been used for treatment of various diseases. In recent years, there have been many clinical trials investigating the pharmaceutical effect of medical herbs like ginseng, *Scutellaria barbata*, a perennial herb in the family *Lamiaceae* and *Panax notoginseng* in cancer prevention and treatment (Chen et al., 2017; Liu et al., 2019; Wang et al., 2007; Yun, 2001).

1.4. Hallmarks of cancer

Cancer is a multifactorial disease, resulting from the combined influence of genetic and environmental factors and which have specific characteristics, or hallmarks, that are specific to the development of cancer (Sarkar et al., 2013; Seyfried & Huysentruyt, 2013). The DNA mutation is central in the development of cancer. The manifestation of cancer appears when pro-oncogenes are activated and/or tumor suppressor genes are deactivated, modifying normal cell cycle progression as well as inactivation of apoptotic mechanisms in human cells. Cancerous cells invade and spread from the primary tumor to healthy tissues and distant organs with their metastatic properties, causing changes and destruction of the normal cells. The outcome of these events leads to cancer morbidity and mortality (HHP, 2021; Sarkar et al., 2013) (**Figure 1**).

Figure 1. Different between normal cells and cancer cells and metastasis in cancer cells.



There are other hallmarks of cancer, for example, epigenetic alteration, where a small change in DNA residues transfer pro-cancer characteristics to the next generation and may result in the initiation of carcinogenesis (HHP, 2021; Sarkar et al., 2013).

1.5. Ginseng

Ginseng is the root of the Araliaceous plant and have traditionally been used in China and other Asian countries as a strengthening tonic, prophylactic agent and restorative to increase energy, lower blood sugar and boost immunity (Bahrke & Morgan, 1994). More recently, a potential role of ginseng in cancer prevention and treatment has been investigated in several epidemiological studies (Lo et al., 2012; Yun, 2001, 2003; Yun & Choi, 1990, 1995, 1998; Yun, Choi, et al., 2001; Zhang et al., 2017). The name ginseng is adapted from a Chinese term referring to the man-like shape of the root (Wang et al., 2016). Traditionally, the ginseng root was available in white or red, where white ginseng is prepared by air-drying, while red ginseng is prepared by a steaming or heating process (Wang et al., 2016). Commercially available preparations of ginseng in the market can be found in the form of fresh slices, juice, extract (tincture or boiled), powder, tea, tablet, capsule and other formulations. Roots are graded according to their source, age, part of root and method of preparation. Therefore, the chemical composition of commercial ginseng products is variable because of the genetic nature of the plant source, the cultivations methods and conditions as well as the drying and curing process(Bahrke & Morgan, 1994).

In Korea, two years old fresh ginseng has been used in a meal named samketang, the special chicken-ginseng soup (Chen et al., 2014; Shin et al., 2000). In Norway, ginseng is use as an energizing supplement and available at pharmacy stores with the name Gerimax, and manufacturer added magnesium and B vitamins to this product. There exist 13 species of ginseng belong to Araliaceae family around the world. The most important ginseng is Panax ginseng C. A. Meyer, which is grown in Korea, Japan, China Russia, the USA and Germany. Three types of Panax ginseng C. A. Meyer are shown in **Figure 2**.

Panax quinquefolius (American ginseng) found in southern Canada and the USA and L, P. japonicus C A Meyer (Japanese ginseng) grown in Japan (Yun, 2001).

Ginseng is rich in active biopharmaceutical substances with pharmacological properties such as neuroprotection and memory enhancer effects on the central nervous system, antipsychotic action, sedative effects, protection from stress ulcers, increase gastrointestinal motility, antifatigue actions, endocrinological effects, enhancement of sexual behaviour, acceleration of metabolism, formation of carbohydrates, lipids, RNA, and proteins (Rokot et al., 2016; Yun, Choi, et al., 2001).

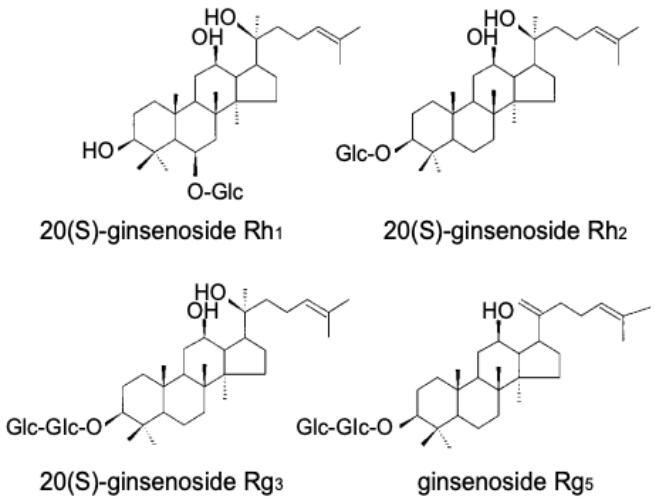
Figure 2. Fresh ginseng (left), white ginseng (center), and red ginseng (right) are tree types of Panax ginseng C.A. Meyer in Korea.

Ginseng is a source of various substances including ginsenosides, polysaccharides, flavonoids, volatile oils, amino acids, and vitamins. A series of saponin glycosides collectively known as the ginsenosides appear to be the main pharmacologically active compound in ginseng and hence responsible for pharmaceutical properties in ginseng species (Shin et al., 2000). Saponin, a triterpenoid glycosides of dammarane type with glucose, arabinose, xylose or rhamnose named ginsenoside-Rx in ginseng species was reported by Shibata and Tanaka's group in 1965 (Chen et al., 2014).

Red ginseng is thought to involve in anti-inflammatory and anti-carcinogenesis pathways by scavenging reactive oxygen species, reducing COX-2 inhibitor, inducible nitric oxide synthase (iNOS), and transcription factor NF-*k*B, which results in inhibition of cell proliferation and pose anti-angiogenetic effect (Wang et al., 2016). There are several possible mechanisms by which ginseng may influence the carcinogenic processes in various cancers from *in-vitro* to animal studies, as discussed later.

A series of ginsenosides were discovered in red ginseng such as 20(S)-ginsenoside Rg_3, ginsenosides Rh_2, Rs_1, or Rs_2, Rs_3, Rs_4, and Rg_5, plus notoginsenoside-R4 in protopanaxadiol group, and 20(R)-ginsenoside Rg_2, (R)-ginsenoside-Rh_1, ginsenoside Rh_4 and F_4 in protopanaxatriol group. However, malonyl ginsenoside- Rb1, -Rb2, -Rc, and Rd are only presented in white ginseng (**Figure 3**) (Yun, Lee, et al., 2001).

Figure 3. Chemical structure of ginsenoside Rh1, Rh2, Rh3 and Rg5 GIc-; β-D-glucopyranosyl-, GIc-GIc-; β-D-glucopyranosyl (1→2) β-D-glucopyranosyl-.



Korean ginseng (Panax ginseng C.A. Meyer) has been used as nutritional supplement to prolong human life and enhance body functions. Intake of ginseng has also been claimed to be useful in the treatment of stress, fatigue, diabetes mellitus as well as cancer (Lee et al., 2010; Yun, 2003). Additionally, ginseng has medical effects to strengthen the immune system and cardiovascular system (Cui et al., 2006).

In vivo study (mice studies) on anticarcinogenic properties of Panax ginseng C.A. Meyer have shown significantly 22% reduction in the incidence of lung adenoma following ginseng treatment, and significantly 75% reduction in the incidence of liver cancer (Wu et al., 2001; Yun, Lee, et al., 2001).

1.6. Epidemiological studies of ginseng use and cancer incidence

Epidemiological observational studies suggest a beneficial effect of ginseng in the prevention of different cancer types (Brasky et al., 2010; Yun, 2001; Yun & Choi, 1990, 1995, 1998; Yun, Choi, et al., 2001; Zhang et al., 2017). A case-control study conducted by Yun & Choi published in 1990 including 905 cases and 905 controls reported an odds ratio (OR) for any cancer of 0.56 (95% CI, 0.45-0.69) for individuals who consumed ginseng compared to those who did not use ginseng (Yun & Choi, 1990). The same study with longer recruitment period (5.4 years) including 3974 participants (1987 cases, 1987 controls) estimated OR of any cancer to be 0.50 (95% CI, 0.44-0.58) for patients who had used ginseng versus those who did not consume ginseng (Yun & Choi, 1995). Regarding specific cancers, ORs were 0.47 (95% CI, 0.29-0.76) for cancer of the lip, oral cavity, and pharynx, 0.20 (95% CI, 0.09-0.38) for esophageal cancer, 0.36 (95% CI, 0.25-0.52) for stomach cancer, 0.42 (95% CI, 0.24-0.74) for colorectal cancer, 0.48 (95% CI, 0.33-0.70) for liver cancer, 0.22 (95% CI, 0.05-0.95) for pancreatic cancer, 0.18 (95% CI, 0.06-0.54) for laryngeal cancer, 0.55 (95% CI, 0.38-0.79) for lung cancer, and 0.15 (95% CI, 0.04-0.60) for ovarian cancer respectively (Yun, 1996).

With respect to ginseng products, ORs for cancer were 0.37 (95% CI, 0.29-0.46) for fresh ginseng extract user, 0.57 (95% CI, 0.48-0.68) for white ginseng extract users, 0.30 (95% CI, 0.22-0.41) for white ginseng powder users, and 0.20 (95% CI, 0.08-0.50) for red ginseng users. However, no significant reductions in cancer risk observed by using fresh ginseng slices, fresh ginseng juice, and white ginseng tea (Yun, Choi, et al., 2001).

A cohort study led by the same researchers including 4634 participants and 137 cancer cases that occurred after mean follow-up of 5.4 years found a relative risk (RR) of 0.40 (95% CI, 0.28-0.56) for ginseng use compared to non-users (Yun & Choi, 1998). Furthermore, there was a dose-response relationship between increasing frequency of use and reduced cancer risk with RRs of 0.46 (95% CI, 0.30-0.69), 0.35 (95% CI, 0.21-0.58) and 0.34 (95% CI, 0.20-0.59) for intakes 1-3 times/year, 4-11 times/year, 1 time/month or more, respectively compared to those who did not use ginseng. Moreover, the reduced risk was reported for stomach cancer (0.33, 95% CI, 0.18-0.57) and lung cancer (0.30, 95% CI, 0.14-0.65), but not for liver cancer (0.86, 95% CI, 0.25-2.94) (Yun & Choi, 1998).

An analysis of the VITamins And Lifestyle (VITAL) study from USA including 66,227 participants suggested a reduced risk for haematological cancers following ginseng use (588 cases, HR 0.79, 95% CI, 0.55-0.88) (Walter et al., 2011). In contrast, some cohort studies reported no association in relation to risk of some other cancer types. For instance, in the Shanghai Women's Health Study from China including 74942 women there was no association between ginseng use and stomach cancer risk (153 cases, HR, 1.03, 95% CI, 0.73-1.44) (Kamangar et al., 2007). Similarly, a study from US including 76512 men and women reported no association with lung cancer (665 cases, HR, 0.97, 95% CI, 0.70-1.33), and colorectal cancer risk (428 cases, HR, 0.86, 95% CI, 0.56-1.33) (Satia et al., 2009). Another study from US including 35016 participants reported no association with breast cancer risk following former use of ginseng (880 cases, HR 0.91, 95% CI, 0.58-1.44), current ginseng use HR 0.94 (95% CI, 0.61-1.46) compared to non-users (Brasky et al., 2010).

Although two previous meta-analyses found on ginseng use and risk of various cancers and for liver cancer, they both had some methodological issues (errors) and limitations. No dose-response analyses were conducted in these studies either. We therefore conducted a systematic review and meta-analysis of the available 2 case-control, 4 cohort and 1 RCT studies to investigate the association of ginseng intake and risk of various cancers. Additionally, the dose-response analysis of frequency of ginseng use and total cancer was performed.

Aim of this study

The aim of this project was to conduct a systematic review and meta-analysis of observational studies (case-control, cohort) and randomized controlled trials to address the impact of ginseng on cancer incidence.

Research question

Is the use of ginseng associated with the risk of developing cancer in the general population?

2. Material and methods

2.1 Meta-analysis

Meta-analysis is a quantitative method that combines the results from several independent studies into a combined summary estimate or treatment effect (e.g. trials). Effect estimates that can be combined include odds ratios, hazard ratios, risk ratios, or risk differences (Egger et al., 1997).

Differences in therapeutic response between control and test groups subjected to different exposures or treatment strategies can be assessed by estimating a combined estimated treatment effect from individual studies. In other words, meta-analysis provides a tool for helping to understand and quantify treatment effects or summary estimates as well as to identify sources of variability in results across studies (Stroup et al., 2000). Meta-analyses therefore provide a more objective appraisal of the evidence than traditional narrative reviews, by providing an overall estimate of a treatment effect, and by investigating potential sources of heterogeneity between studies. However, meta-analyses may be prone to some type of bias including publication bias or small study bias as well as reporting biases (Egger et al., 1997). Publication bias is when usually smaller studies with null results or opposite results of what is generally observed remains unpublished as researchers may not prioritize to write up manuscripts that are inconsistent with the prevailing literature. This can lead to exaggerated summary estimates in many cases, but the impact on the summary estimates depends on the degree of publication bias. In addition, if the quality of the included studies is poor, the summary estimate may not be reliable.

The goal of the random-effects model is to estimate the mean of distribution effect of selected publications by summarizing effect sizes from each study and represent these as a summary estimate. Hence, seven observational studies and one RCT study were used to perform meta-analysis, confidence intervals (95% CI), relevant data, adjusted confounders, and other relevant parameters were reported from selected publications included in this master thesis.

2.2 Search strategy

PubMed and Embase databases were searched for relevant articles up to 23.05.2020, and updated to 30. March 2022 to include any relevant studies that were published after the initial search. The literature search was conducted by using a set of search terms such as: "Ginseng AND (cancer OR tumor OR carcinoma)" as well as terms for specific cancer types. The full search strategy is presented in **Supplement A and B**. Retrieved publications were imported in Reference Manager 11 to screen the potentially relevant studies according to the inclusion criteria.

2.3. Inclusion and exclusion criteria in study selection

Inclusion and exclusion eligibility criteria were established based on the study protocol in order to determine which studies should be included or excluded in this meta-analysis.

2.3.1. Inclusion criteria

To be included in the meta-analysis, the study had to be a case-control study, cohort study, or a randomized trial reporting on the association between ginseng use and cancer risk. Three case-control publications on ginseng intake and cancer were from the same study (Yun & Choi, 1990, 1995; Yun, Choi, et al., 2001), and the study with the largest number of cancer cases and controls was used.

2.3.2. Exclusion criteria

Certain studies were not included in the meta-analysis and reasons for exclusion are cross-sectional studies, reviews, meta-analyses, animal, *in-vitro* and *ex-vivo* studies. Also, studies in others language than English or duplicate studies were excluded.

2.4. Literature search screening

A total of 5606 scientific articles were systematically reviewed and screened manually in Reference Manager 11 program as part of the study selection procedure in order to identify relevant publications for this project. In the first part of the screening procedure, studies were selected based on whether the title and abstract of the articles appeared to be potentially relevant for the project (reported on ginseng and cancer risk). In the second part of the screening, the full text articles of the potentially relevant studies were obtained and inspected and were excluded if they did not meet the criteria for study designs to be included (e.g.

cross-sectional studies, reviews, meta-analyses were excluded). Each record was judged and coded as included or excluded based on the following inclusion criteria described above.

2.5 Data extraction

Relevant data was extracted from each study including name of the first author, publication year, geographic location, name of the study, recruitment and follow-up period, sample size, age, sex, number of cancer cases, type of ginseng product, frequency and duration of use og ginseng products, relative risk (RR) estimates and 95% confidence intervals, and list of adjusted confounders.

2.6 Statistical methods

A random effects model, which take into account heterogeneity within and between studies, was used to calculate summary RRs and 95% confidence intervals (CIs) for the association between ginseng use and cancer risk (DerSimonian & Laird, 1986). The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weights.

A linear dose-response analysis of frequency of ginseng use and overall cancer risk was conducted using the method of Greenland and Longnecker (Greenland & Longnecker, 1992). Linear trends and 95% CIs were computed from the natural logarithm of the RRs and 95% CIs across categories of ginseng use. We estimated the midpoint for each category by calculating the average of the upper and lower cut-off point for each category. For open-ended categories, we used the width of the adjacent category to calculate an upper cut-off point. A potential nonlinear association between frequency of ginseng use and overall cancer risk was examined using restricted cubic splines with three knots at 10%, 50% and 90% percentiles of the distribution, which was combined using multivariable meta-analysis (Jackson et al., 2010). A Wald test was used to test for nonlinearity (Orsini et al., 2012).

Heterogeneity between studies was evaluated using Q and I^2 statistics (Higgins & Thompson, 2002). I^2 is a measure of how much of the heterogeneity that is due to between study variation rather than chance while the Q test provided information on the presence of heterogeneity. I^2-values around 25%, 50%, and 75% are considered to indicate low, moderate and high heterogeneity, respectively. A p-value <0.05 was considered statistically significant and all statistical tests were two-sided. Publication bias was assessed using Egger's test. The

number of studies included in each analysis was considered too limited for using visual inspection of funnel plots in any meaningful way as well as for conducting any meaningful subgroup analyses and influence analyses (leave-one-out analyses). Forest plots are nevertheless shown stratified by study design to ease interpretation of the results considering the various types of biases that can affect different study designs. The statistical analyses were conducted using Stata, version 16.1 software (StataCorp, Collage Station, TX, USA).

2.7. Risk of bias/study quality

Study quality was assessed using the Newcastle Ottawa scale which rates nonrandomized studies according to selection, comparability and outcome assessment with a score range from 0 to 9 (Wells et al., 2021). The star system manual developed by Newcastle Ottawa Scale was used to rate and judge the quality of two case-control studies (Rebbeck et al., 2007; Yun & Choi, 1995) as well as five cohort studies (Brasky et al., 2011; Kamangar et al., 2007; Satia et al., 2009; Walter et al., 2011; Yun & Choi, 1998) in this meta-analysis. A study can be given a maximum one star for each numbered item within the Selection and Exposure categories, while a maximum of two stars for Comparability according to the manual Results from the study quality assessment presented in **Supplement C**.

To assess the quality of one remaining randomized trial, Risk of Bias Excel Tool version 2 (RoB 2) from Cochrane Collaboration was used (Higgins et al., 2019). The RoB 2 provides a framework to considering the risk of bias in the finding in randomized trial. This is done by answering a series of 'signaling questions' structured into five domains based on both empirical evidence and theoretical considerations (Higgins et al., 2019).

The five domains are presented here:

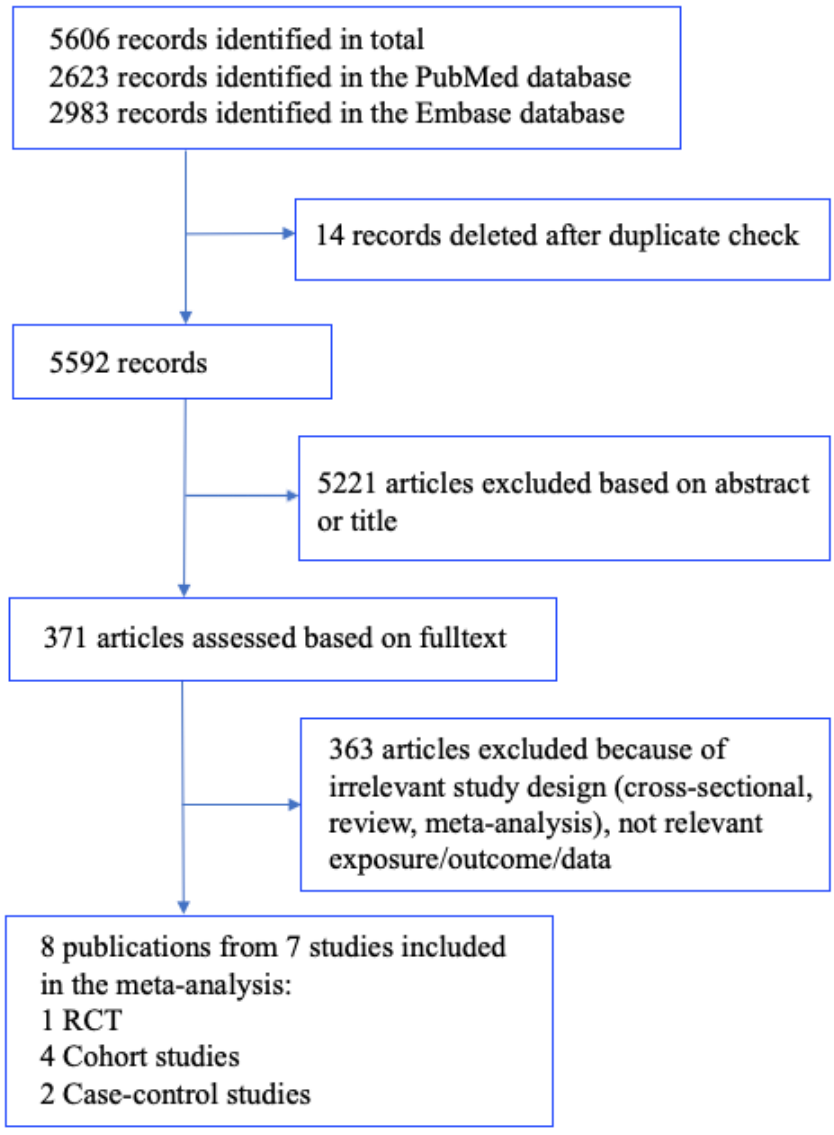
1. bias arising from the randomization process
2. bias due to deviations from intended interventions
3. bias due to missing outcome data
4. bias in measurement of the outcome; and
5. bias in selection of the reported result

Then, the algorithm from the tool maps responses to the signaling questions and allocate different scores to each domain of bias, reaching an overall judgement about risk of bias in the assessed randomized trial. Low risk of bias is reported in green color in the risk of bias summary. A summary of risk of bias appears in yellow, if there are not enough information within the text of study to determine, whether the level of bias is low or high. For example, if there is no information in a paper about how was the randomization done for an intervention in study and placebo groups. Finally, high risk of bias appears in red in the risk of bias summary (Higgins et al., 2019). The summary determination of risk of bias for included RCT study is showed in **Supplement D**.

3. Results

From a total of 5606 records retrieved by the search 8 publications (7 studies) were selected for inclusion in this systematic review and meta-analysis. One RCT (T.-K. Yun et al., 2010), five cohort studies (Brasky et al., 2010; Kamangar et al., 2007; Satia et al., 2009; Walter et al., 2011; Yun & Choi, 1998), and two case-control studies (Rebbeck et al., 2007; Yun & Choi, 1995) were included in the analyses of ginseng and cancer risk including a total of 4954 cancer cases and 235264 participants (**Figure 4, Table 1, 2, 3, 4, 5, and 6**). Of the eight publications on ginseng use and cancer risk, three were from the USA and five studies were from Asia. Two case-control studies and five cohort studies be awarded score from 8 to 9 according to Newcastle Ottawa Scale which consider to having high quality. The assessment of risk of bias using RoB 2 tool showed the overall low risk of bias for RCT study included in this meta-analysis. The flowchart shows the study selection process:

Figure 4. Flowchart of study selection.



3.1. Ginseng usage and its association with developing cancer

Extracted estimates with 95% CIs from cohorts, case-control studies and RCTs on ginseng used and total cancer, stomach cancer, colorectal cancer, liver cancer, lung cancer, and other cancers are presented in **Table 1**, **2**, **3**, **4**, **5, 6 and 7** respectively.

Table 1. Cohort, case-control and randomized controlled studies of ginseng and total cancer.

First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Yun TK et al, 1998, Korea	Kanghwa-eup	1987-1992, 5.4 years follow-up	4634 men & women, age ≥40 years	Ginseng	**No intake vs. ginseng intake**	0.40 (0.28-0.56)	Age, sex, education, smoking & alcohol
					Frequency of use		
					No intake	1.00	
					1-3 times/year	0.46 (0.30-0.69)	
					4-11 times/year	0.35 (0.21-0.58)	
					Once/month or more	0.34 (0.20-0.59)	
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	3974 men & women, age ≥20 years, 1987 cases and 1987 controls	Ginseng	**Ever vs. never**	0.50 (0.44-0.58)	Age, sex, marital status, education, smoking & alcohol
					Frequency of use		
					No intake	1.00	
					1-3 times/ year	0.60 (0.51-0.71)	
					4-11 times/year	0.60 (0.43-0.61)	
					1 time/month or more	0.36 (0.30-0.43)	
					Duration of use		
					1 year	0.64 (0.54-0.77)	
					2 years	0.53 (0.42-0.66)	
					3 years	0.36 (0.28-0.47)	
					4 years	0.45 (0.33-0.61)	
					5 years	0.31 (0.22-0.44)	
Randomized controlled trials							
Yun TK et al, 2010, Korea	Zhejiang University Hospital, Peoples Hospital – Linan, Peoples Hospital Zhuji, and Kuwha Hospital	1997-2008, 8 years follow- up	643 men & women, age 40-69 years, 318 placebo (16 cases) and 325 study group (8 cases)	Ginseng	User vs. non-user Red ginseng extract powder (1 g) once a week for 3 years	0.54 (0.23-1.28)	Age, sex, alcohol, smoking, family history of cancer

Table 2. Cohort, case-control and randomized controlled studies of ginseng and stomach cancer.

First author, publication year,country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Kamangar F et al, 2007, China	Shanghai Women's Health Study	1997-2000 – 2004, 5.7 years follow-up	73452 women, age 40-70 years, 153 stomach cancer cases	Ginseng	No ginseng Any ginseng White ginseng Red ginseng American ginseng Others ginseng	1.00 1.03 (0.73-1.44) 0.78 (0.36-1.70) 1.04 (0.14-7.47) 0.94 (0.66-1.36) 1.27 (0.47-3.48)	Age, smoking history, fruit and vegetables, education, income
Yun TK et al, 1998, Korea	Kanghwa-eup	1987-1992, 5.4 years follow-up	4634 men & women, age≥40 years, 42 stomach cancer cases	Ginseng	No intake Ginseng intake **Fresh ginseng** Sliced, juice Extract **White ginseng** Powder Extract Tea	1.00 0.33 (0.18-0.57) 0.57 (0.17-1.94) 0.33 (0.12-0.88) 0.24 (0.03-1.84) 1.34 (0.30-5.97) 0.64 (0.26-1.61)	Age, sex, education, smoking & alcohol
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	3974 men & women, age ≥20 years, 300 stomach cancer cases 300 hospital controls	Ginseng	Ever vs. never	0.36 (0.25-0.52)	Age, sex, marital status, education, smoking & alcohol
Randomized controlled trials							
Yun TK et al, 2010, Korea	Zhejiang University Hospital, Peoples Hospital – Linan, Peoples Hospital Zhuji, and Kuwha Hospital	1997-2008, 8 years follow-up	643 men & women, age 40-69 years, 318 placebo (16 cases) and 325 study group (8 cases)	Ginseng	User vs. non-user Red ginseng extract powder (1 g) once a week for 3 years	0.99 (0.44-2.21)	Age, sex, alcohol, smoking, family history of cancer

Table 3. Cohort, case-control and randomized controlled studies of ginseng and colorectal cancer.

First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Satia et al 2009, China	The VITamins And Lifestyle (VITAL)	2000-2007, a mean 5 years follow-up	76512 men and women, age 50-76 years: 428 CRC cases	Ginseng	No usage vs. usage	0.86 (0.56-1.33)	Age, gender, education, years smoked, pack-years, and pack-years squared.
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	3974 men & women, age ≥20 years, 118 cases and 118 controls	Ginseng	Ever vs. never taken	0.42 (0.24-0.74)	Age, sex, marital status, education, smoking & alcohol
Randomized controlled trials							
Yun TK et al, 2010, Korea	Zhejiang University Hospital, Peoples Hospital – Linan, Peoples Hospital Zhuji, and Kuwha Hospital	1997-2008, 8 years follow- up	643 men & women, age 40-69 years, 318 placebo (16 cases) and 325 study group (8cases)	Ginseng	User vs. non-user Red ginseng extract powder (1 g) once a week for 3 years	0.98 (0.06-15.60)	Age, sex, alcohol, smoking, family history of cancer, and Chinese ginseng intake

Table 4. Cohort, case-control and randomized controlled studies of ginseng and liver cancer.

First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Yun TK et al, 1998, Korea	Kanghwa-eup	1987-1992, 5.4 years follow-up	4634 men & women, age ≥40 years, 14 cases	Ginseng	No intake Ginseng intake **Fresh ginseng** **White ginseng** Powder Extract	1.00 0.86 (0.25-2.94) 1.97 (0.34-2.95) 1.72 (0.36-8.26) 0.85 (0.15-4.87)	Age, sex, education, smoking & alcohol
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	3974 men & women, age ≥20 years 264 cases and 264 controls	Ginseng	Never vs. ever	0.48 (0.33-0.70)	Age, sex, marital status, education, smoking & alcohol
Randomized controlled trials							
Yun TK et al, 2010, Korea	Zhejiang University Hospital, Peoples Hospital – Linan, Peoples Hospital Zhuji, and Kuwha Hospital	1997-2008, 8 years follow- up	643 men & women, age 40-69 years, 318 placebo (16 cases) and 325 study group (8 cases)	Ginseng	User vs. non-user Red ginseng extract powder (1 g) once a week for 3 years	0.99 (0.25-3.96)	Age, sex, alcohol, smoking, family history of cancer, and Chinese ginseng intake

Table 5. Cohort, case-control and randomized controlled studies of ginseng and lung cancer.

First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Satia et al 2009, China	The VITamins And Lifestyle (VITAL)	2000-2007, 5 years follow-up (mean)	77125 men & women, age 50-76 years, 665 cases	Ginseng	Ginseng use vs. non-use	0.97 (0.70-1.33)	Age, gender, education, years smoked, pack-years, and peak-years squared.
Yun TK et al, 1998, Korea	Kanghwa-eup	1987-1992, 5.4 years follow-up	4634 men & women, age≥40 years, 24 cases	Ginseng	No intake Ginseng intake **Fresh ginseng** Sliced, juice Extract **White ginseng** Tea	1.00 0.30 (0.14-0.65) 0.67 (0.15-3.43) 0.28 (0.04-2.17) 0.80 (0.26-2.44)	Age, sex, education, smoking & alcohol
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	552 men & women, age ≥20 years, 276 cases & 276 controls	Ginseng	Never vs. ever use	0.55 (0.38-0.79)	Age, sex, marital status, education, smoking & alcohol
Randomized controlled trials							
Yun TK et al, 2010, Korea	Zhejiang University Hospital, Peoples Hospital – Linan, Peoples Hospital Zhuji, and Kuwha Hospital	1997-2008, 8 years follow-up	643 men & women, age between 40-69 years, 318 placebo (16 cases) and 325 study group (8 cases)	Ginseng	User vs. non-user Red ginseng extract powder (1 g) once a week for 3 years	0.49 (0.15-1.64)	Age, sex, alcohol, smoking, family history of cancer, and Chinese ginseng intake

Table 6. Case-control studies of ginseng and breast cancer.

First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Case-control studies							
Yun TK et al, 1995, Korea	Korea Cancer Center Hospital	1987-1990	1830 women, age ≥20 years 174 cases and 179 controls	Ginseng	Never vs. ever	0.63 (0.40-1.05)	Age, sex, marital status, education, smoking & alcohol
Rebbeck et al, 2007, USA	Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia	1992-2002	2473 women aged 50-70 years, 72 breast cancer cases and 164 controls	Ginseng	Ever use vs. never use	0.71 (0.54-0.92)	Age at first full-term pregnancy, education menopause status, family history of breast cancer, time from diagnosis/ ascertainment to interview, reference age as a continuous variable, and ever use of hormone replacement therapy

Table 7. Cohort and case-control studies of ginseng and other cancers.

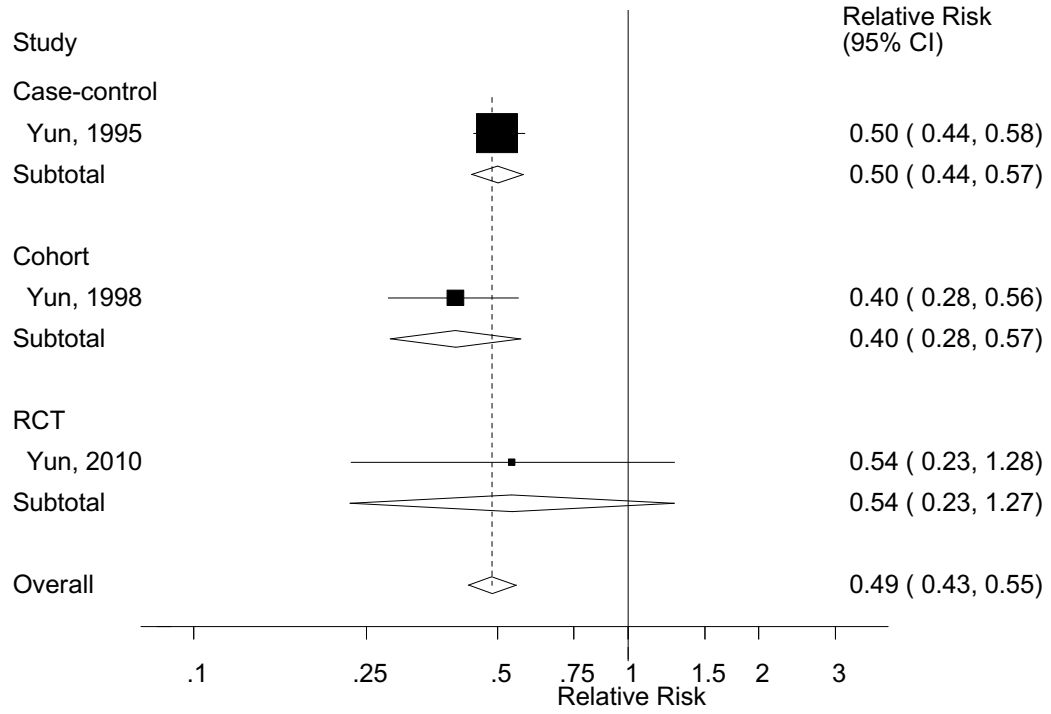
First author, publication year, country	Study Name	Study period	Number of participants, sex, age, number of cases	Exposure, subgroup	Comparison	RR (95% CI)	Adjustment for confounders
Cohort studies							
Brasky M. et al, 2010, USA	VITamins and Lifestyle (VITAL)	2000-2007, 6 years follow-up	35,239 men, age 50-76 years, 1602 prostate cancer cases	Ginseng	Non-user vs. User	0.91 (0.71-1.16)	Age, race, education, BMI, Prostate specific antigen (PSA), history of benign biopsy, number of first-degree relatives with a history of a benign prostate biopsy & diabetes
Walter R. B. Et al., 2011, USA	VITamins and Lifestyle (VITAL)	2000-2002, 10 years follow-up	66227 men and women, age 50- 76 years, 588 hematological cancer cases	Ginseng	Never use vs. ever use	0.79 (0.55-1.12)	Age, sex, race/ethnicity education, smoking, self-reported health, consumption of fruits & vegetables (without potatoes), history of coronary artery disease, history of rheumatoid arthritis, history of fatigue/lack of energy, and family history of leukemia/lymphoma
Case-control studies							
Yun TK et al., 1995, Korea	Korea Cancer Center Hospital	1987-1990	3974 men and women, age≥20 years, 159 oral, pharyngeal, lip cancer cases and 159 hospital control	Ginseng	Ever vs. never	0.47 (0.29-0.76)	Age, sex, marital status, education, smoking & alcohol
			87 esophageal cancer cases, 87 hospital controls			0.20 (0.09-0.38)	
			Pancreas cancer 23 cases & 23 controls			0.22 (0.05-0.95)	
			Larynx cancer 40 cases & 400 controls			0.18 (0.06-0.54)	
			Cervix uteri cancer, women aged≥20, 302 cases & 302 controls			0.72 (0.52-1.01)	
			Ovary cancer, women aged≥20, 23 cases & 22 controls			0.15 (0.04-0.60)	
			Urinary bladder cancer, 63 cases & 63 controls			0.64 (0.28-1.47)	
			Thyroid gland cancer, 40 cases & 40 controls			0.96 (0.38-2.44)	

3.2. Results from meta-analysis

3.3. Total cancer

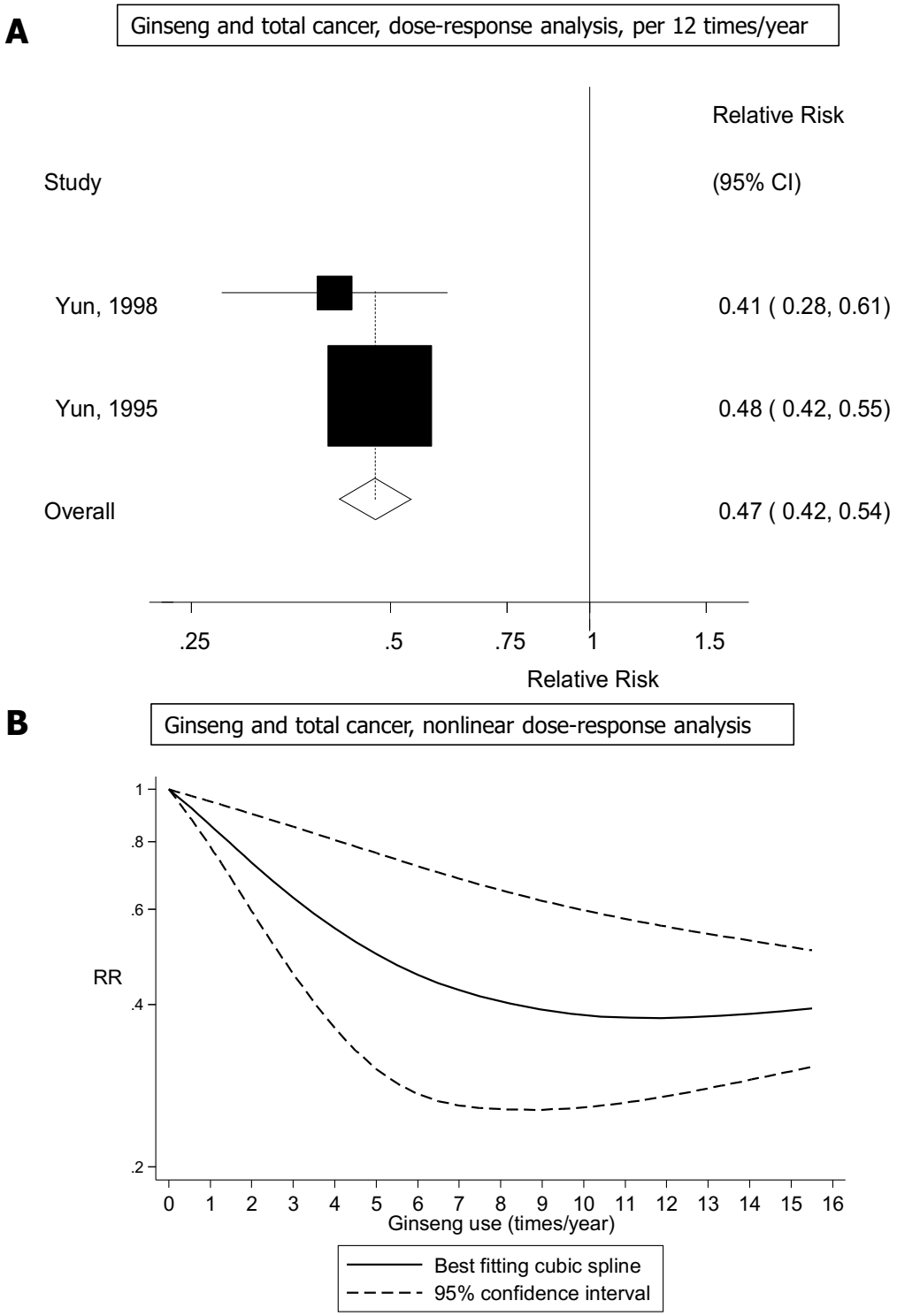
Three studies (1 case-control study, 1 cohort, and 1 RCT) were included in the analysis of ginseng use and total cancer risk and included a total of 2435 cancer cases and 9251 participants (Yun & Choi, 1995, 1998; T. K. Yun et al., 2010). The summary RR was 0.49 (95% CI: 0.43-0.55, I^2=0%, $p_{heterogeneity}$=0.49) (**Figure 5**). Egger's test was not significant (p=0.74).

Figure 5. The summary RR (95% CIs) for total cancer.



Two studies were included in the dose-response analysis of frequency of ginseng use and total cancer risk and included 1987 cases and 4634 participants (Yun & Choi, 1995, 1998). The summary RR per 12 times/year was 0.47 (95% CI: 0.42-0.54, I^2=0%, $p_{heterogeneity}$=0.47) (**Figure 6a**). There was some indication of a nonlinear association between frequency of ginseng use and total cancer risk, although the test for nonlinearity was only borderline significant (p=0.07), and there was a 62% reduction in risk at a frequency of 12 times/year compared to no intake (**Figure 6b**, Supplementary **Table 8**), but no further reduction in risk at intakes up to 15 times/year.

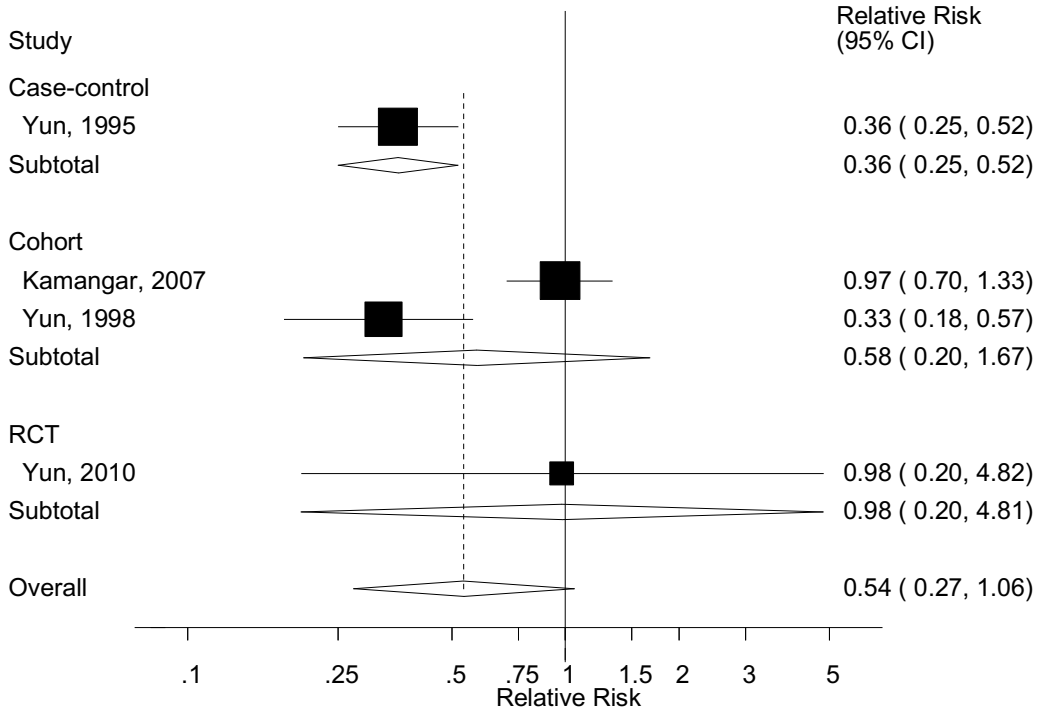
Figure 6. Linear and nonlinear dose-response analysis of frequency of ginseng use and total cancer risk.



3.4. Stomach cancer

Four studies (1 case-control, 2 cohorts, and 1 RCT) were included in the analysis of ginseng use and stomach cancer risk and included a total of 498 cases and 82703 participants (Kamangar et al., 2007; Yun & Choi, 1995, 1998; T. K. Yun et al., 2010). The summary of RR was 0.54 (95% CI: 0.27, 1.06, I^2=85.3%, $p_{heterogeneity}$<0.0001) (**Figure 7**) and there was no indication of publication bias with Egger's test (p=0.83).

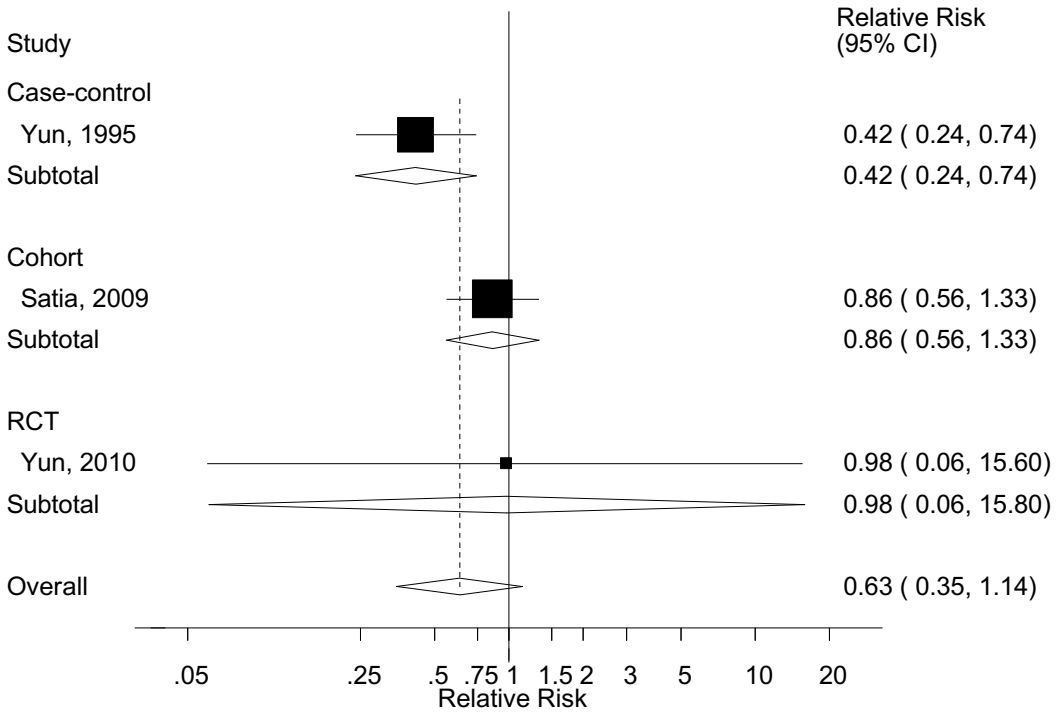
Figure 7. The summary RR (95% CIs) for stomach cancer.



3.5. Colorectal cancer

Three studies (1 case-control, 1 cohort, and 1 RCT) were included in the analysis of ginseng use and colorectal cancer risk and included a total of 547 cases and 81129 participants (Satia et al., 2009; Yun & Choi, 1995; T. K. Yun et al., 2010). The summary RR for ginseng use vs. non-use was 0.63 (95% CI: 0.35, 1.14, I^2=49.9%, $p_{heterogeneity}$=0.14) (**Figure 8**) and there was no indication of publication bias with Egger's test (p=0.95).

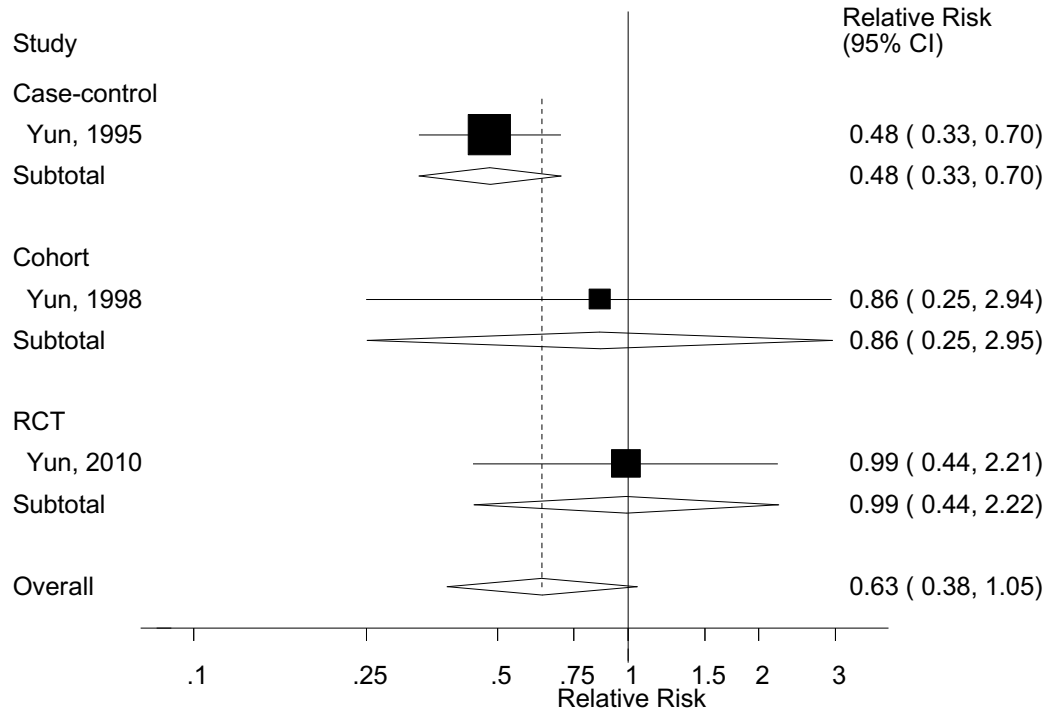
Figure 8.The summary RR (95% CIs) for colorectal cancer.



3.6. Liver cancer

Three studies (1 case-control, 1 cohort, and 1 RCT) were included in the analysis of ginseng use and liver cancer risk and included a total of 275 cases and 9251 participants (Yun & Choi, 1995, 1998; T. K. Yun et al., 2010). The summary RR was 0.63 (95% CI: 0.38-1.05, I^2=33.9%, $p_{heterogeneity}$=0.22) for liver cancer (**Figure 9**). Egger's test was not significant (p=0.31).

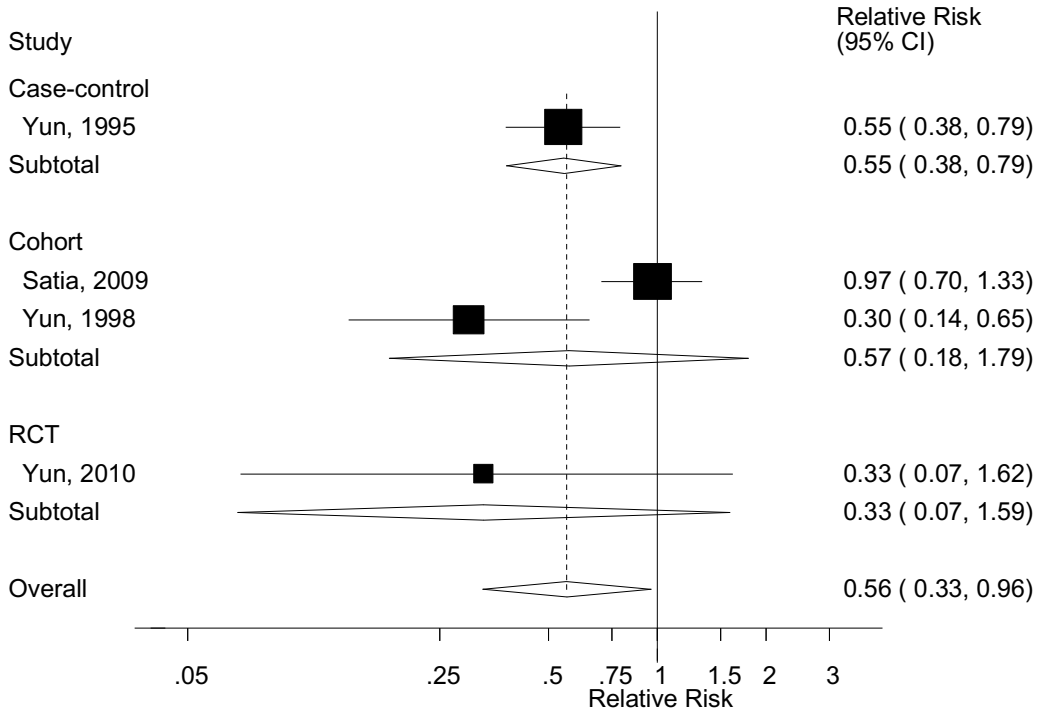
Figure 9. The summary RR (95% CIs) for liver cancer.



3.7. Lung cancer

Four studies (1 case-control, 2 cohorts, and 1 RCT) were included in the analysis of ginseng use and lung cancer risk and included a total of 953 cases and 81742 participants (Satia et al., 2009; Yun & Choi, 1995, 1998; T. K. Yun et al., 2010). The summary RR was 0.56 (95% CI: 0.33-0.96, I^2=73.1%, $p_{heterogeneity}$=0.01) for lung cancer (**Figure 10**). Egger's test was not significant (p=0.32).

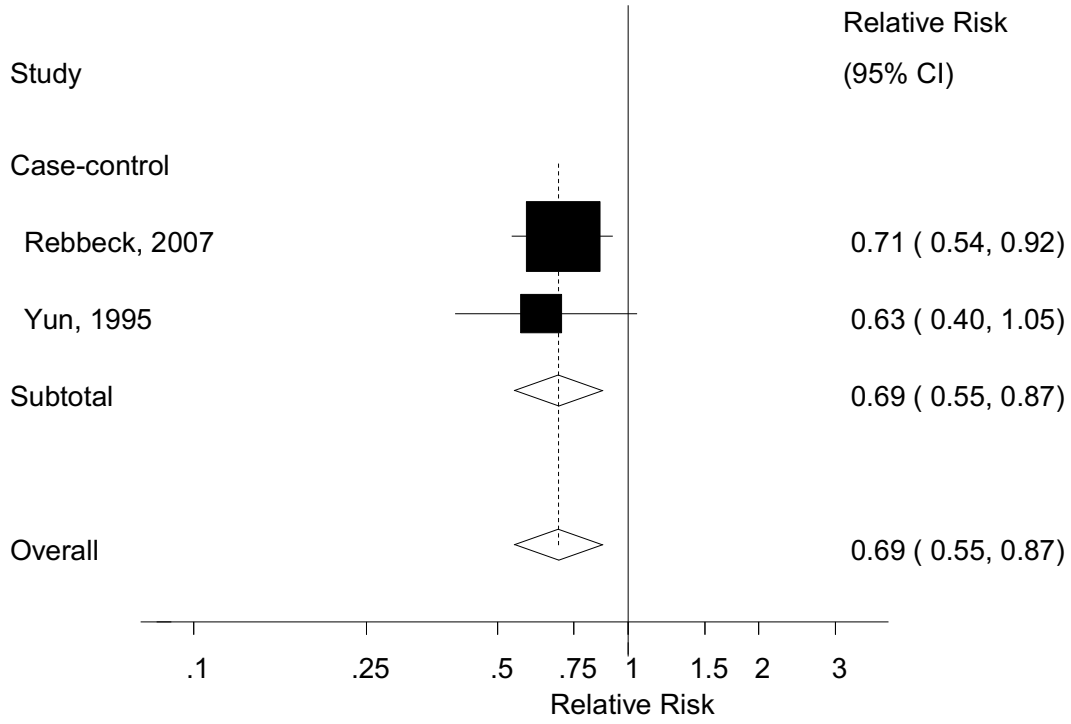
Figure 10. The summary RR (95% CIs) for lung cancer.



3.8. Breast cancer

Two case-control studies with 246 cases and 343 controls were included in the analysis of ginseng use and the breast cancer risk (Rebbeck et al., 2007; Yun & Choi, 1995). The summary RR for ginseng users vs. non-users was 0.69 (95% CI: 0.55-0.87, I^2=0.0%, $p_{heterogeneity}$=0.67) (**Figure 11**).

Figure 11. The summary RR (95% CIs) for breast cancer.



Summary of results of ginseng use and risk of other cancer sites

For several other cancer sites there was only one study available, and formal statistical meta-analyses were not possible for those cancers. In the VITAL study of 35239 men aged 50-76 years and including 1602 incident prostate cancer cases, there was no association between ginseng use and prostate cancer risk and the HR was 0.91 (95% CI: 0.71-1.16) (Brasky et al., 2011). Another publication from the VITAL study including 66227 men and women aged 50-76 years evaluated the effect of ginseng intake on hematological cancer risk (588 cases). This study did not report a significant benefits for this type of malignancy either, and the HR was 0.79 (95% CI: 0.55-1.12) (**Table 5**) (Walter et al., 2011).

A study of the preventive effect of ginseng intake of 3974 men and women aged ≥20 years with 1987 various cancer cases showed associations with ginseng consumption and for cancer of oral, pharyngeal, and lip with 159 cases and 159 controls and an OR of 0.47 (95% CI: 0.29-0.76), for esophageal cancer with 87 cases and 87 controls and an OR of 0.20 (95% CI: 0.09-0.38), for pancreas cancer with 23 cases and 23 controls and an OR of 0.22 (95% CI: 0.05-0.95), for larynx cancer with 40 cases and 40 controls, and an OR of 0.18 (95% CI: 0.06-0.54), and ovary cancer with 23 cases and 22 controls and an OR of 0.15 (95% CI: 0.04-0.60) (**Table 5**) (Yun & Choi, 1995).

However, there was no significant associations between ginseng consumption and risk of some other cancers, including uterine cervix cancer with 302 cases and 302 controls and an OR of 0.72 (95% CI: 0.52-1.01), urinary bladder cancer with 63 cases and 63 controls and an OR of 0.64 (95% CI: 0.28-1.47), and thyroid gland cancer with 40 cases and 40 controls and an OR of 0.96 (95% CI: 0.38-2.44) (**Table 5**) (Yun & Choi, 1995).

4. Discussion

This systematic review and meta-analysis of 8 publications (7 studies) (RCT, cohorts, and case-control studies) including 4954 cancer cases and 235264 participants suggest that the use of ginseng may reduce the risk of cancer overall by 51%, lung cancer by 44%, and breast cancer by 31%. There was a dose-response relationship between frequency of ginseng use and reduced total cancer risk with a 62% reduction in risk in participants that used ginseng monthly, however, this finding was based on only two studies and need to be interpreted with caution. There were non-significant inverse associations with stomach, colorectal and liver cancer, however, all these analyses were based on few studies and need further studies, particularly cohort studies and RCTs, are needed before firm conclusions can be drawn.

The findings of the current meta-analysis are partly consistent with a previous meta-analysis on ginseng intake and cancer, suggesting a role of ginseng in the treatment of cancer patients (Jin et al., 2016). Results from the current meta-analysis suggest that use of ginseng is associated with a statistically significant 51% reduction in risk of total cancer, 44% reduction in lung cancer risk, and 31% reduction in risk of breast cancer and a non-significant 37-46% reduction in risk of stomach, colorectal cancer, and liver cancer. The meta-analysis by Jin et al., 2016 found more modest reductions in cancer risk (24% for colorectal cancer, 22% for lung cancer, 17% for stomach cancer, and 18% for liver cancer) compared to the current meta-analysis, but there appears to be several errors in the extractions of the odds ratios from one Korean case-control study in that meta-analysis as they are considerably different from those reported in the original paper. In addition, for overall cancer risk, studies on different cancer sites were included in the same analysis, which is not good practice and in meta-analysis language is considered mixing apples and oranges. Another meta-analysis from Zhu et al., 2021 indicated that ginseng consumption significantly decreased the risk of developing liver cancer and reported an OR of 0.46 (95% CI: 0.40-0.52) (Zhu et al., 2021), which is partly consistent with our results, however, the summary estimate did not reach significance in the current meta-analysis although it was also in the direction of reduced risk. The difference in the results compared to the current meta-analysis is due to one Korean study reported on in two different publications (Shin et al., 2000; Yun & Choi, 1995) being erroneously included twice in the meta-analysis by Zhu et al., 2021. The current meta-analysis therefore provides better and less biased estimates of the impact of ginseng use on

cancer risk overall as well as for several individual cancer sites compared to the two previous meta-analyses.

Consistent with the inverse dose-response relationship that was observed between increasing frequency of ginseng use in the current meta-analysis, one case-control study also showed that increasing duration of ginseng use was associated with a decreasing trend in total cancer incidence, and ORs were 0.64, 0.53, 0.36, 0.45, and 0.31 for 1, 2, 3, 4, and 5 years respectively (Yun & Choi, 1995). Also, the ORs for individuals who consumed ginseng for 1-5, 6-10, and 11-20 years were 0.51, 0.44, and 0.43, showing a gradual decrease in the ORs up to 20 years (Yun & Choi, 1995). Further studies are needed to assess the impact of frequency and duration of ginseng use in relation to risk of cancer overall as well as risk of specific cancers. The observation of a dose-response relationship between frequency and duration of ginseng use and cancer risk suggest that there may be a biological gradient between higher frequency and duration of ginseng and cancer risk, and use of ginseng may be useful for the prevention of cancer. Ginseng may pose its preventive effect in the primary prevention of cancers by having therapeutic effect in the early initiation stage of carcinogenesis, which have been reported in several animal and lab-scale studies.
Hence, this may indicate that the long-term preventive effect of ginseng is depended on continuous consumption, as ginseng contains antioxidants which have a significant role in neutralizing the damage free radicals may exert on human cells.

Biological mechanisms

Several potential mechanisms could explain the observed beneficial effect of ginseng use on cancer risk in this meta-analysis. As discussed earlier, ginseng contains several bioactive compounds, and ginsenosides are the main pharmacologically active substance in ginseng species. Ginsenosides have shown anti-cancer function by inhibiting angiogenesis and DNA synthesis, decreasing host susceptibility to mutation, protection from DNA damage, promotion of immunosurveillance, and induction of apoptosis in cancer cells (Wang et al., 2019; Yun, Lee, et al., 2001).

Wang X. D. et al., 2019 observed that a novel ginsenoside called 4-XL-PPD has an anticancer activity for gastric cancer (Wang et al., 2019). An *In vivo* study of 4-XL-PPD on gastric cancer cell lines (MGC-803) showed that 4-XL-PPD suppressed the growth of human gastric cancer cells, and induced apoptosis by generating reactive oxygen radicals as well as inhibiting migration and invasion of cancer cells (Wang et al., 2019).
4-XL-PPD is involved in regulation of the expression of the proteins associated with apoptosis through up-regulating of the cleaved caspase-9,8,3 and cleaved Poly (ADP-ribose) polymerase-PARP in MGC-803 cells (Wang et al., 2019). The anti-cancer activity of 4-XL-PPD for gastric cancer may be related to re-active oxygen species-mediated cell apoptosis and inhibition of cancer cell migration and invasion in MGC-803 cells. As known before, apoptosis plays an important role in inhibiting the development of cancer in cells (Wang et al., 2019).

Red ginseng powder may inhibit the growth of preneoplastic lesions in the colon treated with azoxymethane (Wargovich, 2001). Wargovich M. J., 2001 concluded that red ginseng powder at 0.5 mg/kg exhibits moderate inhibition of aberrant crypt foci (ACF), a cluster of abnormal cells present in the colon which is in the initiation phase of carcinogenesis in the development of colon cancer (Wargovich, 2001).

The mechanisms behind this observation may be an inhibitory effect on the proliferation of a number of tumor cells in culture and hence pose a general antiproliferative effect on the colonic epithelium. Another possible explanation would be through the inhibition of anti-inflammatory pathways preferentially inhibit the growth of ACFs (Wargovich, 2001).

An experimental study in rats found red ginseng may reduce the development of liver cancer induced by diethyl-nitrosamine (DEN), which is a cancerous agent. Ginseng may protect hepatocytes from injury by DEN by inhibiting morphological changes in the structure of hepatic tissue, and by maintaining the normal level of DNA and RNA in liver tissue according to a study in rats (Wu & Zhu, 1990).

Xiu-gan W & Da-he Z.,1990 performed an experimental study on the effect of ginseng on liver cancer. They found that ginseng inhibited the development of liver cancer in rats, and the incidence of liver cancer was reduced substantially ($p<0.01$) in the experimental group (14.3%) when compared to the control group (100%) (Wu & Zhu, 1990).

The mechanism by which Rh2- mediated G1 cell cycle arrest is due to downregulation of the protein levels and kinase activities of cyclin-D1, cyclin-e, and Cdk6 as well as upregulation of pRb2/p130 (Cheng et al., 2005). Cheng CH-CH et al., 2005 observed that ginsenoside Rh2 (a triterpene saponin) extracted from ginseng led to G1 cell arrest followed by progression to apoptosis in A540 lung cells at 30lg/ml (Cheng et al., 2005).

In this study, results indicate that different ginseng species and preparations, as well as treatment methods like unsteamed and steamed ginseng may influence the strength of the anti-cancer properties in included scientific papers which are in line with previous studies (Xie et al., 2009). For example, red ginseng may have stronger anticancer activity than Asian ginseng (Xie et al., 2009). This can be explained by ginseng species containing different saponin molecules and different extraction methods give rise to variations in therapeutic effects on cancer cells from available publications (Xie et al., 2009). This may indicate that red ginseng can be useful in treatment of cancer patients in combination with other chemotherapeutic agents.

Wang W. et al.,2008 observed that 25-hydroxyprotopanaxadiol (25-OH-PPD) purified from Panax ginseng inhibited prostate cancer cell growth and proliferation, induced apoptosis, and led to arrest in the G1 phase of the cell cycle in LNCaP and PC3 cell lines (Wang et al., 2008). The determination of the anti-cancer property of 25-OH-PPD in nude mice bearing PC3 xenograft tumors confirmed the inhibition of tumor growth in a dose-dependent manner. They concluded that this compound could be safely combined with chemotherapeutic agents like Taxotere and Gemcitabine or radiation therapy to improve the anti-tumor effects (Wang et al., 2008).

Liu W. K. et al., 2000 observed that saponins from ginseng have an anti-proliferative effect on the human prostate cancer cell line. They also found that ginsenoside Rg-3 was the most effective to inhibit the growth of prostate cancer in the LNCaP cell line (Liu et al., 2000). The molecular mechanism shows that ginsenoside Rg-3 inhibit cell proliferation by suppression of the cell cycle proregression genes (PCNA and cyclin kinase D1) which lead to increased expression of cyclin kinase inhibitors genes (p21 and p27), resulting in G1 cell cycle arrest and apoptosis (Liu et al., 2000).

Duda B. R. et al., 1998 found that American ginseng may have an estrogenic like effect on ER-positive breast cancer using the MCF-7 breast cancer cell line. A molecular mechanism of this effect from ginseng may be explained by inducing the expression of the pS2 gene and its protein products that have positive roles in breast cancer prognosis and overall survival (Duda et al., 1996).

OH M. et al., 1999 identified that the anti-cancer mechanism of ginsenoside Rh2 in MCF-7 human breast carcinoma cells is due to inhibition of the cell growth by inducing G1 arrest in cell cycle progression (Oh et al., 1999). Additionally, G-Rh2 treatment modify protein expression in MCF-7 cell lines by down-regulating the protein level of cyclin D3 and upregulating the expression of cyclin-dependent kinase (Cdk) inhibitor $p21^{WAF1/CIP1}$. A strong inhibitory effect on cell growth was reported to be dependent on the treatment dosage (Oh et al., 1999).

Methodological issues

As discussed earlier, meta-analysis is systematic approach and should be viewed as an observational study of evidence, because in many situations randomized controlled designs are not feasible, and only data from observational studies are available (Stroup et al., 2000).

Randomized controlled trials (RCTs) are considered to provide the strongest evidence regarding an intervention. However, using ginseng as a single anticancer agent in treatment of cancer patients against approved anticancer medications may not be approved due to ethical issues. On the other hand, the anticancer property of ginseng should be evaluated as long-term intake, and that makes it impossible to design a usually randomized comparison study for cancer patients.

Nevertheless, it is possible to design randomized trials to assess the efficacy of ginseng consumption in preventing cancer incidence in healthy people. Another possible option would be to design an RCT study where ginseng is used as adjuvant therapy together with other cancer treatments and to compare it with another anti-cancer therapy alone. The meta-analysis being constructed from such RCTs has the highest level of evidence in medical research.

As mentioned earlier, results from the quality assessment of included studies showed high-quality scores for two case-control studies and five cohort studies as assessed by the Newcastle Ottawa scale and overall low risk of bias for one RCT study in the using the RoB 2 tool.

Role of meta-analyses in medical research

As mentioned earlier, meta-analyses use a systematic approach to assess the available evidence. Meta-analyses have the advantage of providing an overall more precise summary estimate for the association between an exposure and an outcome or for a treatment effect when compared to any single studies. As result, meta-analyses are often used to summarize the available evidence that can be used by policymakers and clinicians in decision making. Meta-analyses, therefore, can provide a higher level of evidence than any individual studies, however, conclusions can be tampered if the published studies are of poor quality or have a poor study design. Randomized controlled trials (RCTs) are considered the strongest study design to test the efficacy of medications in the prevention or treatment of diseases, however, cohort studies and in some cases case-control studies can provide valuable information as well.

Strengths and Limitations

This meta-analysis was conducted using standard search strategies, well-known statistical methods and presented quantitative findings gathered from relevant scientific articles. Strengths of the study includes the comprehensive literature search, prospective cohort, and randomized control design of some of the included studies. However, one major limitation is that part of the available data on cancer risk was based on case-control studies, which could be affected by recall and selection bias.

Recall bias is a type of bias where cases may recall their ginseng use (or other exposures) differentially when compared to the controls, which can result in exaggerated risk estimates and can therefore hamper the interpretation of the results. In addition, case-control studies can be affected by selection bias, where for example health-conscious individuals may be more likely to participate as controls than those that are less health-conscious, and this also can threaten the validity of the results by leading to exaggerated effect estimates. Given that the results, in some cases, were stronger or more pronounced in case-control studies than in the available cohort studies some caution is needed in the interpretation of the results, and further cohort studies and RCTs are therefore needed. Since most of the studies on ginseng and cancer risk were based on observational studies, the possibility that residual confounding by other factors could have impacted the results cannot be excluded. It is possible that ginseng users may have an overall healthier lifestyle than non-users and that inadequate adjustment for other risk factors could explain the observed associations. Nevertheless, most of the studies adjusted for age, sex (when relevant), smoking, and alcohol consumption, and some also adjusted for education or dietary factors, but few studies adjusted for physical activity, BMI, or dietary factors. It is therefore difficult to completely rule out the possibility that residual confounding could explain the observed associations. Another limitation of the study was the small number of studies available for specific cancer sites which limited the robustness of the summary estimates as well as possibilities for conducting meaningful sensitivity analyses, subgroup analyses and more detailed assessments of publication bias using funnel plots.

Publication bias can lead to exaggerated summary estimates as studies with null results or results opposite to the prevailing trend may be less likely to be published. Although the Egger's test did not indicate that there was publication bias, the limited number of studies may have led to too low power for the test to detect such bias. No firm conclusions can therefore be drawn based on the limited data currently available. Lastly, there was some evidence from experimental studies for the potential biological plausibility of the findings as beneficial effects were observed on multiple cancers in *in vitro* and *in vivo* cell and animal studies. This might suggest potential causal associations between ginseng exposure and reduced cancer risk, however, further epidemiological studies are needed.

Conclusion

Results from the current meta-analysis suggests that ginseng use may reduce the risk of cancer overall, with some indication of an inverse dose-response relationship with increasing duration, as well as lung and breast cancer. There was also some suggestion of inverse associations for other cancers including stomach, colorectal and liver cancer, however, the associations were not statistically significant. There is experimental and mechanistic support from *in vitro* and animal studies for several of these findings. However, additional RCTs and cohort studies are needed before firm conclusions can be drawn with regard to the potential of ginseng (including specific types of ginseng) in cancer prevention, as the available epidemiological evidence was limited.

Further research

This project has identified several areas for further research. More prospective cohort studies and RCTs are needed to evaluate the association between ginseng use and the risk of different types of cancers. Any further studies should assess in more detail whether particular subtypes of ginseng are particularly beneficial and assess the dose-response relationship between increasing frequency and duration of ginseng use and cancer risk overall as well as risk of specific cancers. Such endeavours may contribute significantly to research and development of anti-cancer therapies, and open up new platforms for making reliable biopharmaceutical products from ginseng to reduce the burden of cancer in the general population.

References

Bade, B. C., & Dela Cruz, C. S. (2020). Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clinics in Chest Medicine*, *41*(1), 1-24. https://doi.org/https://doi.org/10.1016/j.ccm.2019.10.001

Bahrke, M. S., & Morgan, W. P. (1994). Evaluation of the ergogenic properties of ginseng. *Sports Med*, *18*(4), 229-248. https://doi.org/10.2165/00007256-199418040-00003

Brasky, T. M., Kristal, A. R., Navarro, S. L., Lampe, J. W., Peters, U., Patterson, R. E., & White, E. (2011). Specialty supplements and prostate cancer risk in the VITamins and Lifestyle (VITAL) cohort. *Nutrition and cancer*, *63*(4), 573-582. https://doi.org/10.1080/01635581.2011.553022

Brasky, T. M., Lampe, J. W., Potter, J. D., Patterson, R. E., & White, E. (2010). Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. *Cancer Epidemiol Biomarkers Prev*, *19*(7), 1696-1708. https://doi.org/10.1158/1055-9965.Epi-10-0318

CDC. (2016). *Cancers linked to tobacco use make up 40% of all cancers diagnosed in the United States*. Centers for Disease Control and Prevention. https://www.cdc.gov/media/releases/2016/p1110-vital-signs-cancer-tobacco.html

Chen, C.-C., Kao, C.-P., Chiu, M.-M., & Wang, S.-H. (2017). The anti-cancer effects and mechanisms of Scutellaria barbata D. Don on CL1-5 lung cancer cells. *Oncotarget*, *8*(65), 109340-109357. https://doi.org/10.18632/oncotarget.22677

Chen, S., Wang, Z., Huang, Y., O'Barr, S. A., Wong, R. A., Yeung, S., & Chow, M. S. (2014). Ginseng and anticancer drug combination to improve cancer chemotherapy: a critical review. *Evid Based Complement Alternat Med*, *2014*, 168940. https://doi.org/10.1155/2014/168940

Cheng, C. C., Yang, S. M., Huang, C. Y., Chen, J. C., Chang, W. M., & Hsu, S. L. (2005). Molecular mechanisms of ginsenoside Rh2-mediated G1 growth arrest and apoptosis in human lung adenocarcinoma A549 cells. *Cancer Chemother Pharmacol*, *55*(6), 531-540. https://doi.org/10.1007/s00280-004-0919-6

Cui, Y., Shu, X. O., Gao, Y. T., Cai, H., Tao, M. H., & Zheng, W. (2006). Association of ginseng use with survival and quality of life among breast cancer patients. *Am J Epidemiol*, *163*(7), 645-653. https://doi.org/10.1093/aje/kwj087

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials*, *7*(3), 177-188. https://doi.org/10.1016/0197-2456(86)90046-2

Duda, R. B., Taback, B., Kessel, B., Dooley, D. D., Yang, H., Marchiori, J., Slomovic, B. M., & Alvarez, J. G. (1996). pS2 expression induced by American ginseng in MCF-7 breast cancer cells. *Ann Surg Oncol*, *3*(6), 515-520. https://doi.org/10.1007/bf02306082

Egger, M., Smith, G. D., & Phillips, A. N. (1997). Meta-analysis: principles and procedures. *Bmj*, *315*(7121), 1533-1537. https://doi.org/10.1136/bmj.315.7121.1533

Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*, *144*(8), 1941-1953. https://doi.org/10.1002/ijc.31937

GLOBOCAN. (2021). *GLOBAL CANCER OBSERVATORY*. https://gco.iarc.fr/

Greenland, S., & Longnecker, M. P. (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*, *135*(11), 1301-1309. https://doi.org/10.1093/oxfordjournals.aje.a116237

HHP. (2021). *Cancer*. Harvard Health Publishing, Harvard Medical School. https://www.health.harvard.edu/topics/cancer

Higgins, J. P., Savović, J., Page, M. J., & Sterne, J. A. (2019). *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. https://methods.cochrane.org/risk-bias-2
Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, *21*(11), 1539-1558. https://doi.org/10.1002/sim.1186
Ilbawi, A. V., Cherian (2020). *World Health Organization Report On Cancer*. file:///C:/Users/hamidj/Downloads/9789240001299-eng%20(1).pdf
Jackson, D., White, I. R., & Thompson, S. G. (2010). Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med*, *29*(12), 1282-1297. https://doi.org/10.1002/sim.3602
Jenq, R. R., & van den Brink, M. R. M. (2010). Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer. *Nature Reviews Cancer*, *10*(3), 213-221. https://doi.org/10.1038/nrc2804
Jin, X., Che, D. B., Zhang, Z. H., Yan, H. M., Jia, Z. Y., & Jia, X. B. (2016). Ginseng consumption and risk of cancer: A meta-analysis. *J Ginseng Res*, *40*(3), 269-277. https://doi.org/10.1016/j.jgr.2015.08.007
Kamangar, F., Gao, Y. T., Shu, X. O., Kahkeshani, K., Ji, B. T., Yang, G., Li, H. L., Rothman, N., Chow, W. H., & Zheng, W. (2007). Ginseng intake and gastric cancer risk in the Shanghai Women's Health Study cohort. *Cancer Epidemiol Biomarkers Prev*, *16*(3), 629-630. https://doi.org/10.1158/1055-9965.Epi-06-1009
Lee, J. H., Kwon, K. R., Cho, C. K., Han, S. S., & Yoo, H. S. (2010). Advanced cancer cases treated with cultivated wild ginseng phamacopuncture. *J Acupunct Meridian Stud*, *3*(2), 119-124. https://doi.org/10.1016/s2005-2901(10)60022-2
Liu, W., Yang, B., Yang, L., Kaur, J., Jessop, C., Fadhil, R., Good, D., Ni, G., Liu, X., Mosaiab, T., Yi, Z., & Wei, M. Q. (2019). Therapeutic Effects of Ten Commonly Used Chinese Herbs and Their Bioactive Compounds on Cancers. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 6057837. https://doi.org/10.1155/2019/6057837
Liu, W. K., Xu, S. X., & Che, C. T. (2000). Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. *Life Sci*, *67*(11), 1297-1306. https://doi.org/10.1016/s0024-3205(00)00720-7
Liu, X., Zhou, M., Wang, F., Mubarik, S., Wang, Y., Meng, R., Shi, F., Wen, H., & Yu, C. (2020). Secular Trend of Cancer Death and Incidence in 29 Cancer Groups in China, 1990-2017: A Joinpoint and Age-Period-Cohort Analysis. *Cancer management and research*, *12*, 6221-6238. https://doi.org/10.2147/CMAR.S247648
Lizama, N., Jongenelis, M., & Slevin, T. (2020). Awareness of cancer risk factors and protective factors among Australian adults. *Health Promot J Austr*, *31*(1), 77-83. https://doi.org/10.1002/hpja.248
Lo, L. C., Chen, C. Y., Chen, S. T., Chen, H. C., Lee, T. C., & Chang, C. S. (2012). Therapeutic efficacy of traditional Chinese medicine, Shen-Mai San, in cancer patients undergoing chemotherapy or radiotherapy: study protocol for a randomized, double-blind, placebo-controlled trial. *Trials*, *13*, 232. https://doi.org/10.1186/1745-6215-13-232
Mao, Q.-Q., Xu, X.-Y., Shang, A., Gan, R.-Y., Wu, D.-T., Atanasov, A. G., & Li, H.-B. (2020). Phytochemicals for the Prevention and Treatment of Gastric Cancer: Effects and Mechanisms. *International journal of molecular sciences*, *21*(2), 570. https://doi.org/10.3390/ijms21020570
NIH. (2021a). *Alcohol and Cancer Risk*. National Cancer Institute. https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet

NIH. (2021b). *Obesity and Cancer*. National Cancer Institute https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet
NIPH. (2018). *Cancer in Norway*. Norwegian Institute of Public Health. https://www.fhi.no/nettpub/hin/ikke-smittsomme/kreft/
OECD. (2019). *Health at a Glance* Organisation for Economic Cooperation and Development (OECD). https://doi.org/doi:https://doi.org/10.1787/4dd50c09-en
Oh, M., Choi, Y. H., Choi, S., Chung, H., Kim, K., Kim, S. I., Kim, D. K., & Kim, N. D. (1999). Anti-proliferating effects of ginsenoside Rh2 on MCF-7 human breast cancer cells. *Int J Oncol*, *14*(5), 869-875. https://doi.org/10.3892/ijo.14.5.869
Orsini, N., Li, R., Wolk, A., Khudyakov, P., & Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*, *175*(1), 66-73. https://doi.org/10.1093/aje/kwr265
Park, S. J., Kang, H. J., Jun, H. J., Shin, S. H., & Yoo, H. S. (2020). Multi-center, randomized, double-blind, placebo-controlled, exploratory study to evaluate the efficacy and safety of HAD-B1 for dose-finding in EGFR positive and locally advanced or metastatic NSCLC subjects who need Afatinib therapy: Study protocol clinical trial (SPIRIT Compliant). *Medicine (Baltimore)*, *99*(4), e18735. https://doi.org/10.1097/md.0000000000018735
Pelucchi, C., Gallus, S., Garavello, W., Bosetti, C., & La Vecchia, C. (2006). Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, *29*(3), 193-198. https://pubmed.ncbi.nlm.nih.gov/17373408
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6527045/
Rebbeck, T. R., Troxel, A. B., Norman, S., Bunin, G. R., DeMichele, A., Baumgarten, M., Berlin, M., Schinnar, R., & Strom, B. L. (2007). A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *Int J Cancer*, *120*(7), 1523-1528. https://doi.org/10.1002/ijc.22485
Rokot, N. T., Kairupan, T. S., Cheng, K.-C., Runtuwene, J., Kapantow, N. H., Amitani, M., Morinaga, A., Amitani, H., Asakawa, A., & Inui, A. (2016). A Role of Ginseng and Its Constituents in the Treatment of Central Nervous System Disorders. *Evidence-based complementary and alternative medicine : eCAM*, *2016*, 2614742-2614742. https://doi.org/10.1155/2016/2614742
Sarkar, S., Horn, G., Moulton, K., Oza, A., Byler, S., Kokolus, S., & Longacre, M. (2013). Cancer development, progression, and therapy: an epigenetic overview. *Int J Mol Sci*, *14*(10), 21087-21113. https://doi.org/10.3390/ijms141021087
Satia, J. A., Littman, A., Slatore, C. G., Galanko, J. A., & White, E. (2009). Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. *Cancer Epidemiol Biomarkers Prev*, *18*(5), 1419-1428. https://doi.org/10.1158/1055-9965.Epi-09-0038
Seyfried, T. N., & Huysentruyt, L. C. (2013). On the origin of cancer metastasis. *Crit Rev Oncog*, *18*(1-2), 43-73. https://doi.org/10.1615/critrevoncog.v18.i1-2.40
Shin, H. R., Kim, J. Y., Yun, T. K., Morgan, G., & Vainio, H. (2000). The cancer-preventive potential of Panax ginseng: a review of human and experimental evidence. *Cancer Causes Control*, *11*(6), 565-576. https://doi.org/10.1023/a:1008980200583
Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A., Thacker, S. B., & for the Meta-analysis Of Observational Studies in Epidemiology, G. (2000). Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting. *JAMA*, *283*(15), 2008-2012. https://doi.org/10.1001/jama.283.15.2008

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209-249. https://doi.org/https://doi.org/10.3322/caac.21660

Walter, R. B., Brasky, T. M., Milano, F., & White, E. (2011). Vitamin, mineral, and specialty supplements and risk of hematologic malignancies in the prospective VITamins And Lifestyle (VITAL) study. *Cancer Epidemiol Biomarkers Prev*, *20*(10), 2298-2308. https://doi.org/10.1158/1055-9965.Epi-11-0494

Wang, C.-Z., Xie, J.-T., Zhang, B., Ni, M., Fishbein, A., Aung, H. H., Mehendale, S. R., Du, W., He, T.-C., & Yuan, C.-S. (2007). Chemopreventive effects of Panax notoginseng and its major constituents on SW480 human colorectal cancer cells. *International journal of oncology*, *31*(5), 1149-1156. https://pubmed.ncbi.nlm.nih.gov/17912442 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676859/

Wang, C. Z., Anderson, S., Du, W., He, T. C., & Yuan, C. S. (2016). Red ginseng and cancer treatment. *Chin J Nat Med*, *14*(1), 7-16. https://doi.org/10.3724/sp.J.1009.2016.00007

Wang, W., Rayburn, E. R., Hao, M., Zhao, Y., Hill, D. L., Zhang, R., & Wang, H. (2008). Experimental therapy of prostate cancer with novel natural product anti-cancer ginsenosides. *Prostate*, *68*(8), 809-819. https://doi.org/10.1002/pros.20742

Wang, X., Sun, Y. Y., Qu, F. Z., Su, G. Y., & Zhao, Y. Q. (2019). 4-XL-PPD, a novel ginsenoside derivative, as potential therapeutic agents for gastric cancer shows anti-cancer activity via inducing cell apoptosis medicated generation of reactive oxygen species and inhibiting migratory and invasive. *Biomed Pharmacother*, *118*, 108589. https://doi.org/10.1016/j.biopha.2019.01.050

Wargovich, M. J. (2001). Colon cancer chemoprevention with ginseng and other botanicals. *J Korean Med Sci*, *16 Suppl*(Suppl), S81-86. https://doi.org/10.3346/jkms.2001.16.S.S81

WCRF. (2018). *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. W. C. R. F. International. https://www.wcrf.org/dietandcancer/resources-and-toolkits/

Wells, G., Shea, B., Connell, D. O., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2021). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Wu, X. G., & Zhu, D. H. (1990). Influence of ginseng upon the development of liver cancer induced by diethylnitrosamine in rats. *J Tongji Med Univ*, *10*(3), 141-145, 133. https://doi.org/10.1007/bf02986451

Wu, X. G., Zhu, D. H., & Li, X. (2001). Anticarcinogenic effect of red ginseng on the development of liver cancer induced by diethylnitrosamine in rats. *J Korean Med Sci*, *16 Suppl*(Suppl), S61-65. https://doi.org/10.3346/jkms.2001.16.S.S61

Xie, J. T., Wang, C. Z., Zhang, B., Mehendale, S. R., Li, X. L., Sun, S., Han, A. H., Du, W., He, T. C., & Yuan, C. S. (2009). In vitro and in vivo anticancer effects of American ginseng berry: exploring representative compounds. *Biol Pharm Bull*, *32*(9), 1552-1558. https://doi.org/10.1248/bpb.32.1552

Yun, T.-K., Zheng, S., Choi, S.-Y., Cai, S. R., Lee, Y.-S., Liu, X. Y., Cho, K. J., & Park, K. Y. (2010). Non–Organ-Specific Preventive Effect of Long-Term Administration of Korean Red Ginseng Extract on Incidence of Human Cancers. *Journal of Medicinal Food*, *13*(3), 489-494. https://doi.org/10.1089/jmf.2009.1275

Yun, T. K. (1996). Experimental and epidemiological evidence of the cancer-preventive effects of Panax ginseng C.A. Meyer. *Nutr Rev*, *54*(11 Pt 2), S71-81. https://doi.org/10.1111/j.1753-4887.1996.tb03822.x

Yun, T. K. (2001). Panax ginseng--a non-organ-specific cancer preventive? *Lancet Oncol*, *2*(1), 49-55. https://doi.org/10.1016/s1470-2045(00)00196-0
Yun, T. K. (2003). Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. *Mutat Res*, *523-524*, 63-74. https://doi.org/10.1016/s0027-5107(02)00322-6
Yun, T. K., & Choi, S. Y. (1990). A case-control study of ginseng intake and cancer. *Int J Epidemiol*, *19*(4), 871-876. https://doi.org/10.1093/ije/19.4.871
Yun, T. K., & Choi, S. Y. (1995). Preventive effect of ginseng intake against various human cancers: a case-control study on 1987 pairs. *Cancer Epidemiol Biomarkers Prev*, *4*(4), 401-408.
Yun, T. K., & Choi, S. Y. (1998). Non-organ specific cancer prevention of ginseng: a prospective study in Korea. *Int J Epidemiol*, *27*(3), 359-364. https://doi.org/10.1093/ije/27.3.359
Yun, T. K., Choi, S. Y., & Yun, H. Y. (2001). Epidemiological study on cancer prevention by ginseng: are all kinds of cancers preventable by ginseng? *J Korean Med Sci*, *16 Suppl*(Suppl), S19-27. https://doi.org/10.3346/jkms.2001.16.S.S19
Yun, T. K., Lee, Y. S., Lee, Y. H., Kim, S. I., & Yun, H. Y. (2001). Anticarcinogenic effect of Panax ginseng C.A. Meyer and identification of active compounds. *J Korean Med Sci*, *16 Suppl*(Suppl), S6-18. https://doi.org/10.3346/jkms.2001.16.S.S6
Yun, T. K., Zheng, S., Choi, S. Y., Cai, S. R., Lee, Y. S., Liu, X. Y., Cho, K. J., & Park, K. Y. (2010). Non-organ-specific preventive effect of long-term administration of Korean red ginseng extract on incidence of human cancers. *J Med Food*, *13*(3), 489-494. https://doi.org/10.1089/jmf.2009.1275
Zhang, D., Zheng, J., Ni, M., Wu, J., Wang, K., Duan, X., Zhang, X., & Zhang, B. (2017). Comparative efficacy and safety of Chinese herbal injections combined with the FOLFOX regimen for treating gastric cancer in China: a network meta-analysis. *Oncotarget*, *8*(40), 68873-68889. https://doi.org/10.18632/oncotarget.20320
Zhu, C., Wang, J., Liu, W., Chen, L., Abdelrahim, M. E. A., & Ren, L. (2021). Ginseng Consumption Possible Effect on Liver Cancer: A Meta-Analysis. *Nutrition and cancer*, *73*(9), 1581-1589. https://doi.org/10.1080/01635581.2020.1803929

Supplement

Supplement A: Search strategy in Embase database

# ▲	Searches	Results	Type	Annotations
1	(Oral or pharyngeal or pharynx or oropharyngeal or oropharynx or hypopharyngeal or hypopharynx or nasal or paranasal sinus or Nasopharyngeal or nasopharynx or Laryngeal or larynx or Esophageal or esophagus or oesophageal or oesophagus or Upper aerodigestive tract or Lung or respiratory or Stomach or gastric or Small intestinal or small intestine or small bowel or Pancreatic or pancreas or Liver or hepatocellular or Gallbladder or Bile duct or Colon or rectal or rectum or colorectal or colorectum or large bowel or Breast or mammary or Ovarian or ovary or Endometrial or endometrium or corpus uteri or uterine or Cervical or cervix or Prostate or Testicular or testes or penis or penile or Kidney or renal or renal cell or adrenal or Bladder or urothelial or urinary tract or Brain or Thyroid or anal).ab,ti.	8940036	Advanced	
2	Oral/ or pharyngeal/ or pharynx/ or oropharyngeal/ or oropharynx/ or hypopharyngeal/ or hypopharynx/ or nasal/ or paranasal sinus/ or Nasopharyngeal/ or nasopharynx/ or Laryngeal/ or larynx/ or Esophageal/ or esophagus/ or oesophageal/ or oesophagus/ or Upper aerodigestive tract/ or Lung/ or respiratory/ or Stomach/ or gastric/ or Small intestinal/ or small intestine/ or small bowel/ or Pancreatic/ or pancreas/ or Liver/ or hepatocellular/ or Gallbladder/ or Bile duct/ or Colon/ or rectal/ or rectum/ or colorectal/ or colorectum/ or large bowel/ or Breast/ or mammary/ or Ovarian/ or ovary/ or Endometrial/ or endometrium/ or corpus uteri/ or uterine/ or Cervical/ or cervix/ or Prostate/ or Testicular/ or testes/ or penis/ or penile/ or Kidney/ or renal/ or renal cell/ or adrenal/ or Bladder/ or urothelial/ or urinary tract/ or Brain/ or Thyroid/ or anal/	2460270	Advanced	
3	Cancer/ or carcinoma/ or neoplasm/ or tumor/ or tumour/	806690	Advanced	
4	(Cancer or carcinoma or neoplasm or tumor or tumour).ab,ti.	3898990	Advanced	
5	Cholangiocarcinoma/ or lymphoma/ or non-Hodgkins lymphoma/ or non-Hodgkin lymphoma/ or Hodgkins lymphoma/ or Hodgkin lymphoma/ or Hodgkin disease/ or leukemia/ or myeloma/ or melanoma/ or glioma/ or meningioma/ or sarcoma/	569400	Advanced	

☐	6	(Cholangiocarcinoma or lymphoma or non-Hodgkins lymphoma or non-Hodgkin lymphoma or Hodgkins lymphoma or Hodgkin lymphoma or Hodgkin disease or leukemia or myeloma or melanoma or glioma or meningioma or sarcoma).ab,ti.	901512	Advanced
☐	7	ginseng/	7985	Advanced
☐	8	ginseng.ab,ti.	9204	Advanced
☐	9	1 or 2	9516837	Advanced
☐	10	3 or 4	4075951	Advanced
☐	11	9 and 10	2633953	Advanced
☐	12	5 or 6	1110000	Advanced
☐	13	7 or 8	5826120	Advanced
☐	14	9 or 10	1756480	Advanced
☐	15	11 or 12 or 13 or 14	7714082	Advanced
☐	16	7 or 8	11732	Advanced
☐	17	15 and 16	2983	Advanced

Supplement B: Search strategy in PubMed database

Ginseng and cancer prevention
Ginseng
AND
1) Oral OR pharyngeal OR pharynx OR oropharyngeal OR oropharynx OR hypopharyngeal OR hypopharynx OR nasal OR paranasal sinus OR Nasopharyngeal OR nasopharynx OR Laryngeal OR larynx OR Esophageal OR esophagus OR oesophageal OR esophagus OR "Upper aerodigestive tract" OR "head and neck" OR Lung OR respiratory OR Stomach OR gastric OR "Small intestinal" OR "small intestine" OR "small bowel" OR Pancreatic OR pancreas OR Liver OR hepatocellular OR Gallbladder OR "Bile duct" OR Colon OR rectal OR rectum OR colorectal OR colorectum OR "large bowel" OR Breast OR mammary OR Ovarian OR ovary OR Endometrial OR endometrium OR "corpus uteri" OR uterine OR Cervical OR cervix OR Prostate OR Testicular OR testes OR penis OR penile OR Kidney OR renal OR "renal cell" OR adrenal OR Bladder OR urothelial OR "urinary tract" OR Brain OR Thyroid OR anal

AND

3)
Cancer OR carcinoma OR neoplasm OR tumor OR tumor tumor

OR
4)
Cholangiocarcinoma OR lymphoma OR non-Hodgkin's lymphoma OR non-Hodgkin lymphoma OR Hodgkin's lymphoma OR Hodgkin lymphoma OR Hodgkin disease OR leukemia OR myeloma OR melanoma OR glioma OR meningioma OR sarcoma

OR
5)
Cancer OR carcinoma OR neoplasm OR tumor OR tumor

(ginseng) AND ((((((Oral OR pharyngeal OR pharynx OR oropharyngeal OR oropharynx OR hypopharyngeal OR hypopharynx OR nasal OR paranasal sinus OR Nasopharyngeal OR nasopharynx OR Laryngeal OR larynx OR Esophageal OR esophagus OR oesophageal OR esophagus OR "Upper aerodigestive tract" OR "head and neck" OR Lung OR respiratory OR Stomach OR gastric OR "Small intestinal" OR "small intestine" OR "small bowel" OR Pancreatic OR pancreas OR Liver OR hepatocellular OR Gallbladder OR "Bile duct" OR Colon OR rectal OR rectum OR colorectal OR colorectum OR "large bowel" OR Breast OR mammary OR Ovarian OR ovary OR Endometrial OR endometrium OR "corpus uteri" OR uterine OR Cervical OR cervix OR Prostate OR Testicular OR testes OR penis OR penile OR Kidney OR renal OR "renal cell" OR adrenal OR Bladder OR urothelial OR "urinary tract" OR Brain OR Thyroid OR anal)) AND (Cancer OR carcinoma OR neoplasm OR tumor OR tumor))) OR (Cancer OR carcinoma OR neoplasm OR tumor OR tumor

23.05.2020: 2623 records +

Supplement C: The overview of the assessed study quality using the Newcastle Ottawa scale

Case-Control studies star template	Selection	Comparability	Exposure
Yun Taik-Koo & Choi Soo-Yong., 1995	✵✵✵✵	✵✵	✵✵✵
Rebbeck T. R. et al., 2007	✵✵✵✵	✵✵	✵✵✵

Cohort studies star template	Selection	Comparability	Exposure
Yun Taik-Koo & Choi Soo-Yong., 1998	✵✵✵✵	✵✵	✵✵
Satia J. A. et al., 2009	✵✵✵✵	✵✵	✵✵✵
Brasky T M. et al., 2011	✵✵✵	✵ ✵	✵✵✵
Kamangar F. et al., 2007	✵✵✵✵	✵✵	✵✵✵
Walter B. R et al., 2011	✵✵✵	✵✵	✵✵✵

CODING MANUAL FOR CASE-CONTROL STUDIES

Yun Taik-Koo & Choi Soo-Yong., 1995: 9 *

Selection:

1) a *

2) **a** *

3)b*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b✵

2) a✵

3) a✵

Rebbeck T R. et al., 2007: 9 *

Selection:

1) b *

2) **a** *

3)a*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) c✵

2) a✵

3) a✵

CODING MANUAL FOR COHORT STUDIES

Yun Taik-Koo & Choi Soo-Yong., 1998: 8 *

Selection:

1) **a** *

2) **a** *

3)b*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b✵

2) b

3) b✵

Rebbeck T R. et al., 2007: 9 *

Selection:

1) b *

2) **a** *

3)a*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) c✵

2) a✵

3) a✵

Satia J. A. et al., 2009: 9 *

Selection:

1) **a** *

2) **a** *

3) c*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b✵

2) a ✵

3) b ✵

Brasky T M. et al., 2011: 8 *

Selection:

1) **a** *

2) **a** *

3)c

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b ✵

2) a✵

3) b ✵

Kamangar F. et al., 2007: 9 *

Selection:

1) **a** *

2) **a** *

3)b-c*

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b-c✵

2) b✵

3) b (93% finished)✵

Walter B. R et al., 2011: 8 ✵

Selection:

1) **a** *

2) **a** *

3)c

4) a ✵

Comparability

1)a ✵✵

Exposure

1) b✵

2) a✵

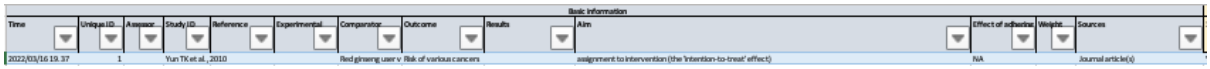
3) b✵

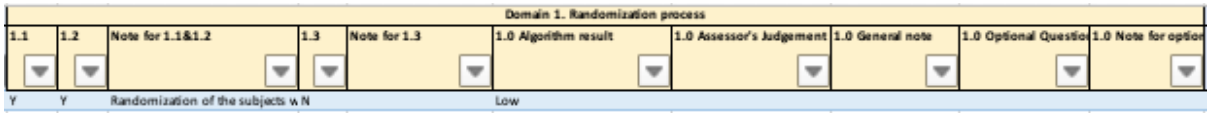
Supplement D: The quality assessment of randomized trial using RoB 2 Tool

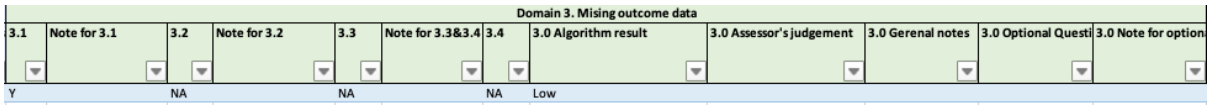
Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Yun TK et al., 2010	NA	Red ginseng user vs. non/use	Risk of various cancers	1	+	+	+	+	+	+

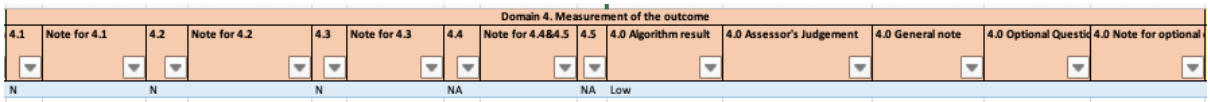
+ Low risk
! Some concerns
- High risk

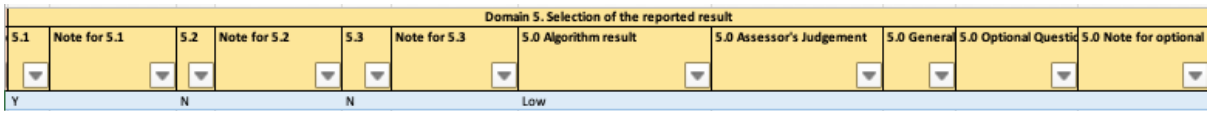
D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result







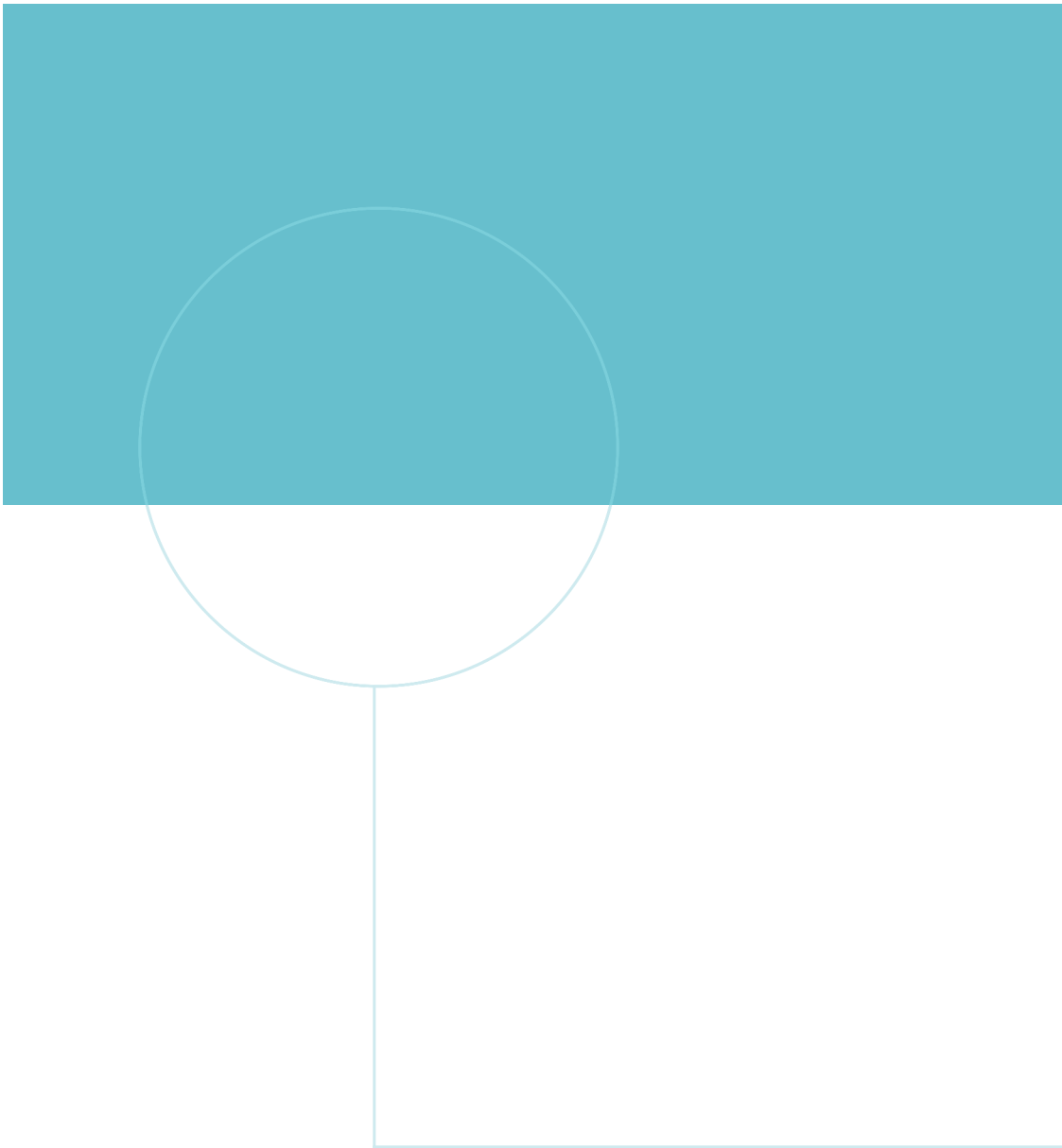




Supplementary Table

Table 8. Relative risks and 95% confidence intervals from nonlinear dose-response analysis of ginseng and total cancer risk.

Frequency per year	RR (95% CI)
0	1.00
1	0.85 (0.77-0.95)
2	0.73 (0.59-0.90)
3	0.63 (0.47-0.85)
4	0.56 (0.38-0.81)
5	0.50 (0.32-0.77)
6	0.46 (0.29-0.72)
7	0.43 (0.26-0.69)
8	0.40 (0.25-0.65)
9	0.39 (0.25-0.61)
10	0.38 (0.25-0.58)
11	0.38 (0.26-0.55)
12	0.38 (0.27-0.52)
13	0.38 (0.29-0.51)
14	0.38 (0.30-0.50)
15	0.39 (0.31-0.50)
$p_{nonlinearity}$	0.07



NTNU

Norwegian University of
Science and Technology