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Geographic Variability and the Association of Flavonoids, Glycemic Index, and Related Single Nucleotide Polymorphisms with Liver Cancer

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Geographic Variability and the Association of Flavonoids, Glycemic Index, and Related Single Nucleotide Polymorphisms with Liver Cancer

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Epidemiology

by

Aileen Baecker

2017

ABSTRACT OF THE DISSERTATION

Geographic Variability and the

Association of Flavonoids, Glycemic Index, and

Related Single Nucleotide Polymorphisms with Liver Cancer

by

Aileen Baecker

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2017

Professor Zuofeng Zhang, Co-Chair

Professor Jian Yu Rao, Co-Chair

Background: Liver cancer is the second most fatal cancer in the world. China is disproportionally affected, accounting for approximately 50% of liver cancer cases and deaths worldwide. Major risk factors for liver cancer include chronic hepatitis B and C viral infections, aflatoxin B1 exposure, alcoholic consumption, and tobacco smoking. **Objective and Methods**: We aimed to update the fraction of liver cancer cases attributable to these known risk factors, as well as estimate attributable risk of obesity for liver cancer at country, regional, and global levels. At the individual level, a population-based case-control study was conducted in a high risk area of China, Jiangsu Province, to evaluate novel associations between dietary intakes of flavonoids as well as glycemic index and load with liver cancer, and to assess original relationships of single nucleotide polymorphisms (SNPs) of NF-κB, the stem cell pathway, and GWAS SNPs with liver cancer. We constructed a genetic risk score, and evaluated the association between these SNPs and liver cancer stratified by flavonoid intake. **Results**: In the global analyses, we found that most liver cancer cases could be attributed to viral hepatitis, particularly in low income regions. Alcohol consumption was responsible for more cases than any other lifestyle risk factor, and patterns varied geographically. In the case-control study, we observed marginal and inverse associations between total flavonoid consumption and liver cancer, driven in large part by the protective association between tea drinking and liver cancer. Carbohydrate intake was associated with increased odds of liver cancer. No obvious association between SNPs of the NF-κB pathway and liver cancer was observed, however, genetic risk scores of SNPs of the stem cell pathway and those identified in GWAS studies were associated with liver cancer. Furthermore, we found that dietary flavonoid intake modified the associations between liver cancer and SNPs associated with the stem cell pathway as well as SNPs identified through GWAS studies. **Conclusion**: This study provides policy-makers updated and regionally specific estimates of the burden of cancer. In addition to confirming established risk factors with the exception of obesity, the results from the case-control study support a marginally protective effect of dietary flavonoid consumption, driven largely by tea drinking, and a marginal increase in susceptibility associated with increased glycemic load and liver cancer in a Chinese population. Furthermore, there was evidence that dietary intake may modify the associations between some SNPs and liver cancer.

The dissertation of Aileen Baecker is approved.

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CHAPTER 1. BACKGROUND

1.1 Liver Cancer

1.1.1 Worldwide Incidence & Mortality

In 2012, approximately 50% of all incident liver cancer cases in the world were in China. Liver cancer is largely seen in less developed regions of the world, where 83% of the world's 782,000 new liver cancer cases in 2012 occurred (Ferlay et al. 2013). 50% of these cases occurred in China alone (Ferlay et al. 2013).

Liver cancer disproportionately affects men. It is the fifth most common cancer in men (554,000 cases) and the ninth most common cancer in women (228,000 cases). Furthermore, it is highly fatal, responsible for around 746,000 deaths a year (Ferlay et al. 2013), making liver cancer the second most common causes of death from cancer worldwide. Due to the poor prognosis associated with liver cancer, the geographical patterns in mortality follow incidence closely.

In the United States, the 5-year survival is 17.5% for all stages, with survival ranging from 30.9% for localized compared to only a 3.1% 5-year survival rate for patients with distant liver cancer (National Cancer Institute 2017). Although lower rates are reported in high income countries of the world, mortality rates from liver cancer have already greatly increased in countries such as the United States (US) (Bertuccio et al. 2017), and are projected to increase even more over the next twenty years (Rahib et al. 2014; Parkin, Boyd, and Walker 2011). Published literature suggests that 5-year survival in China is lower than in the United States. A global surveillance study from 67 countries found a Chinese 5-year survival rate of 12.5% from

2005-2009 (Allemani et al. 2015), with survival rates varying by county. In Dafeng, 5-year net survival in adults 15-99 years old was 11.3% (CI: 4.1, 18.5) from 2000-2004 and 16.0% from 2005-2009. Survival rates in Ganyu were lower, 2.5% (95% CI: 0.9, 4.1) from 2000-2004 and 5.8% (95% CI: 1.8, 9.7) from 2005-2009 (Allemani et al. 2015).

1.1.2 HCC Risk Factors

Accumulated damage over many years can cause liver cancer. This includes chronic inflammation, such as inflammation from chronic hepatitis B virus (HBV) infection or non-alcoholic fatty liver disease. Molecular pathways that have been proposed to affect liver carcinogenesis include inflammation, NF-κB, and stem cell pathways. Patients generally present with liver cancer after a long period of damage, and liver diseases and conditions that commonly precede liver cancer include chronic hepatitis, fibrosis and cirrhosis, alcoholic liver disease, and fatty liver disease.

There are two types of liver cancer in adults. The most common form is called hepatocellular carcinoma (HCC), and originates in the hepatocytes of the liver. Around four out of five incident cases of primary liver cancer are HCC. The other form of liver cancer is cholangiocarcinoma, which starts in the ducts carrying bile from the liver to the gallbladder, or from the gallbladder to the intestines. Most liver cancers are HCC, with approximately 10-25% of liver cancers identified as cholangiocarcinoma. Major risk factors for HCC include chronic infection with HBV, HCV, aflatoxin exposure, tobacco smoking, alcohol drinking, and more recently, obesity. In contrast, known risk factors for cholangiocarcinoma are parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis, and toxins (Tyson and El-Serag 2011).

Most liver cancers in Jiangsu Province, China are cases of HCC. The etiology of HCC is geographically heterogeneous, as the risk factors for HCC vary considerably by region.

Hepatitis Viruses

For over forty years (Sherlock 1970), chronic infection with HBV has been a known etiologic agent in the development of HCC. Approximately 45% of the world population lives in an area where chronic HBV infection is highly endemic, with the highest rates in sub-Saharan Africa, the Amazon basin, China, the Republic of Korea, and several countries in southeast Asia (Custer et al. 2004). Chronic HBV infection is measured using seropositivity for hepatitis B surface antigen (HBsAg). The relative risk associated with seropositivity of HBsAg and liver cancer ranges from 5.3-148 in cohort studies, and 5 to 30 in case control studies (IARC Working Group 2012a).

HCV has been identified as a carcinogen to humans since the early 1990s (IARC Working Group 2012b). The estimated prevalence of HCV worldwide is 2.2%, with region-specific rates as low as <1% in northern Europe and ranging to over 3% in northern Africa (IARC Working Group 2012b). Chronic HCV infection is commonly identified with HCV antibodies (anti-HCV). Chronic infection with HCV has been associated with relative risks ranging from ~15 to 25.

Few large-scale population-based studies have reported the number of HBV/HCV coinfection, making it difficult to estimate the prevalence worldwide. However, some studies have reported that approximately 5-20% of patients with chronic HBV infection are co-infected with HCV (Crespo et al. 1994; Fattovich et al. 1991; Gaeta et al. 2003; Chan et al. 1991; Dai et al. 2001; Sato et al. 1994; Ohkawa et al. 1994; Xess et al. 2001; Pramoolsinsap et al. 1999).

Meta-analyses have reported conflicting results on the joint effects of HBV and HCV, reporting both sub-additive and super-additive effects (sub-additive: (Cho et al. 2011); super-additive: (Donato, Boffetta, and Puoti 1998) and (Shi et al. 2005)). Cho et al. found an overall sub-additive effect on risk of hepatocellular carcinoma in more recent studies (2000-2009), cohort studies, and studies conducted in areas where HBV and HCV infection were uncommon, an additive effect in HBV endemic areas, and a super-additive effect in older studies, case-control studies, and in HCV endemic areas (Cho et al. 2011).

Aflatoxin

Dietary exposure to aflatoxins is common in areas with unsafe practices of food storage and/or contamination of the water supply. Worldwide, millions of people are exposed to these toxic metabolites produced by the *aspergillus* molds. These molds commonly infest staple crops including maize, rice, wheat, and peanuts. Aflatoxin poisoning can be acute, however chronic low-level exposure to aflatoxins is associated with an increased risk of developing HCC in addition to increased risks of impaired immune function and malnutrition.

HBV prevalence is thought to interact with aflatoxin exposure, and together HBV infection and aflatoxin exposure greatly increase risk of liver cancer. A review of available studies concluded that aflatoxin likely plays a causative role in 4.6-28.2% of all global HCC cases (25,000-155,000), with the majority of cases occurring in sub-Saharan Africa, Southeast Asia, and China (Liu et al. 2012). Exposure to aflatoxin in persons with chronic HBV infection is associated with a risk up to 30 times greater than in those exposed to aflatoxin alone (Groopman, Kensler, and Wild 2008). Estimates for HBV infected individuals in regions where aflatoxin exposure is common, such as parts of Africa and Asia, are likely underestimates.

Alcohol

Since 1988, IARC has classified alcohol as a group 1 carcinogen. Heavy drinking is thought to lead to cirrhosis, a major risk factor for liver cancer. The countries with the highest per capita alcohol consumption are located in Eastern and Western Europe. The National Institute on Alcohol Abuse and Alcoholism defines heavy or "at-risk" alcohol drinking as more than 4 drinks on any single day or more than 14 drinks per week for men, and more than 3 drinks on any day or more than 7 drinks per week for women (National Institute on Alcohol Abuse and Alcoholism). A meta-analysis by Turati et al. found that drinking 37.5g of ethanol (about 3 drinks) or more per day was associated with a RR of 1.16 (95% CI: 1.01-1.34) for liver cancer among heavy drinkers compared to non-drinkers, and that risk increases with drinking (Turati et al. 2014).

Tobacco Smoking

Studies providing evidence for the carcinogenicity of smoking date back to the 1950s (Doll and Hill 1950; Wynder and Graham 1950), including studies showing an association between smoking and liver cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2004). There are over 60 known carcinogens in cigarette smoke (US Department of Health and Human Services 2010), including polycyclic aromatic hydrocarbons and aromatic amines, both which have been associated with risk of HCC (Wang et al. 1998; Chen et al. 2002).

In 2012, Eastern Asia and Eastern Europe had the highest prevalence of daily smokers (Ng et al. 2014). Recent meta-analyses by Lee et al. (Lee et al. 2009) and Gandini et al. (Gandini et al. 2008) found that current smokers had about 1.5 times the risk for liver cancer compared to never smokers (Lee et al: 1.51 [1.37,1.67]; Gandini et al: 1.56 [1.29,1.87]). This is consistent with IARC's 2004 findings in their monograph on tobacco smoke and involuntary smoking that an association between tobacco smoking and liver cancer has been consistently observed in cohort and case control studies (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2004).

Those who smoke tend to drink alcohol as well. A meta-analysis by Lee et al. found that the RR for current smokers was slightly lower after adjusting for alcohol (before adjustment: 1.51, 95% CI: 1.37, 1.67; after adjustment: 1.43, 95% CI: 1.21, 1.68), while Chuang et al. found that the risk ratio for alcohol and liver cancer was 1.29 (95% 95% CI: 1.08, 1.50) before adjusting for smoking and 1.33 (95% CI: 1.15, 1.52) after adjusting for smoking (Lee et al. 2009; Chuang et al. 2015).

Obesity

Obesity has been proposed as a risk factor for liver cancer. The marked increase in the worldwide prevalence of obesity, particularly in children, suggests that even a small associated increased risk of liver cancer can have wide-reaching future effects. Obesity-induced liver inflammation results in elevated production of cytokines and adipokines, and a chronic state of inflammation can lead to NAFLD, NASH, fibrosis, and cirrhosis (Sun and Karin 2012). Meta-analyses looking at obesity (BMI of 30 or more) have found associated RRs ranging from 1.35-1.89 (Rui et al. 2012; Larsson and Wolk 2007).

Obesity may interact with other lifestyle risk factors. Those who drink alcohol are more likely to be obese, and it may be difficult to assess the individual effect of each risk factor as they often co-occur. A meta-analysis of 26 prospective studies by Chen et al. found that the risk of liver cancer associated with obesity, adjusted for alcohol was 1.46 (95% CI: 1.25, 1.69) (Chen et al. 2012). This estimate is similar to the estimate of the association between obesity and liver cancer, unadjusted for alcohol intake.

1.1.3 Previous Descriptive Epidemiology of HCC

Traditional risk factors that were included in the analysis were chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol drinking, and tobacco smoking. Recently, evidence has emerged that obesity may also increase risk of HCC through chronic inflammation of the liver (Sun and Karin 2012). The distribution of these risk factors varies geographically, creating variability in the disease risk profiles for HCC by geographic region.

Previously published studies on the major attributable risk factors of liver cancer use outdated data, and have often looked at a limited number of risk factors. Two studies estimated the worldwide risk of liver cancer due to infectious agents only (de Martel et al. 2012; Parkin 2006), while another has estimated risk from alcohol intake only (Praud et al. 2016). Studies in France, the United Kingdom, the United States (USA), Japan, and China have also looked at the fraction of liver cancer cases attributable to both infectious and lifestyle risk factors; nevertheless, these studies are country-specific and lack global and regional perspectives (IARC Working Group 2007; Parkin, Boyd, and Walker 2011; Inoue et al. 2012; Fan et al. 2013; Makarova-Rusher et al. 2016). The Global Burden of Disease Project has focused on mortality outcomes, estimating the years of life lost associated with subtypes of liver cancer (Mortality and Causes of Death 2016). There is a pressing need for an updated and comprehensive study of global trends of liver cancer risk factors.

1.2 Diet and Liver Cancer

Changes in the disease risk profile of liver cancer have already been observed in some regions of the world. Studies reporting the underlying causes of liver cancer and other liver diseases increasingly report a large proportion of HCC cases arising from cryptogenic cirrhosis (El-Serag and Rudolph 2007), where the cause of disease is unknown and not related to traditional viral liver cancer risk factors. Globally, HCC associated with cryptogenic cirrhosis accounts for around 15-30% of HCC (Michelotti, Machado, and Diehl 2013).

It is theorized that a large proportion of these cryptogenic cases may be due to a novel risk factor: obesity. While viral risk factors for HCC may be projected to decline, obesity has been steadily increasing on a global scale, and there is evidence that the increasing rates of non-alcoholic fatty liver disease (NAFLD) are linked to an increased risk of HCC (Yang et al. 2012; Hucke et al. 2011; Ertle et al. 2011; Malik et al. 2009). Lifestyle risk factors will likely play a larger role in the etiology of liver cancer in years to come. A better understanding of lifestyle-related risk factors and how they affect established risk factors is essential to understanding and preventing future liver cancer cases.

1.2.1 Glycemic Index and Glycemic Load

Diet may affect liver cancer risk through a several pathways, including through glycemic index and glycemic load. Diets with low daily glycemic index and glycemic load are linked to favorable lipid profiles and lower concentrations of c-reactive protein in overweight and obese persons, and may improve glucose intolerance and hyperinsulinemia (Valtuena et al. 2006). High carbohydrate intake may contribute to insulin resistance and increased inflammation, and dietary glycemic index has been associated with liver steatosis, a condition which commonly precedes liver cancer (Valtuena et al. 2006).

Glycemic index (GI) measures how rapidly a carbohydrate is digested and released as glucose into the bloodstream, and foods with a high GI raise blood sugar to a greater extent than foods with medium or low GI. On a scale of 0 to 100, pure glucose is given a value of 100. However, GI does not take into account the amount of carbohydrate in a food. Foods such as watermelon may have a high glycemic index, but one serving of watermelon contains very few carbohydrates (about 6g of carbohydrates per 100g of watermelon; versus about 73 g in 100g of rice). Glycemic load (GL) is adjusted for the amount of carbohydrate a food contains, giving a better measure of not only how much glucose enters the bloodstream, but also how much glucose is delivered.

One meta-analysis of six studies of liver cancer did not find strong evidence of an association with GI (RR: 1.11, 95% CI: 0.80, 1.53) or GL (RR: 1.14, 95% CI: 0.78, 1.67). However, five of the six studies were conducted in Western populations. It is possible that different dietary patterns between Western and Asian populations may modify the association between liver cancer and GI or GL. One high GI food commonly eaten in China is white rice, while breads and pastas are more common in Western populations. Furthermore, Asian populations tend to experience the adverse metabolic effects at lower BMIs, indicating that there could be a biological basis for a different association between these two populations as well. One study has been conducted in a Chinese population, including 139 female and 208 male cases, and found an association between glycemic index and liver cancer among women. No association was observed among men or with glycemic load (Vogtmann et al. 2013).

1.2.2 Flavonoids

Plant-based diets, particularly those rich in vegetables and fruits, have consistently been associated with a protective effect against cancers of various sites (World Cancer Research Fund/American Institute for Cancer Research 1997). This effect is likely due to the low energy content of these foods as well as their constituent parts, including vitamins, minerals, and bioactive compounds. Flavonoids are one such bioactive compound produced by plants which may reduce the risk of cancer.

Flavonoids are present in many dietary plants, are relatively abundant in the diet, and are generally heat stable (Ren et al. 2003). They are characterized by their general structure of a 15-carbon skeleton, consisting of two phenyl rings linked to a heterocyclic ring (Aherne and O'Brien 2002). Flavonoids can be further subdivided into subclasses of flavones, flavonols, flavanones, catechins and epicatechins, anthocyanins, and isoflavones. Human dietary intake from flavonoids is estimated to be anywhere from dozens of mg/day (Hertog et al. 1993), to over a hundred mg/day (Li et al. 2013). Flavonoid uptake and metabolism is complex, and for this reason plasma measurements of flavonoids can be a misleading indication of bioavailability (Batra and Sharma 2013; Hollman 2004). Dietary measures of flavonoids may give a better estimate of flavonoid intake for this reason.

Dietary intake from flavonoids has shown a protective association against cardiovascular disease and several cancers (Mulvihill and Huff 2010; Garcia-Lafuente et al. 2009; Hooper et al. 2008). Flavonoids have a wide variety of biological effects which are thought to have anti-carcinogenic properties. These mechanisms for anti-carcinogenesis include antiproliferative effects and strong antioxidant capacity, in addition to involvement in cell signaling, cell cycle regulation, cell differentiation, and angiogenesis (Ren et al. 2003). Another putative mechanism, which has mainly been described in breast tissue, is the modulation of estrogen signaling by isoflavones. Recently, flavonoids have been investigated in the treatment of ovarian, breast, cervical, pancreatic, and prostate cancers, even entering several late phase clinical trials for oncological indications (Ferry et al. 1996; Lazarevic, Karlsen, and Saatcioglu 2008; Lin et al. 2009).

Flavonoid-mediated chemoprevention is likely due in part to the anti-inflammatory and antioxidant activities of flavonoids. Flavonoids are able to scavenge reactive oxygen species (ROS) and growth promoting oxidants that are the major catalysts for tumor promotion (Ren et al. 2003; Ravishankar et al. 2013). Furthermore, there is evidence that there exists a close association among reactive oxygen species (ROS), chronic inflammation, and cancer (Gupta et al. 2012). While acute inflammation is therapeutic, chronic inflammation is a risk factor for several diseases, including cancer. ROS regulates several well-known mediators of inflammation and tumorigenesis, including COX-2, inflammatory cytokines (TNF-, IL-1, IL-6), chemokines (IL-8, CXCR4), and pro-inflammatory transcription factors (NF-κB) (Gupta et al. 2012).

Flavonoids may also affect immune function and directly work to inhibit fungal and viral growth. One in vitro study found that the flavonoid apigenin inhibits HCV replication (Shibata et al. 2014). Another study tested six different plant flavonoids against a spectrum of bacteria and fungi, and found that flavonoids were generally good antimicrobial and antifungal agents (Orhan et al. 2010).

Several studies have shown a chemoprotective effect of flavonoids *in vitro* and in animal studies. Fang et al. isolated flavonoids from a Chinese herb and applied them to human cancer cells, and found that the flavonoids had the strongest inhibitory effect on SK-Hep-1 human hepatocellular carcinoma cells (Fang et al. 2010). Other studies observed inhibition of proliferation and inducement of apoptosis in hepatocellular carcinoma cells (Hep3B, SMMC-7721, and HepG2) after exposure to flavonoids from milkvetch and milk thistle as well as genistein (Yeh et al. 2007; Hu et al. 2009; Ramakrishnan et al. 2009). Another study by Siess et al. found that rats with several flavonoids during two stages of aflatoxin B1 induced hepatocarcinogenesis had decreased numbers of preneoplastic foci (Siess et al. 2000), suggesting that flavonoids may act as an anti-initiator and anti-promoter in rat hepatocarcinogenesis.

Many epidemiological studies have been conducted on flavonoid intake and cancer; however few studies have focused on their association with HCC. One case-control study and one cohort study, both in western populations, have looked at total flavonoid intake and HCC. Flavone intake was inversely associated with HCC risk in a Greek case-control study described by Lagiou et al. (Lagiou et al. 2008). This effect was observed both in participants positive for chronic hepatitis virus (highest vs lowest flavonoid quintile, OR=0.50, 95% CI: 0.27-0.94) as well as in participants negative for chronic hepatitis (highest vs lowest, OR=0.41, 95% CI: 0.16-1.06) (Lagiou et al. 2008). In this population, the main sources of flavonoids were spinach and peppers, and were inversely associated in both hepatitis positive and hepatitis negative participants. The study included six cholangiocarcinoma cases. A suggestion of an inverse association with flavonoids and cholangiocarcinoma was found, however the sample size limits the significance of these findings.

In addition, a cohort study by Zamora-Ros et al. has also been conducted in the European Prospective Investigation Into Cancer and Nutrition study (Zamora-Ros, Fedirko, et al. 2013). This study included 191 incident HCC cases over a follow-up of 11years, and found a borderline association of HCC with total flavonoid intake when comparing the highest tertile to the lowest (HR=0.65, 95% CIL 0.40-1.04). Among the flavonoid subclasses, flavanols were inversely associated with HCC (HR=0.62, 95% CI 0.31-0.79).

Flavonoid Consumption in an Asian Diet

The sources of flavonoids in Asian diets are different from Western diets. Whereas spinach and peppers were the main source of flavonoids in the Greek case-control study by Lagiou et al. (Lagiou et al. 2008), soy and tea are commonly consumed sources of flavonoids. In China, Li et al. found that the richest sources of total flavonoids in commonly consumed fruits and vegetables were apple, plum, pear, peach, lotus root, and taro (Li et al. 2013), while Xu et al. looked at a wider variety of foods and beverages and found tea to be the top source of flavonoids (Xu et al. 2016). Flavonoid studies in China have found that nearly 50% of flavonoids come from tea consumption (Xu et al. 2016), while a large cohort study of European countries found that tea consumption was responsible for a much smaller portion of total flavonoid intake. In non-Mediterranean European countries, tea consumption was responsible for 25.7% of total flavonoid intake, while 6.8% of total flavonoid intake in Mediterranean countries came from tea (Zamora-Ros, Knaze, et al. 2013). In two Chinese studies of diet, the daily intake of total flavonoids was found to be around 165.6-395 mg/day (Li et al. 2013; Xu et al. 2016) .

Although flavonoids are common in dietary plants, the subclasses of flavonoids are not uniformly distributed in plants. For example, catechins and epicatechins are more abundant in tea, while isoflavones are common in soy. In addition, variation in flavonoids may vary in concentration depending on the part of the fruit or vegetable is consumed. For many fruits and vegetables, the skins of the fruit or the leaves of the plant contain the most concentrated sources of flavonoids. Regional norms and personal preferences in fruit and vegetable preparation may affect flavonoid intake. For example, skinning a fruit such as an apple or a pear will reduce flavonoid intake.

Furthermore, food preparation and processing also affect flavonoid intake, and conventions vary regionally and culturally. For example, the consumption of salads and raw vegetables is more common in a Western diet, while most vegetable dishes are cooked in a Chinese diet. Xu et al. measured flavonoids in nine kinds of vegetables from a Tianjin market after frying, boiling, stewing, and microwaving (Xu et al. 2007). The authors found that the percentage of flavonoids reserved after frying ranged from 54.6-115.6%, while boiling resulted in a 33.6-107.8% reserve rate, stewing 31.7-100.5%, and microwaving 43.1-109.6%. Additionally, pickling has also been thought to affect flavonoid content. A study conducted in China by Chun et al. found that total flavonoid content was higher in fresh red cabbage samples (108.1 ± 9.3 mg catechin equivalents /100g fresh sample) compared to pickled red cabbage (72.4 ± 4.4 mg catechin equivalents/100g fresh sample) (Chun et al. 2004).

Variation in flavonoid intake between a Western and Asian diet may be due to a variety of factors. Variation due to common sources of dietary flavonoids likely plays a large role. Other factors are inherent to the biology and growth cycle of the plant, while others can be influenced by the processing and preparation of the plant after it has reached the market. While most studies of flavonoids have been conducted in Western populations, it is likely that there are large differences in flavonoid consumption between Asian and Western populations due to differences in flavonoid sources, cultivation methods, and preparation methods.

Current and commonly used databases have been developed by Western countries, including the USDA Database for the Flavonoid Content of Selected Foods (US Department of Agriculture 2013, 2008), Phenol-Explorer (Neveu et al. 2010), and the UK Food Standards Agency database (Ward et al. 2010). Food items common in a Chinese diet are not always reflected in these databases, necessitating construction of a database that includes Chinese food items and reflecting Chinese cultivation and preparation methods.

1.2.3 Genetic Pathways

By impacting cell function and the molecular environment, diet may modify the risk between these genetic polymorphisms and risk of liver cancer. Of particular interest are diet and diabetes-related single nucleotide polymorphisms (SNPs). The associations between SNPs located in genes associated with nutrient metabolism (such as BCM01) with liver cancer are likely to be modified by diet and molecular changes associated with diet.

Another pathway that may be related to diet and liver cancer is the NF-κB pathway. NF-κB is a protein that controls transcription of DNA, and is involved in cellular responses to stress, cytokines, free radicals, and viral antigens (Gilmore 2006, 1999; Brasier 2006). A variety of diseases, including cancer, inflammatory diseases, and viral infection have been linked to dysregulation in NF-κB signaling. One role of NF-κB is to regulate genes controlling cell proliferation and cell survival. Thus, many human tumors have activated NF-κB.

The putative chemopreventive effects of flavonoids are not limited to scavenging ROS, they have also been shown in several studies of tumor cell lines to inhibit tumor growth and more directly inhibit NF-κB signaling (Singh et al. 2005; Shin et al. 2011). Sing et al. observed inhibition of NF-κB signaling in the suppression of tumor xenograft growth by the flavonoid silibinin (Singh et al. 2005). In addition, several chalcones, which are similar in structure to flavonoids, have also been observed to repress NF-κB pathways in endothelial cell lines (Chang et al. 2007; Bertl et al. 2004; Zhao et al. 2016) Thus, NF-κB signaling is dysregulated in tumor cells, and flavonoids may affect tumor growth through inhibition of NF-κB signaling in addition to mechanisms through tumor-related oxidative stress.

Other pathways of interest that may be related to liver carcinogenesis are the stem cell pathway and micro RNA (miRNA) pathways. Wnt/β-catenin signaling plays a crucial role in hepatic development and regeneration, and dysregulation of this pathway may contribute to liver carcinogenesis by affecting cell proliferation, apoptosis, oxidative stress, and differentiation (Monga et al. 2003; Monga et al. 2001). Additionally, miRNAs have been linked to enhanced hepatitis virus replication, regulation of lipid metabolism, and hepatocellular carcinoma (Otsuka et al. 2017).

1.3 Gaps in the Literature

Gaps in the literature that are filled by this study are summarized in Table 1-1. Previous studies estimating the number of cases of liver cancer that can be attributed to major risk factors have either looked at a limited number of factors or have only looked at a variety of risk factors for a single country (de Martel et al. 2012; Parkin 2006; Parkin, Boyd, and Walker 2011; Praud et al. 2016; IARC Working Group 2007; Inoue et al. 2012; Fan et al. 2013; Makarova-Rusher et al. 2016). There is a need for updated comprehensive estimates for a variety of risk factors for liver cancer on a global, regional, and country level. Very few studies have investigated dietary factors and liver cancer, especially in high risk populations. Although dietary intake of flavonoids has been associated with a variety of cancers, the association has only been explored for liver cancer in two studies with small sample size in Europe. This study is the first to look at the association between flavonoid intake and liver cancer in a high-risk population in China, and it is the largest study to assess whether flavonoid intake, glycemic index, or glycemic load are associated with liver cancer. Additionally, this study assessed interaction between these dietary factors and established risk factors of liver cancer. Furthermore, the associations between liver cancer and SNPs associated with NF-κB, stem cell pathways, and GWAS studies were assessed. This is the first study to evaluate how flavonoid intake modifies the associations between established and novel related SNPs on liver cancer susceptibility. SNPs significantly associated with liver cancer and included in the genetic risk score were also assessed for interaction with established liver cancer risk factors.

CHAPTER 2. RESEARCH OBJECTIVES

For Specific Aim 1, we aim to estimate the distribution and determinants of liver cancer at the country, regional, global levels. Current literature is either out-of-date or confined to regional localities. Many excluded more recently identified risk factors for liver cancer. There have been no such estimates at country level worldwide. Understanding how risk factors vary geographically is integral to constructing appropriate health policies to address major country-level and regional risk factors. We studied the global burden of liver cancer and explored geographic heterogeneity in terms of attributable risks for established and novel risk factors for liver cancer at global, regional and country levels. The methods, results, and conclusions of Specific Aim 1 are described in Chapter 3.

Specific Aim2 was conducted in a population-based case-control study in Jiangsu Province, China, allowing the study of known and novel risk/protective factors for liver cancer at the individual level. Protective dietary factors are less commonly studied for liver cancer. Dietary flavonoid intake as well as glycemic index and load, are dietary factors thought to be associated liver cancer. Furthermore, these dietary factors vary between Western and Asian populations. Animal and in vitro studies have shown promising evidence of an anti-hepatocarcinogenic effect of dietary flavonoid intake, and observational studies of total flavonoid and isoflavone intake in Western and Japanese populations have generally supported this observation. Similarly, observational studies have found a statistically insignificant association between glycemic index and glycemic load with liver cancer, however there is evidence that this risk is higher in certain subpopulations. Elucidating the association between dietary intake of flavonoids, glycemic index, and glycemic load will help improve understanding of the differential effects of an Asian diet on liver cancer risk. The methods, results, and conclusions of Specific Aim 2 are described in Chapter 4.

For Specific Aim 3, we aim to assess the potential impact of genetic predisposition on the development of liver cancer. Animal models indicate that SNPs involved in inflammation, stem cell pathways, as well as candidate SNPs identified through GWAS may be involved in liver carcinogenesis. Furthermore, these pathways are affected by diet, and may interact to modify risk of liver cancer. No study has yet explored the association of these SNPs with liver cancer, or their potential interactions with dietary factors. This study will shed a light on the potential interactions between genetics and diet on liver cancer development. The study design of Specific Aim 3 is described in Chapter 4, while methods, results, and conclusions are described in Chapter 5.

Specific aims are as follows: 1. To describe and update regionally-specific determinants of liver cancer throughout the world in 2012 using estimates of incident cancer, regional prevalence, and risk estimates of four established risk factors and one novel risk factor from the literature. 2. To evaluate the effect of dietary intake of total flavonoids, subclasses of flavonoids, glycemic index, and glycemic load on risk of liver cancer, adjusting for potential confounders. 3. To analyze the relationship between selected SNPs, both individually and in a genetic risk score, with liver cancer, stratifying on diet and adjusting for potential confounders.

CHAPTER 3. GLOBAL POPULATION ATTRIBUTABLE FRACTIONS METHODS, RESULTS, AND DISCUSSION

3.1 Methods

3.1.1 HCC Case Estimation

The 2012 age-standardized estimated numbers of new cancer cases by country and gender are available for 27 of the major cancers in GLOBOCAN 2012 (Ferlay et al. 2013). In 2012 there were 782,451 incident cases of liver cancer worldwide, with over two-thirds of cases occurring in men. Most cases of liver cancer are HCC, however in some regions where the risk factors for cholangiocarcinoma (parasitic infections, particularly) are more common, a larger percentage of liver cancer cases are cholangiocarcinoma. Since Globocan only reports liver cancer cases, we estimated the percentage of HCC cases by country and by geographic region using IARC's age-standardized world incidence rates of microscopically verified cases by histological type (IARC 2014). Cases of HCC were estimated due to the fact that risk factors for HCC are very different from cholangiocarcinoma.

The age-standardized incidence rates by histological type are reported by country, and for some larger countries rates were reported for multiple regions within the country. Country-wide data from large registries were prioritized, and if that wasn't available than country-wide data were estimated from regional studies using averages weighted by verified study sample size. While most studies reported all histological subtypes, a couple studies did have a high proportion of unspecified liver carcinoma or cancer. Studies where more than half of the cases were unspecified were not used to calculate the percent of HCC cases. These studies were primarily in

Algeria and parts of China, where HCC is predominant. The median percentage of unspecified cases in males was 4.1% with an IQR of 0-10%, and for women this was 2.0% (IQR: 0-11.1%).

The HCC rates for the 66 countries that had data were used to calculate the gender-specific rates in each Global Burden of Disease region (GBD) for countries that were missing data. Rates were weighted by number of cases in each region. No studies were conducted in Central Asia, Oceania, Central Sub-Saharan Africa, or West Sub-Saharan Africa. For these regions, percent HCC was estimated using the percentages calculated for other regions in the same continental division.

3.1.2 Prevalence Data for HCC Risk Factors

Prevalence data for major HCC risk factors was extracted from the literature and publicly accessible databanks. Prevalence estimates were limited to what was available in the literature and from databases. Specific sources used are as follows. HBV prevalence was obtained from a study of 161 countries, estimating HBsAg seroprevalence worldwide from 1965-2012 (Schweitzer et al. 2015). Estimates for both genders from 1990-2013 were used. HCV prevalence data came from a study of anti-HCV prevalence in 87 countries for both genders, estimated from 2000-2010 data (Gower et al. 2014). Alcohol exposure estimates by country were obtained from a study of 241 countries and territories, estimating the 2005 distribution of drinking in men and women ages 15 and older (Shield et al. 2013). Prevalence estimates were given for never drinkers, former drinkers, and in increments of 20 and 40g alcohol consumed per day. Prevalence of male and female ever smokers and never smokers in 1996 was obtained a study of 187 countries (Ng et al. 2014), while prevalence of overweight and obese in men and women in 1996 was obtained from the WHO data repository (World Health Organization 2017b, 2017a).

3.1.3 Geographic Divisions

The proportion of HCC cases attributable to each risk factor was estimated for each country that had available data. In order to look at trends on a regional level, global estimates were grouped into the 21 Global Burden of Disease (GBD) Regions. These regional divides partition the world into regions based on geography and similar epidemiological profiles (World Health Organization 2002). The specific countries included in each grouping in this study are reported in Table 3-1. Gender-specific PAFs on the regional level were estimated using the countries for which data were available, weighted by the number of HCC cases in each region.

3.1.4 Relative Risk Estimates

To assess the RRs associated with individual risk factors and liver cancer, we systematically searched publications on PubMed. The search words used with "liver cancer," "HCC," and "hepatocellular carcinoma" included: HBV, hepatitis B virus, HCV, hepatitis C virus, aflatoxin, alcohol, drinking, smoking, tobacco smoking, obesity, adiposity, and meta-analysis. Meta-analyses were given the highest priority. Separate RRs were abstracted when there was indication of variation by gender, geographical location, level of alcohol drinking, and/or HBV/HCV status (See Table 3-2).

Risk ratios for HBV and HCV were extracted from a meta-analysis using RRs of measurements using second generation measurement techniques (Donato, Boffetta, and Puoti 1998). For HBV, the RR used was 22.5 (CI: 19.5-26), and for HCV this was 17.3 (CI: 13.9-21.6). The risk associated with a 25g increase in alcohol consumption per day was reported in a meta-analysis of 27 cohort studies and 63 case control studies (Chuang et al. 2015). A trend line was fitted to the gender-specific reported risk ratios and estimates for the risk associated with a 20g increase in daily alcohol intake were estimated in order to correspond to prevalence data. A risk ratio of 1.43 (CI: 1.21-1.68) was used to estimate the risk associated with ever smoking on liver cancer risk (Lee et al. 2009). This estimate was adjusted for alcohol consumption. The gender-specific estimates of risk associated with an overweight BMI (>=25) and an obese BMI (>=30) were obtained from a meta-analysis of 26 prospective studies (Chen et al. 2012). For risk factors with evidence from the literature of possible super- or sub-additive interaction, the potential impact this would have on the fraction of attributable cases was hypothesized.

3.1.5 Calculation of PAF

The fraction of new liver cancer cases attributable to each infectious risk factor was calculated using Levin’s formula, given the prevalence of the risk factor and the associated relative risk:

$$PAF_{Levin} = \frac{p(RR-1)}{1+p(RR-1)}$$

The population attributable fraction, or PAF, represents the proportion of cases of liver cancer that could be avoided had exposure to a major risk factor was removed (e.g. through vaccination). The population attributable cases (PAC), representing the number of cases that could have been avoided had exposure to the risk factor been removed, can be calculated by multiplying the number of HCC cases in each region by the PAF.

For alcohol consumption and BMI, data on the prevalence and risk associated at different levels of exposure (e.g. for those who consume 0g, 0-20g, 20-40g, 40-60g, and 60+g alcohol daily or for those who have a BMI of 18.5-25, 25-30, 30-35, 35+) was widely available. The population attributable fraction was then calculated as a summary measure of these categories to reflect varying risk as exposure level increases using the following formula,

$$PAF_{Summary} = \frac{p_1(RR_1 - 1) + p_2(RR_2 - 1) + \cdots + p_n(RR_n - 1)}{1 + p_1(RR_1 - 1) + p_2(RR_2 - 1) + \cdots + p_n(RR_n - 1)}$$

Risk ratio data was extracted from meta-analysis, and the risk associated with each level of alcohol drinking or BMI was extracted. For alcohol drinking, risk ratio data was available for increments of 25g alcohol/day, while the prevalence data for alcohol consumption was reported in 20 gram increments. In order to estimate the risk associated with the available prevalence data, a trend line was fitted to risk ratio data and the risk associated with 20 gram increments was estimated. For tobacco smoking, continuous or categorical data that reflected the population distribution of tobacco smoking was not available, and Levin's formula was used as an approximation of the fraction of cases attributable to ever smoking.

3.1.6 Confidence Intervals and Uncertainty

95% confidence intervals (CIs) were calculated using the 95% CI limits of the reported risk ratios and prevalence data. Another factor that contributes to uncertainty in estimation is that individuals may have more than one risk factor and these risk factors may interact with one another.

3.2 Results

Worldwide, viral risk factors for liver cancer play a larger role compared to behavioral risk factors. Chronic infection with HBV contributes to 43.6% of all HCC cases worldwide, while 21% of HCC cases can be attributed to HCV (Table 3-3). Alcohol consumption was the strongest lifestyle risk factor, contributing to 25.9% of HCC cases, while smoking contributed to 12.6%

and obesity to 8.9%. This discrepancy between infectious and lifestyle risk factors is especially pronounced in Asian and African regions, as well as Oceania.

3.2.1 Hepatitis B

Worldwide, more cases of HCC can be attributed to chronic infection with HBV than any other risk factor. 43.6% of the world total of liver cancer cases can be attributed to HBV (Table 3-3). The vast majority of cases attributable to chronic infection with HBV occurred in Asia, and in particular East Asia (166,977). PAFs were highest (>50%) in Oceania and Sub-Saharan Africa, as well as Central, East, and Southeast Asia.

3.2.2 Hepatitis C

About 122,132 cases of HCC (21% of all HCC cases) can be attributed to chronic HCV infection (Table 3-3). Similar to patterns observed with HBV, Central Asia, Central Sub-Saharan Africa, and West Sub-Saharan Africa had a high PAFs due to HCV (>30%), with high proportions of attributable cases also in North Africa and the Middle East and Eastern Europe. North Africa and the Middle East had the largest PAF due to HCV (56.3%), due to a large PAF (70.6%) for Egypt (Table 3-7), where HCV is prevalent and is exacerbated by a possible interaction with schistosoma (Bedwani et al. 1996).

Meta-analyses have reported conflicting results on the joint effects of HBV and HCV, reporting both sub-additive (Cho et al. 2011) and super-additive effects (Donato, Boffetta, and Puoti 1998; Shi et al. 2005). Cho et al. stratified studies and found an overall sub-additive effect on risk of HCC in more recent studies (2000-2009), cohort studies, and studies conducted in areas where HBV and HCV infection were uncommon. If the effects are in fact sub-additive, then the sum of the PAFs reported here for HBV and HCV are an overestimate. Conversely, if the effects are super-additive, then those who are co-infected have a risk of HCC exceeding the sum of their risk from HBV and HCV individually, and the sum of these estimates would be an underestimate.

Aflatoxin is another risk factor for liver cancer thought to interact with HBV exposure. A review of available studies concluded that aflatoxin likely plays a causative role in 4.6-28.2% of all global HCC cases (25,000-155,000), with the majority of cases occurring in sub-Saharan Africa, Southeast Asia, and China (Liu et al. 2012). Exposure to aflatoxin in persons with chronic HBV infection is associated with a risk up to 30 times greater than in those exposed to aflatoxin alone (Groopman, Kensler, and Wild 2008). Estimates for HBV infected individuals in regions where aflatoxin exposure is common, such as parts of Africa and Asia, are likely underestimates.

3.2.3 Alcohol

About 150, 629 cases of HCC can be attributed to alcohol drinking, or 25.9% of the worldwide total (Table 3-3). Although infectious diseases had larger PAFs in Asia and Africa, PAFs for alcohol drinking were largest (>35%) in Central and Eastern Europe and Tropical Latin America. PAFs were larger for men in most regions of the world compared to women due to the higher prevalence of drinking among men (Table 3-4). However, in some regions of the world including Southern and Andean Latin America, drinking prevalence was similar among men and women resulting in higher PAFs due to the increased risk of HCC at lower levels of alcohol consumption.

3.2.4 Tobacco Smoking

Overall, around 73,279 cases of liver cancer can be attributed to tobacco smoking, or 12.6% of the world total (Table 3-3). Men in all regions had higher attributable fractions compared to women due to a higher prevalence of smoking; however, this disparity was more pronounced in Asia and Africa. The largest number of cases was in East Asia, due to a large attributable fraction among men (18.7%), but not among women (1.7%) (Table 3-4). Central and Western Europe, Australasia, North America, and Southern Latin America had high attributable fractions among women (>8%).

The meta-analysis by Lee et al. suggests that adjustment for alcohol may slightly lower the RR for smoking and liver cancer (Lee et al. 2009). The RR used in this study for smoking was adjusted for alcohol consumption, and likely a reasonable estimate of tobacco smoking independent of alcohol consumption. The estimates of alcohol are not adjusted for smoking. However, if adjustment for smoking were to lower the associated RRs, then the estimates presented here would be an overestimate.

3.2.5 Obesity

Body fatness, encompassing those overweight and obese, has been proposed as a risk factor for liver cancer. The World Cancer Research Fund has found that there is limited but suggestive evidence that body fatness is associated with liver cancer, but without more data it is still unclear what the associated magnitude of risk might be (World Cancer Research Fund/American Institute for Cancer Research 2007). However, even a small increased risk of liver cancer could have wide-reaching future effects.

Overall, 51,760 HCC cases worldwide in 2012 can be attributed to obesity, or 8.9% of the world total (Table 3-3). Australasia, Western Europe, and North America had the highest attributable fractions of liver cancer cases due to a high prevalence of overweight and obese (>20%), while parts of Asia and Africa had the lowest attributable fractions (<5%) (Table 3-4). Although the worldwide prevalence of obesity was generally higher in women, the risk of HCC associated with obesity is higher in men, leading to higher PAFs in many geographic regions. If adjustment for alcohol lowers the risk ratio by a very slight margin, as might be expected from the results of Chen et al., then these estimates for obesity might be slightly overestimated (Chen et al. 2012).

The five countries with the largest number of HCC cases are: China, Japan, the USA, India, and Vietnam. China alone accounts for over half of the cases of HCC worldwide. More cases can be attributed to HBV than any other risk factor in China, India, and Vietnam (Table 3-5). Alcohol drinking and HCV were major risk factors in Japan and the USA, while obesity was also a main risk factor in the USA. Smoking was responsible for a high proportion of cases in men but not women in China, Japan, India, and Vietnam. Estimations of percent HCC by country are presented in Table 3-6. Table 3-7, Table 3-8, and Table 3-9 include additional country-specific estimates of HCC cases attributable to HBV, HCV, alcohol drinking, tobacco smoking, and obesity.

High income regions of the world (Asia Pacific, Australasia, Western Europe, and North America) had a distinct disease profile compared to other regions of the world (Figure 3-1). Lifestyle risk factors were responsible for a larger percentage of HCC cases in high income regions compared to other regions of the world. On average the PAF for alcohol drinking in high income regions was 29.5% (vs. 26.5% in other regions), 11.2% for smoking (vs. 9.0%), and 18.4% for obesity (vs. 12.5%), while the average PAF for HBV (14.0%) and HCV (18.0%) was much smaller in these regions compared to other regions of the world (42.3% and 27.0%, respectively). When comparing high income regions to other regions of the world, the disparity in PAFs was largest for HBV and smallest for tobacco smoking.

3.3 Discussion

This study provides an estimate of the contribution of known modifiable risk factors of HCC cases worldwide. In 2012, liver cancer was the second leading cause of cancer mortality worldwide, and many incident cases of liver cancer are due to preventable causes.

The majority of HCC cases can be attributed to viral infections. For both HBV and HCV, regions in Asia and Africa had the highest attributable risk fractions. These regions have the highest burden of liver cancer disease worldwide, and the effects of vaccination programs in these areas will likely have a large impact on liver cancer incidence in years to come. Although the burden of disease in areas that do have vaccination programs is still high, this is because of the long lag time between chronic hepatitis infection and liver cancer. Compounding the risk associated with hepatitis infection, aflatoxin exposure is also seen more commonly in Asia and Africa. Aflatoxin exposure can be prevented and monitored in these regions through regulatory measures and improved food storage.

While infectious disease and contamination are responsible for the majority of cases in Asia and Africa, a comparatively higher percentage of cases of liver cancer are due to tobacco smoking, alcohol drinking, and obesity in more developed regions of the world such as Europe, America, and Australasia. Many HCC cases are due to lifestyle risk factors, and these cases are likely to grow in number. The prevalence of lifestyle risk factors are increasing in many developing countries, and as infectious diseases and aflatoxin contaminants become more controlled, these lifestyle risk factors will likely play a larger role in the global burden of liver cancer in both developed and developing countries.

Results from this study were comparable to the results from similar studies conducted in individual countries around the world. These studies, conducted in France (IARC Working Group, 2007), the United Kingdom (Parkin et al., 2011), Japan (Inoue et al., 2012), and China (Fan et al., 2013) found that the population attributable fractions due to infectious diseases (HBV and HCV) in Europe were much lower (64.4% and 41.6% for France and the United Kingdom, respectively) than the percent of cases due to infectious disease in Asia (92.1% in Japan and over 70% in China). Similarly, we found that the burden of disease due to infectious agents and contaminants were much higher in Asia and Africa than in western populations.

CHAPTER 4. DIETARY FACTORS METHODS, RESULTS, AND DISCUSSION

4.1 Jiangsu Case-Control Study Design

4.1.1 Study Population

A population-based case-control study was designed to evaluate the risk factors for the four most common cancers in Jiangsu province, China, from 2003-2010. Jiangsu province is one of the highest risk areas for liver cancer in China. In 2007, the incidence from liver cancer in Jiangsu province was 32/100,000, while mortality rates were very similar (30/100,000) (Liu 2014). Counties from the north of Jiangsu province (Dafeng, Ganyu, Chuzhou, and Tongshan) were included in this study. Esophageal, stomach, lung, and liver cancer were all investigated.

4.1.2 Recruitment and Selection

Pathologically or clinically confirmed diagnoses of liver cancer from January 2003 to December 2010 were reported to each county tumor registry. Diagnostic methods included computed tomography (CT), ultrasound, alpha-fetoprotein (AFP), cytology, surgery, magnetic resonance imaging (MRI), among others. Cases were restricted to newly diagnosed patients, participants 20 or older, in stable medical condition, without a previous history of cancer, and those who gave informed consent to participate in the study. Only participants who had lived in the study area for 5 or more years were included in the study. Liver cancer cases include both HCC and cholangiocarcinoma, with only a very small number of cases of cholangiocarcinoma. A total of 2,011 patients with primary liver cancer were included and interviewed during the study period. The response rate was 44%.

Eligibility criteria for controls were the same as for cases. Each control was frequency matched to the cases by cancer site for each village or city resident block using sex and age group (± 5 years) in a 1:1 ratio; however these matches were later pooled to increase statistical power. A sensitivity analysis was conducted in order to assess the impact of breaking the matches, and estimates were similar. If a control did not fit the criteria or refused to be interviewed, basic demographics were recorded and the same selection process was used to choose another control. 5-8 ml of blood was drawn from each control. A total of 8,720 controls were interviewed, 7,933 completed questionnaires, and 6,529 had blood samples drawn. The response rates exceeded 90% at all study sites. A total of 2,011 liver cancer cases and 7,933 controls were recruited into the Jiangsu Four Cancer Study.

4.1.3 In-Person Interview and Questionnaire

Cases and controls were interviewed using a standard questionnaire by trained interviewers. Furthermore, in-person interviews were monitored by professional staff in the Division of Chronic Disease Prevention of the county CDC. Interviews took place in either the hospital or at home. The collected information included: (1) socio-demographic characteristics, including age, gender, residence, place of birth, education, annual income, blood type, and disease diagnostic information; (2) residence and drinking water history, including "raw water" intake history as a proxy for aflatoxin exposure; (3) detailed dietary history using a pretested Chinese food frequency questionnaire, including 90 food items; (4) detailed tobacco smoking history; (5) alcohol drinking habits and history; (6) tea drinking habits; (7) detailed information on disease history; (8) occupation history and related exposures; (9) family history of liver cancer and other cancers; and (10) physical activities. For female cases and controls, reproductive factors were also collected.

The Food Frequency Questionnaire (FFQ) asked participants to recall diet over the past year. This was asked in order to capture diet before diagnosis of disease. Frequency consumed was reported for each food item, with the option of saying none consumed. The participant could state the number of times they ate a standard amount (g) of a food item per day, month, or year. Lastly, the questionnaire also asked how many months out of the year the participant consumed each food item, in order to reflect seasonal variations in diet.

Five percent of the face-to-face interviews were conducted twice to verify the quality of the data. The questionnaire data collected from the first interview was reviewed by a research staff at the county level and then by an epidemiologist at the provincial CDC. Data were doubly entered into an epidemiology database designed using EpiData (Odense, Denmark) at each county CDC and then cleaned and managed at Jiangsu Provincial CDC.

4.1.4 Collection and Measurement of Biologic Samples

Five to eight ml of blood was collected for each consenting participant following the in-person interview. Blood samples were collected in EDTA or heparin coated tubes, and assigned an identification number. The samples were then separated into serum, red blood cells, and white blood cells, and then stored under -20 degrees Celsius at local branches of the CDC. Samples from all study sites were then sent to the Jiangsu Provincial CDC, which was responsible for storing all samples at -70 degrees or colder for future examination. DNA samples were then extracted in a molecular epidemiology lab at the Department of NCD at the Jiangsu Provincial CDC.

HBV and HCV markers were measured at the Jiangsu CDC. Presence of serum HBsAg, HBsAb, HBeAg, HBeAb, HBcAb and anti-HCV IgG were measured using enzyme-linked immunosorbant assay (ELISA) kits from Shanghai Kehua Biological Pharmacy (Shanghai, China), according to the manufacturer's instructions (Liu 2014). Genotyping was performed at the UCLA Genotype and Sequencing Core, using a customized Fluidigm Dynamic 96.96 Array™ Assay (Fluidigm, South San Francisco, CA). Assays were based on allele-specific PCR SNP detection and Dynamic Array™ integrated fluidic circuits (IFCs). The SNP assay tagged allele-specific PCR primers and a common reverse primer. A universal probe set was used in every reaction, producing uniform fluorescence; furthermore, Fluidigm provided locus-specific primer sequences that allowed confirmation of target locations.

4.1.5 Calculation of Daily Caloric Intake

For each FFQ food item, a corresponding food item or list of food items was found in the China Food Composition 2010, released by the China CDC (Institute of Nutrition and Food Safety 2010). Three graduate students worked to match FFQ items to food items in the China Food Composition data, one of them a Chinese national.

In addition to the food name and food code, the edible percentage of food, energy in calories, carbohydrates (g), proteins (g), fat (g), fiber (g), and cholesterol (mg) was extracted. Each food item was reported in terms of 100g of fresh food. For food categories that were composite categories (e.g. apples and pears), constituent food categories were averaged together. Some foods were weighted more heavily to reflect more common consumption in the population, or to reflect preparation methods. Two FFQ items could not be found in the China Food Composition data, frog and sugar cane. Estimates from the Japanese Food Composition Table were used for frog and data from the USDA database for sugar cane (Watanabe 2015; USDA 2017). Caloric intake from foods was calculated using grams of food consumption*edible percentage of food*kcal/g of food. Calories from alcohol were calculated from grams of reported consumption of liquor (both >=38% and <38% alcohol by volume) and beer from one year prior. Calorie information for representative liquors and beers were taken from the China Food Composition data and converted into kcal/gram.

4.1.6 Flavonoid Database Construction and Coverage

A database listing the flavonoid values for common Chinese foods was constructed in order to assess the impact of flavonoid intake on liver cancer within the study, and used along with a validated FFQ administered to participants of the Jiangsu study to describe consumption of foods and flavonoids one year prior to inclusion in the study.

Total flavonoid intake (mg/week) was calculated for each participant, as well as constituent flavonoid categories including flavonols (isorhamnetin, kaempferol, myricetin, quercetin), flavones (apigenin, luteolin), flavanones (eriodictyol, hesperetin, naringenin), flavan-3-ols (catechin, catechin-3-gallate, epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, gallocatechin, gallocatechin-3-gallate), theaflavins (theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, theaflavin-3,3'-digallate), anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin) and isoflavones (daidzein, genistein).

Figure 4-1 illustrates the process of developing the flavonoid database. In order to reflect foods eaten in Jiangsu province, Chinese articles reporting flavonoid values were reviewed for inclusion into the database. These articles measured flavonoid intake in fruits and vegetables that were not available in the USDA database or the European databases (Guo et al. 2008a, 2008b; Li, Ling, et al. 2010; Cao et al. 2002; Huang et al. 2012; Li, Yao, et al. 2010), and covered approximately forty different fruits and fifty different vegetables from different areas in China. Additionally, articles from countries outside of China that reported values for common Chinese food items (e.g. Japan, Fiji, and Hawaii) were also considered (Arai et al. 2000; Lako et al. 2006; Sakakibara et al. 2003; San and Yildirim 2010; Franke et al. 2004; Kevers et al. 2007). Pre-existing databases were also considered due to the large number of studies on a variety of flavonoids that these databases represent. Data from the USDA Flavonoid Database and the USDA Isoflavone Database were used instead Phenol Explorer or the UK Food Standards Agency database because of the diversity of international foods represented, as well as the detailed information included on preparation method (e.g. pan-fried, boiled, etc.).

Only articles that used high quality measurement techniques, including high-performance liquid chromatography (HPLC), were included. In addition, studies that reported total flavonoids instead of totals by flavonoid subclass were excluded. There were only a handful of food items where articles for total flavonoids could be found, but not for subclasses of flavonoids (e.g. articles on wood ear and sugar cane), and these items were not a major source of flavonoids in this population.

From each article, flavonoid measurements by subclass were extracted, along with the units of measurement, sample size, and standard deviation. The method of sample preparation was noted, as well as whether the sample was of fresh food or cooked food. In addition, the location of the study (Guangzhou, Shanghai, Beijing, etc.) and type or variety of food (e.g. Fuji apple) was also collected. If units were not already reported in mg/100g fresh weight of edible food, then values were converted. For beverages, values for brewed teas from the USDA database were used. These values were reported as mg flavonoid/1g dry tea, which corresponded to grams of tea reported in the questionnaire. Wine was dropped from the analysis as only a handful of participants drank grape wines. For values reported as "trace," values were reported by multiplying the Limit of Quantitation, when reported, by 0.71 (US Department of Agriculture 2013; Mangels et al. 1993). Most foods and flavonoid subclasses did not have a reported value. Often this represents a lack of data, rather than a true zero value.

Where multiple data sources were available for the same food item, preparation method and sample size were prioritized over location. For example, if cooked values were available from the USDA databases for a food that is almost exclusively eaten cooked (e.g. eggplant), this was prioritized over raw foods so long as sample size was similar. If a food is commonly eaten raw (e.g. bananas), this was not a point of consideration. If a food item was not available, but values were available from a similar variety or from a variety of the same botanical family, this was used instead (e.g. members of *lactuca sativa* for asparagus lettuce).

For food categories that encapsulated more than one food item, an average of the constituent food categories was calculated. Following an informal consultation with three Chinese nationals, certain foods were weighted more heavily to reflect foods more commonly consumed. If a food category did not have any flavonoid value reported in the main data source used, all other data sources were searched to fill in missing values. Weekly milligrams of intake from total flavonoids and flavonoid subclasses were derived from g weekly consumption of food items. Tea was reported in the questionnaire as grams of dry tea consumption per month, and converted into individual grams of black, green, flower, or oolong tea consumed per week before multiplying by mg flavonoid intake/g of dry tea.

Of the 54 fruit, vegetable, legume, and nut food items, 50 were covered. This is equivalent to a 93.6% coverage rate. The four items not covered, including pumpkin seeds, wood ear, sugar cane, and wheat gluten, are not expected to be a major source of dietary flavonoids in this population. The developed flavonoid database covered all fruits on the FFQ, except for sugar cane. While one study has been conducted on Chinese sugarcane, this study reported totals for the subclass of anthocyanins and total flavonoids, not individual flavonoids (Li, Yao, et al. 2010). Wheat gluten was the only food item in the vegetable section that was not covered (95.8% coverage), and likely only has minimal flavonoid content. 95.8% of vegetable food items were covered. No articles on pumpkin seeds could be found, and one study was found on one variety of wood ear, *auricularia auricular-judae*, however this study only reported total flavonoid content, not individual flavonoids (Packialakshmi, Sudha, and Charumathy 2015). 100% of the tofu and legume category was covered.

4.1.7 Dietary Glycemic Index, Glycemic Load, and Macronutrients

Glycemic Index values for major carbohydrate-containing food items were obtained from the 2002 and 2008 International Table of Glycemic Index and Glycemic Load Values as well as the

National Cancer Institute's Glycemic Load Values (Atkinson, Foster-Powell, and Brand-Miller 2008; Flood et al. 2006; Foster-Powell, Holt, and Brand-Miller 2002). Of the 65 FFQ items that were not meat or fish dishes, GI values could not be found for salty dishes, pickled kohlrabi, garlic leaves, wheat gluten, ginger, wood ear fungus, sugar cane, and ginkgo. Of these, salty dishes, ginger, and garlic leaves are the most commonly eaten foods (consumed by >30% of population), and are not likely to contribute greatly to individual glycemic index due to their lower GI values and the smaller portion sizes of these foods. Glycemic index and load were calculated for food items only.

Glycemic index (GI) was calculated by multiplying the GI value for each food by the available carbohydrates in each food. For each individual, these values were summed together and then divided by the total available carbohydrates. Glycemic load (GL) was calculated in the same way, except the denominator was 100 instead of total available carbohydrates. GI and GL were calculated as daily values, and the grams of available carbohydrates for each food item was obtained from the Chinese Food Composition Tables (Institute of Nutrition and Food Safety 2010).

The percent of kcals from fat, protein, and carbohydrates was calculated by summing the grams of each macronutrient and multiplying by the corresponding number of kcals/gram. For fat this was 9 kcals/gram, for protein and carbohydrates this was 4 kcals/gram. This was then divided by the total number of calories consumed.

4.2 Excluded and Missing Data

Of the 9,944 participants in the study, 2,557 controls and 745 cases were dropped due to insufficient or implausible dietary data. Daily caloric intake from food only was used to exclude individuals who consumed less than 500 or more than 5,000 calories per day, and those who ate only one food item per day were excluded. After reviewing implausible values by county, approximately 50% of the dietary data from Tongshan was found to be missing or implausible. Much of this data showed individuals who reported eating only 1 food item over the course of the year. Of those controls who did eat more than 1 food item per year, the number of food items consumed was much less on average (23) compared to the number of food items consumed in other counties (40), even though participants from Tongshan were better educated and had similar income. Furthermore, the median number of food items consumed in Tongshan County was associated to case status. This suggests that these differences were caused by a systematic disparity in the collection of data from Tongshan, rather than a real difference in diet between Tongshan and the other counties, and that this data could affect the outcome of this study. For these reasons, the dietary data collected from Tongshan was considered unreliable and excluded from the dietary study. Those with invalid dietary data were less likely to be from Dafeng, and more likely to have lower income and to eat fewer food items and fewer calories. Gender, age, and education were similar between both groups.

704 cases and 963 controls were missing biological measures of HbsAg. Those missing covariate data were more likely to be from Ganyu or Chuzhou counties, to be less than 60, to be better educated, and to have reported eating fewer calories. Crude, adjusted, and semi-Bayes adjusted logistic models are reported for the restricted dataset. Multiple imputation was used to compare

imputed values of HBsAg in the full dataset to the complete case analysis. For those who reported smoking or drinking, but were missing any of the variables needed to calculate either pack-years or grams of alcohol consumption, imputation using the median in controls was used for missing values.

4.3 Statistical Analysis

Distributions of outcomes within categorical variables were compared using Chi-square tests or Fisher's exact tests. Wilcoxon rank sum tests were used to compare median values. Unless otherwise specified, p-values of less than 0.05 were considered significant. Unconditional logistic regression was used to obtain odds ratios (OR) with 95% confidence intervals (CI) to assess the relationship between the outcome of interest, liver cancer, and dietary factors. Models were adjusted for gender (male or female), age, county (Dafeng, Ganyu, Chuzhou), education (illiteracy, primary school, middle school, high school and above), HBsAg status (positive or negative), past alcohol consumption (non-drinker, <500 g/week, >500 g/week during the 90s), pack-years smoking, daily kcal (except SNP) and family history of liver cancer (yes or no). Odds ratios for the adjusted logistic models (aOR) were compared to results using multiple imputation (miOR) and semi-Bayes adjustment (sbOR). Two-tailed trend tests for tertiles of dietary factors were calculated by testing the significance of the regression parameter for tertiles treated as a continuous variable in the logistic regression model. Continuous associations were reported using odds ratios in the crude (cOR) and adjusted models using the interquartile range of the dietary variable of interest.

Potential additive and multiplicative interactions were assessed using the relative excess risk due to interaction (RERI) and the ratio of odds ratios (ROR), respectively. Preventive factors were re-coded as risk factors and the stratum with the lowest risk was set as the reference category for examining the joint effect in all analyses for interaction. Continuous dietary and genetic measures were recoded as binary variables using the median in controls to assess interaction. All statistical analyses were performed using SAS 9.4.

4.3.1 Multiple Imputation

Missing values for HBsAg status were imputed using 5 rounds of imputation. The missing data were generated from the observed data using proc mi and the Markov chain Monte Carlo (MCMC) option. All variables included in the logistic regression models (including gender, county, age, education, past alcohol consumption, pack-years smoking, HBsAg status, family history of liver cancer, and daily kcal consumption) were included in the imputation model. The logistic regression parameters were combined using proc mianalyze for the final adjusted models.

4.3.2 Semi-Bayes Adjustment

To mitigate the effects of multiple comparisons and sparse-data bias, the data augmentation approach of the semi-Bayes shrinkage method was used (Greenland 2007). Shrinkage estimation (including semi-Bayes shrinkage estimation) works by pulling or ‘shrinking’ the regression coefficient toward prior patterns or values. Parameter estimates are regressed to a degree proportional to their estimated variance, therefore pulling unstable coefficients more than stable coefficients. When prior values are zero, the coefficients are pulled toward zero (thus, the term ‘shrinkage’).

Practically, this was implemented in our data using a null prior to generate posterior estimates of effect measures for risk associated with food categories, macronutrients, flavonoids, and SNPs. Few epidemiology studies have been conducted on these associations, justifying the use of the more conservative null prior. Information weighting was used to carry out the adjustment, using a coefficient prior with median 0 (OR=1) and a prior variance of 0.50 (95% probability of falling within 0.25-4.00). This simulated prior was merged with the study data, weighted, and then logistic regression models were run in the merged and weighted dataset to calculate semi-Bayes adjusted estimates.

4.3.3 Adjustment for Energy Intake

Adjusting for energy intake can control for confounding by total energy intake and reduce extraneous variation in nutrient intake (Willett, Howe, and Kushi 1997). Additionally, adjustment is helpful in mitigating the effects of measurement error in data collected from self-reported dietary instruments, as individuals tend to under or over report foods to a similar degree in the same direction (National Cancer Institute), and is commonly used for analysis of Food Frequency Questionnaire data.

Total energy intake (including diet and alcohol) was adjusted for using the residual method. In this method, residuals are obtained from a regression model where total energy intake is the predictor variable and absolute nutrient intake is the dependent variable, making the residual an estimate of nutrient intake uncorrelated with total energy intake. Standard diagnostics for regression were conducted, including plotting residuals to assess distribution in the linear models as well as identifying observations with high leverage. Proc robustreg was used with M estimation and Huber weights, which down weights observations with larger residuals.

Residuals were calculated for all food items other than macronutrients, which are already calculated as a percentage of caloric intake. Tertiles of the residual were used as the predictor of interest in the logistic regression model, and other covariates added into the model include gender, age, county, education, past alcohol consumption, pack-years of smoking, HBsAg status, family history of liver cancer, and daily caloric intake. Residual values were standardized to the mean caloric consumption in controls in order to give results better interpretability, and tables are reported in both tertiles and the standardized residual equivalents.

4.4 Results

4.4.1 Socio-Demographic Characteristics

A total of 1,266 cases and 5,376 controls were included in the dietary analysis. Table 4-1 shows the distribution of demographic and socio-demographic characteristics among cases and controls in the analysis dataset. Most cases were recruited from Dafeng (48.7%), followed by Ganyu (29.2%), and Chuzhou (22.1%). Cases tended to be younger than controls, and a larger proportion were male (77.2%) compared to controls (72.8%). In general, cases had slightly higher levels of education. Cases were much more likely to have a family history of liver cancer ($p<0.001$).

4.4.2 Established Risk Factors

Table 4-2 shows major worldwide liver cancer risk factors, chronic hepatitis B infection, aflatoxin exposure, alcohol drinking, tobacco smoking, and BMI, and their association with liver cancer in this case-control study. The association between HBsAg status and liver cancer was very strong in this study (aOR: 20.56, 95% CI 16.41, 25.76), and is comparable to estimates from meta-analysis. 60% of cases were HBsAg positive, while 5.5% of controls were HBsAg positive. Reports of mildew were associated with a slight increase in liver cancer susceptibility, while clean grain storage was associated with a slight decrease. However, neither proxy for aflatoxin exposure was significantly associated with liver cancer. Ever drinking alcohol was associated with liver cancer in the adjusted models (aOR: 1.39, 95% CI: 1.04, 1.87), however this association did not remain significant after semi-Bayes adjustment or multiple imputation. Consumption of 500 or more grams of alcohol per week, the equivalent of about 5 drinks per day, was significantly associated with liver cancer in both the adjusted and multiple imputation models. Ever smoking was marginally associated with liver cancer, and the association for those who smoked 0-20 pack-years compared to never smokers (aOR: 1.27, 95% CI: 0.91, 1.77) was similar to the association for those who smoked 20 or more pack-years (aOR: 1.28, 95% CI: 0.84, 1.95). BMI was significantly protective in this study, with a BMI of at least 27.5 (obese among Asians) associated with an aOR of 0.23 (95% CI: 0.13, 0.41) compared to those with a BMI less than 18.5.

4.4.3 Food Categories

Table 4-3 shows food categories and constituent foods, while median food consumption values among those with complete dietary data are shown in Table 4-4. Median daily kcal consumption, including dietary and alcohol intake, was not significantly different between cases (2,210 kcal/day) and controls (2,160 kcal/day). The distribution of macronutrients was similar in cases and controls. The most commonly consumed foods were grains and vegetables. Controls consumed an average of 3,426 g/week of grains, an equivalent of a little less than 3 cups cooked rice/day, and 1,666 g/week of vegetables (equivalent to a little less than 1 1/2 cups of cooked vegetable per day). Median values of fruits and vegetables were higher in cases, while median values of soy and legumes and fish were lower in cases. Median total flavonoid consumption was lower in cases than controls (p=0.025), as well as the subgroups catechins and epicatechins and isoflavonoids. Flavone consumption was higher in cases.

Although a number of food items in the crude model were associated with liver cancer, most associations disappeared after adjusting for covariates. Table 4-5 presents the association between food categories and liver cancer. Fruit consumption did not appear to be associated with liver cancer, especially after using multiple imputation. Vegetable consumption was not significantly associated with liver cancer when categorized into tertiles, however a 1,261g increase in vegetable consumption was marginally associated with increased odds of liver cancer (aOR: 1.12, 95% CI: 1.01, 1.24). No statistically significant associations were found after looking at the association between liver cancer and vegetable subcategories, including red vegetables, green vegetables, starch vegetables, and other vegetables.

The third tertile of meat consumption was marginally protective against liver cancer (aOR: 0.76, 95% CI: 0.57, 1.02), while a 135g increase in fish consumption was associated with increased odds of liver cancer (aOR: 1.05, 95% CI: 1.00, 1.09). The third tertile of grain consumption was associated with an increased odds in liver cancer in the adjusted model (aOR: 1.39, 95% CI: 1.04, 1.85) as well as the semi-Bayes adjusted model (sbOR: 1.37, 95% CI: 1.03, 1.81). The p for trend for grains was also significant (p=0.020), although the second tertile of grain consumption was not associated with liver cancer (aOR: 0.98, 95% CI: 0.74, 1.31). A 937g increase in grain consumption was significantly associated with liver cancer (aOR: 1.25, 95% CI: 1.09, 1.42).

4.4.4 Glycemic Index, Glycemic Load, and Macronutrients

The main source of glycemic load among controls with complete dietary data was rice, accounting for 89.9% of the daily glycemic load. After rice, noodles were responsible for the second largest percentage of daily glycemic load (6.3%). These two food items were responsible for the vast majority of the variation in glycemic load. White rice is a high GI food, while noodles are medium GI food.

Table 4-6 shows the associations between GI, GL, and macronutrients with liver cancer. Liver cancer did not appear to be associated with percent of calories from protein or fat, however those who consumed a higher percentage of carbohydrates appeared to have higher odds of liver cancer. Those in the second and third tertile of carbohydrate consumption had an odds ratio of 1.33 (95% CI 0.99, 1.79) and 1.72 (1.24, 2.39), compared to those in the first tertile. The association in the third tertile persisted after semi-Bayes adjustment and after using multiple imputation. There appeared to be a monotonic trend, with the association with liver cancer increasing with higher consumption of carbohydrates (p=0.001). Furthermore, an 18% increase in percent of calories from carbohydrates was associated with an odds ratio of 1.31 (95% CI: 1.08, 1.59).

Although glycemic index was not obviously associated with liver cancer, glycemic load appeared to be marginally associated with liver cancer. Those in the third tertile had an adjusted odds ratio of 1.36 (95% CI: 0.98, 1.87), and there was a marginally significant trend with increasing glycemic load (p=0.055). Furthermore, a 125 unit increase in glycemic load was associated with an odds ratio of 1.22 (95% CI: 1.02, 1.46). Along with the results showing increased odds of liver cancer associated with percent calories from carbohydrates and the highest tertile of grain consumption, this provides compelling evidence that carbohydrates and carbohydrate-rich foods may be associated with liver cancer.

Conversely, cholesterol appeared to be marginally and inversely associated with liver cancer. Although the p for trend was not significant, the second tertile was associated with decreased odds of liver cancer (aOR: 0.73, 95% CI: 0.56, 0.95), although this did not remain statistically significant after multiple imputation. As carbohydrate consumption is correlated with consumption of fat and cholesterol, it is likely that those who consumed higher amounts of cholesterol may have a lower percentage of carbohydrate intake as well.

4.4.5 Dietary Flavonoids

Table 4-7 shows the main sources of flavonoids in this population. Among controls, the main source of flavonoids was green tea (77.7%), followed by tofu (3.9%) and dried bean curd (2.7%). Green tea is rich in flavonoids (135.6 mg/1 gram dried tea leaf), particularly catechins and epicatechins as well as theaflavins. Green tea consumption was relatively common in this population, and about 30% of controls drank tea daily with the majority (80%) of regular tea drinkers preferring green tea. Tea consumption was reported in grams of dried tea leaf, which is an especially potent source of flavonoids. Controls used 10.1 grams of green tea leaves per week on average.

Dietary sources of flavonoid subclasses tended to correlate with specific food categories. The dietary sources of flavonols were diverse, including onions, grapes, and bananas, while most dietary flavonols in the control population came from green tea (43.5%), green vegetables (11.1%), and onions (4.6%). Green vegetables were the largest source of dietary flavones (45.5%), followed by green pepper (10.2%) and green tea (9.6%). Citrus fruits are rich in flavanones, and tangerines (75.7%) provided the majority of dietary flavanones, followed by oranges (24.3%). Catechins and epicatechins were found primarily in teas in this population, particularly green tea (92.5%), oolong tea (3.0%), and black tea (2.4%). In the dietary items measured, green tea was the only source of theaflavins. Anthocyanidins were found primarily in radishes (46%), salted vegetables (21%), and beans (12%). Isoflavones are found primarily in soy products, although some vegetables, teas, and eggs contain smaller amounts. In the control population, tofu was the main source of isoflavones (41.4%), followed by dried bean curd (31.1%) and soybeans (19.1%).

Table 4-8 presents the associations between total flavonoids and flavonoid subgroups with liver cancer. Increasing consumption of total flavonoids appeared to be inversely and marginally associated with liver cancer (p=0.074), with an adjusted odds ratio of 0.77 (95% CI: 0.58, 1.01) when comparing the highest tertile of total flavonoid consumption to the lowest. The associations between flavonoid subgroups and liver cancer appeared to vary by subgroup.

The subgroups of flavonols, flavones, flavanones, and anthocyanidins did not appear to be associated with liver cancer. For these subgroups, the p for trend ranged from 0.194 to 0.906, and adjusted odds ratios for individual tertiles varied substantially as well. Three subcategories of flavonoids appeared to have a significant or marginally significant protective effect against liver cancer. The evidence for a protective effect was strongest for catechins and epicatechins, with an adjusted odds ratio of 0.70 (95% CI: 0.53, 0.92) and a p for trend of 0.01. This association persisted after semi-Bayes adjustment and multiple imputation. Isoflavonoids appeared to have a marginally protective effect as well, as those in the third tertile had an adjusted odds ratio of 0.79 (95% CI: 0.60, 1.02). The p for trend was 0.069. There was some evidence that the highest tertile of theaflavins, which exclusively came from green tea in this study, was associated with a marginal protective effect (aOR: 0.81, 95% CI: 0.59, 1.10), and the association after semi-Bayes adjustment and multiple imputation were similar. None of the continuous measures for flavonoids and flavonoid subclasses were statistically significant.

4.4.6 Tea Consumption

Table 4-9 shows tea consumption patterns for cases and controls with complete dietary data. 338 (31%) controls reported ever drinking tea regularly, compared to 26.7% of cases. Regular tea drinking was defined as drinking at least one cup of tea once a day. 28.2% of controls were current tea drinkers compared to 13.7% of cases. Cases generally started drinking later than controls. The most common type of tea consumed among controls was green tea, with over 78% of regular tea drinkers preferring green tea. Most tea drinkers had one or two cups per day, and re-brewed tea from the same set of tea leaves 3 or more times. Controls generally drank more cups of tea every day, and re-brewed more often than cases. Tap water, purified water, and well water were used most commonly to brew tea, and most tea drinkers used between 0 and 50 grams of tea leaves per month.

Ever drinking tea was inversely associated with liver cancer (aOR: 0.73, 95% CI: 0.56, 0.94). This protective effect remained even after semi-Bayes adjustment and after imputing missing covariates. Current tea drinking had a strong protective association (aOR: 0.42, 95% CI: 0.31, 0.56), while former tea drinking was associated with an increased odds (aOR: 4.30, 95% CI: 2.81, 6.56).

The length of time a person had been drinking did not seem to make a large difference, as those who started drinking at age 35 or later and those who had been drinking tea for less than 30 years both were inversely associated with liver cancer (aOR for 35+ years of age: 0.59, 95% CI: 0.41, 0.84; aOR for <30 years tea drinking: 0.53, 95% CI: 0.39, 0.73), while the associations for those who had started drinking tea younger than 35 years old or had been drinking tea for longer than 30 years were not statistically significant. Green tea drinking was protective against liver cancer in the crude (cOR: 0.77, 95% CI: 0.62, 0.97) and adjusted models (aOR: 0.75, 95% CI: 0.57, 1.00), but this association did not hold after semi-Bayes adjustment and multiple imputation. The odds ratios for other types of tea appeared to be protective, but the sample size was not large enough for statistical significance.

Drinking as few as one cup per day had a protective effect in crude and adjusted models (aOR: 0.48, 95% CI: 0.32, 0.72), and this association held even after semi-Bayes adjustment and multiple imputation. There was not much evidence that drinking more than one cup per day gave additional protection against liver cancer, however. Although drinking 3 cups of tea had a significant protective effect (cOR: 0.60, 95% CI 0.37, 0.98), this effect was only marginally significant in the adjusted model, and no association was observed with 2 cups/day or 4 or more cups/day. Similarly, re-brewing tea one to two times using the same tea leaves had a protective effect in the adjusted and semi-Bayes adjusted models (aOR: 0.50, 95% CI: 0.32, 0.77; sbOR: 0.54, 95% CI 0.36, 0.81), but this protective effect was only marginally significant for re-brewing three or more times. Monthly consumption of up to 50 grams of tea leaves had a significant protective effect in the adjusted, semi-Bayes adjusted, and multiple imputation adjusted models (aOR: 0.72, 95% CI: 0.54, 0.95). The protective effect intensified with increasing tea monthly tea leaf consumption, although these associations were not significant as only a small number of participants used 50 or more grams of tea leaves each month. The source of water used to brew the tea might affect risk, as tea brewed using deep well water was inversely associated with liver cancer in the adjusted models, but tea brewed from other sources was not.

4.4.7 Effect Measure Modification

Interaction on the additive and multiplicative scale was assessed for major liver cancer risk factors and dietary factors, including total flavonoid intake, glycemic index, glycemic load, and percent calories from carbohydrate. The results are presented in Table 4-10. No statistically significant interaction on the additive or multiplicative scale was observed between flavonoid intake and GI, GL, or percent calories from carbohydrates. Unclean tools associated with grain storage, a surrogate risk factor for aflatoxin exposure, was associated with an increased odds of liver cancer in this population. The ROR for the joint associations of unclean grain storage and low flavonoid intake on liver cancer was statistically significant (ROR: 0.59, 95% CI: 0.38, 0.92), while RERI suggested sub-additive biological interaction (RERI: -0.70, 95% CI: -1.39, 0.00). Similarly, the ROR for HBsAg+ and low flavonoid intake was statistically significant (ROR: 0.62, 95% CI: 0.40, 0.97). There was no strong evidence that chronic hepatitis interacted with any other dietary factor. Alcohol consumption (ever/never drinker) and tobacco smoking (ever/never smoker) did not appear to modify the association between dietary factors and liver cancer.

4.5 Discussion

Our results confirm associations between chronic hepatitis B infection, alcohol drinking, and tobacco smoking with liver cancer. Obesity is not a risk factor, but in fact associated with a decreased risk in this study. There are two likely explanations for this association. First, BMI was measured after inclusion into the study. One of the first signs of liver cancer is rapid weight loss, and reverse causation could explain this association. Furthermore, the metabolic effects of obesity may vary with ethnicity.

Evidence is emerging that diet may play a role in the development of chronic liver disease and liver cancer. A meta-analysis of 19 studies found that as little as a 100g/day increase in vegetable intake was associated with a reduction in liver cancer risk, and that the association with fruit intake was in the same direction, but was not statistically significant (Yang, Zhang, et al. 2014). We found a non-significant association with tertile of vegetable intake and liver cancer (p for trend=0.176), and a marginally significant association when looking at vegetable intake continuously (aOR: 1.12, 95% CI: 1.01, 1.24). After assessing the association by vegetable subgroup, no clear trends were observed. Fruit consumption had a moderately protective association, although the p for trend was not significant (p=0.331).

While most studies have been conducted on fruit and vegetable consumption, several studies have assessed the association between liver cancer and red meat, saturated fat, and dairy. A meta-analysis of 7 cohort and 10 case-control studies as well the multi-center prospective cohort study EPIC found no association between red meat consumption or total meat consumption with liver cancer (Luo et al. 2014; Fedirko et al. 2013). Our study found a marginally protective effect of meat consumption, including both red and white meat consumption, on liver cancer (p for trend=0.071), however it is possible that the inclusion of white meat, which was found to be protective against liver cancer in the meta-analysis, could bring the estimate down. It is also possible that the ability to regularly purchase meat might also be a proxy for higher socioeconomic status in this population, although additionally adjusting for income in the model resulted in similar estimates. Furthermore, meat consumption in this population was very low compared to diets in most Western populations. A 135g increase in fish consumption was associated with increased odds of liver cancer. It is possible that this might be linked to pollution in this population. Two Italian case-control studies have found a protective effect of milk and eggs on hepatocellular carcinoma risk (La Vecchia et al. 1988; Talamini et al. 2006), while a Japanese case-control study found an increased risk (Fukuda et al. 1993). Our results were not significant, although the direction of the association was protective, suggesting that the difference between the Italian and Japanese studies was likely not due to a difference between Western and Asian diets.

One study of glycemic load, glycemic index, and carbohydrate intake and liver cancer was conducted in a cohort study in Shanghai, China. The dietary patterns described in this study are similar to ours. Rice was the main contributor, responsible for approximately 81% of the glycemic load (90% in our study), followed by noodles and bread. This study did not find strong evidence of an association between glycemic index, glycemic load, and carbohydrates with liver cancer overall, however this study did find a significant association with glycemic index and liver cancer in women. Our study supports the results from two case-control studies conducted in the Mediterranean that found evidence of a positive association between glycemic load and liver cancer (Rossi et al. 2009; Lagiou et al. 2008), making it unlikely that the different results from the Shanghai study were due to a difference between a Western and Asian diet. Estimates additionally adjusted for mildew and clean grain storage, proxies for aflatoxin exposure, were very similar for GI, GL, carbohydrate intake, and grain consumption, making it unlikely that these associations were due to residual confounding by aflatoxin exposure.

To the best of our knowledge, no study has looked at the association between total flavonoid intake and liver cancer in a Chinese population. One study of colorectal cancer described flavonoid intake in a similar case control study conducted in Guangdong Province in China (Xu et al. 2016). In this population, approximately 50% of total flavonoid intake came from tea compared to 78% in our study, although the absolute mg of flavonoid consumption per day from tea was similar in both studies (Guangdong: 211.90 mg/day Jiangsu: 199.23 mg/day). Fruits and vegetables were other main sources of flavonoids in Guangdong and Guangzhou (Li et al. 2013; Xu et al. 2016), while tofu products and vegetables contributed substantially to flavonoid intake in our study.

Results from European countries have found nonsignificant or marginal associations between total flavonoid intake and liver cancer, with stronger results for a protective effect of catechins and epicatechins against liver cancer (Zamora-Ros, Fedirko, et al. 2013; Lagiou et al. 2008). We found similar results in our study showing a marginally significant protective association between total flavonoid intake and liver cancer (p for trend=0.074), with the protective association most evident in the third tertile of total flavonoid consumption (aOR: 0.77, 95% CI: 0.58, 1.01). Compared to the study by Lagiou et al., we found limited evidence of sub-multiplicative effect measure modification of hepatitis infection on the association between total flavonoid intake and liver cancer.

Tea is a rich source of catechins and epicatechins. Isoflavonoids, a flavonoid subgroup that is strongly influenced by tea intake, also had a marginally protective association with liver cancer (isoflavonoids p for trend: 0.069). Tea was protective against liver cancer in our study, and results reflect the strong association tea consumption has on the relationship between flavonoid intake and liver cancer. There was no evidence that flavonoid-rich vegetables were inversely associated with liver cancer; however there did appear to be a marginally protective association with fruits. It is possible that, as the association with liver cancer varies by flavonoid source, there may be some aspect of tea consumption that confers an additional protective benefit beyond the posited benefit of high flavonoid intake. One possibility is a difference in bioavailability or dosage between tea and whole foods, as well as other co-factors that exist within the beverage or food itself that may affect the association with liver cancer.

Although individual food categories were not strongly associated with liver cancer risk, tea consumption did have a clear inverse association with of liver cancer in this study. A meta-analysis of nine prospective cohort studies conducted in Asian populations found that green tea consumption was associated with a reduced risk of liver cancer (RR: 0.88, 95% CI: 0.81, 0.97), but that this association was only marginally significant for one additional daily cup of tea (RR: 0.97, 95% CI: 0.95, 1.00). Our results found a similar protective effect associated with regular tea consumption (aOR: 0.73, 95% CI: 0.56, 0.94), driven largely by consumption of green tea. However, our study results suggested that drinking more than one cup of tea per day, or re-brewing tea from the same teapot more often did not confer additional health benefits. The majority of flavonoids in tea leaves are released during the first time the tea leaves are brewed. Consumption of as little as one cup of tea every day had a beneficial association with liver cancer (aOR: 0.48, 95% CI: 0.32, 0.72).

CHAPTER 5. GENETIC POLYMORPHISMS METHODS, RESULTS, AND DISCUSSION

5.1 Methods

The study of genetic polymorphisms was conducted in the Jiangsu population-based case-control study, the details of which can be found in the "study design" section of Chapter 4.

5.1.1 Selection Criteria

SNP selection was completed in the following manner. Nonsynonymous SNPs from NF-kB, stem cell, and miRNA pathways were identified, as well as SNPs from GWAS studies. Published data indicating the functionality of the SNPs was reviewed before selecting SNPs. All SNPs included in the analysis had a genotyping call rate greater than 90%, a minor allele frequency greater than 5%, and were in Hardy-Weinberg equilibrium among the controls using a Bonferonni adjusted p-value cutoff of 0.000521 (0.05/96). One pair of SNPs was in linkage disequilibrium (rs1538660 and rs3204145). The results for only rs3204145 are shown here. Table 5-1 shows the dbsnp no. of the 43 SNPs included in the study, as well as the gene they are associated with.

5.1.2 Statistical Analysis

Unconditional logistic regression models were used to estimate genotype-specific ORs and 95% CIs for 43 SNPs in a subgroup of the study population. Heterozygous and homozygous carriers of the variant were compared to homozygous carriers of the wild type allele, and additional ORs were reported assuming a log-additive, dominant, and recessive models. Models were adjusted for gender (male or female), age, county (Dafeng, Ganyu, Chuzhou), education (illiteracy, primary school, middle school, high school and above), HbsAg status (positive or negative), past alcohol consumption (non-drinker, <500 g/week, >500 g/week during the 90s), pack-years smoking, and family history of liver cancer (yes or no). Stratified dietary analyses were additionally adjusted for daily kcals. Because there were some cells with sparse data, the semi-Bayes shrinkage method using data augmentation was used with a null prior of OR=1 and a variance of 0.5. Analyses were also stratified by low (less than or equal to the median in controls) and high (greater than the median in controls) total flavonoid intake, and we assessed additive and multiplicative effect measure modification between SNPs and total flavonoid intake using RERI and ROR (Hosmer and Lemeshow 1992). Glycemic index, glycemic load, and percent carbohydrates were similarly stratified by low or high intake, and interaction with established risk factors, such as grain storage (aflatoxin proxy), hepatitis B status, alcohol drinking (ever/never), or smoking (ever/never), was assessed. All variables were re-coded to be risk factors when calculating RERI and ROR.

5.1.3 Genetic Risk Scores

Genetic risk scores were constructed as a parsimonious way of summarizing the effects across several genetic variants in individual subjects. A polygenic risk score (PRS) assesses the number of risk alleles an individual has, while the multigenetic index (MGI) includes the number of risk genotypes (Mu et al. 2005; Garcia-Closas et al. 2013). The PRS was calculated using the log-additive models using the weighted sum of all SNPs associated with liver cancer with a p-value less than 0.1 in the adjusted model. A weighted variant of the MGI was calculated using the weighted sum of all risk genotypes from the dominant models that were associated with liver cancer with p value of less than 0.1 in the adjusted model. The genetic risk scores were categorized into tertiles based on their distribution in controls, and is estimated only for those with complete genotype data on all SNPs. Median imputation among controls was used as a comparison to the complete case analysis. PRS was stratified into low PRS (less than the median in controls) and high PRS (greater than or equal to median in controls), and additive and multiplicative interaction with dietary factors (flavonoid intake and glycemic index) as well as established risk factors (hepatitis B, mildew exposure, alcohol drinking, and smoking) was assessed using RERI and ROR. All continuous factors were re-coded as binary variables, and preventive factors were re-coded as risk factors.

5.2 Results

Table 5-2 shows the adjusted and semi-Bayes adjusted odds ratios for the associations between selected SNPs and liver cancer. Positive associations were observed in the full sample for a SNP involved in the micro RNA pathway, *rs42031* (aOR for A:T vs A:A: 1.78, 95% CI: 1.11, 2.86), while protective associations were observed for a SNP involved in the stem cell pathway, *rs3734637* (aOR for A:C vs A:A: 0.71, 95% CI: 0.50, 1.00). These results remained significant, even after semi-Bayes adjustment in the log-additive and dominant models.

In addition, Table 5-2 shows the adjusted and semi-Bayes adjusted odds ratios after stratifying for total flavonoid intake. Among those in the upper half of flavonoid intake, the associations observed for *rs42031* (CDK6) in the overall population persisted in all models and in the dominant model for *rs3734637* (HEY2). For both SNPs, estimates were slightly further from the null compared to the full dataset. Associations were observed among those with low flavonoid intake with *rs12934922* (BCM01), *rs2269700* (stem cell pathway), *rs3729629* (stem cell pathway), *rs738722* (CHEK2), and *rs9267673* (ZBTB12-C2), and among those with high flavonoid intake associations were observed with stem cell pathway SNPs *rs3130932* (Oct-4) and *rs3740535* (Ctbp2). There were no associations between NF-kB SNPs and liver cancer in the full or stratified dataset.

The association between two SNPs associated with liver cancer and the stem cell pathway, *rs374053* (Ctbp2) and *rs3729629* (WNT2), appeared to vary with total flavonoid intake. Ctbp2, a gene associated with liver cancer initiation and progression, was marginally associated with increased odds of liver cancer among those with low flavonoid intake, and inversely and marginally associated with liver cancer among those with high flavonoid intake. The AG and AA genotypes were protective against liver cancer compared to GG, and the log-additive model was significantly associated with a decreased susceptibility (aOR: 0.68, 95% CI: 0.47, 0.99), however this association did not remain after semi-Bayes adjustment. Among those who consumed a low level of flavonoid intake, the AG and AA genotypes were a risk factor for liver cancer. Statistically significant interaction (Table 5-3) was observed on the multiplicative scale (ROR: 0.53, 95% CI: 0.29, 0.98), but did not remain after semi-Bayes adjustment. For *rs3729629* (WNT2), the CG genotype had an adjusted odds ratio of 0.62 (95% CI: 0.40, 0.97) compared to the GG genotype. The log-additive and dominant models were significantly protective (log-additive: 0.64, 95% CI: 0.46, 0.90; dominant: 0.59, 95% CI 0.39, 0.90), and this association remained after semi-Bayes adjustment. Furthermore, statistically significant interaction was observed on the additive and multiplicative scale (RERI: -1.19, 95% CI: -2.26, -0.11; ROR: 0.43, 95% CI: 0.23, 0.79), and these associations persisted even after semi-Bayes adjustment.

Three other SNPs appeared to vary with flavonoid intake, including *rs12934922* (BCM01), *rs9267673* (ZBTB12-C2), and *rs738722* (CHEK2). Among those with low flavonoid intake, *rs12934922* (BCM01) was inversely associated with liver cancer. Those who had the TT genotype had an adjusted odds ratio of 4.84 (95% CI 1.50, 15.58) among those with low flavonoid intake, while the TT and AT genotypes were not associated with liver cancer among those with high flavonoid intake (aOR TT vs AA: 0.44, 95% CI: 0.07, 2.59). Statistically significant interaction was observed (ROR: 0.46, 95% CI: 0.23, 0.93), but did not persist after semi-Bayes adjustment. For *rs738722*, the CT genotype compared to CC was protective against liver cancer (aOR: 0.62, 95% CI: 0.38, 0.99), among those with low total flavonoid intake, and this association remained after semi-Bayes adjustment. Statistically significant interaction was observed on both the additive and multiplicative scale (RERI: -1.12, 95% CI: -2.24, -0.01; ROR: 0.47, 95% CI: 0.25, 0.89), and these remained significant after semi-Bayes adjustment. One other SNP, *rs9267673* (ZBTB12-C2) is an HBV-related SNP that was associated with liver cancer for those with low flavonoid intake (TT vs CC aOR: 4.53, 95% CI: 1.57, 13.02), but not among those with low flavonoid intake (TT vs CC aOR: 0.93, 95% CI: 0.24, 3.60). Although no statistically significant interaction was observed, the direction of the association varies clearly after stratification.

5.2.1 Genetic Risk Scores

Three SNPs were associated with liver cancer with a p-value of less than 0.1 in the log-additive model, including: *rs3734637* (HEY 2, stem cell pathway), *rs42031* (CDK6, micro RNA pathway), and *rs4730775* (WNT2, stem cell pathway). The association between tertiles of the polygenic risk score with liver cancer is presented in Table 5-4. The second and third tertiles of the PRS are associated with an increased risk of liver cancer (T3 vs T1, OR: 2.89, 95% CI: 1.68, 4.95). After stratifying for total flavonoid intake, the third tertile of the PRS remained significant (OR: 3.50, 95% CI: 1.70, 7.24) among those with low flavonoid intake, while median imputation of missing genotypes generally increased estimates of the first tertile and lowered estimates of the third. Increasing PRS was associated with increasing risk of liver cancer in the full dataset (p for trend <0.001, as well as in both the low and high flavonoid subgroups (low flavonoid p=0.001; high flavonoid p=0.071).

Four SNPs were associated with liver cancer with a p-value of less than 0.1 in the dominant model, including: *rs222851* (DVL2, stem cell pathway), *rs3734637* (HEY 2, stem cell pathway), *rs42031* (CDK6, micro RNA pathway), and *rs4730775* (WNT2, stem cell pathway), and included in the multigenetic index. The associations between the weighted MGI and liver cancer were slightly more modest than for the PRS. The third tertile of the weighted MGI was significantly associated with liver cancer in the full dataset (aOR: 2.09, 95% CI 1.45, 3.02), as well as in the low flavonoid stratified analysis, however, it was not significantly associated with liver cancer in the high flavonoid analysis. The trends for the weighted MGI in the full dataset and in the low flavonoid dataset were similarly significant (p<0.001), and median imputation slightly increased estimates of most associations.

Table 5-5 shows the joint associations between high and low genetic risk scores with proposed dietary and established risk factors on liver cancer. Low flavonoid intake and high GI did not have any significant interactions, however estimates were in the direction of super-additivity and super-multiplicativity. Chronic hepatitis B infection interacted with weighted MGI on the additive scale (RERI: 18.27, 95% CI: 1.65, 34.88), however this association did not remain after semi-Bayes adjustment. Furthermore, there was no evidence of multiplicative interaction. Mildew exposure, ever drinking, and ever smoking did not significantly interact with either PRS or weighted MGI.

5.3 Discussion

It is thought that flavonoids may affect risk of liver cancer by influencing cell signaling pathways and inflammation. We analyzed the association between genetic polymorphisms and liver cancer stratified by total flavonoid consumption in order to assess how diet can impact the molecular environment for the SNPs associated with the NFKB, microRNA, and stem cell pathways, as well as selected SNPs hypothesized to be associated with cancer. Total flavonoid intake did not alter associations between *rs3734637* (HEY2) and *rs42031* (CDK6) and liver cancer, however associations were observed among those with low flavonoid intake with rs12934922 (BCM01), rs2269700 (stem cell pathway), rs3729629 (stem cell pathway), rs738722 (CHEK2), and rs9267673 (ZBTB12-C2), and among those with high flavonoid intake associations were observed with stem cell pathway SNPs rs3130932 (Oct-4) and rs3740535 (Ctbp2). Furthermore, statistical interactions were observed between total flavonoid intake and *rs738722* (CHEK2), *rs3729629* (WNT2), and *rs3740535* (CTBP2), and *rs12934922* (BCM01). There was no association between NF-kB SNPs and liver cancer in the full or stratified dataset.

Several SNPs associated with the stem cell pathway were differentially expressed among those with low and high flavonoid intake, including DEC1, Oct-4, CTBP2, and WNT2. DEC1 is a presumed tumor suppressor for squamous cell carcinomas of the esophagus and head and neck. More specifically, the C variant of *rs2269700* has been associated with decreased susceptibility to head and neck cancer in non-Hispanic Whites (Huang et al. 2010), although there has been evidence that DEC1 is upregulated in hepatocellular carcinoma but regulated by the tumor promoter HIF1A (Ma et al. 2013). In our study, the C variant of *rs2269700* was associated with a decreased susceptibility to liver cancer in the full dataset as well as among those with low flavonoid intake; however sample size was very limited. The SNP *rs3130932* (Oct-4) has been previously associated with cancer initiation (Katafigiotis et al. 2011), in our study the G variant was associated with increased susceptibility to liver cancer among those with high flavonoid intake. Polymorphisms of *rs3740535* (CTBP2) and *rs3729629* (WNT2) have been associated with liver cancer initiation and progression (Li et al. 2017; Zheng et al. 2015). For *rs3729629* (WNT2), this is through the Wnt/beta catenin pathway which flavonoids and isoflavonoids have been shown to suppress in *in vitro* studies (Park et al. 2005; Li et al. 2008). We observed that low flavonoid intake was associated with liver cancer for those with the AG and AA genotypes for *rs3740535* (Ctbp2), while the CC and CG genotypes were marginally preventively associated with liver cancer for *rs3729629* (WNT2). Statistically significant sub-additive and sub-multiplicative associations persisted after semi-Bayes adjustment between total flavonoid intake and *rs3729629*, while a sub-multiplicative association was observed with *rs3740535* and total flavonoid intake.

The T variant of *rs12934922* (BCM01) has been shown to reduce the catalytic activity of beta-carotene (Leung et al. 2009). In our study the T variant was associated with an increased susceptibility to liver cancer among those with low flavonoid intake (T:T vs. A:A aOR: 1.87, 95% CI: 1.50, 15.58; A:T vs. A:A aOR: 1.69, 95% CI: 1.04, 2.76), but a null association with liver cancer among those with a high flavonoid intake (T:T vs. A:A aOR: 0.44, 95% CI: 0.07, 2.59; A:T vs. A:A aOR: 0.86, 95% CI: 0.50, 1.49). Increased intake of total flavonoids likely corresponds to an increased intake of beta carotene from shared sources, and the harmful association between the *rs12934922* (BCM01) SNP with liver cancer is possibly mitigated by increased vegetable intake. A statistically significant interaction between *rs12934922* and total flavonoid intake was observed on the multiplicative scale (ROR: 0.46, 95% CI: 0.23, 0.93).

GWAS studies have shown *rs9267673* to be associated with hepatitis-related liver cirrhosis and cancer (Jiang et al. 2015). We found an association between the T variant and liver cancer in those with low flavonoid intake, but not among those who consumed higher amounts of flavonoids, suggesting that diet may have some impact on the progression of viral hepatitis to liver cancer. Flavonoids and isoflavonoids have been associated with downregulation of CHEK2 in an *in vitro* study (Moskot et al. 2015). CHEK2 is a tumor promoter, and the T variant of *rs738722* has been associated with esophageal squamous cell carcinoma, but not breast cancer (Yang, Wu, et al. 2014; Baynes et al. 2007). There was evidence of sub-additive and sub-multiplicative interaction between flavonoid intake and *rs738722* (RERI: -1.12, 95% CI: -2.23, -0.01; ROR 0.47, 95% CI: 0.25, 0.89).

Construction of genetic risk scores, including the PRS and weighted MGI, was associated with increased odds of liver cancer. These scores did not appear to interact with dietary factors total flavonoid intake or glycemic index, or with established risk factors mildew exposure, alcohol drinking, or tobacco smoking. However, there was some evidence of super-additive interaction between hepatitis B infection and the weighted multigenetic index.

To our knowledge, the present study is the first to report associations *rs12934922* (BCM01) and *rs738722* (CHEK2) with liver cancer, and furthermore is the first to report effect measure modification of total flavonoid intake on the association between any SNPs and liver cancer.

CHAPTER 6. CONCLUSION AND PUBLIC HEALTH IMPLICATIONS

6.1 Limitations and Strengths

For Specific Aim 1, there are several limitations for estimating global population attributable fractions. The risk factors presented often co-occur and it is possible that these factors may interact with one another in order to synergistically increase susceptibility of liver cancer (e.g. aflatoxin and HBV), or alternatively the co-occurrence of two risk factors may mask in part the carcinogenicity of a co-factor (e.g. Cho et al.'s theory of HBV & HCV co-infection). In order to take this into account, we hypothesized the effect interactions would have on the population attributable fractions reported in this study.

Another limitation of this study is the available data for estimation of continuous variables such as alcohol drinking, adiposity, and tobacco smoking. PAFs for alcohol drinking and obesity were estimated using categorical prevalence and risk estimates, while these measures were not available for tobacco smoking. It is likely that the reported estimates for tobacco do not adequately reflect the population distribution of smoking within each GBD region. Furthermore, the GBD regions themselves are aggregate measures of country-level data, and thus do not reflect the variation that may exist between countries in the same GBD region. However, Table 3-7, Table 3-8, and Table 3-9 include country-specific estimates of HCC attributable risk to HBV, HCV, alcohol drinking, tobacco smoking, and adiposity, reflecting these variations within broader regions.

For Specific Aim 2, the study based on the Jiangsu Province case-control study, recall bias may have influenced the measurement of dietary factors. Participants were asked to recall their general dietary patterns one year before diagnosis to capture dietary history; however cases may have over reported known risk behaviors such as alcohol consumption after experiencing symptoms of liver cancer. Cases over-reporting alcohol consumption would lead to differential misclassification away from the null, while other dietary risk factors are not likely to vary by case status, and therefore non-differential misclassification towards the null is more likely. Furthermore, measurement of diet through the FFQ is subject to systematic error which was mitigated in this study through residual energy adjustment. In addition, exclusion of participants from the analysis due to missing data, either from invalid dietary data or missing measures of HbsAg, may have caused selection bias in this study if data were not missing at random. Those missing measures of HBsAg were more likely to be from Chuzhou or Ganyu, less than 60, better educated, and to have reported eating fewer calories. Those with invalid dietary data were less likely to be from Dafeng and more likely to have lower income. Estimates from multiple imputation were used in the dietary analysis to compare against the complete case analysis.

For Specific Aim 3, although the study enrolled a large number of cases and controls, the subsample that had SNP data was much smaller, and we did not have sufficient statistical power for some SNPs to obtain stable estimates after stratifying for flavonoid intake. Additionally, multiple comparisons may have also resulted in false positives as we investigated a large number of genetic and dietary factors. We applied a semi-Bayesian shrinkage approach to our estimates in order to mitigate the effects of sparse data bias and multiple comparisons; however there still might be false positive results. Future studies with large sample sizes are warranted to confirm the findings in this study, especially as this study is the first to explore several of these associations, and their modification by flavonoid status. Furthermore, the genetic risk scores are calculated by summing the individual associations of risk alleles or genotypes from different pathways. This may not completely capture individual genetic risk, as individual SNPs may interact with one another, and individual SNPs may amplify or mask the effect of another.

Despite these limitations, this study comprehensively updates global estimations of major risk factors and is the first study to summarize and report attributable risk of obesity on liver cancer on country, regional, and global levels. This is the first study to evaluate the relationship between flavonoid intake and liver cancer risk in a Chinese population. Strengths of the Jiangsu study include the large number of cases available as well as biological measures of HBV infection and SNPs. Furthermore, novel associations between SNPs and liver cancer were the first of their kind to be identified, and no other study has looked at the effect modification by flavonoid intake on the relationship between these SNPs and liver cancer.

6.2 Conclusions and Public Health Implications

The number of hepatocellular carcinoma cases was estimated that can be attributed to major liver cancer risk factors, giving researchers and policymakers an updated estimation of the geographical distribution of the number of incident cases of liver cancer worldwide. This is the first estimate of liver cancer cases attributable to obesity. Our results may be informative for policy-making and program planning for HCC prevention and control in both developing and developed countries. Furthermore, this is the first study to assess the association between flavonoid intake and liver cancer in a Chinese population, and the largest conducted thus far on glycemic index and glycemic load. Tea appeared to be protective against liver cancer in this study, however, no clear association was observed between vegetable sources of flavonoids and liver cancer. The differences in diet between a Western and Asian diet do not affect the direction of the association of flavonoids with liver cancer, but that the association may vary by food source. Our study also added to the body of evidence suggesting that higher glycemic index and carbohydrate intake may be associated with increased odds of liver cancer. Lastly, this study is the first of its kind to assess the potential effect modification of flavonoid intake on the associations between genetic polymorphisms and liver cancer. We found that dietary factors may modify genetic predisposition by altering the relationship between several SNPs and liver cancer. With the increasing interest in precision medicine, more studies are needed that look at the interaction between genetics and lifestyle risk factors, and how this affects cancer risk and prognosis.

Historically hepatocellular carcinoma is primarily thought of as a result of chronic viral infection with hepatitis B and hepatitis C. This has been largely proven, as about 43.6% of global HCC cases can be attributed to infection with HBV, while 21% of the global risk can be attributed to HCV infection based on estimates in this study. However as HBV vaccine and HCV treatment options become more widely available, the dominant effect of HBV and HCV on the development of HCC will likely decline as more of the population becomes vaccinated and treated. Lifestyle risk factors will most likely play a larger role in the etiology of liver cancer in the future, and may interact with established risk factors, modifying their association with liver cancer.

A better understanding of lifestyle-related factors and how they affect established risk and preventative factors is paramount to understanding liver cancer etiology to provide effective prevention and control measures to reduce liver cancer incidence and mortality

TABLES AND FIGURES

Table 1-1. Gaps in the Literature

	Aim 1			Aim 2		Aim 3		
	Country	**Regional**	**Global**	**Flavonoid**	**GI/GL**	**NF-κB**	**Stem cell**	**GWAS**
Liver Cancer	?	Yes	Yes	?	?	???	?	?
HBV/HCV	?	?	Yes	?	???	---	?	?
Alcohol	?	Yes	Yes	???	???	---	?	???
Smoking	?	?	Yes	???	???	---	?	???
Aflatoxin B1	---	---	Yes	???	???	---	???	???
Obesity	??	??	??	---	---	---	---	---
Flavonoid	---	---	---	---	???	???	???	???
GI/GL	---	---	---	???	---	???	???	???

Yes = association established by studies
--- = not applicable or not examined in this study
??? = no studies on this interaction (shaded region represents interaction)
?? =no studies on this association
? = few studies on this association/interaction

Table 3-1. Constituent countries of Global Burden of Disease Regions

	Region	Constituent Countries
Asia	*Asia Pacific*	*Brunei, Japan, Republic of Korea, Singapore*
	Central Asia	Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan
	East Asia	China, Democratic Republic of Korea
	South Asia	Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan
	Southeast Asia	Cambodia, Indonesia, Lao PDR, Malaysia, Maldives, Mauritius, Myanmar, Philippines, La Reunion (France), Sri Lanka, Thailand, Timor-Leste, Viet Nam
Europe & Western Pacific	*Australasia*	*Australia, New Zealand*
	Central Europe	Albania, Bosnia Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, FYR Macedonia
	Eastern Europe	Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
	Western Europe	*Austria, Belgium, Cyprus, Denmark, Finland, France (Metropolitan), Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Norway, Portugal, Spain, Sweden, Switzerland, The Netherlands, United Kingdom*
	Oceania	Fiji, French Polynesia, Guam, New Caledonia, Papua New Guinea, Samoa, Solomon Islands, Vanuatu
Americas	Caribbean	Bahamas, Barbados, Belize, Cuba, Dominican Republic, French Guyana (France), Guadeloupe (France), Guyana, Haiti, Jamaica, Martinique (France), Puerto Rico, Suriname, Trinidad and Tobago
	Andean Latin America	Bolivia, Ecuador, Peru
	Central Latin America	Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela
	Southern Latin America	Argentina, Chile, Uruguay
	Tropical Latin America	Brazil, Paraguay
	North America	*Canada, United States of America*
Africa & E. Mediterranean	North Africa & Middle East	Algeria, Bahrain, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, State of Palestine, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Western Sahara, Yemen
	Central Sub-Saharan Africa	Angola, Central African Republic, Democratic Republic of Congo, Republic of Congo, Equatorial Guinea, Gabon
	East Sub-Saharan Africa	Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, Sudan, Tanzania, Uganda, Zambia, South Sudan
	Southern Sub-Saharan Africa	Botswana, Lesotho, Namibia, South African Republic, Swaziland, Zimbabwe
	West Sub-Saharan Africa	Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Cote D'Ivoire, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, The Gambia, Togo

Regions in *italics* are high income

Table 3-2. Summary of risk estimates of major risk factors for hepatocellular carcinoma

Study	Study Design	Overall RR (95% CI)	Measure of Exposure	Heterogeneity by Region	Heterogeneity by Gender		Heterogeneity by Hepatitis	Other Adjustments
					men	women		
HBV								
Donato, Boffeta & Puoti, 1998	32 studies, 21 case-control studies	20.4 (18.0, 23.2)	HBsAg positivity vs HBsAg negative, in HCV-negative	20.8 (17.8, 24.3) in Africa, China, & southeast Asia;18.8 (11.8, 30.3) in Japan & Mediterranean	NA		135 (79.7, 242) in anti-HCV/HCV RNA positive	22.5 (19.5, 26) in 2nd generation HBsAg measurement
This Study: 22.5 (19.5, 26)								
HCV								
Donato, Boffeta & Puoti, 1998	32 studies, 21 case-control studies	23.6 (20.0, 28.1)	Anti-HCV/HCV-RNA positivity vs negativity, in HBsAg negative	11.5 (8.8, 15.0) in Africa, China, & southeast Asia; 31.2 (20.9, 47.4) in Japan & Mediterranean	NA		135 (79.7, 242) in HBsAG positive	17.3 (13.9, 21.6) in 2nd generation anti-HCV
This Study: 17.3 (13.9, 21.6)								
Alcohol								
Chuang et al., 2015	27 cohort studies; 63 case control	1.2 (1.1, 1.3)	25g/day vs never	1.28 (1.13, 1.44) in Asia, 1.39 (0.93, 1.85) in Europe, 1.20 (0.86, 1.54) in North America, ever vs never	1.2 (1.1,1.3)	1.3 (1.1,1.5)	1.12 (0.82,1.52)	2.06 (1.31, 2.81) in former vs never drinkers
		1.5 (1.4, 1.7)	50g/day vs never		1.5 (1.3,1.7)	2.1 (1.2,3.6)	1.74 (1.25,2.41)	
		2.1 (1.7, 2.6)	75g/day vs never		1.8 (1.5,2.3)	4.7 (1.5,14.5)	3.68 (2.15,6.29)	
		3.2 (2.3, 4.4)	100g/day vs never		2.3 (1.7,3.1)		10.6 (3.66,30.7)	
This Study: Chuang et al. gender-specific estimates and former vs never estimate								
Smoking								
Lee et al., 2009	13 case-control; 7 cohort	1.51 (1.37, 1.67)	Current smokers vs never tobacco smokers	1. 56 (1.36, 1.79) in Asia	1.61 (1.38, 1.89)	1.86 (1.33, 2.60)	1.38 (1.01, 1.88) adjusted for HBV, 1.55 (1.00, 2.38) adjusted for HCV	1.43 (1.21, 1.68) adjusted for alcohol
This Study: 1.43 (1.21, 1.68)								
Obesity								
Chen et al., 2012	26 prospective studies	1.48 (1.31, 1.67)	Overweight vs normal weight	1.35 (1.18, 1.54) in Asia, 1.65 (1.36, 2.02) in non-Asian countries	1.42 (1.22, 1.65)	1.18 (1.08, 1.30)	1.74 (1.35, 2.25) adjusted for HBV and/or HCV	1.46 (1.25, 1.69) adjusted for alcohol
		1.83 (1.59, 2.11)	Obese vs normal weight		1.91 (1.51, 2.41)	1.55 (1.30, 1.85)		
This Study: Chen et al. gender-specific estimates								

Table 3-3. Fraction of cases of hepatocellular carcinoma attributable to major risk factors by geographic region

Region	HCC (N=)	HBV PAF (CI)	HCV PAF (CI)	Alcohol PAF (CI)	Smoking PAF (CI)	Obesity PAF (CI)
Asia Pacific	40,303	22.7% (20.4%, 25.7%)	17.4% (5.4%, 31.9%)	27.6% (13.9%, 40.5%)	14.1% (7.2%, 21.3%)	7.7% (4.3%, 11.4%)
Central Asia	4,687	57.4% (48.1%, 67.8%)	49.7% (33.0%, 66.9%)	27.0% (12.1%, 40.9%)	8.5% (4.0%, 13.9%)	14.3% (7.0%, 23.5%)
East Asia	310,366	53.8% (50.0%, 58.5%)	17.5% (5.3%, 30.2%)	26.6% (12.9%, 39.8%)	14.3% (7.4%, 21.1%)	6.5% (3.5%, 9.6%)
South Asia	24,900	26.7% (23.6%, 30.8%)	17.1% (6.7%, 25.4%)	12.6% (5.2%, 20.4%)	8.4% (4.0%, 13.3%)	3.9% (2.1%, 6.0%)
Southeast Asia	57,264	50.9% (46.6%, 56.0%)	20.3% (11.7%, 38.6%)	19.4% (8.9%, 30.3%)	14.0% (7.1%, 21.0%)	4.3% (2.4%, 6.5%)
Australasia	1,457	15.5% (13.5%, 18.2%)	22.0% (13.7%, 28.6%)	27.7% (13.8%, 40.8%)	9.7% (4.7%, 15.1%)	21.3% (11.7%, 31.4%)
Central Europe	5,198	28.5% (23.8%, 35.3%)	19.9% (13.3%, 30.3%)	35.4% (17.4%, 51.4%)	12.3% (5.9%, 19.5%)	19.0% (9.8%, 29.4%)
Eastern Europe	5,475	39.3% (34.5%, 45.4%)	38.8% (14.3%, 52.9%)	38.5% (18.2%, 56.5%)	13.2% (6.5%, 20.4%)	17.8% (9.4%, 27.2%)
Western Europe	32,766	12.1% (9.8%, 15.3%)	15.4% (8.3%, 32.0%)	30.4% (15.4%, 44.3%)	12.1% (6.0%, 18.7%)	20.1% (11.0%, 29.9%)
Oceania	496	78.9% (73.5%, 83.8%)	3.2% (2.7%, 16.3%)	20.8% (9.7%, 30.8%)	13.5% (6.3%, 21.8%)	16.3% (7.7%, 26.9%)
Caribbean	836	47.9% (33.6%, 62.7%)	NA	27.7% (11.7%, 42.2%)	6.7% (2.9%, 11.6%)	13.1% (6.4%, 21.2%)
Andean Latin America	1,960	24.3% (18.7%, 32.6%)	16.4% (5.3%, 25.7%)	29.9% (12.7%, 44.6%)	4.9% (2.1%, 8.8%)	14.6% (7.0%, 23.8%)
Central Latin America	7,231	8.5% (6.5%, 11.4%)	18.7% (12.0%, 27.1%)	26.3% (11.1%, 40.9%)	6.3% (2.8%, 10.8%)	17.0% (8.6%, 26.7%)
Southern Latin America	1,648	14.2% (12.5%, 16.9%)	19.6% (6.5%, 35.1%)	30.1% (13.8%, 43.8%)	11.3% (5.0%, 19.1%)	19.6% (10.0%, 30.5%)
Tropical Latin America	7,841	12.1% (10.4%, 14.5%)	20.7% (13.3%, 25.7%)	36.8% (16.8%, 54.4%)	7.3% (3.1%, 13.1%)	15.3% (8.0%, 23.7%)
North America	25,898	5.8% (4.4%, 7.7%)	17.3% (13.9%, 33.4%)	31.6% (15.5%, 46.8%)	8.9% (4.3%, 13.9%)	23.6% (13.2%, 34.3%)
North Africa & Middle East	22,147	27.8% (24.3%, 32.3%)	56.3% (45.0%, 67.2%)	20.8% (7.7%, 35.0%)	8.9% (4.1%, 14.6%)	18.5% (9.6%, 28.6%)
Central Sub-Saharan Africa	3,778	59.5%	41.4%	26.7%	4.1%	4.6%

Region	HCC (N=)	HBV PAF (CI)	HCV PAF (CI)	Alcohol PAF (CI)	Smoking PAF (CI)	Obesity PAF (CI)
		(54.2%, 65.3%)	(30.7%, 74.8%)	(11.2%, 40.6%)	(1.6%, 7.5%)	(2.4%, 7.6%)
East Sub-Saharan Africa	5,124	57.9% (51.5%, 64.8%)	17.1% (9.2%, 46.3%)	21.4% (9.0%, 34.0%)	5.7% (2.4%, 9.9%)	4.2% (2.2%, 6.9%)
Southern Sub-Saharan Africa	2,449	62.0% (56.0%, 68.6%)	21.5% (12.2%, 41.3%)	22.5% (10.1%, 36.6%)	9.1% (4.3%, 14.7%)	12.6% (6.3%, 20.3%)
West Sub-Saharan Africa	19,754	69.2% (64.3%, 74.4%)	53.0% (31.1%, 73.4%)	27.5% (12.6%, 42.1%)	4.4% (1.9%, 8.0%)	5.8% (3.0%, 9.3%)
WORLD	581,579	43.6% (40.0%, 48.1%)	21.0% (9.7%, 34.9%)	25.9% (12.3%, 39.0%)	12.6% (6.4%, 19.0%)	8.9% (4.8%, 13.3%)

Table 3-4. Fraction of cases of hepatocellular carcinoma attributable to major lifestyle risk factors by geographic region and gender

	Men				Women			
GBDR	**HCC (N=)**	**Alcohol PAF (CI)**	**Smoking PAF (CI)**	**Obesity PAF (CI)**	**HCC (N=)**	**Alcohol PAF (CI)**	**Smoking PAF (CI)**	**Obesity PAF (CI)**
Asia Pacific	27,417	28.7% (16.8%, 40.1%)	18.7% (9.7%, 27.7%)	9.3% (5.4%, 13.2%)	12,886	25.4% (7.6%, 41.3%)	4.5% (2.1%, 7.6%)	4.2% (1.8%, 7.4%)
Central Asia	2,688	27.8% (15.0%, 40.6%)	13.1% (6.2%, 20.9%)	17.0% (9.0%, 26.3%)	1,999	25.8% (8.0%, 41.2%)	2.4% (1.0%, 4.4%)	10.7% (4.2%, 19.8%)
East Asia	230,372	27.8% (14.8%, 41.1%)	18.7% (9.7%, 27.4%)	7.2% (4.1%, 10.4%)	79,995	23.2% (7.4%, 36.2%)	1.7% (0.7%, 2.9%)	4.2% (1.8%, 7.5%)
South Asia	15,679	15.4% (6.8%, 24.5%)	12.5% (6.0%, 19.7%)	4.3% (2.6%, 6.1%)	9,220	8.0% (2.4%, 13.4%)	1.3% (0.5%, 2.5%)	3.1% (1.2%, 5.7%)
Southeast Asia	41,782	23.8% (11.4%, 36.7%)	18.3% (9.4%, 27.3%)	4.5% (2.7%, 6.3%)	15,482	7.2% (2.1%, 12.6%)	2.2% (0.9%, 3.9%)	3.7% (1.5%, 7.0%)
Australasia	1,033	27.5% (16.1%, 38.7%)	9.9% (4.9%, 15.4%)	24.7% (14.0%, 35.6%)	424	28.4% (8.4%, 45.8%)	9.0% (4.3%, 14.3%)	13.0% (6.1%, 21.3%)
Central Europe	3,293	35.9% (21.2%, 50.1%)	14.5% (7.1%, 22.5%)	22.5% (12.2%, 33.4%)	1,904	34.5% (11.0%, 53.6%)	8.5% (3.8%, 14.3%)	12.9% (5.5%, 22.4%)
Eastern Europe	3,134	39.0% (22.8%, 54.9%)	18.7% (9.5%, 27.9%)	19.9% (11.0%, 29.4%)	2,341	37.8% (12.0%, 58.6%)	5.9% (2.6%, 10.4%)	15.0% (7.3%, 24.3%)
Western Europe	23,137	30.2% (18.0%, 42.1%)	13.1% (6.5%, 20.0%)	23.5% (13.2%, 33.9%)	9,629	30.7% (9.1%, 49.8%)	9.7% (4.7%, 15.4%)	12.1% (5.6%, 20.2%)
Oceania	322	20.4% (11.1%, 29.8%)	16.8% (8.1%, 26.1%)	18.2% (9.3%, 28.8%)	175	21.5% (7.1%, 32.5%)	7.5% (3.1%, 13.8%)	12.7% (4.9%, 23.4%)
Caribbean	446	28.1% (14.3%, 42.4%)	8.7% (3.9%, 14.7%)	13.6% (7.3%, 20.8%)	390	27.1% (8.9%, 41.9%)	4.4% (1.8%, 8.0%)	12.4% (5.3%, 21.6%)
Andean Latin America	882	28.4% (15.2%, 41.9%)	7.5% (3.3%, 12.8%)	17.0% (9.1%, 25.8%)	1,078	31.1% (10.7%, 46.8%)	2.8% (1.1%, 5.5%)	12.6% (5.3%, 22.2%)
Central Latin America	3,523	29.1% (15.2%, 43.5%)	9.5% (4.3%, 15.8%)	19.8% (10.8%, 29.5%)	3,708	23.6% (7.3%, 38.5%)	3.3% (1.4%, 6.1%)	14.3% (6.5%, 24.0%)
Southern Latin America	912	26.9% (15.7%, 37.9%)	12.3% (5.6%, 20.2%)	23.5% (12.7%, 34.9%)	736	34.0% (11.4%, 51.2%)	10.2% (4.4%, 17.7%)	14.8% (6.6%, 25.0%)
Tropical Latin America	4,654	36.4% (19.1%, 54.3%)	8.4% (3.6%, 14.6%)	17.7% (9.8%, 26.2%)	3,187	37.5% (13.4%, 54.5%)	5.8% (2.3%, 10.9%)	11.9% (5.4%, 20.1%)
North America	19,132	31.9% (17.5%, 46.4%)	9.1% (4.5%, 14.3%)	26.5% (15.1%, 37.7%)	6,767	30.7% (9.7%, 48.0%)	8.1% (3.9%, 12.8%)	15.5% (7.6%, 24.6%)
North Africa & Middle East	15,076	26.7% (10.2%, 45.1%)	12.6% (5.8%, 20.4%)	19.5% (10.5%, 29.6%)	7,071	8.2% (2.5%, 13.4%)	1.1% (0.4%, 2.1%)	16.4% (7.8%, 26.6%)
Central Sub-Saharan Africa	2,292	26.1% (12.3%, 40.5%)	6.3% (2.6%, 11.5%)	4.5% (2.9%, 6.4%)	1,486	27.5% (9.5%, 40.7%)	0.6% (0.2%, 1.3%)	4.7% (1.7%, 9.4%)

GBDR	Men				Women			
	HCC (N=)	**Alcohol PAF (CI)**	**Smoking PAF (CI)**	**Obesity PAF (CI)**	**HCC (N=)**	**Alcohol PAF (CI)**	**Smoking PAF (CI)**	**Obesity PAF (CI)**
East Sub-Saharan Africa	3,023	23.3% (11.3%, 35.8%)	8.4% (3.7%, 14.5%)	4.3% (2.7%, 6.1%)	2,101	18.8% (5.7%, 31.3%)	1.6% (0.6%, 3.4%)	4.1% (1.5%, 8.0%)
Southern Sub-Saharan Africa	1,452	27.1% (14.3%, 40.4%)	13.1% (6.3%, 20.6%)	11.0% (5.9%, 17.0%)	996	15.9% (4.0%, 31.0%)	3.3% (1.4%, 6.0%)	15.0% (6.9%, 25.1%)
West Sub-Saharan Africa	13,229	27.7% (14.6%, 41.1%)	5.8% (2.5%, 10.3%)	5.9% (3.4%, 8.7%)	6,525	27.2% (8.4%, 44.3%)	1.6% (0.6%, 3.1%)	5.7% (2.3%, 10.8%)
WORLD	413,479	27.5% (14.5%, 40.7%)	16.5% (8.5%, 24.7%)	9.8% (5.6%, 14.1%)	168,100	22.0% (6.9%, 34.9%)	2.9% (1.3%, 5.0%)	6.5% (2.9%, 11.2%)

Table 3-5. Hepatocellular carcinoma cases attributable to major risk factors in top five countries worldwide

Country	Risk Factor	PAF Males	PAF Females	PAC Males	PAC Females
1. China				N= 306,508	
	HCC Cases			227,739	78,770
	HBV	53.8% (50.0%, 58.5%)		164,813 (153,177, 179,421)	
	HCV	17.5% (5.3%, 30.2%)		53,593 (16,144, 92,466)	
	Alcohol	27.8% (14.8%, 41.1%)	23.2% (7.4%, 36.2%)	63,368 (33,659, 93,569)	18,247 (5,837, 28,529)
	Smoking	18.7% (9.8%, 27.4%)	1.7% (0.8%, 2.9%)	42,593 (22,226, 62,399)	1,332 (591, 2,288)
	Obesity	7.2% (4.1%, 10.4%)	4.2% (1.8%, 7.4%)	16,461 (9,423, 23,643)	3,334 (1,446, 5,865)
2. Japan				N=28,591	
	HCC Cases			18,696	9,895
	HBV	12.4% (10.7%, 14.6%)		3,553 (3,069, 4,188)	
	HCV	19.6% (6.5%, 32.2%)		5,617 (1,858, 9,210)	
	Alcohol	25.6% (14.8%, 36.3%)	23.9% (6.9%, 39.6%)	4,795 (2,767, 6,793)	2,369 (680, 3,914)
	Smoking	18.2% (9.4%, 27.3%)	5.2% (2.4%, 8.7%)	3,411 (1,764, 5,096)	512 (237, 860)
	Obesity	9.1% (5.3%, 13.0%)	3.9% (1.7%, 6.8%)	1,703 (985, 2,427)	387 (166, 675)
3. USA				N=24,223	
	HCC Cases			17,932	6,291
	HBV	5.3% (4.1%, 7.0%)		1,282 (989, 1,698)	
	HCV	17.5% (14.3%, 34.1%)		4,235 (3,463, 8,270)	
	Alcohol	32.0% (17.5%, 46.5%)	30.7% (9.8%, 48.0%)	5,730 (3,141, 8,342)	1,934 (614, 3,022)
	Smoking	9.0% (4.5%, 14.1%)	8.0% (3.8%, 12.6%)	1,620 (799, 2,534)	500 (241, 793)
	Obesity	26.6% (15.2%, 37.8%)	15.6% (7.7%, 24.8%)	4,765 (2,733, 6,775)	981 (485, 1,558)
4. India				N=19,104	
	HCC Cases			12,011	7,094
	HBV	23.6% (20.9%, 27.4%)		4,516 (3,997, 5,230)	
	HCV	11.5% (5.3%, 17.8%)		2,204 (1,006, 3,394)	
	Alcohol	18.8% (8.4%, 29.9%)	10.0% (3.0%, 16.9%)	2,259 (1,005, 3,590)	713 (214, 1,200)
	Smoking	12.1% (5.9%, 18.9%)	1.1% (0.5%, 2.1%)	1,449 (705, 2,266)	81 (34, 146)

Country	Risk Factor	PAF Males	PAF Females	PAC Males	PAC Females
	Obesity	4.1% (2.5%, 5.7%)	2.9% (1.2%, 5.4%)	495 (295, 684)	207 (85, 380)
5. Vietnam				N=15,738	
	HCC Cases			12,030	3,708
	HBV	69.8% (65.5%, 74.6%)		10,988 (10,304, 11,736)	
	HCV	NA		NA	
	Alcohol	23.9% (11.9%, 36.4%)	4.3% (1.2%, 7.6%)	2,880 (1,432, 4,382)	158 (45, 282)
	Smoking	20.0% (10.5%, 29.3%)	1.9% (0.8%, 3.4%)	2,408 (1,258, 3,519)	69 (29, 124)
	Obesity	2.8% (1.8%, 3.5%)	2.2% (0.9%, 4.0%)	341 (222, 421)	81 (32, 149)

Figure 3-1. Average PAF in high income countries versus low and middle income countries

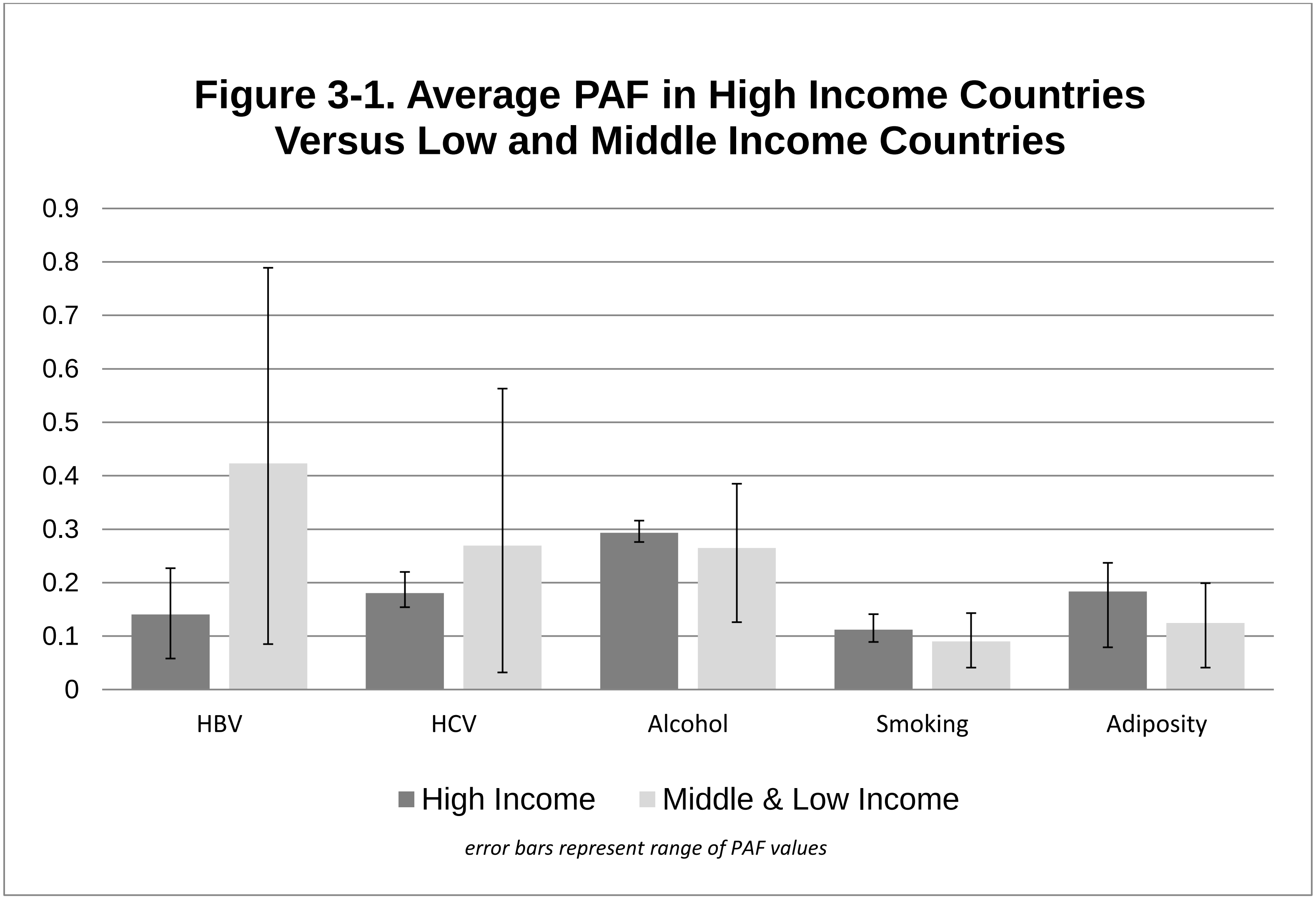

Table 3-6. Percent and number of hepatocellular carcinoma cases by country

Country	Males			Females			All
	Liver Cancer Cases	% HCC	HCC Cases	Liver Cancer Cases	% HCC	HCC Cases	HCC Cases
Afghanistan	477	69.7%	332	283	51.5%	197	530
Albania	104	58.3%	61	67	45.0%	39	100
Algeria	214	87.0%	186	213	71.4%	185	372
Angola	309	81.6%	252	203	66.8%	166	418
Argentina	1,059	55.4%	587	821	41.2%	455	1,042
Armenia	260	76.1%	198	204	62.8%	155	353
Australia	1,180	74.8%	883	478	46.1%	358	1,241
Austria	644	68.1%	439	311	42.9%	212	651
Azerbaijan	254	76.1%	193	212	62.8%	161	354
Bahrain	17	66.7%	11	9	50.0%	6	17
Bangladesh	1,837	69.7%	1,280	1185	51.5%	826	2,106
Barbados	4	36.8%	1	7	37.9%	3	4
Belarus	201	41.7%	84	126	33.3%	53	136
Belgium	446	74.2%	331	199	54.5%	148	479
Belize	8	36.8%	3	6	37.9%	2	5
Benin	471	81.6%	384	249	66.8%	203	587
Bhutan	18	69.7%	13	7	51.5%	5	17
Bolivia	128	71.3%	91	148	66.0%	106	197
Bosnia and Herzegovina	170	58.3%	99	144	45.0%	84	183
Botswana	50	87.9%	44	25	62.2%	22	66
Brazil	5,766	79.7%	4,596	3912	56.8%	3,118	7,715
Brunei	14	74.5%	10	6	64.7%	4	15
Bulgaria	418	73.9%	309	222	66.7%	164	473
Burkina Faso	779	81.6%	636	475	66.8%	388	1,023
Burundi	151	61.4%	93	114	58.8%	70	163
Cambodia	1,444	71.5%	1,033	820	57.4%	587	1,620
Cameroon	550	81.6%	449	177	66.8%	144	593
Canada	1,619	74.1%	1,199	642	50.0%	476	1,675
Cape Verde	35	81.6%	29	21	66.8%	17	46
Central African Republic	115	81.6%	94	62	66.8%	51	144
Chad	307	81.6%	250	140	66.8%	114	365
Chile	561	48.3%	271	529	26.7%	255	526
China	293,318	77.6%	227,739	101452	65.1%	78,770	306,508
Colombia	613	59.0%	362	681	40.7%	402	763
Comoros	10	61.4%	6	5	58.8%	3	9
Congo	137	81.6%	112	98	66.8%	80	192
Costa Rica	123	64.7%	80	83	44.4%	54	133
Côte d'Ivoire	1,590	81.6%	1,297	647	66.8%	528	1,825

Country	Males			Females			All
	Liver Cancer Cases	% HCC	HCC Cases	Liver Cancer Cases	% HCC	HCC Cases	HCC Cases
Croatia	329	66.7%	219	137	50.0%	91	311
Cuba	361	23.5%	85	364	28.6%	86	171
Cyprus	36	50.0%	18	20	42.9%	10	28
Czech Republic	581	60.5%	351	338	41.2%	204	556
Democratic Republic of the Congo	2,215	81.6%	1,807	1444	66.8%	1,178	2,985
Denmark	227	65.7%	149	84	50.0%	55	204
Djibouti	11	61.4%	7	7	58.8%	4	11
Dominican Republic	441	36.8%	162	410	37.9%	151	313
Ecuador	324	71.3%	231	381	66.0%	272	503
Egypt	12,493	88.5%	11,059	5128	76.9%	4,540	15,599
El Salvador	181	59.9%	108	266	41.1%	159	268
Equatorial Guinea	16	81.6%	13	4	66.8%	3	16
Eritrea	43	61.4%	26	36	58.8%	22	49
Estonia	34	52.0%	18	30	41.7%	16	33
Ethiopia	418	61.4%	257	578	58.8%	355	612
Fiji	45	69.0%	31	25	49.3%	17	48
Finland	407	65.9%	268	213	46.7%	140	409
France	6,500	76.6%	4,981	1832	47.8%	1,404	6,385
Gabon	17	81.6%	14	11	66.8%	9	23
Georgia	250	76.1%	190	189	62.8%	144	334
Germany	6,396	72.0%	4,607	2806	44.5%	2,021	6,628
Ghana	1,502	81.6%	1,225	421	66.8%	343	1,569
Greece	708	72.7%	515	346	48.9%	252	766
Guatemala	725	59.9%	434	817	41.1%	490	924
Guinea	673	81.6%	549	429	66.8%	350	899
Guinea-Bissau	86	81.6%	70	44	66.8%	36	106
Guyana	21	36.8%	8	13	37.9%	5	13
Haiti	256	36.8%	94	204	37.9%	75	169
Honduras	292	59.9%	175	306	41.1%	183	358
Hungary	434	58.3%	253	196	45.0%	114	367
Iceland	6	56.5%	3	4	50.0%	2	6
India	17,236	69.7%	12,011	10180	51.5%	7,094	19,104
Indonesia	13,365	71.5%	9,562	4756	57.4%	3,403	12,965
Iran	889	94.7%	842	678	54.5%	642	1,485
Iraq	318	87.0%	277	360	71.4%	313	590
Ireland	152	58.8%	89	87	42.9%	51	141
Israel	158	85.7%	135	85	71.4%	73	208
Italy	7,188	76.3%	5,485	3545	58.1%	2,705	8,191
Jamaica	76	100.0%	76	55	100.0%	55	131
Japan	23,651	79.0%	18,696	12517	70.4%	9,895	28,591

Country	Males			Females			All
	Liver Cancer Cases	% HCC	HCC Cases	Liver Cancer Cases	% HCC	HCC Cases	HCC Cases
Jordan	100	87.0%	87	59	71.4%	51	138
Kazakhstan	790	76.1%	601	547	62.8%	416	1,017
Kenya	634	61.4%	389	486	58.8%	298	688
Kuwait	43	82.8%	36	9	66.7%	7	43
Kyrgyzstan	186	76.1%	141	138	62.8%	105	246
Laos	1,486	71.5%	1,063	630	57.4%	451	1,514
Latvia	96	83.3%	80	58	80.0%	48	128
Lebanon	69	87.0%	60	47	71.4%	41	101
Lesotho	65	87.9%	57	18	62.2%	16	73
Liberia	248	81.6%	202	144	66.8%	117	320
Libya	123	77.8%	96	94	33.3%	73	169
Lithuania	111	58.3%	65	64	33.3%	37	102
Luxembourg	46	72.7%	33	22	48.9%	16	49
Macedonia	86	58.3%	50	49	45.0%	29	79
Madagascar	317	61.4%	195	159	58.8%	98	292
Malawi	111	95.5%	106	95	82.4%	91	197
Malaysia	1,111	69.1%	768	416	33.3%	287	1,055
Maldives	6	71.5%	4	0	57.4%	0	4
Mali	257	81.6%	210	114	66.8%	93	303
Malta	13	47.8%	6	6	22.2%	3	9
Mauritania	194	81.6%	158	94	66.8%	77	235
Mauritius	15	71.5%	11	18	57.4%	13	24
Mexico	3,068	59.9%	1,839	3319	41.1%	1,989	3,828
Micronesia, Federated States of	31	69.0%	21	4	49.3%	3	24
Moldova	277	57.3%	159	171	54.3%	98	257
Mongolia	888	76.1%	676	630	62.8%	479	1,155
Montenegro	31	58.3%	18	20	45.0%	12	30
Morocco	195	87.0%	170	145	71.4%	126	296
Mozambique	419	61.4%	257	239	58.8%	147	404
Myanmar	3,421	71.5%	2,448	1491	57.4%	1,067	3,514
Namibia	19	87.9%	17	8	62.2%	7	24
Nepal	109	69.7%	76	77	51.5%	54	130
Netherlands	338	71.4%	241	137	50.0%	98	339
New Zealand	205	73.1%	150	91	44.4%	67	216
Nicaragua	225	59.9%	135	208	41.1%	125	260
Niger	377	81.6%	308	139	66.8%	113	421
Nigeria	7,875	81.6%	6,425	4172	66.8%	3,404	9,828
North Korea	3,391	77.6%	2,633	1578	65.1%	1,225	3,858
Norway	118	81.3%	96	72	50.0%	59	154
Oman	42	87.0%	37	17	71.4%	15	51

Country	Males			Females			All
	Liver Cancer Cases	% HCC	HCC Cases	Liver Cancer Cases	% HCC	HCC Cases	HCC Cases
Pakistan	2,824	69.7%	1,968	1500	51.5%	1,045	3,013
Palestine	50	87.0%	44	23	71.4%	20	64
Panama	98	59.9%	59	77	41.1%	46	105
Papua New Guinea	334	69.0%	231	209	49.3%	144	375
Paraguay	73	79.7%	58	86	56.8%	69	127
Peru	785	71.3%	560	982	66.0%	700	1,260
Philippines	5,441	80.5%	4,378	2293	74.7%	1,845	6,222
Poland	1,071	54.1%	579	927	42.8%	502	1,081
Portugal	772	63.2%	488	232	25.0%	147	634
Qatar	44	100.0%	44	5	85.3%	5	49
Romania	1,485	58.3%	866	729	45.0%	425	1,291
Russia	3,848	61.5%	2,368	2964	60.0%	1,824	4,192
Rwanda	472	61.4%	290	275	58.8%	169	459
Samoa	3	69.0%	2	1	49.3%	1	3
Saudi Arabia	516	84.3%	435	206	76.0%	174	609
Senegal	451	81.6%	368	282	66.8%	230	598
Serbia	522	35.5%	185	277	36.8%	98	284
Sierra Leone	343	81.6%	280	199	66.8%	162	442
Singapore	588	84.1%	494	175	68.4%	147	641
Slovakia	258	66.7%	172	140	46.2%	93	265
Slovenia	157	82.5%	130	59	46.2%	49	178
Solomon Islands	32	69.0%	22	9	49.3%	6	28
Somalia	99	61.4%	61	88	58.8%	54	115
South Africa	1,165	90.0%	1,049	807	50.0%	726	1,775
South Korea	12,559	65.4%	8,216	4341	48.3%	2,840	11,056
South Sudan	224	61.4%	138	154	58.8%	95	232
Spain	4,006	75.1%	3,007	1516	52.7%	1,138	4,145
Sri Lanka	527	71.5%	377	279	57.4%	200	577
Sudan	646	61.4%	397	279	58.8%	171	568
Suriname	20	36.8%	7	15	37.9%	6	13
Swaziland	60	87.9%	53	15	62.2%	13	66
Sweden	319	62.5%	199	171	41.2%	107	306
Switzerland	623	76.0%	473	188	47.9%	143	616
Syria	321	87.0%	279	244	71.4%	212	492
Tajikistan	156	76.1%	119	117	62.8%	89	208
Tanzania	405	61.4%	249	190	58.8%	117	365
Thailand	14,739	68.4%	10,088	5716	52.2%	3,912	14,000
The Bahamas	5	36.8%	2	3	37.9%	1	3
The Gambia	176	81.6%	144	62	66.8%	51	194
Timor-Leste	29	71.5%	21	15	57.4%	11	31
Togo	302	81.6%	246	189	66.8%	154	401

Country	Males			Females			All
	Liver Cancer Cases	% HCC	HCC Cases	Liver Cancer Cases	% HCC	HCC Cases	HCC Cases
Trinidad and Tobago	18	36.8%	7	19	37.9%	7	14
Tunisia	70	80.0%	56	44	50.0%	35	91
Turkey	1,537	72.4%	1,112	690	52.4%	499	1,611
Turkmenistan	153	76.1%	116	110	62.8%	84	200
Uganda	783	60.6%	475	568	58.3%	344	819
Ukraine	904	40.0%	362	663	33.3%	265	627
United Arab Emirates	51	87.0%	44	17	71.4%	15	59
United Kingdom	2,721	57.8%	1,572	1465	36.8%	847	2,419
United States	22,541	79.6%	17,932	7908	61.1%	6,291	24,223
Uruguay	70	76.9%	54	33	60.0%	25	79
Uzbekistan	597	76.1%	454	481	62.8%	366	820
Vanuatu	21	69.0%	15	5	49.3%	3	18
Venezuela	554	59.9%	332	434	41.1%	260	592
Vietnam	16,815	71.5%	12,030	5182	57.4%	3,708	15,738
Western Sahara	9	87.0%	8	0	71.4%	0	8
Yemen	222	87.0%	193	127	71.4%	111	304
Zambia	128	61.4%	79	102	58.8%	63	141
Zimbabwe	287	81.3%	233	261	85.0%	212	445

Table 3-7. Fraction and number of hepatocellular carcinoma cases attributable to chronic hepatitis B and hepatitis C infection by country

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
Afghanistan	26.00%	137	15.20%	81
	(19.4%, 34.7%)	(103 , 184)	(7.7%, 29.1%)	(41 , 154)
Albania	62.60%	62	.	.
	(58.3%, 67.6%)	(58 , 67)	.	.
Algeria	36.20%	135	18.60%	69
	(29.1%, 44.9%)	(108 , 167)	(2.7%, 35.1%)	(10 , 130)
Angola	73.30%	306	.	.
	(67.8%, 78.8%)	(283 , 329)		
Argentina	14.20%	148	19.60%	205
	(12.5%, 16.9%)	(130 , 176)	(6.5%, 35.1%)	(68 , 365)
Australia	10.10%	125	21.70%	269
	(8.5%, 12.3%)	(105 , 153)	(14.3%, 28.0%)	(177 , 347)
Austria	35.00%	227	7.50%	49
	(16.5%, 59.8%)	(107 , 389)	(1.4%, 13.1%)	(9 , 85)
Azerbaijan	.	.	33.60%	119
			(12.2%, 59.1%)	(43 , 210)
Bahrain	20.50%	4	.	.
	(14.7%, 28.7%)	(3 , 5)		
Bangladesh	39.90%	841	17.50%	368
	(35.6%, 45.5%)	(750 , 958)	(2.7%, 32.2%)	(57 , 678)
Belarus	.	.	17.50%	24
			(11.1%, 38.5%)	(15 , 52)
Belgium	13.10%	63	12.80%	61
	(8.2%, 21.0%)	(39 , 100)	(1.4%, 20.6%)	(7 , 99)
Belize	50.40%	3	.	.
	(42.0%, 59.7%)	(2 , 3)		
Benin	.	.	37.00%	217
			(33.4%, 73.4%)	(196 , 431)
Bhutan	55.60%	10	.	.
	(47.6%, 64.2%)	(8 , 11)		
Bolivia	5.30%	10	.	.
	(1.5%, 17.2%)	(3 , 34)		
Bosnia and Herzegovina	19.30%	35	.	.
	(14.4%, 26.0%)	(26 , 48)		
Brazil	12.10%	933	20.70%	1,596
	(10.4%, 14.5%)	(805 , 1,115)	(13.3%, 25.7%)	(1,023 , 1,981)
Bulgaria	45.60%	216	15.20%	72

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(37.0%, 55.5%)	(175 , 262)	(4.0%, 34.1%)	(19 , 162)
Burkina Faso	72.20%	738	.	.
	(68.5%, 76.3%)	(700 , 781)		
Burundi	50.30%	82	.	.
	(28.7%, 71.9%)	(47 , 117)		
Cambodia	46.50%	753	27.30%	442
	(39.8%, 54.4%)	(644 , 880)	(24.2%, 76.0%)	(392 , 1,232)
Cameroon	68.30%	405	65.40%	388
	(63.3%, 73.7%)	(375 , 437)	(37.4%, 86.5%)	(222 , 513)
Canada	12.40%	208	15.20%	255
	(8.9%, 17.6%)	(150 , 294)	(7.7%, 21.9%)	(129 , 367)
Central African Republic	75.30%	109	.	.
	(69.6%, 80.9%)	(100 , 117)		
China	53.80%	164,813	17.50%	53,593
	(50.0%, 58.5%)	(153,177 , 179,421)	(5.3%, 30.2%)	(16,144 , 92,466)
Colombia	36.10%	276	.	.
	(28.2%, 45.8%)	(215 , 349)		
Congo	76.30%	146	.	.
	(69.1%, 82.7%)	(132 , 159)		
Côte d'Ivoire	66.70%	1,218	35.00%	638
	(61.2%, 72.6%)	(1,117 , 1,325)	(10.0%, 73.4%)	(183 , 1,340)
Croatia	19.10%	59	.	.
	(14.8%, 25.3%)	(46 , 78)		
Cuba	21.80%	37	.	.
	(10.4%, 40.9%)	(18 , 70)		
Cyprus	38.70%	11	8.90%	2
	(32.1%, 46.8%)	(9 , 13)	(6.5%, 29.1%)	(2 , 8)
Czech Republic	6.80%	38	10.20%	57
	(3.2%, 14.3%)	(18 , 79)	(2.7%, 13.1%)	(15 , 73)
Democratic Republic of the Congo	55.50%	1,658	41.20%	1,230
	(50.4%, 61.4%)	(1,505 , 1,834)	(30.8%, 74.7%)	(919 , 2,231)
Denmark	17.80%	36	10.20%	21
	(14.9%, 21.6%)	(31 , 44)	(6.5%, 13.1%)	(13 , 27)
Djibouti	69.10%	8	.	.
	(64.4%, 74.2%)	(7 , 8)		
Egypt	26.00%	4,048	70.60%	11,006
	(22.7%, 30.3%)	(3,546 , 4,723)	(58.9%, 79.5%)	(9,184 , 12,408)
Equatorial Guinea	65.40%	11	.	.
	(58.6%, 72.4%)	(10 , 12)		
Eritrea	34.90%	17	.	.

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(30.0%, 41.1%)	(15 , 20)		
Ethiopia	50.00%	306	17.50%	107
	(44.8%, 56.2%)	(274 , 344)	(8.9%, 55.6%)	(54 , 340)
Fiji	41.50%	20	.	.
	(33.5%, 51.0%)	(16 , 25)		
Finland	.	.	10.20%	42
			(7.7%, 16.3%)	(31 , 67)
France	5.10%	326	8.90%	569
	(4.3%, 6.3%)	(271 , 404)	(5.3%, 19.2%)	(336 , 1,226)
Gabon	72.50%	17	64.60%	15
	(67.7%, 77.5%)	(15 , 18)	(22.6%, 81.7%)	(5 , 19)
Georgia	30.80%	103	52.20%	174
	(22.1%, 42.2%)	(74 , 141)	(43.8%, 61.2%)	(146 , 204)
Germany	10.10%	667	8.90%	590
	(8.0%, 12.9%)	(530 , 855)	(4.0%, 16.3%)	(265 , 1,079)
Ghana	73.60%	1,154	.	.
	(69.8%, 77.8%)	(1,095 , 1,220)		
Greece	12.60%	96	23.60%	181
	(10.7%, 15.2%)	(82 , 117)	(6.5%, 36.0%)	(50 , 276)
Guatemala	4.50%	42	.	.
	(2.7%, 7.7%)	(25 , 71)		
Guinea	76.30%	686	.	.
	(72.0%, 80.6%)	(648 , 725)		
Haiti	76.80%	130	.	.
	(57.3%, 88.6%)	(97 , 150)		
Hungary	7.70%	28	11.50%	42
	(2.9%, 20.3%)	(11 , 75)	(5.3%, 36.8%)	(19 , 135)
India	23.60%	4,516	11.50%	2,204
	(20.9%, 27.4%)	(3,997 , 5,230)	(5.3%, 17.8%)	(1,006 , 3,394)
Indonesia	28.20%	3,661	11.50%	1,496
	(24.2%, 33.4%)	(3,143 , 4,332)	(5.3%, 30.2%)	(683 , 3,911)
Iran	16.70%	247	7.50%	112
	(14.7%, 19.6%)	(218 , 292)	(2.7%, 17.8%)	(40 , 264)
Iraq	12.60%	74	34.30%	202
	(10.7%, 15.4%)	(63 , 91)	(4.0%, 40.9%)	(24 , 241)
Ireland	0.60%	1	15.20%	21
	(0.2%, 1.8%)	(0 , 3)	(8.9%, 25.7%)	(12 , 36)
Israel	15.10%	32	24.60%	51
	(12.9%, 18.3%)	(27 , 38)	(11.1%, 30.2%)	(23 , 63)
Italy	23.80%	1,947	24.60%	2,014

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(20.3%, 28.3%)	(1,666 , 2,320)	(18.2%, 61.2%)	(1,490 , 5,012)
Jamaica	44.50%	58	.	.
	(32.8%, 57.7%)	(43 , 76)		
Japan	12.40%	3,553	19.60%	5,617
	(10.7%, 14.6%)	(3,069 , 4,188)	(6.5%, 32.2%)	(1,858 , 9,210)
Jordan	28.50%	39	.	.
	(23.6%, 34.8%)	(33 , 48)		
Kazakhstan	45.00%	458	35.00%	356
	(28.4%, 63.5%)	(288 , 645)	(12.2%, 59.1%)	(124 , 601)
Kenya	53.30%	367	.	.
	(47.6%, 59.9%)	(327 , 412)		
Kuwait	14.70%	6	.	.
	(10.7%, 20.1%)	(5 , 9)		
Kyrgyzstan	.	.	29.00%	71
			(18.2%, 59.1%)	(45 , 146)
Laos	65.30%	988	.	.
	(60.5%, 70.6%)	(916 , 1,068)		
Latvia	.	.	28.10%	36
			(19.1%, 41.6%)	(25 , 53)
Lebanon	18.70%	19	.	.
	(14.9%, 23.8%)	(15 , 24)		
Liberia	64.60%	207	.	.
	(35.1%, 85.3%)	(112 , 273)		
Libya	31.70%	54	16.40%	28
	(27.5%, 37.1%)	(46 , 63)	(14.3%, 33.2%)	(24 , 56)
Lithuania	26.80%	27	32.10%	33
	(22.3%, 32.6%)	(23 , 33)	(8.9%, 39.3%)	(9 , 40)
Luxembourg	.	.	12.80%	6
			(7.7%, 16.3%)	(4 , 8)
Madagascar	49.80%	146	16.40%	48
	(45.0%, 55.5%)	(132 , 162)	(10.0%, 26.9%)	(29 , 79)
Malawi	72.30%	142	.	.
	(64.3%, 79.6%)	(126 , 157)		
Malaysia	13.20%	140	19.60%	207
	(11.0%, 16.1%)	(116 , 170)	(4.0%, 62.5%)	(42 , 659)
Mali	72.90%	221	.	.
	(69.2%, 77.0%)	(209 , 233)		
Mauritania	74.00%	174	23.60%	56
	(68.1%, 79.7%)	(160 , 187)	(13.3%, 69.8%)	(31 , 164)
Mexico	3.90%	150	18.60%	711

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(3.2%, 4.9%)	(123 , 189)	(13.3%, 25.7%)	(508 , 983)
Micronesia, Federated States of	44.00%	11	.	.
	(33.8%, 55.6%)	(8 , 13)		
Moldova	66.90%	172	42.30%	109
	(60.6%, 73.4%)	(156 , 188)	(24.2%, 49.3%)	(62 , 127)
Mongolia	66.10%	763	63.80%	736
	(60.9%, 71.8%)	(703 , 829)	(54.7%, 77.1%)	(632 , 890)
Morocco	18.80%	56	20.70%	61
	(16.0%, 22.6%)	(47 , 67)	(7.7%, 29.1%)	(23 , 86)
Mozambique	58.50%	236	.	.
	(51.7%, 65.9%)	(209 , 266)		
Myanmar	42.20%	1,484	21.70%	763
	(37.6%, 47.9%)	(1,322 , 1,684)	(12.2%, 36.8%)	(429 , 1,295)
Namibia	62.80%	15	.	.
	(57.4%, 68.7%)	(14 , 16)		
Nepal	15.00%	19	.	.
	(12.9%, 17.9%)	(17 , 23)		
Netherlands	7.60%	26	3.20%	11
	(6.4%, 9.2%)	(22 , 31)	(1.4%, 8.0%)	(5 , 27)
New Zealand	46.60%	101	23.60%	51
	(42.5%, 51.8%)	(92 , 112)	(10.0%, 32.2%)	(22 , 70)
Nicaragua	10.10%	26	.	.
	(4.6%, 21.3%)	(12 , 55)		
Niger	76.90%	324	.	.
	(72.7%, 81.2%)	(306 , 342)		
Nigeria	67.80%	6,667	57.80%	5,680
	(64.0%, 72.2%)	(6,295 , 7,096)	(35.2%, 73.4%)	(3,455 , 7,218)
Norway	0.20%	0	10.20%	16
	(0.0%, 0.5%)	(0 , 1)	(7.7%, 16.3%)	(12 , 25)
Oman	54.30%	28	.	.
	(45.3%, 63.9%)	(23 , 33)		
Pakistan	37.20%	1,120	52.20%	1,573
	(33.5%, 42.0%)	(1,009 , 1,264)	(18.2%, 68.4%)	(548 , 2,060)
Palestine	27.90%	18	.	.
	(16.7%, 43.8%)	(11 , 28)		
Papua New Guinea	86.10%	323	.	.
	(81.5%, 90.0%)	(305 , 337)		
Peru	27.20%	343	16.40%	206
	(21.4%, 35.0%)	(269 , 441)	(5.3%, 25.7%)	(66 , 324)
Philippines	47.30%	2,945	12.80%	796

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(43.0%, 52.7%)	(2,676 , 3,277)	(4.0%, 30.2%)	(249 , 1,877)
Poland	17.80%	193	12.80%	138
	(12.5%, 25.6%)	(135 , 276)	(7.7%, 19.2%)	(83 , 208)
Portugal	16.80%	107	22.70%	144
	(11.3%, 25.0%)	(72 , 158)	(6.5%, 38.5%)	(41 , 244)
Qatar	27.10%	13	12.80%	6
	(17.5%, 40.4%)	(9 , 20)	(6.5%, 24.5%)	(3 , 12)
Romania	54.90%	709	34.30%	443
	(50.6%, 60.0%)	(654 , 775)	(28.7%, 43.7%)	(371 , 565)
Russia	40.20%	1,686	40.10%	1,679
	(35.8%, 45.8%)	(1,499 , 1,920)	(14.3%, 54.7%)	(599 , 2,295)
Samoa	.	.	3.20%	0
			(2.7%, 16.3%)	(0 , 0)
Saudi Arabia	38.00%	231	19.60%	120
	(34.0%, 43.1%)	(207 , 262)	(7.7%, 61.2%)	(47 , 373)
Senegal	71.70%	429	.	.
	(67.0%, 76.7%)	(400 , 459)		
Serbia	9.40%	27	.	.
	(7.4%, 12.5%)	(21 , 35)		
Sierra Leone	64.20%	284	.	.
	(52.4%, 75.1%)	(232 , 332)		
Singapore	39.00%	250	.	.
	(33.7%, 45.6%)	(216 , 292)		
Slovakia	27.20%	72	18.60%	49
	(23.3%, 32.5%)	(62 , 86)	(11.1%, 30.2%)	(30 , 80)
Slovenia	5.70%	10	.	.
	(4.4%, 7.2%)	(8 , 13)		
Solomon Islands	82.00%	23	.	.
	(78.5%, 85.5%)	(22 , 24)		
Somalia	80.60%	93	.	.
	(76.0%, 85.0%)	(87 , 98)		
South Africa	58.50%	1,038	21.70%	385
	(52.0%, 65.6%)	(922 , 1,165)	(12.2%, 35.1%)	(217 , 622)
South Korea	48.40%	5,349	11.50%	1,275
	(44.6%, 53.2%)	(4,936 , 5,880)	(2.7%, 31.2%)	(299 , 3,450)
Spain	6.10%	251	21.70%	899
	(4.9%, 7.7%)	(204 , 318)	(5.3%, 36.0%)	(218 , 1,491)
Sri Lanka	35.00%	202	.	.
	(25.9%, 46.2%)	(149 , 266)		
Sudan	54.40%	309	.	.

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(47.5%, 62.1%)	(270 , 353)		
Sweden	14.20%	44	10.20%	31
	(10.3%, 20.0%)	(32 , 61)	(6.5%, 13.1%)	(20 , 40)
Switzerland	.	.	19.60%	121
			(8.9%, 28.0%)	(55 , 173)
Syria	36.00%	177	.	.
	(28.6%, 45.1%)	(141 , 222)		
Tajikistan	.	.	33.60%	70
			(13.3%, 59.1%)	(28 , 123)
Tanzania	60.00%	219	.	.
	(54.1%, 66.4%)	(198 , 243)		
Thailand	56.80%	7,954	30.60%	4,278
	(52.9%, 61.6%)	(7,405 , 8,629)	(20.0%, 44.4%)	(2,802 , 6,219)
The Gambia	64.50%	125	25.50%	50
	(58.2%, 71.2%)	(113 , 138)	(16.3%, 38.5%)	(32 , 75)
Togo	70.10%	281	.	.
	(58.2%, 80.3%)	(233 , 321)		
Tunisia	56.50%	52	17.50%	16
	(51.8%, 62.0%)	(47 , 57)	(4.0%, 35.1%)	(4 , 32)
Turkey	46.20%	745	14.00%	226
	(42.5%, 51.1%)	(684 , 823)	(7.7%, 31.2%)	(124 , 503)
Turkmenistan	.	.	47.70%	95
			(13.3%, 59.1%)	(27 , 118)
Uganda	67.90%	556	.	.
	(63.0%, 73.1%)	(516 , 599)		
Ukraine	23.80%	149	37.00%	232
	(17.0%, 32.9%)	(107 , 207)	(11.1%, 49.3%)	(70 , 309)
United Arab Emirates	12.80%	8	.	.
	(6.9%, 23.3%)	(4 , 14)		
United Kingdom	0.20%	5	8.90%	215
	(0.0%, 0.3%)	(0 , 6)	(5.3%, 20.6%)	(127 , 498)
United States	5.30%	1,282	17.50%	4,235
	(4.1%, 7.0%)	(989 , 1,698)	(14.3%, 34.1%)	(3,463 , 8,270)
Uzbekistan	71.50%	586	64.80%	531
	(65.0%, 77.9%)	(533 , 638)	(47.1%, 73.9%)	(386 , 606)
Vanuatu	69.40%	12	.	.
	(59.4%, 78.4%)	(11 , 14)		
Venezuela	7.90%	47	19.60%	116
	(6.4%, 10.1%)	(38 , 60)	(4.0%, 36.0%)	(24 , 213)
Vietnam	69.80%	10,988	.	.

Country	HBV		HCV	
	PAF (CI)	PAC (CI)	PAF (CI)	PAC (CI)
	(65.5%, 74.6%)	(10,304 , 11,736)		
Yemen	63.80%	194	26.40%	80
	(58.9%, 69.2%)	(179 , 210)	(13.3%, 43.1%)	(40 , 131)
Zambia	56.50%	80	.	.
	(49.6%, 64.1%)	(70 , 91)		
Zimbabwe	76.00%	338	20.70%	92
	(71.8%, 80.3%)	(320 , 358)	(12.2%, 66.3%)	(54 , 295)

Table 3-8. Fraction and number of hepatocellular carcinoma cases attributable to lifestyle risk factors in men by country

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Afghanistan	8.60%	28	.	.	4.20%	14
	(3.7%, 15.0%)	(12 , 50)			(2.6%, 5.9%)	(9 , 19)
Albania	14.60%	9	.	.	17.90%	11
	(6.9%, 23.2%)	(4 , 14)			(9.5%, 27.2%)	(6 , 17)
Algeria	13.20%	25	12.70%	24	17.10%	32
	(6.1%, 21.4%)	(11 , 40)	(4.6%, 21.3%)	(9 , 40)	(9.0%, 26.1%)	(17 , 49)
Angola	7.00%	18	.	.	4.90%	12
	(2.9%, 12.7%)	(7 , 32)			(2.9%, 7.2%)	(7 , 18)
Argentina	11.10%	65	26.80%	157	24.10%	141
	(4.9%, 18.7%)	(29 , 110)	(16.0%, 37.3%)	(94 , 219)	(13.0%, 35.6%)	(77 , 209)
Armenia	19.70%	39	33.70%	67	16.80%	33
	(9.9%, 29.4%)	(20 , 58)	(20.0%, 47.1%)	(39 , 93)	(8.8%, 26.0%)	(17 , 51)
Australia	9.90%	88	27.20%	240	24.70%	219
	(4.9%, 15.5%)	(43 , 137)	(16.0%, 38.2%)	(141 , 337)	(14.1%, 35.5%)	(124 , 314)
Austria	12.90%	57	31.80%	140	22.40%	98
	(6.4%, 19.8%)	(28 , 87)	(19.1%, 44.1%)	(84 , 193)	(12.2%, 33.1%)	(54 , 145)
Azerbaijan	15.60%	30	.	.	17.00%	33
	(7.3%, 24.7%)	(14 , 48)			(9.1%, 26.3%)	(18 , 51)
Bahrain	7.70%	1	.	.	23.30%	3
	(3.5%, 12.9%)	(0 , 1)			(12.5%, 34.8%)	(1 , 4)
Bangladesh	16.40%	209	6.40%	82	3.60%	47
	(7.9%, 25.6%)	(102 , 327)	(2.3%, 10.5%)	(30 , 134)	(2.3%, 5.0%)	(29 , 64)
Barbados	4.60%	0	29.10%	0	16.60%	0
	(1.8%, 8.7%)	(0 , 0)	(14.9%, 43.7%)	(0 , 1)	(8.9%, 25.5%)	(0 , 0)
Belarus	18.60%	16	35.50%	30	20.20%	17
	(9.3%, 28.2%)	(8 , 24)	(21.6%, 48.4%)	(18 , 41)	(10.5%, 31.1%)	(9 , 26)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Belgium	13.80%	46	29.20%	97	23.90%	79
	(6.7%, 21.5%)	(22 , 71)	(17.1%, 41.1%)	(57 , 136)	(13.5%, 34.5%)	(45 , 114)
Belize	7.70%	0	33.90%	1	14.80%	0
	(3.3%, 13.5%)	(0 , 0)	(17.0%, 51.9%)	(1 , 2)	(7.9%, 23.1%)	(0 , 1)
Benin	5.80%	22	21.90%	84	5.00%	19
	(2.3%, 11.1%)	(9 , 43)	(10.7%, 33.3%)	(41 , 128)	(2.9%, 7.5%)	(11 , 29)
Bhutan	7.00%	1	18.60%	2	5.40%	1
	(2.9%, 12.5%)	(0 , 2)	(8.1%, 29.5%)	(1 , 4)	(3.3%, 7.9%)	(0 , 1)
Bolivia	16.90%	15	22.50%	21	15.70%	14
	(8.1%, 26.4%)	(7 , 24)	(11.9%, 33.2%)	(11 , 30)	(8.5%, 24.0%)	(8 , 22)
Bosnia and Herzegovina	16.20%	16	29.70%	29	15.50%	15
	(7.8%, 25.3%)	(8 , 25)	(15.3%, 44.8%)	(15 , 44)	(8.4%, 23.8%)	(8 , 24)
Botswana	9.20%	4	31.80%	14	8.50%	4
	(4.0%, 15.9%)	(2 , 7)	(16.5%, 47.7%)	(7 , 21)	(4.6%, 13.5%)	(2 , 6)
Brazil	8.40%	386	36.40%	1,674	17.70%	813
	(3.6%, 14.5%)	(165 , 668)	(19.2%, 54.4%)	(882 , 2,500)	(9.8%, 26.2%)	(451 , 1,204)
Brunei	5.60%	1	.	.	13.90%	1
	(2.3%, 10.5%)	(0 , 1)			(7.3%, 22.2%)	(1 , 2)
Bulgaria	15.40%	48	31.40%	97	23.30%	72
	(7.5%, 24.0%)	(23 , 74)	(18.8%, 43.5%)	(58 , 134)	(12.5%, 34.8%)	(39 , 108)
Burkina Faso	7.80%	49	22.80%	145	4.40%	28
	(3.3%, 13.6%)	(21 , 86)	(11.1%, 35.2%)	(71 , 224)	(2.6%, 6.4%)	(17 , 41)
Burundi	9.00%	8	.	.	2.60%	2
	(3.9%, 15.4%)	(4 , 14)			(1.9%, 3.3%)	(2 , 3)
Cambodia	17.60%	182	.	.	2.90%	30
	(8.7%, 26.8%)	(90 , 277)			(1.9%, 3.8%)	(20 , 40)
Cameroon	6.40%	29	23.40%	105	6.60%	30
	(2.6%, 11.4%)	(12 , 51)	(12.8%, 34.1%)	(57 , 153)	(3.8%, 9.9%)	(17 , 45)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Canada	10.50%	126	31.10%	373	24.70%	296
	(5.2%, 16.5%)	(62 , 198)	(17.5%, 44.6%)	(210 , 535)	(13.7%, 35.8%)	(165 , 429)
Cape Verde	4.90%	1	25.90%	7	6.80%	2
	(2.0%, 9.1%)	(1 , 3)	(13.7%, 38.2%)	(4 , 11)	(3.8%, 10.4%)	(1 , 3)
Central African Republic	6.60%	6	.	.	3.90%	4
	(2.7%, 12.1%)	(3 , 11)			(2.6%, 5.5%)	(2 , 5)
Chad	5.80%	14	17.10%	43	4.40%	11
	(2.4%, 10.5%)	(6 , 26)	(8.1%, 26.6%)	(20 , 67)	(2.6%, 6.3%)	(7 , 16)
Chile	14.40%	39	26.50%	72	22.60%	61
	(6.8%, 23.0%)	(18 , 62)	(14.9%, 38.1%)	(40 , 103)	(12.2%, 33.6%)	(33 , 91)
China	18.70%	42,593	27.80%	63,368	7.20%	16,461
	(9.8%, 27.4%)	(22,226,	(14.8%, 41.1%)	(33,659,	(4.1%, 10.4%)	(9,423, 23,643)
		62,399)		93,569)		
Colombia	7.40%	27%	25.70%	93%	17.80%	64%
	(3.1%, 13.3%)	(11 , 48)	(14.0%, 37.4%)	(51 , 135)	(9.6%, 26.8%)	(35 , 97)
Comoros	7.30%	0	3.40%	0	4.90%	0
	(3.0%, 13.1%)	(0 , 1)	(1.2%, 5.7%)	(0 , 0)	(3.0%, 7.0%)	(0 , 0)
Congo	6.60%	7	17.20%	19	6.30%	7
	(2.7%, 11.9%)	(3 , 13)	(9.1%, 25.6%)	(10 , 29)	(3.7%, 9.5%)	(4 , 11)
Costa Rica	5.60%	4	29.60%	24	18.80%	15
	(2.4%, 9.6%)	(2 , 8)	(14.8%, 45.0%)	(12 , 36)	(10.0%, 28.8%)	(8 , 23)
Côte d’Ivoire	5.60%	73	25.50%	331	6.70%	87
	(2.4%, 10.2%)	(31 , 132)	(12.9%, 38.8%)	(167 , 503)	(3.9%, 10.1%)	(50 , 131)
Croatia	12.30%	27	37.90%	83	20.90%	46
	(5.9%, 19.5%)	(13 , 43)	(21.7%, 54.0%)	(48 , 118)	(11.1%, 31.4%)	(24 , 69)
Cuba	9.70%	8	26.90%	23	17.40%	15
	(4.2%, 16.9%)	(4 , 14)	(14.1%, 40.0%)	(12 , 34)	(9.2%, 26.6%)	(8 , 23)
Cyprus	17.30%	3	.	.	22.60%	4

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(8.4%, 26.9%)	(2 , 5)			(12.0%, 33.9%)	(2 , 6)
Czech Republic	12.10%	42	35.40%	124	25.60%	90
	(5.7%, 19.1%)	(20 , 67)	(21.4%, 48.7%)	(75 , 171)	(14.1%, 37.4%)	(50 , 131)
Democratic Republic of the Congo	6.20%	112	26.60%	481	4.30%	77
	(2.5%, 11.3%)	(46 , 204)	(12.5%, 41.4%)	(226 , 749)	(2.8%, 6.0%)	(51 , 108)
Denmark	13.10%	20	29.60%	44	23.10%	34
	(6.6%, 19.9%)	(10 , 30)	(18.2%, 40.4%)	(27 , 60)	(12.8%, 33.7%)	(19 , 50)
Djibouti	14.60%	1	.	.	7.80%	1
	(6.8%, 23.4%)	(0 , 2)			(4.4%, 12.6%)	(0 , 1)
Dominican Republic	8.40%	14	28.20%	46	13.70%	22
	(3.8%, 13.7%)	(6 , 22)	(14.5%, 42.3%)	(24 , 69)	(7.3%, 21.1%)	(12 , 34)
Ecuador	6.50%	15	28.40%	66	16.90%	39
	(2.9%, 10.9%)	(7 , 25)	(15.0%, 42.3%)	(35 , 98)	(9.1%, 25.8%)	(21 , 60)
Egypt	12.80%	1,411	29.20%	3,234	19.40%	2,146
	(5.9%, 20.7%)	(651 , 2,285)	(11.0%, 49.6%)	(1,219 , 5,485)	(10.4%, 29.6%)	(1,147 , 3,268)
El Salvador	7.60%	8	.	.	16.70%	18
	(3.2%, 13.6%)	(3 , 15)			(8.8%, 25.9%)	(10 , 28)
Equatorial Guinea	7.60%	1	.	.	5.10%	1
	(3.1%, 13.5%)	(0 , 2)			(3.1%, 7.5%)	(0 , 1)
Eritrea	5.60%	1	8.20%	2	3.90%	1
	(2.3%, 10.4%)	(1 , 3)	(4.9%, 11.5%)	(1 , 3)	(2.4%, 5.5%)	(1 , 1)
Estonia	16.00%	3	40.40%	7	20.50%	4
	(8.0%, 24.2%)	(1 , 4)	(23.7%, 56.7%)	(4 , 10)	(11.2%, 30.5%)	(2 , 5)
Ethiopia	3.40%	9	20.70%	53	3.40%	9
	(1.4%, 6.2%)	(4 , 16)	(9.7%, 32.2%)	(25 , 83)	(2.2%, 4.7%)	(6 , 12)
Fiji	10.10%	3	29.60%	9	22.60%	7
	(4.5%, 17.2%)	(1 , 5)	(13.2%, 47.2%)	(4 , 15)	(11.5%, 35.0%)	(4 , 11)
Finland	10.30%	28	30.90%	83	22.80%	61

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(5.1%, 15.9%)	(14 , 43)	(18.5%, 42.8%)	(50 , 115)	(12.8%, 33.1%)	(34 , 89)
France	14.00%	698	30.90%	1,538	24.00%	1,194
	(7.0%, 21.3%)	(348 , 1,063)	(18.9%, 42.3%)	(942 , 2,106)	(13.2%, 35.0%)	(658 , 1,744)
Gabon	6.70%	1	.	.	10.30%	1
	(2.8%, 12.2%)	(0 , 2)			(5.5%, 16.6%)	(1 , 2)
Georgia	15.50%	30	29.90%	57	17.30%	33
	(7.4%, 24.3%)	(14 , 46)	(15.7%, 44.4%)	(30 , 84)	(9.1%, 27.1%)	(17 , 52)
Germany	12.40%	569	29.50%	1,360	23.50%	1,082
	(6.2%, 19.0%)	(284 , 875)	(18.2%, 40.4%)	(836 , 1,860)	(13.4%, 33.7%)	(616 , 1,554)
Ghana	4.20%	51	20.60%	252	5.80%	71
	(1.7%, 7.6%)	(21 , 93)	(9.2%, 32.6%)	(112 , 399)	(3.4%, 8.4%)	(41 , 103)
Greece	18.80%	97	29.80%	153	23.60%	122
	(9.8%, 27.6%)	(50 , 142)	(17.2%, 42.2%)	(88 , 217)	(12.8%, 35.0%)	(66 , 180)
Guatemala	6.00%	26	20.50%	89	15.50%	67
	(2.5%, 10.9%)	(11 , 47)	(10.5%, 30.9%)	(46 , 134)	(8.3%, 23.7%)	(36 , 103)
Guinea	5.10%	28	.	.	5.30%	29
	(2.1%, 9.4%)	(12 , 52)			(3.2%, 7.6%)	(18 , 42)
Guinea-Bissau	5.20%	4	.	.	6.10%	4
	(2.1%, 9.5%)	(1 , 7)			(3.5%, 9.0%)	(2 , 6)
Guyana	9.50%	1	.	.	12.90%	1
	(4.1%, 16.4%)	(0 , 1)			(6.9%, 20.2%)	(1 , 2)
Haiti	7.00%	7	.	.	8.70%	8
	(3.1%, 12.0%)	(3 , 11)			(4.8%, 13.2%)	(5 , 12)
Honduras	9.50%	17	.	.	14.60%	26
	(4.2%, 16.0%)	(7 , 28)			(7.8%, 22.5%)	(14 , 39)
Hungary	14.20%	36	37.30%	94	25.00%	63
	(6.9%, 22.2%)	(17 , 56)	(22.4%, 51.6%)	(57 , 131)	(13.6%, 36.6%)	(35 , 93)
Iceland	11.00%	0	24.20%	1	23.20%	1

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(5.5%, 16.8%)	(0 , 1)	(13.4%, 35.0%)	(0 , 1)	(12.6%, 34.4%)	(0 , 1)
India	12.10%	1,449	18.80%	2,259	4.10%	495
	(5.9%, 18.9%)	(705 , 2,266)	(8.4%, 29.9%)	(1,005 , 3,590)	(2.5%, 5.7%)	(295 , 684)
Indonesia	19.30%	1,845	20.40%	1,947	4.50%	428
	(10.0%, 28.3%)	(961 , 2,705)	(7.5%, 34.1%)	(715 , 3,264)	(2.7%, 6.2%)	(257 , 597)
Iran	9.20%	77	17.00%	143	17.90%	151
	(4.0%, 15.6%)	(34 , 131)	(6.0%, 28.6%)	(51 , 241)	(9.9%, 26.7%)	(83 , 224)
Iraq	13.60%	38	5.10%	14	18.80%	52
	(6.3%, 21.9%)	(17 , 61)	(1.9%, 8.6%)	(5 , 24)	(9.9%, 29.0%)	(27 , 80)
Ireland	12.20%	11	31.20%	28	23.20%	21
	(5.9%, 19.3%)	(5 , 17)	(18.7%, 43.4%)	(17 , 39)	(12.6%, 34.5%)	(11 , 31)
Israel	12.10%	16	17.00%	23	24.80%	34
	(5.7%, 19.4%)	(8 , 26)	(9.0%, 25.0%)	(12 , 34)	(13.5%, 36.4%)	(18 , 49)
Italy	12.20%	667	27.10%	1,485	23.30%	1,277
	(6.0%, 18.8%)	(329 , 1,030)	(16.3%, 37.6%)	(892 , 2,062)	(13.2%, 33.3%)	(725 , 1,827)
Jamaica	10.60%	8	29.10%	22	14.70%	11
	(4.7%, 17.8%)	(4 , 14)	(14.1%, 44.7%)	(11 , 34)	(8.0%, 22.2%)	(6 , 17)
Japan	18.20%	3,411	25.60%	4,795	9.10%	1,703
	(9.4%, 27.3%)	(1,764 , 5,096)	(14.8%, 36.3%)	(2,767 , 6,793)	(5.3%, 13.0%)	(985 , 2,427)
Jordan	16.70%	15	.	.	22.10%	19
	(8.1%, 25.9%)	(7 , 23)			(11.8%, 33.3%)	(10 , 29)
Kazakhstan	9.80%	59	30.10%	181	19.40%	117
	(4.5%, 16.2%)	(27 , 97)	(16.8%, 43.4%)	(101 , 261)	(10.1%, 30.1%)	(61 , 181)
Kenya	9.20%	36	24.00%	93	5.40%	21
	(4.0%, 15.8%)	(16 , 61)	(11.0%, 37.7%)	(43 , 147)	(3.2%, 7.9%)	(12 , 31)
Kuwait	11.60%	4	16.60%	6	26.90%	10
	(5.2%, 19.3%)	(2 , 7)	(5.7%, 28.0%)	(2 , 10)	(15.1%, 38.8%)	(5 , 14)
Kyrgyzstan	14.10%	20	27.40%	39	15.40%	22

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(6.9%, 21.8%)	(10 , 31)	(13.6%, 41.6%)	(19 , 59)	(8.3%, 23.8%)	(12 , 34)
Laos	20.60%	219	28.50%	304	3.00%	32
	(10.3%, 30.8%)	(110 , 328)	(14.9%, 42.6%)	(158 , 453)	(2.0%, 4.0%)	(21 , 42)
Latvia	17.00%	14	34.30%	27	21.20%	17
	(8.5%, 25.8%)	(7 , 21)	(20.4%, 47.6%)	(16 , 38)	(11.0%, 32.5%)	(9 , 26)
Lebanon	17.50%	11	16.40%	10	23.00%	14
	(8.7%, 26.7%)	(5 , 16)	(8.6%, 24.1%)	(5 , 14)	(12.2%, 34.7%)	(7 , 21)
Lesotho	17.80%	10	28.90%	17	5.60%	3
	(8.8%, 27.0%)	(5 , 15)	(14.7%, 43.7%)	(8 , 25)	(3.2%, 8.5%)	(2 , 5)
Liberia	6.50%	13	.	.	4.90%	10
	(2.8%, 11.6%)	(6 , 23)			(3.1%, 6.9%)	(6 , 14)
Libya	7.70%	7	.	.	23.20%	22
	(3.2%, 13.6%)	(3 , 13)			(12.4%, 34.7%)	(12 , 33)
Lithuania	14.70%	10	35.20%	23	21.50%	14
	(7.4%, 22.3%)	(5 , 14)	(21.5%, 48.0%)	(14 , 31)	(11.6%, 32.4%)	(7 , 21)
Luxembourg	12.50%	4	.	.	24.20%	8
	(6.1%, 19.5%)	(2 , 7)			(12.7%, 36.3%)	(4 , 12)
Macedonia	17.00%	9	.	.	20.90%	10
	(8.3%, 26.3%)	(4 , 13)			(11.0%, 31.8%)	(6 , 16)
Madagascar	14.30%	28	14.40%	28	4.80%	9
	(6.6%, 23.0%)	(13 , 45)	(6.9%, 22.0%)	(13 , 43)	(3.0%, 7.0%)	(6 , 14)
Malawi	10.60%	11	19.90%	21	3.80%	4
	(4.9%, 17.4%)	(5 , 18)	(8.3%, 32.2%)	(9 , 34)	(2.4%, 5.2%)	(3 , 6)
Malaysia	15.10%	116	12.80%	98	9.70%	74
	(7.1%, 24.0%)	(54 , 184)	(4.7%, 21.4%)	(36 , 164)	(5.4%, 14.7%)	(41 , 113)
Maldives	11.90%	1	.	.	6.20%	0
	(5.3%, 19.6%)	(0 , 1)			(3.8%, 8.5%)	(0 , 0)
Mali	7.60%	16	4.60%	10	5.30%	11

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(3.2%, 13.5%)	(7 , 28)	(2.0%, 7.6%)	(4 , 16)	(3.1%, 7.7%)	(7 , 16)
Malta	12.80%	1	.	.	24.90%	2
	(5.9%, 20.8%)	(0 , 1)			(13.4%, 37.0%)	(1 , 2)
Mauritania	7.10%	11	1.80%	3	6.80%	11
	(3.0%, 12.6%)	(5 , 20)	(0.6%, 3.0%)	(1 , 5)	(3.8%, 10.6%)	(6 , 17)
Mauritius	14.00%	2	24.20%	3	10.70%	1
	(6.8%, 22.0%)	(1 , 2)	(11.9%, 36.8%)	(1 , 4)	(5.8%, 16.5%)	(1 , 2)
Mexico	11.20%	206	31.10%	571	21.90%	403
	(5.3%, 18.0%)	(97 , 331)	(16.3%, 46.3%)	(299 , 851)	(12.1%, 32.3%)	(222 , 593)
Micronesia, Federated States of	15.40%	3	24.90%	5	27.80%	6
	(7.3%, 24.6%)	(2 , 5)	(13.2%, 37.0%)	(3 , 8)	(15.0%, 40.8%)	(3 , 9)
Moldova	15.40%	24	39.60%	63	16.60%	26
	(7.3%, 24.2%)	(12 , 38)	(24.5%, 53.5%)	(39 , 85)	(8.7%, 25.6%)	(14 , 41)
Mongolia	15.10%	102	23.50%	159	16.10%	109
	(7.3%, 23.9%)	(49 , 161)	(12.1%, 35.1%)	(82 , 237)	(8.7%, 24.7%)	(59 , 167)
Montenegro	13.60%	2	.	.	21.90%	4
	(6.3%, 21.9%)	(1 , 4)			(11.5%, 33.5%)	(2 , 6)
Morocco	10.80%	18	14.50%	25	16.20%	27
	(4.9%, 17.9%)	(8 , 30)	(5.9%, 23.6%)	(10 , 40)	(8.6%, 24.9%)	(15 , 42)
Mozambique	8.90%	23	19.80%	51	3.60%	9
	(3.9%, 15.3%)	(10 , 39)	(9.6%, 30.1%)	(25 , 77)	(2.3%, 4.8%)	(6 , 12)
Myanmar	14.90%	365	16.40%	401	2.90%	71
	(7.1%, 23.5%)	(174 , 575)	(6.3%, 26.9%)	(154 , 659)	(2.0%, 3.7%)	(49 , 89)
Namibia	11.20%	2	26.70%	4	7.40%	1
	(5.1%, 18.4%)	(1 , 3)	(14.4%, 39.3%)	(2 , 7)	(4.0%, 11.5%)	(1 , 2)
Nepal	18.60%	14	21.40%	16	4.20%	3
	(9.3%, 28.0%)	(7 , 21)	(9.7%, 33.7%)	(7 , 26)	(2.6%, 6.0%)	(2 , 5)
Netherlands	11.40%	28	31.60%	76	21.10%	51

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(5.7%, 17.5%)	(14 , 42)	(18.0%, 45.0%)	(44 , 109)	(11.7%, 30.9%)	(28 , 75)
New Zealand	10.00%	15	29.20%	44	24.70%	37
	(5.0%, 15.4%)	(7 , 23)	(16.6%, 41.7%)	(25 , 62)	(13.8%, 35.8%)	(21 , 54)
Nicaragua	7.40%	10	39.90%	54	15.10%	20
	(3.1%, 13.2%)	(4 , 18)	(19.4%, 62.5%)	(26 , 84)	(8.0%, 23.3%)	(11 , 31)
Niger	3.40%	10	.	.	3.90%	12
	(1.3%, 6.5%)	(4 , 20)			(2.5%, 5.6%)	(8 , 17)
Nigeria	5.10%	328	33.50%	2,152	6.10%	394
	(2.1%, 9.1%)	(137 , 584)	(18.3%, 48.8%)	(1,177 , 3,138)	(3.5%, 9.0%)	(227 , 578)
North Korea	16.80%	443	.	.	7.00%	185
	(8.1%, 26.2%)	(213 , 689)			(4.2%, 10.0%)	(109 , 264)
Norway	12.30%	12	24.50%	24	22.90%	22
	(6.2%, 18.7%)	(6 , 18)	(14.3%, 34.6%)	(14 , 33)	(12.7%, 33.5%)	(12 , 32)
Oman	6.10%	2	.	.	20.70%	8
	(2.8%, 10.1%)	(1 , 4)			(11.0%, 31.0%)	(4 , 11)
Pakistan	13.30%	262	0.00%	1	6.20%	122
	(6.2%, 21.5%)	(121 , 423)	(0.0%, 0.1%)	(0 , 1)	(3.6%, 9.5%)	(70 , 187)
Palestine	18.70%	8	.	.	.	.
	(9.5%, 28.0%)	(4 , 12)				
Panama	6.60%	4	.	.	18.80%	11
	(3.0%, 11.2%)	(2 , 7)			(10.0%, 28.5%)	(6 , 17)
Papua New Guinea	18.20%	42	18.60%	43	16.90%	39
	(8.8%, 27.9%)	(20 , 64)	(10.8%, 26.1%)	(25 , 60)	(8.5%, 27.1%)	(20 , 63)
Paraguay	9.90%	6	30.60%	18	16.60%	10
	(4.4%, 16.8%)	(3 , 10)	(16.2%, 45.3%)	(9 , 26)	(8.7%, 25.7%)	(5 , 15)
Peru	6.40%	36	29.40%	165	17.20%	96
	(2.6%, 11.4%)	(15 , 64)	(15.8%, 43.2%)	(89 , 242)	(9.3%, 26.1%)	(52 , 146)
Philippines	17.60%	771	28.10%	1,232	6.20%	272

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(8.8%, 26.7%)	(387 , 1,168)	(14.6%, 42.1%)	(638 , 1,843)	(3.6%, 9.0%)	(157 , 394)
Poland	16.00%	93	34.70%	201	23.10%	134
	(8.1%, 24.0%)	(47 , 139)	(20.6%, 48.3%)	(119 , 280)	(12.8%, 33.7%)	(74 , 195)
Portugal	12.50%	61	35.80%	175	20.20%	99
	(6.2%, 19.4%)	(30 , 95)	(20.3%, 51.2%)	(99 , 250)	(11.2%, 29.9%)	(55 , 146)
Qatar	7.80%	3	.	.	26.10%	12
	(3.3%, 13.8%)	(1 , 6)			(14.2%, 38.5%)	(6 , 17)
Romania	15.50%	135	38.50%	334	21.90%	190
	(7.7%, 23.7%)	(67 , 205)	(22.6%, 54.0%)	(196 , 468)	(11.7%, 32.7%)	(101 , 283)
Russia	19.20%	454	39.40%	932	20.00%	475
	(9.8%, 28.4%)	(233 , 672)	(22.8%, 55.6%)	(540 , 1,316)	(11.2%, 29.2%)	(266 , 690)
Rwanda	9.90%	29	.	.	2.90%	8
	(4.4%, 16.7%)	(13 , 48)			(2.2%, 3.5%)	(6 , 10)
Samoa	15.80%	0	26.80%	1	28.60%	1
	(7.5%, 24.8%)	(0 , 1)	(13.1%, 41.1%)	(0 , 1)	(15.5%, 41.8%)	(0 , 1)
Saudi Arabia	7.90%	34	.	.	24.00%	105
	(3.4%, 13.6%)	(15 , 59)			(13.4%, 35.2%)	(58 , 153)
Senegal	8.20%	30	5.00%	18	6.10%	23
	(3.5%, 14.2%)	(13 , 52)	(2.0%, 8.2%)	(7 , 30)	(3.5%, 9.1%)	(13 , 33)
Serbia	12.80%	24	.	.	21.00%	39
	(5.9%, 20.9%)	(11 , 39)			(11.4%, 31.2%)	(21 , 58)
Sierra Leone	12.00%	33	32.20%	90	5.40%	15
	(5.3%, 19.7%)	(15 , 55)	(16.6%, 48.5%)	(46 , 136)	(3.1%, 8.0%)	(9 , 22)
Singapore	9.80%	49	25.00%	123	11.10%	55
	(4.5%, 16.3%)	(22 , 80)	(11.9%, 38.5%)	(59 , 190)	(6.3%, 16.4%)	(31 , 81)
Slovakia	13.20%	23	36.90%	63	22.70%	39
	(6.1%, 21.3%)	(11 , 37)	(21.3%, 52.2%)	(37 , 90)	(12.4%, 33.5%)	(21 , 58)
Slovenia	11.40%	15	32.90%	43	22.20%	29

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(5.0%, 19.2%)	(7 , 25)	(20.2%, 45.0%)	(26 , 58)	(11.7%, 33.4%)	(15 , 43)
Solomon Islands	14.80%	3	23.30%	5	15.50%	3
	(6.8%, 23.9%)	(2 , 5)	(10.7%, 36.4%)	(2 , 8)	(7.9%, 25.0%)	(2 , 6)
Somalia	8.40%	5	.	.	5.10%	3
	(3.6%, 14.7%)	(2 , 9)			(3.1%, 7.5%)	(2 , 5)
South Africa	14.20%	149	27.20%	285	12.50%	132
	(6.9%, 22.1%)	(73 , 232)	(14.7%, 40.2%)	(154 , 421)	(6.7%, 19.5%)	(71 , 204)
South Korea	20.20%	1,658	35.70%	2,935	9.70%	797
	(10.5%, 29.4%)	(866 , 2,417)	(21.7%, 48.9%)	(1,787 , 4,019)	(5.7%, 13.6%)	(469 , 1,118)
South Sudan	.	.	.	.	.	.
Spain	15.00%	451	36.60%	1,101	23.80%	716
	(7.6%, 22.6%)	(227 , 680)	(20.0%, 53.6%)	(600 , 1,612)	(13.5%, 34.1%)	(405 , 1,027)
Sri Lanka	9.80%	37	17.80%	67	4.30%	16
	(4.4%, 16.3%)	(17 , 61)	(7.0%, 29.1%)	(26 , 110)	(2.7%, 5.9%)	(10 , 22)
Sudan	3.40%	14	18.40%	73	6.30%	25
	(1.2%, 7.3%)	(5 , 29)	(8.0%, 29.5%)	(32 , 117)	(3.7%, 9.5%)	(15 , 38)
Suriname	4.30%	0	.	.	16.70%	1
	(1.7%, 8.1%)	(0 , 1)			(8.7%, 26.2%)	(1 , 2)
Swaziland	5.00%	3	26.40%	14	7.80%	4
	(2.1%, 9.0%)	(1 , 5)	(13.0%, 40.5%)	(7 , 21)	(4.4%, 12.3%)	(2 , 6)
Sweden	7.80%	16	27.80%	56	22.20%	44
	(3.8%, 12.4%)	(7 , 25)	(16.3%, 39.1%)	(33 , 78)	(12.5%, 32.1%)	(25 , 64)
Switzerland	13.20%	62	27.30%	129	23.50%	111
	(6.6%, 20.0%)	(31 , 95)	(16.4%, 37.9%)	(78 , 179)	(13.0%, 34.4%)	(61 , 163)
Syria	11.10%	31	18.80%	52	18.60%	52
	(4.9%, 18.6%)	(14 , 52)	(7.3%, 31.1%)	(20 , 87)	(9.9%, 28.3%)	(28 , 79)
Tajikistan	13.40%	16	.	.	14.10%	17
	(6.2%, 21.8%)	(7 , 26)			(7.7%, 21.6%)	(9 , 26)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Tanzania	9.50%	24	25.80%	64	4.60%	11
	(4.2%, 16.3%)	(10 , 41)	(12.5%, 40.0%)	(31 , 99)	(2.8%, 6.5%)	(7 , 16)
Thailand	16.90%	1,708	27.30%	2,757	6.20%	630
	(8.5%, 25.4%)	(862 , 2,567)	(14.7%, 40.3%)	(1,481 , 4,069)	(3.6%, 9.2%)	(365 , 925)
The Bahamas	7.00%	0	.	.	21.70%	0
	(2.9%, 12.5%)	(0 , 0)			(11.3%, 33.2%)	(0 , 1)
The Gambia	10.70%	15	.	.	6.20%	9
	(4.8%, 18.0%)	(7 , 26)			(3.5%, 9.4%)	(5 , 13)
Timor-Leste	20.90%	4	.	.	2.60%	1
	(10.7%, 30.8%)	(2 , 6)			(1.8%, 3.4%)	(0 , 1)
Togo	17.60%	43	.	.	4.90%	12
	(8.7%, 27.1%)	(21 , 67)			(2.9%, 7.3%)	(7 , 18)
Trinidad and Tobago	11.40%	1	.	.	15.10%	1
	(5.0%, 19.1%)	(0 , 1)			(7.9%, 23.8%)	(1 , 2)
Tunisia	15.80%	9	17.00%	10	18.20%	10
	(7.7%, 24.5%)	(4 , 14)	(6.8%, 27.8%)	(4 , 16)	(9.8%, 27.5%)	(5 , 15)
Turkey	15.60%	174	22.60%	251	21.50%	240
	(7.5%, 24.6%)	(84 , 274)	(9.7%, 36.3%)	(108 , 404)	(11.9%, 31.6%)	(133 , 352)
Turkmenistan	15.00%	17	.	.	17.30%	20
	(7.0%, 23.9%)	(8 , 28)			(9.1%, 26.7%)	(11 , 31)
Uganda	10.10%	48	34.40%	163	3.40%	16
	(4.5%, 16.7%)	(21 , 79)	(18.6%, 50.5%)	(88 , 240)	(2.3%, 4.1%)	(11 , 19)
Ukraine	18.40%	67	39.10%	141	20.10%	73
	(9.2%, 28.0%)	(33 , 101)	(22.5%, 55.3%)	(82 , 200)	(10.4%, 31.1%)	(38 , 112)
United Arab Emirates	8.50%	4	6.90%	3	26.50%	12
	(3.9%, 14.1%)	(2 , 6)	(2.7%, 11.3%)	(1 , 5)	(14.5%, 38.8%)	(6 , 17)
United Kingdom	11.60%	182	29.10%	458	23.70%	373
	(5.8%, 17.6%)	(92 , 277)	(18.0%, 39.9%)	(282 , 627)	(13.7%, 33.6%)	(216 , 528)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
United States	9.00%	1,620	32.00%	5,730	26.60%	4,765
	(4.5%, 14.1%)	(799 , 2,534)	(17.5%, 46.5%)	(3,141 , 8,342)	(15.2%, 37.8%)	(2,733 , 6,775)
Uruguay	14.10%	8	29.70%	16	22.10%	12
	(6.6%, 22.8%)	(4 , 12)	(15.8%, 43.9%)	(9 , 24)	(11.7%, 33.5%)	(6 , 18)
Uzbekistan	8.80%	40	.	.	16.20%	74
	(3.8%, 14.9%)	(17 , 68)			(8.7%, 25.1%)	(39 , 114)
Vanuatu	14.50%	2	18.30%	3	18.10%	3
	(6.9%, 22.6%)	(1 , 3)	(7.7%, 29.3%)	(1 , 4)	(9.2%, 28.7%)	(1 , 4)
Venezuela	10.00%	33	.	.	21.70%	72
	(4.4%, 17.1%)	(15 , 57)			(11.6%, 32.8%)	(38 , 109)
Vietnam	20.00%	2,408	23.90%	2,880	2.80%	341
	(10.5%, 29.3%)	(1,258 , 3,519)	(11.9%, 36.4%)	(1,432 , 4,382)	(1.8%, 3.5%)	(222 , 421)
Western Sahara	.	.	.	.	.	.
Yemen	12.40%	24	.	.	12.60%	24
	(5.7%, 20.3%)	(11 , 39)			(6.9%, 19.3%)	(13 , 37)
Zambia	9.20%	7	22.50%	18	6.10%	5
	(4.1%, 15.7%)	(3 , 12)	(10.3%, 35.5%)	(8 , 28)	(3.5%, 9.3%)	(3 , 7)
Zimbabwe	9.40%	22	25.30%	59	6.70%	16
	(4.2%, 16.0%)	(10 , 37)	(12.2%, 39.3%)	(28 , 92)	(3.8%, 10.3%)	(9 , 24)

Table 3-9. Fraction and number of hepatocellular carcinoma cases attributable to lifestyle risk factors in women by country

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Afghanistan	1.10%	2	.	.	2.80%	6
	(0.4%, 2.2%)	(1 , 4)			(1.0%, 5.9%)	(2 , 12)
Albania	1.40%	1	.	.	10.30%	4
	(0.5%, 2.8%)	(0 , 1)			(4.0%, 19.3%)	(2 , 8)
Algeria	0.40%	1	5.30%	10	14.30%	27
	(0.1%, 0.8%)	(0 , 2)	(1.3%, 11.1%)	(2 , 21)	(6.3%, 24.5%)	(12 , 45)
Angola	0.60%	1	.	.	5.30%	9
	(0.2%, 1.3%)	(0 , 2)			(1.8%, 11.1%)	(3 , 18)
Argentina	8.70%	40	34.80%	158	14.40%	66
	(3.5%, 15.8%)	(16 , 72)	(11.7%, 52.1%)	(53 , 237)	(6.4%, 24.5%)	(29 , 111)
Armenia	1.20%	2	34.70%	54	11.10%	17
	(0.5%, 2.6%)	(1 , 4)	(11.5%, 53.1%)	(18 , 82)	(4.4%, 20.5%)	(7 , 32)
Australia	8.90%	32	28.30%	101	12.90%	46
	(4.2%, 14.1%)	(15 , 50)	(8.4%, 45.8%)	(30 , 164)	(6.1%, 21.2%)	(22 , 76)
Austria	9.70%	20	33.40%	71	10.20%	22
	(4.7%, 15.4%)	(10 , 33)	(10.0%, 53.4%)	(21 , 113)	(4.3%, 17.9%)	(9 , 38)
Azerbaijan	0.30%	1	.	.	11.80%	19
	(0.1%, 0.8%)	(0 , 1)			(4.7%, 21.4%)	(8 , 34)
Bahrain	3.40%	0	.	.	18.50%	1
	(1.4%, 6.0%)	(0 , 0)			(8.8%, 29.7%)	(1 , 2)
Bangladesh	0.80%	7	0.10%	1	2.60%	21
	(0.3%, 1.7%)	(3 , 14)	(0.0%, 0.1%)	(0 , 1)	(1.0%, 5.1%)	(8 , 42)
Barbados	0.90%	0	37.90%	1	14.10%	0
	(0.3%, 2.1%)	(0 , 0)	(13.7%, 54.9%)	(0 , 1)	(6.1%, 24.3%)	(0 , 1)
Belarus	4.50%	2	34.60%	18	13.30%	7
	(1.7%, 8.7%)	(1 , 5)	(10.4%, 55.3%)	(5 , 29)	(5.5%, 23.8%)	(3 , 12)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Belgium	10.90%	16	29.00%	43	12.30%	18
	(5.1%, 17.9%)	(7 , 26)	(8.5%, 47.4%)	(13 , 70)	(5.7%, 20.5%)	(8 , 30)
Belize	0.90%	0	24.10%	1	13.00%	0
	(0.3%, 1.9%)	(0 , 0)	(7.8%, 37.9%)	(0 , 1)	(5.4%, 23.0%)	(0 , 1)
Benin	1.60%	3	24.50%	50	5.60%	11
	(0.6%, 3.2%)	(1 , 6)	(8.3%, 36.5%)	(17 , 74)	(2.1%, 10.6%)	(4 , 22)
Bhutan	1.60%	0	17.60%	1	3.80%	0
	(0.5%, 3.4%)	(0 , 0)	(5.6%, 27.2%)	(0 , 1)	(1.3%, 7.9%)	(0 , 0)
Bolivia	9.30%	10	28.00%	30	11.80%	12
	(3.9%, 16.6%)	(4 , 17)	(9.5%, 41.6%)	(10 , 44)	(4.8%, 21.3%)	(5 , 22)
Bosnia and Herzegovina	11.00%	9	13.80%	12	9.40%	8
	(4.7%, 18.7%)	(4 , 16)	(3.8%, 25.5%)	(3 , 21)	(3.5%, 18.1%)	(3 , 15)
Botswana	2.60%	1	23.90%	5	12.00%	3
	(1.0%, 5.3%)	(0 , 1)	(7.4%, 38.9%)	(2 , 9)	(4.7%, 22.2%)	(1 , 5)
Brazil	5.80%	182	37.60%	1,173	11.90%	372
	(2.3%, 11.0%)	(72 , 343)	(13.5%, 54.6%)	(420 , 1,703)	(5.4%, 20.1%)	(169 , 628)
Brunei	3.50%	0	.	.	10.10%	0
	(1.3%, 7.0%)	(0 , 0)			(3.7%, 19.6%)	(0 , 1)
Bulgaria	9.10%	15	26.80%	44	12.80%	21
	(3.9%, 15.8%)	(6 , 26)	(7.5%, 45.6%)	(12 , 75)	(5.3%, 22.8%)	(9 , 37)
Burkina Faso	4.20%	16	24.50%	95	3.70%	14
	(1.6%, 8.0%)	(6 , 31)	(6.8%, 43.1%)	(26 , 167)	(1.4%, 7.2%)	(6 , 28)
Burundi	4.00%	3	.	.	3.00%	2
	(1.5%, 7.9%)	(1 , 6)			(1.1%, 6.2%)	(1 , 4)
Cambodia	2.40%	14	.	.	2.30%	14
	(1.0%, 4.7%)	(6 , 28)			(0.9%, 4.5%)	(5 , 26)
Cameroon	1.30%	2	25.60%	37	6.70%	10
	(0.5%, 2.7%)	(1 , 4)	(7.3%, 43.1%)	(11 , 62)	(2.7%, 12.5%)	(4 , 18)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Canada	9.60%	45	30.40%	145	13.80%	66
	(4.6%, 15.1%)	(22 , 72)	(9.6%, 47.3%)	(46 , 225)	(6.4%, 23.0%)	(30 , 109)
Cape Verde	1.40%	0	21.50%	4	6.30%	1
	(0.5%, 3.0%)	(0 , 1)	(6.7%, 34.5%)	(1 , 6)	(2.3%, 12.2%)	(0 , 2)
Central African Republic	0.60%	0	.	.	4.20%	2
	(0.2%, 1.2%)	(0 , 1)			(1.5%, 8.7%)	(1 , 4)
Chad	1.00%	1	13.10%	15	4.30%	5
	(0.4%, 2.2%)	(0 , 3)	(3.0%, 27.3%)	(3 , 31)	(1.6%, 8.5%)	(2 , 10)
Chile	12.90%	33	33.00%	84	15.50%	39
	(5.8%, 21.3%)	(15 , 54)	(11.0%, 50.0%)	(28 , 128)	(7.0%, 25.8%)	(18 , 66)
China	1.70%	1,332	23.20%	18,247	4.20%	3,334
	(0.8%, 2.9%)	(591 , 2,288)	(7.4%, 36.2%)	(5,837 , 28,529)	(1.8%, 7.4%)	(1,446 , 5,865)
Colombia	3.20%	13	27.80%	111	13.10%	52
	(1.2%, 6.6%)	(5 , 27)	(9.1%, 42.1%)	(36 , 169)	(5.7%, 22.3%)	(23 , 90)
Comoros	4.40%	0	1.00%	0	5.40%	0
	(1.6%, 8.5%)	(0 , 0)	(0.2%, 2.7%)	(0 , 0)	(2.0%, 10.6%)	(0 , 0)
Congo	0.60%	0	16.00%	13	7.00%	6
	(0.2%, 1.3%)	(0 , 1)	(4.5%, 28.0%)	(4 , 22)	(2.6%, 13.4%)	(2 , 11)
Costa Rica	1.90%	1	36.80%	20	13.30%	7
	(0.8%, 3.6%)	(0 , 2)	(13.5%, 52.4%)	(7 , 28)	(5.7%, 23.2%)	(3 , 12)
Côte d'Ivoire	1.40%	7	20.00%	106	6.70%	35
	(0.5%, 2.8%)	(3 , 15)	(5.9%, 34.3%)	(31 , 181)	(2.6%, 12.7%)	(14 , 67)
Croatia	9.40%	9	38.40%	35	12.10%	11
	(4.3%, 15.7%)	(4 , 14)	(12.2%, 59.4%)	(11 , 54)	(5.0%, 21.8%)	(5 , 20)
Cuba	5.60%	5	20.60%	18	14.50%	12
	(2.1%, 10.6%)	(2 , 9)	(6.5%, 32.7%)	(6 , 28)	(6.4%, 24.7%)	(5 , 21)
Cyprus	9.30%	1	.	.	13.10%	1
	(3.8%, 16.5%)	(0 , 2)			(5.5%, 23.1%)	(1 , 2)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Czech Republic	8.50%	17	39.90%	82	14.70%	30
	(3.9%, 13.9%)	(8 , 28)	(12.7%, 61.0%)	(26 , 125)	(6.6%, 24.8%)	(13 , 51)
Democratic Republic of the Congo	0.60%	7	28.30%	334	4.40%	52
	(0.2%, 1.3%)	(2 , 15)	(9.9%, 41.6%)	(116 , 490)	(1.6%, 8.9%)	(19 , 104)
Denmark	13.00%	7	32.20%	18	10.90%	6
	(6.5%, 20.0%)	(4 , 11)	(9.5%, 51.8%)	(5 , 29)	(4.7%, 19.2%)	(3 , 11)
Djibouti	3.20%	0	.	.	7.10%	0
	(1.2%, 6.4%)	(0 , 0)			(2.5%, 14.2%)	(0 , 1)
Dominican Republic	5.60%	9	29.00%	44	12.30%	19
	(2.5%, 9.7%)	(4 , 15)	(9.4%, 45.0%)	(14 , 68)	(5.3%, 21.4%)	(8 , 32)
Ecuador	1.30%	4	22.50%	61	12.50%	34
	(0.5%, 2.5%)	(1 , 7)	(6.0%, 41.1%)	(16 , 112)	(5.0%, 22.5%)	(14 , 61)
Egypt	0.40%	18	9.00%	408	17.00%	772
	(0.1%, 0.7%)	(7 , 34)	(2.8%, 14.4%)	(127 , 655)	(8.2%, 27.4%)	(372 , 1,243)
El Salvador	1.30%	2	.	.	13.00%	21
	(0.5%, 2.6%)	(1 , 4)			(5.5%, 22.9%)	(9 , 36)
Equatorial Guinea	0.60%	0	.	.	5.50%	0
	(0.2%, 1.3%)	(0 , 0)			(1.9%, 11.1%)	(0 , 0)
Eritrea	0.40%	0	6.80%	2	3.60%	1
	(0.1%, 0.8%)	(0 , 0)	(1.8%, 12.1%)	(0 , 3)	(1.4%, 7.1%)	(0 , 2)
Estonia	7.90%	1	37.70%	6	13.50%	2
	(3.6%, 13.2%)	(1 , 2)	(12.0%, 58.3%)	(2 , 9)	(6.1%, 22.8%)	(1 , 4)
Ethiopia	0.50%	2	16.60%	59	3.30%	12
	(0.2%, 1.1%)	(1 , 4)	(4.7%, 28.8%)	(17 , 102)	(1.3%, 6.4%)	(4 , 23)
Fiji	2.10%	0	12.80%	2	16.90%	3
	(0.8%, 4.0%)	(0 , 1)	(4.0%, 20.4%)	(1 , 4)	(7.1%, 29.2%)	(1 , 5)
Finland	7.80%	11	29.80%	42	11.30%	16
	(3.8%, 12.4%)	(5 , 17)	(8.3%, 49.7%)	(12 , 70)	(5.1%, 19.0%)	(7 , 27)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
France	11.50%	161	32.50%	456	12.00%	168
	(5.6%, 18.0%)	(78 , 253)	(9.5%, 52.3%)	(134 , 735)	(5.2%, 20.8%)	(73 , 291)
Gabon	1.10%	0	.	.	9.90%	1
	(0.4%, 2.4%)	(0 , 0)			(3.7%, 18.9%)	(0 , 2)
Georgia	2.40%	3	26.10%	38	11.60%	17
	(0.9%, 4.5%)	(1 , 6)	(8.4%, 41.1%)	(12 , 59)	(4.5%, 21.4%)	(6 , 31)
Germany	9.10%	183	29.40%	594	11.20%	227
	(4.3%, 14.5%)	(88 , 293)	(8.3%, 48.7%)	(167 , 984)	(5.2%, 18.7%)	(106 , 377)
Ghana	0.60%	2	15.90%	55	7.00%	24
	(0.2%, 1.1%)	(1 , 4)	(4.5%, 27.3%)	(16 , 94)	(2.8%, 13.0%)	(10 , 45)
Greece	11.50%	29	34.10%	86	13.50%	34
	(5.4%, 18.3%)	(14 , 46)	(10.9%, 53.1%)	(27 , 133)	(5.9%, 23.5%)	(15 , 59)
Guatemala	1.10%	6	11.60%	57	12.10%	59
	(0.4%, 2.4%)	(2 , 12)	(3.4%, 19.7%)	(17 , 96)	(5.1%, 21.3%)	(25 , 104)
Guinea	0.70%	3	.	.	5.00%	17
	(0.3%, 1.5%)	(1 , 5)			(1.9%, 9.7%)	(7 , 34)
Guinea-Bissau	1.10%	0	.	.	5.60%	2
	(0.4%, 2.5%)	(0 , 1)			(2.0%, 10.9%)	(1 , 4)
Guyana	1.40%	0	.	.	12.80%	1
	(0.5%, 2.9%)	(0 , 0)			(5.2%, 23.0%)	(0 , 1)
Haiti	2.30%	2	.	.	8.30%	6
	(0.9%, 4.5%)	(1 , 3)			(3.2%, 15.7%)	(2 , 12)
Honduras	1.40%	3	.	.	11.30%	21
	(0.5%, 3.0%)	(1 , 5)			(4.6%, 20.4%)	(8 , 37)
Hungary	9.40%	11	36.80%	42	12.90%	15
	(4.2%, 15.8%)	(5 , 18)	(11.3%, 57.6%)	(13 , 66)	(5.6%, 22.5%)	(6 , 26)
Iceland	10.90%	0	23.40%	1	11.70%	0
	(5.4%, 16.8%)	(0 , 0)	(7.0%, 37.6%)	(0 , 1)	(5.0%, 20.6%)	(0 , 0)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
India	1.10%	81	10.00%	713	2.90%	207
	(0.5%, 2.1%)	(34 , 146)	(3.0%, 16.9%)	(214 , 1,200)	(1.2%, 5.4%)	(85 , 380)
Indonesia	1.10%	36	3.20%	109	3.90%	134
	(0.5%, 1.9%)	(16 , 64)	(1.0%, 5.4%)	(32 , 183)	(1.5%, 7.5%)	(52 , 254)
Iran	1.40%	9	9.30%	60	14.50%	93
	(0.5%, 3.0%)	(3 , 19)	(2.9%, 15.1%)	(18 , 97)	(6.9%, 23.7%)	(44 , 152)
Iraq	1.00%	3	0.30%	1	15.20%	48
	(0.4%, 2.1%)	(1 , 6)	(0.1%, 0.6%)	(0 , 2)	(6.7%, 25.9%)	(21 , 81)
Ireland	11.30%	6	32.00%	16	10.90%	6
	(5.3%, 18.2%)	(3 , 9)	(8.8%, 53.7%)	(4 , 27)	(4.6%, 19.3%)	(2 , 10)
Israel	9.20%	7	13.90%	10	15.10%	11
	(4.1%, 15.6%)	(3 , 11)	(4.0%, 23.3%)	(3 , 17)	(6.8%, 25.5%)	(5 , 19)
Italy	8.40%	228	27.40%	740	12.30%	333
	(4.0%, 13.6%)	(108 , 367)	(7.8%, 45.6%)	(210 , 1,235)	(5.8%, 20.3%)	(157 , 550)
Jamaica	3.00%	2	31.80%	18	14.70%	8
	(1.2%, 5.9%)	(1 , 3)	(11.0%, 47.4%)	(6 , 26)	(6.6%, 24.6%)	(4 , 14)
Japan	5.20%	512	23.90%	2,369	3.90%	387
	(2.4%, 8.7%)	(237 , 860)	(6.9%, 39.6%)	(680 , 3,914)	(1.7%, 6.8%)	(166 , 675)
Jordan	3.80%	2	.	.	17.90%	9
	(1.4%, 7.3%)	(1 , 4)			(8.7%, 28.7%)	(4 , 15)
Kazakhstan	6.10%	25	28.00%	117	12.40%	52
	(2.7%, 10.6%)	(11 , 44)	(7.9%, 47.7%)	(33 , 198)	(5.0%, 22.3%)	(21 , 93)
Kenya	1.00%	3	10.00%	30	4.90%	15
	(0.4%, 2.1%)	(1 , 6)	(2.5%, 19.8%)	(8 , 59)	(1.9%, 9.6%)	(6 , 29)
Kuwait	1.40%	0	9.00%	1	20.70%	2
	(0.5%, 2.9%)	(0 , 0)	(2.8%, 14.4%)	(0 , 1)	(10.4%, 32.1%)	(1 , 2)
Kyrgyzstan	0.70%	1	23.50%	25	9.40%	10
	(0.3%, 1.4%)	(0 , 1)	(7.5%, 36.7%)	(8 , 39)	(3.6%, 17.8%)	(4 , 19)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Laos	5.30%	24	18.30%	82	2.50%	11
	(2.0%, 10.3%)	(9 , 46)	(5.3%, 31.5%)	(24 , 142)	(1.0%, 5.0%)	(4 , 23)
Latvia	7.20%	3	34.60%	17	14.50%	7
	(3.1%, 12.5%)	(1 , 6)	(11.0%, 53.7%)	(5 , 26)	(6.2%, 25.0%)	(3 , 12)
Lebanon	12.60%	5	9.40%	4	16.40%	7
	(5.8%, 20.6%)	(2 , 8)	(2.6%, 16.1%)	(1 , 7)	(7.4%, 27.5%)	(3 , 11)
Lesotho	0.50%	0	19.10%	3	10.00%	2
	(0.2%, 1.1%)	(0 , 0)	(5.7%, 32.4%)	(1 , 5)	(3.8%, 19.0%)	(1 , 3)
Liberia	0.60%	1	.	.	4.80%	6
	(0.2%, 1.2%)	(0 , 1)			(1.7%, 9.6%)	(2 , 11)
Libya	0.40%	0	.	.	18.20%	13
	(0.1%, 1.3%)	(0 , 1)			(8.6%, 29.5%)	(6 , 22)
Lithuania	4.00%	1	34.30%	13	15.10%	6
	(1.8%, 7.0%)	(1 , 3)	(10.3%, 55.0%)	(4 , 21)	(6.8%, 25.4%)	(3 , 9)
Luxembourg	10.40%	2	.	.	10.70%	2
	(4.9%, 16.9%)	(1 , 3)			(4.2%, 19.7%)	(1 , 3)
Macedonia	10.40%	3	.	.	12.50%	4
	(4.4%, 18.2%)	(1 , 5)			(5.1%, 22.3%)	(1 , 6)
Madagascar	3.20%	3	9.90%	10	4.10%	4
	(1.2%, 6.5%)	(1 , 6)	(2.9%, 16.4%)	(3 , 16)	(1.5%, 7.9%)	(2 , 8)
Malawi	2.10%	2	6.60%	6	4.00%	4
	(0.8%, 4.4%)	(1 , 4)	(1.9%, 11.7%)	(2 , 11)	(1.5%, 7.8%)	(1 , 7)
Malaysia	0.90%	3	3.00%	9	6.70%	19
	(0.3%, 1.9%)	(1 , 5)	(0.8%, 5.6%)	(2 , 16)	(2.6%, 12.8%)	(8 , 37)
Maldives	4.00%	0	.	.	4.90%	0
	(1.6%, 7.8%)	(0 , 0)			(1.8%, 10.0%)	(0 , 0)
Mali	1.50%	1	1.50%	1	4.80%	4
	(0.6%, 3.2%)	(1 , 3)	(0.4%, 2.6%)	(0 , 2)	(1.8%, 9.3%)	(2 , 9)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Malta	8.60%	0	.	.	14.70%	0
	(3.5%, 15.4%)	(0 , 0)			(6.3%, 25.4%)	(0 , 1)
Mauritania	1.40%	1	1.60%	1	6.20%	5
	(0.5%, 3.0%)	(0 , 2)	(0.5%, 2.8%)	(0 , 2)	(2.3%, 12.3%)	(2 , 9)
Mauritius	1.30%	0	16.20%	2	9.10%	1
	(0.5%, 2.5%)	(0 , 0)	(4.8%, 26.5%)	(1 , 3)	(3.6%, 16.9%)	(0 , 2)
Mexico	4.00%	80	24.90%	495	15.60%	310
	(1.7%, 7.1%)	(34 , 142)	(7.5%, 41.6%)	(149 , 827)	(7.3%, 25.4%)	(146 , 505)
Micronesia, Federated States of	4.60%	0	11.40%	0	21.20%	1
	(1.8%, 8.9%)	(0 , 0)	(3.3%, 20.1%)	(0 , 1)	(10.3%, 33.5%)	(0 , 1)
Moldova	2.10%	2	39.60%	39	11.70%	12
	(0.8%, 3.9%)	(1 , 4)	(11.9%, 62.1%)	(12 , 61)	(4.7%, 21.3%)	(5 , 21)
Mongolia	2.40%	11	21.40%	103	9.90%	47
	(0.9%, 4.5%)	(4 , 22)	(6.9%, 32.6%)	(33 , 156)	(3.8%, 18.5%)	(18 , 89)
Montenegro	8.00%	1	.	.	12.50%	1
	(3.2%, 14.6%)	(0 , 2)			(5.0%, 22.5%)	(1 , 3)
Morocco	0.30%	0	0.10%	0	13.20%	17
	(0.1%, 0.6%)	(0 , 1)	(0.0%, 0.2%)	(0 , 0)	(5.6%, 22.9%)	(7 , 29)
Mozambique	1.80%	3	16.90%	25	4.00%	6
	(0.7%, 3.7%)	(1 , 5)	(5.3%, 26.7%)	(8 , 39)	(1.5%, 7.7%)	(2 , 11)
Myanmar	3.00%	32	1.60%	18	2.50%	27
	(1.2%, 5.8%)	(13 , 62)	(0.5%, 2.8%)	(5 , 30)	(0.9%, 4.9%)	(10 , 53)
Namibia	5.20%	0	24.40%	2	10.30%	1
	(2.1%, 9.6%)	(0 , 1)	(6.5%, 44.2%)	(0 , 3)	(4.0%, 19.0%)	(0 , 1)
Nepal	10.40%	6	11.70%	6	2.70%	1
	(4.6%, 17.4%)	(2 , 9)	(3.6%, 18.8%)	(2 , 10)	(1.0%, 5.4%)	(1 , 3)
Netherlands	9.80%	10	34.60%	34	10.40%	10
	(4.8%, 15.5%)	(5 , 15)	(11.1%, 53.5%)	(11 , 52)	(4.6%, 18.1%)	(5 , 18)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
New Zealand	9.90%	7	28.90%	19	13.30%	9
	(4.9%, 15.4%)	(3 , 10)	(8.8%, 46.2%)	(6 , 31)	(6.1%, 22.2%)	(4 , 15)
Nicaragua	2.30%	3	32.10%	40	12.20%	15
	(0.9%, 4.7%)	(1 , 6)	(11.6%, 46.8%)	(14 , 58)	(5.1%, 21.4%)	(6 , 27)
Niger	1.10%	1	.	.	3.80%	4
	(0.4%, 2.4%)	(0 , 3)			(1.4%, 7.3%)	(2 , 8)
Nigeria	1.40%	48	33.40%	1,135	5.90%	200
	(0.5%, 2.8%)	(18 , 95)	(10.4%, 53.4%)	(355 , 1,817)	(2.4%, 10.9%)	(81 , 370)
North Korea	1.30%	16	.	.	4.80%	59
	(0.5%, 2.7%)	(6 , 33)			(1.7%, 9.6%)	(21 , 118)
Norway	11.90%	7	25.60%	15	12.30%	7
	(5.9%, 18.4%)	(3 , 11)	(7.7%, 41.0%)	(4 , 24)	(5.6%, 20.8%)	(3 , 12)
Oman	0.50%	0	.	.	16.00%	2
	(0.2%, 1.0%)	(0 , 0)			(7.3%, 26.5%)	(1 , 4)
Pakistan	2.60%	28	0.00%	0	4.40%	46
	(1.0%, 5.3%)	(10 , 55)	(0.0%, 0.0%)	(0 , 0)	(1.6%, 8.7%)	(17 , 91)
Palestine	1.60%	0	.	.	.	.
	(0.6%, 3.2%)	(0 , 1)				
Panama	1.70%	1	.	.	13.90%	6
	(0.7%, 3.2%)	(0 , 1)			(6.0%, 24.1%)	(3 , 11)
Papua New Guinea	8.40%	12	23.50%	34	11.90%	17
	(3.4%, 15.4%)	(5 , 22)	(7.8%, 35.3%)	(11 , 51)	(4.5%, 22.4%)	(6 , 32)
Paraguay	3.30%	2	31.80%	22	10.50%	7
	(1.3%, 6.5%)	(1 , 4)	(10.4%, 49.1%)	(7 , 34)	(4.1%, 19.7%)	(3 , 14)
Peru	2.40%	17	35.00%	245	12.80%	90
	(0.9%, 4.9%)	(6 , 34)	(12.7%, 49.8%)	(89 , 349)	(5.5%, 22.2%)	(39 , 156)
Philippines	4.70%	86	17.10%	316	4.40%	81
	(2.0%, 8.4%)	(36 , 154)	(4.9%, 30.2%)	(89 , 556)	(1.8%, 8.1%)	(33 , 149)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Poland	9.20%	46	31.70%	159	13.70%	69
	(4.3%, 15.0%)	(22 , 75)	(9.6%, 50.7%)	(48 , 254)	(6.2%, 23.0%)	(31 , 115)
Portugal	4.10%	6	38.50%	56	11.00%	16
	(1.8%, 7.0%)	(3 , 10)	(12.6%, 58.8%)	(18 , 86)	(4.6%, 19.5%)	(7 , 29)
Qatar	0.60%	0	.	.	20.60%	1
	(0.2%, 1.4%)	(0 , 0)			(10.1%, 32.4%)	(1 , 2)
Romania	7.40%	31	40.50%	172	12.70%	54
	(3.4%, 12.3%)	(14 , 52)	(14.1%, 59.7%)	(60 , 254)	(5.3%, 22.4%)	(23 , 95)
Russia	6.20%	113	38.00%	692	15.40%	281
	(2.7%, 10.8%)	(49 , 197)	(12.1%, 58.7%)	(221 , 1,071)	(7.7%, 24.3%)	(140 , 444)
Rwanda	4.20%	7	.	.	3.40%	6
	(1.7%, 7.9%)	(3 , 13)			(1.2%, 6.7%)	(2 , 11)
Samoa	6.50%	0	15.80%	0	22.60%	0
	(2.6%, 12.1%)	(0 , 0)	(4.9%, 25.4%)	(0 , 0)	(11.2%, 35.1%)	(0 , 0)
Saudi Arabia	0.40%	1	.	.	18.80%	33
	(0.2%, 0.9%)	(0 , 2)			(9.5%, 29.4%)	(16 , 51)
Senegal	0.90%	2	1.50%	3	6.10%	14
	(0.3%, 1.7%)	(1 , 4)	(0.4%, 3.1%)	(1 , 7)	(2.3%, 11.6%)	(5 , 27)
Serbia	9.40%	9	.	.	11.70%	12
	(4.0%, 16.6%)	(4 , 16)			(5.0%, 20.5%)	(5 , 20)
Sierra Leone	2.60%	4	31.90%	52	5.40%	9
	(0.9%, 5.3%)	(2 , 9)	(9.7%, 51.9%)	(16 , 84)	(2.0%, 10.5%)	(3 , 17)
Singapore	1.50%	2	28.30%	42	6.10%	9
	(0.6%, 3.0%)	(1 , 4)	(9.8%, 41.6%)	(14 , 61)	(2.4%, 11.5%)	(4 , 17)
Slovakia	6.20%	6	33.40%	31	12.20%	11
	(2.5%, 11.5%)	(2 , 11)	(10.6%, 51.8%)	(10 , 48)	(5.2%, 21.3%)	(5 , 20)
Slovenia	8.60%	4	37.50%	18	12.60%	6
	(3.4%, 15.7%)	(2 , 8)	(11.5%, 58.7%)	(6 , 29)	(5.1%, 22.5%)	(3 , 11)

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
Solomon Islands	6.40%	0	13.10%	1	12.50%	1
	(2.5%, 12.1%)	(0 , 1)	(4.1%, 20.8%)	(0 , 1)	(4.7%, 23.2%)	(0 , 1)
Somalia	1.30%	1	.	.	4.00%	2
	(0.5%, 2.8%)	(0 , 2)			(1.4%, 8.2%)	(1 , 4)
South Africa	4.00%	29	17.80%	130	16.40%	119
	(1.7%, 7.0%)	(12 , 51)	(4.4%, 35.3%)	(32 , 256)	(7.7%, 26.8%)	(56 , 195)
South Korea	2.20%	62	30.50%	866	5.00%	143
	(0.9%, 3.9%)	(27 , 111)	(9.8%, 47.2%)	(279 , 1,340)	(2.0%, 9.2%)	(58 , 261)
South Sudan	.	.	.	.	.	.
Spain	10.60%	121	39.00%	444	13.00%	148
	(5.1%, 16.8%)	(58 , 191)	(13.4%, 58.0%)	(153 , 660)	(6.1%, 21.4%)	(70 , 243)
Sri Lanka	0.70%	1	1.20%	2	4.00%	8
	(0.3%, 1.5%)	(1 , 3)	(0.3%, 2.0%)	(1 , 4)	(1.5%, 7.9%)	(3 , 16)
Sudan	0.40%	1	19.90%	34	5.60%	10
	(0.1%, 1.7%)	(0 , 3)	(6.6%, 30.4%)	(11 , 52)	(2.0%, 11.0%)	(3 , 19)
Suriname	1.00%	0	.	.	15.10%	1
	(0.4%, 2.3%)	(0 , 0)			(6.5%, 26.1%)	(0 , 1)
Swaziland	1.30%	0	14.90%	2	11.40%	2
	(0.5%, 2.7%)	(0 , 0)	(4.5%, 24.2%)	(1 , 3)	(4.4%, 21.1%)	(1 , 3)
Sweden	9.60%	10	30.60%	33	10.90%	12
	(4.6%, 15.2%)	(5 , 16)	(9.4%, 48.6%)	(10 , 52)	(4.8%, 18.5%)	(5 , 20)
Switzerland	11.30%	16	27.20%	39	11.00%	16
	(5.5%, 17.5%)	(8 , 25)	(7.6%, 45.8%)	(11 , 65)	(4.7%, 19.3%)	(7 , 28)
Syria	2.70%	6	9.50%	20	14.20%	30
	(1.0%, 5.5%)	(2 , 12)	(2.9%, 15.6%)	(6 , 33)	(6.1%, 24.6%)	(13 , 52)
Tajikistan	1.40%	1	.	.	8.90%	8
	(0.5%, 2.9%)	(0 , 3)			(3.3%, 16.9%)	(3 , 15)
Tanzania	1.10%	1	21.40%	25	4.70%	5

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(0.4%, 2.3%)	(0 , 3)	(5.7%, 39.3%)	(7 , 46)	(1.8%, 8.9%)	(2 , 10)
Thailand	1.70%	68	9.70%	380	5.10%	199
	(0.7%, 3.1%)	(29 , 121)	(2.8%, 17.0%)	(108 , 665)	(2.0%, 9.8%)	(78 , 381)
The Bahamas	2.40%	0	.	.	17.80%	0
	(0.9%, 5.0%)	(0 , 0)			(8.0%, 29.6%)	(0 , 0)
The Gambia	0.40%	0	.	.	5.80%	3
	(0.1%, 0.9%)	(0 , 0)			(2.2%, 11.3%)	(1 , 6)
Timor-Leste	1.90%	0	.	.	2.20%	0
	(0.7%, 4.0%)	(0 , 0)			(0.8%, 4.2%)	(0 , 0)
Togo	5.90%	9	.	.	5.30%	8
	(2.4%, 10.9%)	(4 , 17)			(2.0%, 10.4%)	(3 , 16)
Trinidad and Tobago	3.20%	0	.	.	13.30%	1
	(1.2%, 6.6%)	(0 , 0)			(5.4%, 23.9%)	(0 , 2)
Tunisia	0.80%	0	0.00%	0	14.90%	5
	(0.3%, 1.6%)	(0 , 1)	(0.0%, 0.0%)	(0 , 0)	(6.7%, 25.0%)	(2 , 9)
Turkey	5.60%	28	7.40%	37	16.60%	83
	(2.4%, 10.0%)	(12 , 50)	(2.0%, 14.0%)	(10 , 70)	(8.1%, 26.4%)	(40 , 132)
Turkmenistan	1.60%	1	.	.	11.00%	9
	(0.5%, 3.3%)	(0 , 3)			(4.3%, 20.4%)	(4 , 17)
Uganda	1.80%	6	36.00%	124	3.60%	12
	(0.6%, 3.6%)	(2 , 12)	(11.6%, 55.9%)	(40 , 192)	(1.3%, 7.1%)	(5 , 25)
Ukraine	5.60%	15	37.70%	100	14.10%	37
	(2.4%, 9.9%)	(6 , 26)	(12.0%, 58.5%)	(32 , 155)	(6.0%, 24.6%)	(16 , 65)
United Arab Emirates	0.30%	0	3.30%	0	20.10%	3
	(0.1%, 0.7%)	(0 , 0)	(1.0%, 5.6%)	(0 , 1)	(9.8%, 31.7%)	(1 , 5)
United Kingdom	11.30%	95	29.80%	253	13.10%	111
	(5.6%, 17.3%)	(47 , 146)	(8.2%, 50.2%)	(69 , 425)	(6.4%, 21.1%)	(54 , 178)
United States	8.00%	500	30.70%	1,934	15.60%	981

Country	Smoking PAF (CI)	Smoking PAC (CI)	Alcohol PAF (CI)	Alcohol PAC (CI)	Adiposity PAF (CI)	Adiposity PAC (CI)
	(3.8%, 12.6%)	(241 , 793)	(9.8%, 48.0%)	(614 , 3,022)	(7.7%, 24.8%)	(485 , 1,558)
Uruguay	9.50%	2	29.90%	8	14.70%	4
	(4.1%, 16.6%)	(1 , 4)	(9.4%, 47.4%)	(2 , 12)	(6.3%, 25.4%)	(2 , 6)
Uzbekistan	0.60%	2	.	.	9.80%	36
	(0.2%, 1.2%)	(1 , 4)			(3.8%, 18.4%)	(14 , 67)
Vanuatu	2.20%	0	6.00%	0	13.80%	0
	(0.9%, 4.1%)	(0 , 0)	(1.8%, 10.1%)	(0 , 0)	(5.5%, 24.8%)	(0 , 1)
Venezuela	5.20%	13	.	.	15.40%	40
	(2.0%, 10.0%)	(5 , 26)			(6.9%, 25.9%)	(18 , 67)
Vietnam	1.90%	69	4.30%	158	2.20%	81
	(0.8%, 3.4%)	(29 , 124)	(1.2%, 7.6%)	(45 , 282)	(0.9%, 4.0%)	(32 , 149)
Western Sahara	.	.	.	.	.	.
Yemen	4.60%	5	.	.	9.90%	11
	(1.8%, 8.8%)	(2 , 10)			(3.9%, 18.4%)	(4 , 20)
Zambia	1.90%	1	12.70%	8	6.30%	4
	(0.7%, 3.8%)	(0 , 2)	(3.4%, 24.2%)	(2 , 15)	(2.4%, 11.9%)	(2 , 7)
Zimbabwe	1.60%	3	8.00%	17	11.30%	24
	(0.6%, 3.2%)	(1 , 7)	(2.1%, 15.6%)	(5 , 33)	(4.7%, 20.3%)	(10 , 43)

Figure 4-1. Flow chart of flavonoid database development

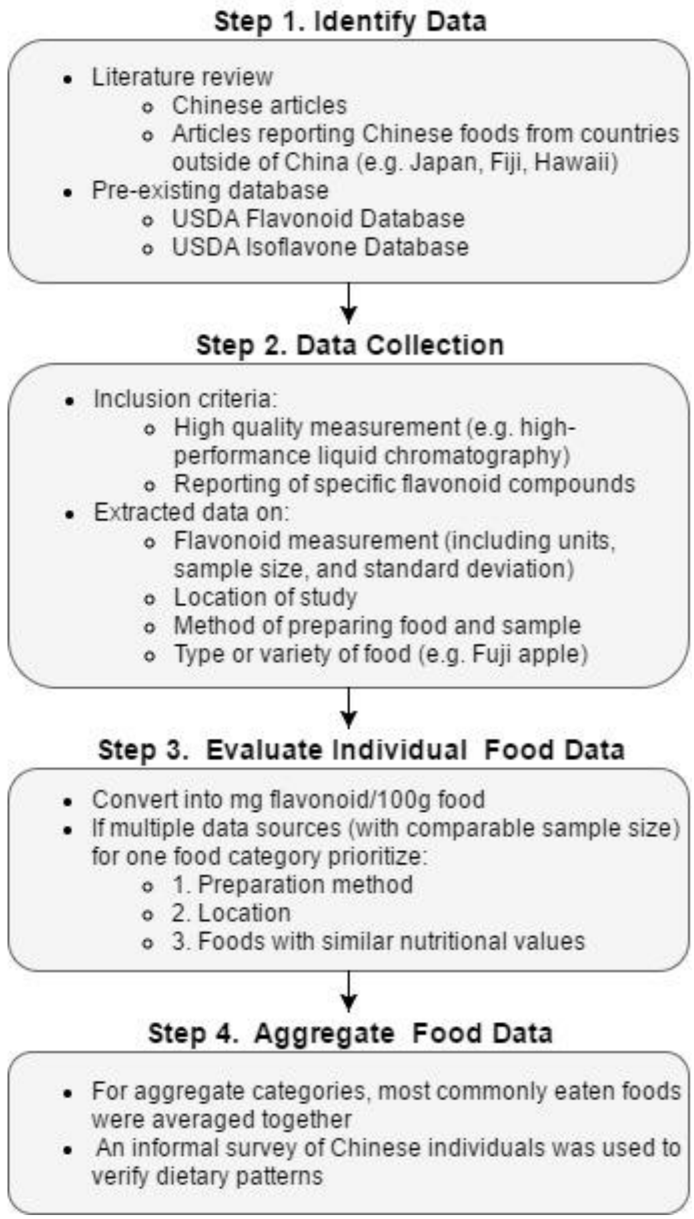

Table 4-1. Socio-demographic characteristics of participants in dietary analysis of Jiangsu case-control study

Characteristics	Case (%)	Control (%)	p-value*
Total	N=1,266	N=5,376	
Study area			
Dafeng	616 (48.7)	2498 (46.5)	**0.004**
Ganyu	370 (29.2)	1824 (33.9)	
Chuzhou	280 (22.1)	1054 (19.6)	
Gender			
Female	289 (22.8)	1461 (27.2)	**0.002**
Male	977 (77.2)	3915 (72.8)	
Age group			
<50	318 (25.1)	557 (10.4)	**<0.001**
50-59	357 (28.2)	1202 (22.4)	
60-69	322 (25.4)	1756 (32.7)	
70-79	219 (17.3)	1518 (28.2)	
80-	50 (3.9)	343 (6.4)	
Education level			
Illiteracy	508 (40.1)	2722 (50.6)	**<0.001**
Primary	397 (31.4)	1643 (30.6)	
Middle	282 (22.3)	775 (14.4)	
High School and Above	79 (6.2)	236 (4.4)	
Family History of Liver Cancer			
No	435 (77.7)	4208 (95.5)	**<0.001**
Yes	125 (22.3)	199 (4.5)	

*Chisq p-value

Table 4-2. Major liver cancer risk factors in dietary analysis of Jiangsu case-control study

	ca/co	p[b]	aOR (95% CI)[a]	p_{trend}	sbOR (95% CI)[a]	miOR (95% CI)[a]
HBsAg						
Negative	223/4,169	<0.001	1.00 (Ref)	**<0.001**	1.00 (Ref)	1.00 (Ref)
Positive	337/242		**20.56 (16.41, 25.76)**		**19.06 (15.28, 23.77)**	**4.94 (4.29, 5.69)**
Mildew						
Unexposed	1,126/4,928	0.006	1.00 (Ref)	0.588	1.00 (Ref)	1.00 (Ref)
Exposed	119/383		1.12 (0.74, 1.71)		1.13 (0.75, 1.68)	1.11 (0.94, 1.31)
Grain storage						
Unclean	709/2,727	0.001	1.00 (Ref)	0.779	1.00 (Ref)	1.00 (Ref)
Clean	557/2,649		0.97 (0.78, 1.21)		0.96 (0.77, 1.19)	0.95 (0.87, 1.03)
Ever drink alcohol						
No	551/2,503	0.051	1.00 (Ref)	0.105	1.00 (Ref)	1.00 (Ref)
Yes	715/2,873		**1.39 (1.04, 1.87)**		1.18 (0.93, 1.50)	1.04 (0.95, 1.14)
Grams ethanol/week in the 1990's						
Never	551/2,503	<0.001	1.00 (Ref)	**0.027**	1.00 (Ref)	1.00 (Ref)
1-500	273/1,364		1.10 (0.82, 1.47)		1.06 (0.80, 1.41)	0.89 (0.79, 1.02)
500+	442/1,509		**1.39 (1.04, 1.87)**		1.29 (0.98, 1.70)	**1.20 (1.06, 1.37)**
Ever smoke						
No	539/2,393	0.212	1.00 (Ref)	0.059	1.00 (Ref)	1.00 (Ref)
Yes	727/2,983		1.27 (0.93, 1.74)		1.25 (0.98, 1.60)	1.04 (0.95, 1.15)
Pack-years smoking						
Never	539/2,393	0.094	1.00 (Ref)	0.084	1.00 (Ref)	1.00 (Ref)
0-20	195/707		1.27 (0.91, 1.77)		1.25 (0.91, 1.71)	0.95 (0.81, 1.12)
20+	532/2,276		1.28 (0.84, 1.95)		1.24 (0.96, 1.62)	1.10 (0.96, 1.25)
BMI						
<18.5	152/343	<0.001	1.00 (Ref)	**<0.001**	1.00 (Ref)	1.00 (Ref)
18.5-23	711/2,617		**0.41 (0.29, 0.58)**		**0.51 (0.37, 0.71)**	1.11 (0.96, 1.28)
23-27.5	333/2,004		**0.18 (0.12, 0.26)**		**0.23 (0.16, 0.33)**	**0.58 (0.49, 0.68)**
>=27.5	62/388		**0.23 (0.13, 0.41)**		**0.33 (0.20, 0.55)**	**0.65 (0.50, 0.85)**

ca, cases; co, controls; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; miOR, multiple imputation adjusted odds ratio

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day, if not outcome of interest), pack-years of smoking (continuous, if not outcome of interest), and HBsAg status (positive, negative, if not outcome of interest)

[b]p for Chisq

Table 4-3. Food categories and constituent foods in the Jiangsu case-control study

Food categories and constituent foods in the Jiangsu case-control study	
Fruits	apples and pears, peaches, tangerines, oranges, grapes, pineapple, melon, watermelon, persimmon, banana, gingko, jujubes
Vegetables	Includes all of the vegetables included in vegetable subclasses (red, green, starch, other)
Red Vegetables	red hot chili peppers, carrot, pumpkin and other winter gourds, tomato
Green Vegetables	seaweed, kelp, green vegetables (including: bok choi, spinach, broccoli, asparagus, cabbage, cauliflower), wosun or asparagus lettuce
Starch Vegetables	potato, taro
Other Vegetables	green onions, onion, garlic leaves, garlic bulb, green pepper, mushrooms, leeks, eggplant, seitan, bamboo shoots, ginger, beans, radishes, pickled cucumber, pickled mustard stem, pickled kohlrabi, salted vegetables, wood ear
Legumes & Seeds	soybeans, soy milk, tofu, fried tofu, bean sprouts, broad bean paste, dried bean curd and other bean curd products (e.g. vegetarian meat), fermented beans, stinky tofu, fermented tofu, peanuts, pumpkin seeds
Meat	stir-fried pork, braised meat, meatballs, shredded pork, preserved pork, beef and mutton, poultry, ham sausage, salted meat, animal liver, viscera, smoked fish, smoked meat, shrimp sauce, deep fried meat
Fish	fresh fish, salted fish, shellfish, shrimp, crab, snails, eel, squid, frog
Dairy & Eggs	chicken eggs, other eggs, fresh milk, powdered milk
Grains	rice, noodles, barley porridge, maize gruel, glutinous rice, sesame seed bread, deep fried dough sticks, oil fried pancakes

Table 4-4. Description of dietary consumption in dietary analysis in Jiangsu study

	Case	Control	Case			Control			p[a]
	Mean (SD)	**Mean (SD)**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
Daily Total Calories	2,318 (914)	2,259 (901)	2,210	1,656	2,895	2,160	1,630	2,832	0.057
Percent Calories from Macronutrients (%)									
Carbohydrates	67 (13)	68 (13)	69	59	77	70	60	78	0.231
Protein	12 (3)	12 (3)	12	10	14	12	10	13	0.814
Fat	14 (9)	14 (8)	12	8	18	11	7	17	0.688
Alcohol	8 (13)	8 (12)	0	0	14	0	0	14	0.178
Glycemic Index and Load									
Glycemic Index	96 (12)	95 (12)	101	91	104	100	88	104	0.1011
Glycemic Load	363 (159)	356 (160)	381	257	482	379	253	465	0.3221
Food Categories (g/week)									
Fruits	305 (411)	278 (386)	178	80	383	163	73	336	**0.022**
Vegetables	1,766 (1,353)	1,666 (1,350)	1,391	857	2,234	1,308	775	2,177	**0.003**
Soy and Legumes	513 (520)	556 (555)	383	171	676	414	208	721	**0.001**
Meat	352 (376)	334 (352)	237	107	467	225	111	432	0.284
Fish	198 (339)	173 (275)	115	44	231	100	40	202	**0.001**
Dairy and Eggs	316 (431)	290 (351)	200	83	365	200	92	350	0.980
Grains	3,451 (1,401)	3,426 (1,369)	3,247	2,317	4,321	3,279	2,404	4,296	0.862
Flavonoids (mg/week)									
Total flavonoids	1,806 (5,282)	1,794 (3,480)	346	169	993	369	184	1,681	**0.025**
Flavonol	113 (193)	112 (139)	60	33	131	63	30	137	0.898
Flavones	34 (27)	32 (27)	27	16	43	25	14	41	**0.001**
Flavanones	4 (15)	4 (11)	0	0	4	0	0	3	**0.020**
Catechins & Epicatechins	1,456 (5,033)	1,439 (3,293)	31	13	369	36	14	1,517	**0.034**
Theaflavins	12 (44)	12 (29)	0	0	0	0	0	0	0.087
Anthocyanidins	36 (56)	38 (65)	20	9	39	21	10	41	0.134
Isoflavonoids	150 (151)	159 (150)	108	52	205	120	60	208	**0.006**

[a]Wilcoxon signed-rank test, with p<0.05 considered significant

Table 4-5. Associations between food categories and liver cancer in dietary analysis of Jiangsu case-control study

	cOR	**p_{trend}**	**aOR[a]**	**p_{trend}**	**sbOR[a]**	**miOR[a]**
Fruits (g/week)						
T1 (0-113)	1.00 (Ref)	0.173	1.00 (Ref)	0.331	1.00 (Ref)	1.00 (Ref)
T2 (113-270)	1.05 (0.90, 1.22)		0.84 (0.64, 1.09)		0.84 (0.65, 1.10)	0.97 (0.86, 1.09)
T3 (270+)	1.11 (0.96, 1.29)		0.88 (0.67, 1.15)		0.88 (0.68, 1.15)	1.01 (0.90, 1.14)
per 257g increase	1.04 (1.00, 1.08)	0.055	1.00 (0.92, 1.09)	0.984		
Vegetables (g/week)						
T1 (0-1,041)	1.00 (Ref)	0.071	1.00 (Ref)	0.176	1.00 (Ref)	1.00 (Ref)
T2 (1,041-1,822)	1.10 (0.95, 1.29)		1.13 (0.87, 1.46)		1.12 (0.87, 1.44)	0.95 (0.83, 1.08)
T3 (1,822+)	1.15 (0.99, 1.34)		1.21 (0.92, 1.60)		1.20 (0.91, 1.57)	1.13 (0.99, 1.28)
per 1,261g increase	1.06 (1.00, 1.12)	0.064	**1.12 (1.01, 1.24)**	**0.040**		
Soy & Legumes (g/week)						
T1 (0-292)	1.00 (Ref)	**0.004**	1.00 (Ref)	0.237	1.00 (Ref)	1.00 (Ref)
T2 (292-598)	0.88 (0.76, 1.02)		0.86 (0.66, 1.11)		0.87 (0.67, 1.12)	1.00 (0.89, 1.13)
T3 (598+)	**0.80 (0.69, 0.93)**		0.86 (0.66, 1.12)		0.86 (0.66, 1.12)	0.91 (0.81, 1.02)
per 490g increase	**0.90 (0.84, 0.96)**	**0.001**	0.91 (0.80, 1.02)	0.107		
Meat (g/week)						
T1 (0-176)	1.00 (Ref)	0.497	1.00 (Ref)	0.071	1.00 (Ref)	1.00 (Ref)
T2 (176-351)	0.91 (0.78, 1.06)		0.97 (0.74, 1.26)		0.97 (0.75, 1.26)	0.95 (0.84, 1.09)
T3 (351+)	1.05 (0.91, 1.22)		0.76 (0.57, 1.02)		0.77 (0.59, 1.02)	0.92 (0.81, 1.05)
per 285g increase	1.03 (0.98, 1.08)	0.275	0.93 (0.82, 1.06)	0.274		
Fish (g/week)						
T1 (0-75)	1.00 (Ref)	**0.014**	1.00 (Ref)	0.450	1.00 (Ref)	1.00 (Ref)
T2 (75-158)	0.98 (0.84, 1.14)		1.07 (0.80, 1.41)		1.06 (0.81, 1.40)	0.96 (0.85, 1.08)
T3 (158+)	**1.22 (1.05, 1.41)**		1.11 (0.85, 1.45)		1.10 (0.85, 1.43)	1.06 (0.95, 1.19)
per 135g increase	**1.03 (1.01, 1.06)**	**0.008**	**1.05 (1.00, 1.09)**	**0.043**		
Dairy & Eggs (g/week)						
T1 (0-114)	1.00 (Ref)	0.981	1.00 (Ref)	0.235	1.00 (Ref)	1.00 (Ref)

	cOR	p_{trend}	aOR[a]	p_{trend}	sbOR[a]	miOR[a]
T2 (114-295)	0.94 (0.81, 1.09)		0.87 (0.68, 1.13)		0.88 (0.68, 1.13)	0.93 (0.83, 1.05)
T3 (295+)	1.00 (0.86, 1.16)		0.85 (0.63, 1.13)		0.85 (0.64, 1.14)	1.09 (0.97, 1.24)
per 271g increase	**1.05 (1.00, 1.09)**	**0.037**	1.03 (0.93, 1.13)	0.569		
Grains (g/week)						
T1 (0-3,171)	1.00 (Ref)	**0.024**	1.00 (Ref)	**0.020**	1.00 (Ref)	1.00 (Ref)
T2 (3,171-3,762)	**0.82 (0.71, 0.96)**		0.93 (0.70, 1.24)		0.93 (0.70, 1.22)	0.94 (0.83, 1.06)
T3 (3,762+)	**0.85 (0.73, 0.98)**		**1.39 (1.04, 1.85)**		**1.37 (1.03, 1.81)**	1.06 (0.93, 1.20)
per 937g increase	0.94 (0.88, 1.00)	0.070	**1.25 (1.09, 1.42)**	**0.001**		

cOR, crude odds ratio; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; miOR, multiple imputation adjusted odds ratio

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-years of smoking (continuous), daily kcal, and HBsAg status (positive, negative)

Table 4-6. Associations between glycemic index, glycemic load, and macronutrients with liver cancer in dietary analysis of Jiangsu case-control study

	cOR	p_{trend}	aOR[a]	p_{trend}	sbOR[a]	miOR[a]
Glycemic Index						
T1 (0-93)	1.00 (Ref)	0.276	1.00 (Ref)	0.507	1.00 (Ref)	1.00 (Ref)
T2 (93-103)	**1.20 (1.03, 1.39)**		0.84 (0.59, 1.20)		0.84 (0.60, 1.19)	0.94 (0.83, 1.05)
T3 (103+)	1.09 (0.94, 1.27)		1.03 (0.70, 1.52)		1.04 (0.72, 1.50)	1.05 (0.91, 1.22)
per 16.47 increase	1.08 (1.00, 1.18)	0.064	1.01 (0.82, 1.25)	0.915		
Glycemic Load						
T1 (0-323)	1.00 (Ref)	0.799	1.00 (Ref)	**0.055**	1.00 (Ref)	1.00 (Ref)
T2 (323-402)	1.00 (0.86, 1.17)		1.03 (0.77, 1.39)		1.02 (0.77, 1.36)	1.03 (0.91, 1.16)
T3 (402+)	0.98 (0.84, 1.14)		1.36 (0.98, 1.87)		1.33 (0.97, 1.82)	1.06 (0.92, 1.21)
per 124.88 increase	0.97 (0.90, 1.05)	0.425	1.22 (1.02, 1.46)	0.028		
Carbohydrates (% kcal)						
T1(0-0.64)	1.00 (Ref)	0.302	1.00 (Ref)	**0.001**	1.00 (Ref)	1.00 (Ref)
T2 (0.64-0.75)	1.02 (0.88, 1.18)		1.33 (0.99, 1.79)		1.30 (0.98, 1.72)	1.03 (0.91, 1.16)
T3 (0.75+)	0.92 (0.79, 1.07)		**1.72 (1.24, 2.39)**		**1.66 (1.21, 2.28)**	**1.14 (1.00, 1.30)**
per 18% increase	0.95 (0.88, 1.03)	0.252	**1.31 (1.08, 1.59)**	**0.006**		
Protein (% kcal)						
T1 (0-0.11)	1.00 (Ref)	0.683	1.00 (Ref)	0.568	1.00 (Ref)	1.00 (Ref)
T2(0.11-0.13)	0.89 (0.77, 1.04)		1.11 (0.84, 1.46)		1.10 (0.84, 1.44)	0.96 (0.85, 1.08)
T3 (0.13+)	1.03 (0.89, 1.19)		1.09 (0.81, 1.46)		1.08 (0.81, 1.44)	1.11 (0.98, 1.25)
per 3% increase	0.96 (0.89, 1.03)	0.241	1.06 (0.92, 1.23)	0.406		
Fat (% kcal)						
T1 (0-0.09)	1.00 (Ref)	0.357	1.00 (Ref)	0.129	1.00 (Ref)	1.00 (Ref)
T2 (0.09-0.15)	1.01 (0.86, 1.17)		1.07 (0.83, 1.39)		1.08 (0.84, 1.38)	1.02 (0.91, 1.15)
T3 (0.15+)	1.07 (0.92, 1.25)		0.79 (0.59, 1.05)		0.80 (0.60, 1.05)	0.96 (0.84, 1.08)
per 1% increase	1.03 (0.96, 1.11)	0.358	0.93 (0.80, 1.08)	0.327		
Fiber (g/week)						

	cOR	p_{trend}	aOR[a]	p_{trend}	sbOR[a]	miOR[a]
T1 (0-51)	1.00 (Ref)	0.536	1.00 (Ref)	0.275	1.00 (Ref)	1.00 (Ref)
T2 (51-68)	1.01 (0.87, 1.17)		1.08 (0.83, 1.41)		1.08 (0.83, 1.40)	0.95 (0.85, 1.07)
T3 (68+)	1.05 (0.90, 1.22)		1.17 (0.88, 1.54)		1.16 (0.88, 1.52)	1.06 (0.93, 1.21)
per 27.21g increase	1.02 (0.97, 1.09)	0.424	1.08 (0.97, 1.21)	0.14		
Cholesterol (mg/week)						
T1 (0-980)	1.00 (Ref)	0.945	1.00 (Ref)	0.212	1.00 (Ref)	1.00 (Ref)
T2 (980-1,963)	0.91 (0.78, 1.06)		**0.73 (0.56, 0.95)**		**0.74 (0.57, 0.96)**	0.87 (0.77, 0.98)
T3 (1,963+)	1.01 (0.87, 1.17)		0.86 (0.65, 1.14)		0.87 (0.66, 1.15)	1.06 (0.94, 1.20)
per 1,544 mg increase	1.03 (0.98, 1.08)	0.289	1.00 (0.90, 1.12)	0.975		

cOR, crude odds ratio; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; miOR, multiple imputation adjusted odds ratio

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-years of smoking (continuous), daily kcal, and HBsAg status (positive, negative)

Table 4-7. Main sources of dietary flavonoids in Jiangsu case-control study

	Foods Richest in Subclass of Flavonoid	Main Dietary Sources of Flavonoid Among Controls (% of Subclass)
Flavonols	Onion (37.2 mg/100g) Grape (20.8 mg/100g) Banana (10.2 mg/100g)	Green tea (43.5%) Green vegetables (11.1%) Onion (4.6%)
Flavones	Green pepper (5.4 mg/100g) Carrot (4.4mg/100g) Ginkgo (4.3mg/100g)	Green vegetables (45.5%) Green pepper (10.2%) Green tea (9.6%)
Flavanones	Tangerine (18.0 mg/100g) Orange (42.6 mg/100g)	Tangerine (75.7%) Orange (24.3%)
Catechins and Epicatechins	Soybeans (37.4 mg/100g) Green tea (131.7 mg/1g) Oolong tea (49.7 mg/1g)	Green tea (92.5%) Oolong tea (3.0%) Black tea (2.4%)
Theaflavins	Green tea (1.2 mg/1g)	Green tea (100%)
Anthocyanidins	Radishes (63.1 mg/100g) Grapes (49.0 mg/100g) Beans (8.0 mg/100g)	Radishes (46%) Salted vegetables (21%) Beans (12%)
Isoflavones	Stinky tofu and fermented tofu (35.6 mg/100g) Soybeans (65.8 mg/100g) Dried tofu (45.0 mg/100g)	Tofu (41.4%) Dried bean curd and other bean curd products (31.1%) Soybeans (19.1%)
Total Flavonoids	Green tea (135.6 mg/1g) Soybeans (103.8 mg/100g) Salted vegetables (80.2 mg/100g)	Green tea (77.7%) Tofu (3.9%) Dried bean curd and other bean curd products (2.7%)

Table 4-8. Associations between total flavonoid intake and flavonoid subgroups with liver cancer in dietary analysis of Jiangsu case-control study

	cOR	p_{trend}	aOR[a]	p_{trend}	sbOR[a]	miOR[a]
Total Flavonoids (mg/week)						
T1 (0-273.23)	1.00 (Ref)	**0.010**	1.00 (Ref)	0.074	1.00 (Ref)	1.00 (Ref)
T2 (273.23-635.83)	0.99 (0.86, 1.15)		1.01 (0.77, 1.31)		1.01 (0.78, 1.31)	1.07 (0.95, 1.20)
T3 (635.83+)	**0.82 (0.71, 0.96)**		0.77 (0.58, 1.01)		0.78 (0.59, 1.02)	**0.85 (0.75, 0.97)**
per 1,425.6 increase	1.00 (0.98, 1.02)	0.986	0.96 (0.90, 1.01)	0.112		
Flavonol (mg/week)						
T1 (0-43.13)	1.00 (Ref)	0.882	1.00 (Ref)	0.906	1.00 (Ref)	1.00 (Ref)
T2 (43.13-98.53)	1.14 (0.98, 1.32)		1.24 (0.95, 1.60)		1.23 (0.95, 1.58)	1.09 (0.96, 1.23)
T3 (98.53+)	0.99 (0.85, 1.15)		0.96 (0.72, 1.28)		0.96 (0.72, 1.27)	0.94 (0.82, 1.09)
per 95.27 increase	1.00 (0.96, 1.04)	0.985	0.94 (0.86, 1.04)	0.242		
Flavones (mg/week)						
T1 (0-19.21)	1.00 (Ref)	**0.020**	1.00 (Ref)	0.194	1.00 (Ref)	1.00 (Ref)
T2 (19.21-34.41)	1.16 (1.00, 1.36)		1.15 (0.88, 1.49)		1.14 (0.88, 1.47)	1.03 (0.92, 1.16)
T3 (34.41+)	**1.20 (1.03, 1.40)**		1.20 (0.91, 1.57)		1.18 (0.91, 1.55)	1.10 (0.97, 1.24)
per 24.52 increase	1.06 (1.00, 1.12)	0.036	1.06 (0.96, 1.17)	0.242		
Flavanones (mg/week)						
T1 (0-0.27)	1.00 (Ref)	0.060	1.00 (Ref)	0.364	1.00 (Ref)	1.00 (Ref)
T2 (0.27-2.07)	0.96 (0.82, 1.12)		0.92 (0.68, 1.24)		0.92 (0.69, 1.24)	0.99 (0.87, 1.12)
T3 (2.07+)	1.15 (0.99, 1.33)		1.12 (0.87, 1.46)		1.12 (0.87, 1.45)	1.11 (0.99, 1.25)
per 3.07 increase	1.01 (1.00, 1.03)	0.079	0.99 (0.96, 1.03)	0.786		
Catechins Epicatechins (mg/week)						
T1 (0-26.56)	1.00 (Ref)	**<0.001**	1.00 (Ref)	**0.010**	1.00 (Ref)	1.00 (Ref)
T2 (26.56-86.46)	0.99 (0.86, 1.15)		0.84 (0.63, 1.11)		0.85 (0.64, 1.12)	1.11 (0.98, 1.26)
T3 (86.46+)	**0.80 (0.68, 0.93)**		**0.70 (0.53, 0.92)**		**0.71 (0.54, 0.93)**	**0.80 (0.71, 0.91)**
per 1,477.95 increase	1.00 (0.98, 1.03)	0.887	0.95 (0.90, 1.01)	0.119		
Theaflavins (mg/week)						

	cOR	p_{trend}	aOR[a]	p_{trend}	sbOR[a]	miOR[a]
T1(0)	1.00 (Ref)	**0.02**	1.00 (Ref)	0.134	1.00 (Ref)	1.00 (Ref)
T2 (0-0.7)	0.97 (0.84, 1.12)		1.03 (0.75, 1.42)		1.04 (0.76, 1.41)	1.13 (0.99, 1.28)
T3 (0.7+)	**0.84 (0.72, 0.98)**		0.81 (0.59, 1.10)		0.81 (0.60, 1.10)	0.88 (0.77, 1.00)
per 0.7 increase	1.00 (1.00, 1.00)	0.66	1.00 (1.00, 1.00)	0.195		
Anthocyanidins (mg/week)						
T1(0-14.01)	1.00 (Ref)	**0.03**	1.00 (Ref)	0.343	1.00 (Ref)	1.00 (Ref)
T2 (14.01-32.11)	0.93 (0.80, 1.08)		0.94 (0.73, 1.21)		0.94 (0.73, 1.21)	1.02 (0.91, 1.15)
T3 (32.11+)	**0.85 (0.73, 0.98)**		0.87 (0.66, 1.16)		0.88 (0.66, 1.16)	0.95 (0.84, 1.07)
per 29.96 increase	0.98 (0.95, 1.01)	0.274	1.00 (0.93, 1.08)	0.990		
Isoflavonoids (mg/week)						
T1 (0-89.09)	1.00 (Ref)	**0.013**	1.00 (Ref)	0.069	1.00 (Ref)	1.00 (Ref)
T2 (89.09-170.99)	**0.78 (0.67, 0.91)**		0.83 (0.63, 1.08)		0.83 (0.64, 1.08)	0.96 (0.85, 1.08)
T3 (170.99+)	**0.83 (0.72, 0.97)**		0.79 (0.60, 1.02)		0.79 (0.61, 1.03)	0.91 (0.81, 1.04)
per 129.08 increase	**0.92 (0.87, 0.98)**	**0.009**	0.93 (0.84, 1.03)	0.182		

cOR, crude odds ratio; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; miOR, multiple imputation adjusted odds ratio

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-years of smoking (continuous), daily kcal, and HBsAg status (positive, negative)

Table 4-9. Associations between tea consumption and liver cancer in dietary analysis of Jiangsu case-control study

	ca/co	p[b]	aOR[a] (95% CI)	sbOR[a] (95% CI)	miOR[a] (95% CI)
Total	1266/5376				
Ever drink tea regularly					
No	928/3711	**0.003**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	338/1665		**0.73 (0.56, 0.94)**	**0.74 (0.57, 0.95)**	**0.85 (0.78, 0.94)**
Regular tea drinking					
No	928/3711	**<0.001**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Former	164/148		**4.30 (2.81, 6.56)**	**3.82 (2.54, 5.75)**	**3.59 (2.81, 4.60)**
Current	174/1517		**0.42 (0.31, 0.56)**	**0.43 (0.32, 0.57)**	**0.34 (0.28, 0.41)**
Age at start of tea drinking					
Never drink	928/3711	**<0.001**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<35	225/963		0.86 (0.63, 1.18)	0.87 (0.64, 1.18)	1.07 (0.91, 1.27)
35-	113/702		**0.59 (0.41, 0.84)**	**0.61 (0.43, 0.86)**	**0.73 (0.61, 0.88)**
Total years of tea drinking					
Never drink	928/3711	**0.01**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<30	187/889		**0.53 (0.39, 0.73)**	**0.55 (0.40, 0.74)**	**0.70 (0.59, 0.83)**
30-	151/776		1.18 (0.83, 1.67)	1.18 (0.84, 1.65)	1.20 (1.00, 1.43)
Type of tea					
Never drink	928/3711	**0.028**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Black tea	33/208		0.63 (0.36, 1.12)	0.68 (0.40, 1.15)	0.96 (0.54, 1.71)
Green tea	271/1295		**0.75 (0.57, 1.00)**	0.77 (0.59, 1.01)	1.22 (0.78, 1.91)
Floral tea	16/55		0.96 (0.35, 2.65)	0.98 (0.43, 2.23)	1.68 (0.77, 3.65)
Oolong tea	1/14		0.53 (0.04, 6.33)	0.85 (0.26, 2.80)	0.32 (0.05, 2.17)
Other	13/80		0.59 (0.23, 1.55)	0.70 (0.33, 1.52)	0.95 (0.44, 2.08)
Cups of new tea every day					
Never drink	928/3711	**0.016**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	98/582		**0.48 (0.32, 0.72)**	**0.51 (0.35, 0.74)**	**0.70 (0.53, 0.92)**
2	149/671		0.94 (0.67, 1.32)	0.95 (0.68, 1.32)	0.94 (0.75, 1.18)
3	55/273		0.70 (0.39, 1.25)	0.74 (0.44, 1.25)	0.97 (0.70, 1.35)
4+	30/115		1.59 (0.78, 3.25)	1.45 (0.76, 2.78)	1.31 (0.84, 2.03)
Times re-brewed					
Never drink	928/3711	**0.028**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1~2	72/355		**0.55 (0.34, 0.89)**	**0.59 (0.38, 0.92)**	0.87 (0.68, 1.12)
3+	260/1286		0.80 (0.61, 1.05)	0.81 (0.62, 1.06)	0.93 (0.78, 1.11)
Type of water used					
Never drink	928/3711	**0.001**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Tap water	154/729		0.80 (0.57, 1.12)	0.82 (0.59, 1.13)	1.13 (0.87, 1.46)
Deep well water	65/437		**0.50 (0.32, 0.77)**	**0.54 (0.36, 0.81)**	**0.64 (0.46, 0.90)**
Shallow well water	108/412		1.14 (0.72, 1.83)	1.14 (0.74, 1.78)	**1.52 (1.11, 2.09)**

	ca/co	p[b]	aOR[a] (95% CI)	sbOR[a] (95% CI)	miOR[a] (95% CI)
Pool/ditch/river/rain	10/70		0.44 (0.15, 1.29)	0.60 (0.27, 1.34)	0.65 (0.33, 1.25)
Monthly g of tea leaves					
Never drink	928/3711	**0.016**	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
0-50	212/1130		**0.72 (0.54, 0.95)**	**0.73 (0.56, 0.97)**	**0.81 (0.66, 0.99)**
50-250	84/361		0.88 (0.54, 1.42)	0.90 (0.57, 1.42)	1.12 (0.84, 1.51)
500+	31/134		0.47 (0.20, 1.10)	0.58 (0.29, 1.16)	0.91 (0.59, 1.41)

ca/co, cases/controls; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; miOR, multiple imputation adjusted odds ratio

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-years of smoking (continuous), daily kcal, and HBsAg status (positive, negative)

[b]p for Chisq or Fisher's Exact Test

Table 4-10. Joint associations between flavonoid intake, glycemic index, glycemic load, carbohydrate intake, and major liver cancer risk factors in Jiangsu case-control study

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Total Flavonoid Intake				
High Flavonoid and Low GI	1.00 (Ref)	1.00 (Ref)	RERI: -0.15 (-0.72, 0.42)	ROR: 0.88 (0.55, 1.39)
Low Flavonoid and Low GI	1.37 (0.97, 1.93)	1.31 (0.93, 1.84)	sbRERI: -0.11 (-0.67, 0.45)	sbROR: 0.9 (0.58, 1.4)
High Flavonoid and High GI	1.10 (0.76, 1.59)	1.13 (0.79, 1.63)		
Low Flavonoid and High GI	1.32 (0.96, 1.81)	1.33 (0.98, 1.81)		
High Flavonoids and Low GL	1.00 (Ref)	1.00 (Ref)	RERI: -0.11 (-0.71, 0.48)	ROR: 0.88 (0.55, 1.39)
Low Flavonoid and Low GL	1.33 (0.94, 1.86)	1.28 (0.92, 1.80)	sbRERI: -0.10 (-0.67, 0.48)	sbROR: 0.9 (0.58, 1.39)
High Flavonoid and High GL	1.30 (0.90, 1.87)	1.25 (0.87, 1.79)		
Low Flavonoid and High GL	**1.51 (1.10, 2.07)**	**1.43 (1.06, 1.94)**		
High Flavonoid and Low Carbs	1.00 (Ref)	1.00 (Ref)	RERI: 0.25 (-0.27, 0.78)	ROR: 1.17 (0.75, 1.84)
Low Flavonoid and Low Carbs	1.13 (0.82, 1.56)	1.10 (0.80, 1.51)	sbRERI: 0.25 (-0.26, 0.77)	sbROR: 1.17 (0.76, 1.79)
High Flavonoid and High Carbs	1.17 (0.82, 1.66)	1.16 (0.81, 1.64)		
Low Flavonoid and High Carbs	**1.55 (1.14, 2.12)**	**1.50 (1.11, 2.03)**		
Unclean Grain Storage				
Clean Storage and Low GI	1.00 (Ref)	1.00 (Ref)	RERI: -0.44 (-1.04, 0.17)	ROR: 0.69 (0.44, 1.08)
Unclean Storage and Low GI	1.29 (0.91, 1.83)	1.31 (0.93, 1.85)	sbRERI: -0.46 (-1.08, 0.15)	sbROR: 0.7 (0.46, 1.08)
Clean Storage and High GI	1.36 (0.94, 1.95)	1.40 (0.99, 1.99)		
Unclean Storage and High GI	1.21 (0.83, 1.76)	1.25 (0.87, 1.78)		
Clean Storage and Low GL	1.00 (Ref)	1.00 (Ref)	RERI: -0.4 (-1.02, 0.21)	ROR: 0.72 (0.46, 1.12)
Unclean Storage and Low GL	1.26 (0.90, 1.77)	1.26 (0.90, 1.76)	sbRERI: -0.40 (-1.00, 0.21)	sbROR: 0.74 (0.49, 1.13)
Clean Storage and High GL	**1.53 (1.07, 2.18)**	**1.48 (1.04, 2.09)**		
Unclean Storage and High GL	1.38 (0.97, 1.98)	1.34 (0.95, 1.90)		
Clean Storage and Low Carbs	1.00 (Ref)	1.00 (Ref)	RERI: -0.28 (-0.87, 0.3)	ROR: 0.79 (0.51, 1.22)
Unclean Storage and Low Carbs	1.18 (0.86, 1.62)	1.18 (0.86, 1.62)	sbRERI: -0.29 (-0.87, 0.29)	sbROR: 0.8 (0.53, 1.21)
Clean Storage and High Carbs	**1.51 (1.07, 2.12)**	**1.50 (1.07, 2.11)**		

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Unclean Storage and High Carbs	1.40 (0.99, 1.98)	1.39 (1.00, 1.95)		
Clean Storage and High Flavonoid	1.00 (Ref)	1.00 (Ref)	RERI: -0.70 (-1.39, 0.00)	**ROR: 0.59 (0.38, 0.92)**
Unclean Storage and High Flavonoid	**1.41 (1.01, 1.98)**	**1.41 (1.01, 1.97)**	sbRERI: -0.69 (-1.37, -0.00)	**sbROR: 0.62 (0.41, 0.94)**
Clean Storage and Low Flavonoid	**1.70 (1.22, 2.35)**	**1.65 (1.20, 2.28)**		
Unclean Storage and Low Flavonoid	**1.41 (1.01, 1.99)**	1.38 (0.99, 1.92)		
Hepatitis B				
HBsAg- and Low GI	1.00 (Ref)	1.00 (Ref)	RERI: 0.89 (-7.66, 9.44)	ROR: 0.9 (0.57, 1.41)
HBsAg+ and Low GI	**22.00 (15.52, 31.18)**	**20.34 (14.43, 28.67)**	sbRERI: -0.79 (-8.24, 6.67)	sbROR: 0.9 (0.59, 1.39)
HBsAg- and High GI	1.17 (0.84, 1.63)	1.08 (0.79, 1.48)		
HBsAg+ and High GI	**23.06 (16.02, 33.19)**	**19.63 (13.94, 27.64)**		
HBsAg- and Low GL	1.00 (Ref)	1.00 (Ref)	RERI: 1.53 (-8.02, 11.08)	ROR: 0.76 (0.49, 1.19)
HBsAg+ and Low GL	**24.29 (17.17, 34.36)**	**22.34 (15.88, 31.41)**	sbRERI: -1.51 (-9.63, 6.60)	sbROR: 0.78 (0.51, 1.2)
HBsAg- and High GL	**1.42 (1.04, 1.94)**	1.25 (0.92, 1.69)		
HBsAg+ and High GL	**26.24 (18.37, 37.47)**	**21.07 (15.03, 29.54)**		
HBsAg- and Low Carbs	1.00 (Ref)	1.00 (Ref)	RERI: 0.58 (-9.1, 10.26)	ROR: 0.68 (0.44, 1.06)
HBsAg+ and Low Carbs	**25.34 (18.20, 35.27)**	**23.59 (17.04, 32.66)**	sbRERI: -2.09 (-10.46, 6.29)	sbROR: 0.7 (0.46, 1.07)
HBsAg- and High Carbs	**1.54 (1.13, 2.09)**	**1.41 (1.04, 1.90)**		
HBsAg+ and High Carbs	**26.46 (18.62, 37.59)**	**21.91 (15.69, 30.58)**		
HBsAg- and High Flavonoid	1.00 (Ref)	1.00 (Ref)	RERI: -1.73 (-11.13, 7.66)	**ROR: 0.62 (0.4, 0.97)**
HBsAg+ and High Flavonoid	**27.01 (19.12, 38.16)**	**24.85 (17.70, 34.88)**	sbRERI: -3.75 (-12.05, 4.56)	sbROR: 0.65 (0.43, 1.00)
HBsAg- and Low Flavonoid	**1.54 (1.16, 2.05)**	**1.40 (1.06, 1.84)**		
HBsAg+ and Low Flavonoid	**25.82 (18.62, 35.80)**	**21.50 (15.73, 29.38)**		
Ever Drink Alcohol				
Never Drinker and Low GI	1.00 (Ref)	1.00 (Ref)	RERI: 0.19 (-0.27, 0.66)	ROR: 1.17 (0.75, 1.82)
Drinker and Low GI	1.12 (0.78, 1.62)	0.96 (0.65, 1.42)	sbRERI: 0.18 (-0.25, 0.61)	sbROR: 1.16 (0.76, 1.77)
Never Drinker and High GI	1.02 (0.70, 1.48)	1.05 (0.73, 1.51)		
Drinker and High GI	1.33 (0.91, 1.96)	1.19 (0.80, 1.76)		

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Never Drinker and Low GL	1.00 (Ref)	1.00 (Ref)	RERI: 0.07 (-0.47, 0.62)	ROR: 1.01 (0.64, 1.61)
Drinker and Low GL	1.28 (0.86, 1.90)	1.01 (0.66, 1.54)	sbRERI: 0.12 (-0.36, 0.61)	sbROR: 1.08 (0.7, 1.68)
Never Drinker and High GL	1.20 (0.81, 1.77)	1.17 (0.80, 1.71)		
Drinker and High GL	**1.55 (1.02, 2.37)**	1.30 (0.87, 1.96)		
Never Drinker and Low Carbs	1.00 (Ref)	1.00 (Ref)	RERI: 0.29 (-0.22, 0.81)	ROR: 1.22 (0.75, 1.99)
Drinker and Low Carbs	1.16 (0.78, 1.75)	0.84 (0.54, 1.32)	sbRERI: 0.42 (-0.03, 0.88)	sbROR: 1.4 (0.87, 2.25)
Never Drinker and High Carbs	1.08 (0.73, 1.58)	1.07 (0.73, 1.55)		
Drinker and High Carbs	**1.53 (1.00, 2.35)**	1.34 (0.88, 2.02)		
Never Drinker and High Flavonoid	1.00 (Ref)	1.00 (Ref)	RERI: 0.21 (-0.31, 0.72)	ROR: 1.12 (0.72, 1.75)
Drinker and High Flavonoid	1.18 (0.82, 1.68)	1.01 (0.69, 1.46)	sbRERI: 0.15 (-0.33, 0.62)	sbROR: 1.11 (0.73, 1.69)
Never Drinker and Low Flavonoid	1.19 (0.85, 1.68)	1.17 (0.84, 1.64)		
Drinker and Low Flavonoid	**1.58 (1.11, 2.25)**	1.32 (0.92, 1.91)		
Ever Smoke Tobacco				
Never Smoker and Low GI	1.00 (Ref)	1.00 (Ref)	RERI: 0.03 (-0.49, 0.55)	ROR: 1 (0.64, 1.57)
Smoker and Low GI	1.27 (0.87, 1.84)	0.98 (0.66, 1.45)	sbRERI: 0.17 (-0.27, 0.61)	sbROR: 1.14 (0.75, 1.74)
Never Smoker and High GI	1.11 (0.76, 1.62)	1.05 (0.73, 1.52)		
Smoker and High GI	1.41 (0.96, 2.06)	1.20 (0.81, 1.78)		
Never Smoker and Low GL	1.00 (Ref)	1.00 (Ref)	RERI: 0.21 (-0.31, 0.72)	ROR: 1.12 (0.72, 1.76)
Smoker and Low GL	1.17 (0.81, 1.70)	1.03 (0.67, 1.57)	sbRERI: 0.11 (-0.38, 0.60)	sbROR: 1.07 (0.69, 1.66)
Never Smoker and High GL	1.18 (0.82, 1.72)	1.18 (0.81, 1.73)		
Smoker and High GL	**1.56 (1.09, 2.26)**	1.32 (0.88, 1.99)		
Never Smoker and Low Carbs	1.00 (Ref)	1.00 (Ref)	RERI: 0.06 (-0.52, 0.64)	ROR: 0.98 (0.62, 1.54)
Smoker and Low Carbs	1.29 (0.89, 1.85)	0.86 (0.55, 1.35)	sbRERI: 0.86 (0.55, 1.35)	sbROR: 1.39 (0.86, 2.22)
Never Smoker and High Carbs	1.34 (0.93, 1.93)	1.07 (0.74, 1.56)		
Smoker and High Carbs	**1.68 (1.17, 2.43)**	1.35 (0.89, 2.04)		
Never Smoker and High Flavonoid	1.00 (Ref)	1.00 (Ref)	RERI: -0.02 (-0.61, 0.57)	ROR: 0.92 (0.59, 1.45)

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Smoker and High Flavonoid	1.36 (0.94, 1.97)	1.02 (0.70, 1.48)	sbRERI: 0.15 (-0.33, 0.63)	sbROR: 1.11 (0.73, 1.69)
Never Smoker and Low Flavonoid	1.36 (0.95, 1.94)	1.16 (0.83, 1.63)		
Smoker and Low Flavonoid	**1.70 (1.18, 2.44)**	1.33 (0.92, 1.92)		

aOR, adjusted odds ratio; sb, semi-Bayes; OR, odds ratio; RERI, relative excess risk due to interaction; ROR, ratio of odds ratios

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day, when not included in interaction term), pack-year of smoking (continuous, when not included in interaction term), daily kcal, and HBsAg status (positive, negative, when not included in interaction term)

Table 5-1. Gene names and dbsnp numbers of 43 candidate SNPs in Jiangsu case-control study

Gene	SNP	Gene	SNP	Gene	SNP
NFKB Pathway		**Stem Cell Pathway**		**GWAS**	
NFKB-IKBKAP	*rs2230793*	Oct4	*rs13409*	CCR4-GLB1	*rs4678680*
NFKB-IKBKAP	*rs3204145*	Oct4	*rs3130932*	ZBTB12 -C2	*rs9267673*
miR-300	*rs12894467*	Ctbp2	*rs3740535*	HLA-DQB1-	*rs9275572*
Micro RNA pathway		WNT2	*rs3729629*	HLA-DQA2	
CXCL12	*rs1804429*	WNT2	*rs4730775*	CHEK2	*rs738722*
IL15	*rs10519613*	DVL2	*rs222851*	TGM5	*rs748404*
WWOX	*rs12828*	AXIN1	*rs1981492*	RUNX1	*rs2014300*
pre-miR-146a	*rs2910164*	Notch4	*rs915894*	PLCE1	*rs2274223*
miR-26a1	*rs7372209*	HEY1	*rs1046472*	GPC5	*rs2352028*
Gemin3	*rs197412*	HEY2	*rs3734637*	TERT-CLPTM1L	*rs4975616*
KRAS	*rs9266*	Notch4	*rs520692*	IL1RAP	*rs7626795*
CDK6	*rs42031*	JAG1	*rs8708*	SEMA5B	*rs9868873*
DOCK4	*rs3801790*	Dec1	*rs2269700*	HIF1alpha	*rs2057482*
Rbl2	*rs3929*			BCM01	*rs12934922*
THBS1	*rs2292305*				
CTNNB1	*rs2953*				
IL6R	*rs4072391*				

Table 5-2. Associations between selected SNPs and liver cancer by flavonoid intake in Jiangsu case-control study

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Total	458/2,398			258/1,196			208/1,158		
rs1046472									
C:C	266/1423	1.00 (Ref)	1.00 (Ref)	146/712	1.00 (Ref)	1.00 (Ref)	106/686	1.00 (Ref)	1.00 (Ref)
A:C	123/728	0.96 (0.69, 1.34)	0.97 (0.70, 1.34)	71/371	1.10 (0.70, 1.74)	1.13 (0.73, 1.75)	50/342	0.77 (0.46, 1.31)	0.80 (0.49, 1.30)
A:A	19/108	1.29 (0.62, 2.71)	1.22 (0.63, 2.36)	5/52	0.68 (0.17, 2.72)	0.82 (0.32, 2.14)	12/56	1.31 (0.47, 3.66)	1.19 (0.51, 2.77)
Log-Add		1.03 (0.79, 1.35)	1.03 (0.79, 1.35)		1.01 (0.68, 1.48)	1.03 (0.71, 1.49)		0.93 (0.62, 1.40)	0.94 (0.63, 1.39)
Dominant		1.00 (0.73, 1.37)	1.00 (0.73, 1.37)		1.06 (0.68, 1.65)	1.08 (0.71, 1.66)		0.84 (0.51, 1.37)	0.86 (0.54, 1.36)
Recessive		1.31 (0.63, 2.72)	1.23 (0.64, 2.37)		0.66 (0.17, 2.61)	0.80 (0.31, 2.08)		1.41 (0.51, 3.91)	1.25 (0.54, 2.89)
rs10519613									
C:C	150/803	1.00 (Ref)	1.00 (Ref)	89/413	1.00 (Ref)	1.00 (Ref)	57/376	1.00 (Ref)	1.00 (Ref)
C:A	172/1022	1.07 (0.75, 1.51)	1.06 (0.76, 1.48)	91/498	0.98 (0.61, 1.58)	0.99 (0.64, 1.55)	71/503	1.24 (0.71, 2.15)	1.18 (0.72, 1.96)
A:A	85/422	1.31 (0.86, 2.00)	1.29 (0.86, 1.93)	41/216	1.04 (0.57, 1.88)	1.05 (0.61, 1.81)	41/202	1.66 (0.87, 3.13)	1.51 (0.85, 2.68)
Log-Add		1.13 (0.92, 1.40)	1.14 (0.92, 1.40)		1.01 (0.76, 1.36)	1.02 (0.77, 1.36)		1.28 (0.93, 1.77)	1.28 (0.94, 1.75)
Dominant		1.14 (0.82, 1.57)	1.14 (0.83, 1.56)		1.00 (0.64, 1.55)	1.01 (0.66, 1.54)		1.37 (0.82, 2.28)	1.34 (0.83, 2.17)
Recessive		1.26 (0.87, 1.84)	1.25 (0.87, 1.80)		1.05 (0.61, 1.80)	1.05 (0.63, 1.75)		1.46 (0.85, 2.53)	1.39 (0.83, 2.32)
rs12828									
G:G	165/922	1.00 (Ref)	1.00 (Ref)	92/474	1.00 (Ref)	1.00 (Ref)	65/433	1.00 (Ref)	1.00 (Ref)
A:G	163/960	0.91 (0.66, 1.27)	0.91 (0.66, 1.25)	90/476	0.92 (0.59, 1.45)	0.91 (0.59, 1.39)	69/462	1.00 (0.60, 1.67)	1.02 (0.64, 1.63)
A:A	71/320	0.90 (0.57, 1.42)	0.90 (0.58, 1.39)	34/150	1.16 (0.61, 2.21)	1.13 (0.63, 2.03)	34/166	0.78 (0.39, 1.55)	0.82 (0.45, 1.51)
Log-Add		0.94 (0.76, 1.17)	0.94 (0.75, 1.16)		1.03 (0.76, 1.40)	1.02 (0.76, 1.38)		0.91 (0.66, 1.25)	0.91 (0.67, 1.25)
Dominant		0.91 (0.67, 1.24)	0.90 (0.67, 1.22)		0.98 (0.64, 1.49)	0.96 (0.64, 1.44)		0.93 (0.58, 1.50)	0.95 (0.60, 1.48)
Recessive		0.94 (0.61, 1.44)	0.94 (0.63, 1.42)		1.20 (0.66, 2.21)	1.18 (0.67, 2.06)		0.78 (0.42, 1.47)	0.81 (0.46, 1.45)
rs12894467									
T:T	250/1360	1.00 (Ref)	1.00 (Ref)	140/667	1.00 (Ref)	1.00 (Ref)	98/669	1.00 (Ref)	1.00 (Ref)
C:T	122/714	1.01 (0.72, 1.42)	1.01 (0.73, 1.41)	65/370	0.88 (0.55, 1.41)	0.91 (0.59, 1.42)	52/329	1.49 (0.88, 2.52)	1.42 (0.87, 2.32)
C:C	25/126	0.96 (0.49, 1.89)	0.97 (0.53, 1.78)	10/64	0.62 (0.21, 1.81)	0.73 (0.32, 1.68)	13/61	1.55 (0.63, 3.85)	1.37 (0.63, 2.97)

dbSNP no.	All			Low Flavonoid Intake			High Flavonoid Intake		
	ca/co	aOR[a]	sbOR[a]	ca/co	aOR[a]	sbOR[a]	ca/co	aOR[a]	sbOR[a]
Log-Add		1.00 (0.77, 1.29)	1.00 (0.77, 1.29)		0.84 (0.58, 1.22)	0.85 (0.59, 1.22)		1.34 (0.92, 1.94)	1.33 (0.93, 1.92)
Dominant		1.00 (0.73, 1.38)	1.01 (0.74, 1.37)		0.84 (0.54, 1.32)	0.86 (0.56, 1.33)		1.50 (0.92, 2.46)	1.47 (0.92, 2.34)
Recessive		0.96 (0.49, 1.86)	0.97 (0.53, 1.76)		0.65 (0.22, 1.87)	0.75 (0.33, 1.71)		1.35 (0.55, 3.26)	1.25 (0.59, 2.68)
rs12934922									
A:A	286/1671	1.00 (Ref)	1.00 (Ref)	153/847	1.00 (Ref)	1.00 (Ref)	120/798	1.00 (Ref)	1.00 (Ref)
A:T	104/525	1.23 (0.87, 1.75)	1.22 (0.87, 1.71)	57/257	**1.69 (1.04, 2.76)**	1.52 (0.96, 2.41)	42/253	0.86 (0.50, 1.49)	0.88 (0.53, 1.46)
T:T	8/50	1.55 (0.59, 4.06)	1.35 (0.60, 3.05)	5/19	**4.84 (1.50, 15.58)**	2.37 (0.89, 6.29)	3/31	0.44 (0.07, 2.59)	0.72 (0.25, 2.07)
Log-Add		1.24 (0.92, 1.66)	1.23 (0.92, 1.65)		**1.87 (1.24, 2.80)**	**1.76 (1.18, 2.61)**		0.80 (0.50, 1.29)	0.81 (0.52, 1.27)
Dominant		1.26 (0.89, 1.76)	1.25 (0.90, 1.74)		**1.86 (1.16, 2.97)**	**1.71 (1.10, 2.68)**		0.82 (0.48, 1.39)	0.83 (0.50, 1.36)
Recessive		1.47 (0.56, 3.83)	1.31 (0.58, 2.93)		**4.12 (1.30, 13.08)**	2.23 (0.85, 5.86)		0.46 (0.08, 2.67)	0.73 (0.26, 2.10)
rs13409									
C:C	137/818	1.00 (Ref)	1.00 (Ref)	65/413	1.00 (Ref)	1.00 (Ref)	69/388	1.00 (Ref)	1.00 (Ref)
C:T	183/1013	0.93 (0.66, 1.31)	0.93 (0.67, 1.29)	111/498	1.21 (0.75, 1.93)	1.14 (0.73, 1.77)	64/498	0.65 (0.39, 1.10)	0.71 (0.44, 1.16)
T:T	85/421	1.06 (0.69, 1.62)	1.07 (0.71, 1.61)	44/218	1.18 (0.64, 2.16)	1.09 (0.62, 1.89)	34/196	0.78 (0.40, 1.51)	0.85 (0.47, 1.53)
Log-Add		1.01 (0.82, 1.25)	1.02 (0.83, 1.26)		1.10 (0.82, 1.48)	1.07 (0.80, 1.43)		0.84 (0.60, 1.17)	0.86 (0.62, 1.18)
Dominant		0.97 (0.70, 1.33)	0.97 (0.71, 1.32)		1.20 (0.77, 1.87)	1.14 (0.74, 1.74)		0.69 (0.43, 1.12)	0.73 (0.46, 1.16)
Recessive		1.10 (0.75, 1.62)	1.11 (0.76, 1.61)		1.06 (0.62, 1.82)	1.02 (0.61, 1.69)		0.98 (0.54, 1.79)	0.99 (0.57, 1.72)
rs1804429									
T:T	359/1969	1.00 (Ref)	1.00 (Ref)	193/983	1.00 (Ref)	1.00 (Ref)	151/951	1.00 (Ref)	1.00 (Ref)
G:T	49/275	1.02 (0.64, 1.64)	1.03 (0.66, 1.61)	30/141	1.45 (0.79, 2.65)	1.36 (0.78, 2.38)	16/129	0.88 (0.40, 1.92)	0.92 (0.47, 1.81)
G:G	1/12	0.93 (0.07, 12.57)	0.98 (0.29, 3.34)	/6	0.00 (0.00, .0)	0.91 (0.24, 3.44)	1/6	2.25 (0.12, 42.93)	1.13 (0.31, 4.04)
Log-Add		1.02 (0.65, 1.58)	1.03 (0.67, 1.56)		1.36 (0.76, 2.44)	1.29 (0.75, 2.22)		0.97 (0.48, 1.96)	0.99 (0.53, 1.84)
Dominant		1.02 (0.64, 1.62)	1.03 (0.66, 1.60)		1.42 (0.78, 2.59)	1.33 (0.76, 2.33)		0.92 (0.43, 1.97)	0.95 (0.49, 1.85)
Recessive		0.93 (0.07, 12.53)	0.98 (0.29, 3.34)		0.00 (0.00, .0)	0.91 (0.24, 3.41)		2.28 (0.12, 43.60)	1.13 (0.31, 4.05)
rs197412									
T:T	182/1011	1.00 (Ref)	1.00 (Ref)	98/511	1.00 (Ref)	1.00 (Ref)	75/477	1.00 (Ref)	1.00 (Ref)
T:C	171/972	0.94 (0.68, 1.31)	0.94 (0.68, 1.29)	92/482	1.09 (0.69, 1.73)	1.06 (0.69, 1.63)	71/476	0.83 (0.50, 1.38)	0.81 (0.51, 1.31)
C:C	51/247	1.41 (0.87, 2.30)	1.35 (0.85, 2.15)	28/127	1.29 (0.66, 2.51)	1.23 (0.67, 2.24)	21/115	1.81 (0.84, 3.90)	1.60 (0.81, 3.14)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		1.11 (0.88, 1.40)	1.10 (0.88, 1.38)		1.12 (0.83, 1.53)	1.11 (0.82, 1.51)		1.14 (0.79, 1.65)	1.13 (0.79, 1.62)
Dominant		1.03 (0.76, 1.40)	1.02 (0.76, 1.39)		1.14 (0.74, 1.74)	1.11 (0.74, 1.68)		0.96 (0.59, 1.55)	0.96 (0.61, 1.51)
Recessive		1.45 (0.92, 2.30)	1.39 (0.90, 2.16)		1.23 (0.66, 2.31)	1.20 (0.67, 2.13)		1.99 (0.96, 4.11)	1.73 (0.90, 3.33)
rs1981492									
G:G	203/1148	1.00 (Ref)	1.00 (Ref)	112/588	1.00 (Ref)	1.00 (Ref)	80/537	1.00 (Ref)	1.00 (Ref)
A:G	170/864	1.13 (0.81, 1.56)	1.12 (0.82, 1.53)	93/432	1.26 (0.81, 1.96)	1.27 (0.83, 1.92)	71/418	1.00 (0.60, 1.66)	0.99 (0.62, 1.59)
A:A	33/217	0.84 (0.49, 1.43)	0.86 (0.52, 1.41)	15/94	0.58 (0.26, 1.32)	0.69 (0.35, 1.37)	17/119	1.23 (0.59, 2.57)	1.21 (0.63, 2.33)
Log-Add		0.99 (0.79, 1.24)	0.99 (0.79, 1.23)		0.94 (0.68, 1.30)	0.96 (0.70, 1.31)		1.08 (0.77, 1.51)	1.09 (0.78, 1.51)
Dominant		1.06 (0.78, 1.44)	1.05 (0.78, 1.42)		1.10 (0.73, 1.68)	1.11 (0.74, 1.66)		1.05 (0.66, 1.69)	1.05 (0.67, 1.65)
Recessive		0.80 (0.48, 1.33)	0.82 (0.51, 1.33)		0.53 (0.24, 1.16)	0.64 (0.32, 1.25)		1.23 (0.61, 2.49)	1.22 (0.65, 2.29)
rs2014300									
G:G	312/1740	1.00 (Ref)	1.00 (Ref)	170/874	1.00 (Ref)	1.00 (Ref)	128/837	1.00 (Ref)	1.00 (Ref)
A:G	83/478	0.93 (0.64, 1.35)	0.93 (0.65, 1.34)	45/241	0.95 (0.56, 1.59)	0.91 (0.56, 1.48)	35/228	0.86 (0.48, 1.55)	0.88 (0.52, 1.51)
A:A	7/51	0.94 (0.33, 2.72)	0.96 (0.41, 2.21)	3/21	1.04 (0.22, 4.82)	0.97 (0.34, 2.71)	4/29	0.96 (0.20, 4.58)	0.99 (0.35, 2.77)
Log-Add		0.94 (0.68, 1.29)	0.94 (0.69, 1.29)		0.97 (0.62, 1.52)	0.92 (0.60, 1.42)		0.90 (0.55, 1.47)	0.91 (0.58, 1.44)
Dominant		0.93 (0.65, 1.33)	0.93 (0.66, 1.33)		0.95 (0.58, 1.58)	0.91 (0.56, 1.46)		0.87 (0.50, 1.52)	0.89 (0.53, 1.49)
Recessive		0.96 (0.33, 2.75)	0.97 (0.42, 2.23)		1.05 (0.23, 4.85)	0.98 (0.35, 2.74)		0.99 (0.21, 4.69)	1.00 (0.36, 2.80)
rs2057482									
C:C	269/1453	1.00 (Ref)	1.00 (Ref)	139/703	1.00 (Ref)	1.00 (Ref)	119/721	1.00 (Ref)	1.00 (Ref)
T:C	128/676	1.03 (0.74, 1.44)	1.03 (0.75, 1.42)	74/362	0.83 (0.52, 1.32)	0.84 (0.54, 1.30)	48/303	1.08 (0.65, 1.81)	1.08 (0.67, 1.74)
T:T	14/100	0.95 (0.45, 2.04)	0.96 (0.49, 1.86)	7/55	0.83 (0.30, 2.36)	0.91 (0.40, 2.07)	6/45	1.03 (0.33, 3.25)	1.00 (0.41, 2.43)
Log-Add		1.01 (0.77, 1.31)	1.01 (0.77, 1.31)		0.87 (0.60, 1.26)	0.87 (0.61, 1.25)		1.05 (0.70, 1.58)	1.05 (0.71, 1.54)
Dominant		1.02 (0.74, 1.41)	1.02 (0.75, 1.39)		0.83 (0.53, 1.30)	0.84 (0.55, 1.28)		1.07 (0.66, 1.75)	1.07 (0.67, 1.70)
Recessive		0.94 (0.44, 2.00)	0.95 (0.49, 1.84)		0.89 (0.32, 2.48)	0.94 (0.41, 2.14)		1.01 (0.32, 3.14)	0.99 (0.41, 2.38)
rs222851									
A:A	148/886	1.00 (Ref)	1.00 (Ref)	79/438	1.00 (Ref)	1.00 (Ref)	60/430	1.00 (Ref)	1.00 (Ref)
A:G	190/1001	1.29 (0.92, 1.82)	1.26 (0.91, 1.75)	104/504	1.16 (0.72, 1.86)	1.12 (0.72, 1.74)	78/476	1.37 (0.82, 2.30)	1.30 (0.81, 2.11)
G:G	63/327	1.39 (0.86, 2.24)	1.33 (0.84, 2.08)	38/163	1.75 (0.93, 3.28)	1.58 (0.89, 2.82)	25/162	0.98 (0.44, 2.18)	0.97 (0.49, 1.92)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		1.20 (0.96, 1.51)	1.20 (0.96, 1.49)		1.29 (0.95, 1.76)	1.28 (0.94, 1.73)		1.08 (0.76, 1.54)	1.07 (0.76, 1.51)
Dominant		1.31 (0.95, 1.81)	1.29 (0.94, 1.77)		1.28 (0.82, 2.00)	1.26 (0.82, 1.93)		1.28 (0.78, 2.10)	1.23 (0.77, 1.96)
Recessive		1.20 (0.78, 1.86)	1.18 (0.78, 1.79)		1.61 (0.91, 2.84)	1.50 (0.88, 2.56)		0.83 (0.39, 1.73)	0.86 (0.45, 1.65)
rs2230793									
A:A	204/1076	1.00 (Ref)	1.00 (Ref)	108/539	1.00 (Ref)	1.00 (Ref)	87/520	1.00 (Ref)	1.00 (Ref)
A:C	170/934	1.07 (0.77, 1.47)	1.07 (0.78, 1.46)	96/477	1.27 (0.81, 1.97)	1.24 (0.81, 1.88)	66/442	0.87 (0.53, 1.42)	0.88 (0.55, 1.40)
C:C	35/233	0.93 (0.54, 1.59)	0.94 (0.57, 1.55)	15/109	0.68 (0.30, 1.52)	0.76 (0.38, 1.51)	19/116	1.38 (0.65, 2.93)	1.29 (0.67, 2.50)
Log-Add		1.00 (0.79, 1.26)	1.00 (0.80, 1.26)		0.98 (0.71, 1.36)	0.98 (0.72, 1.35)		1.06 (0.75, 1.51)	1.07 (0.76, 1.49)
Dominant		1.04 (0.77, 1.41)	1.04 (0.77, 1.40)		1.14 (0.75, 1.75)	1.12 (0.75, 1.68)		0.96 (0.60, 1.52)	0.97 (0.62, 1.51)
Recessive		0.90 (0.54, 1.51)	0.91 (0.56, 1.47)		0.60 (0.28, 1.32)	0.70 (0.36, 1.37)		1.48 (0.72, 3.02)	1.35 (0.72, 2.57)
rs2269700									
T:T	220/1519	1.00 (Ref)	1.00 (Ref)	116/761	1.00 (Ref)	1.00 (Ref)	98/728	1.00 (Ref)	1.00 (Ref)
C:T	183/652	1.00 (0.72, 1.39)	1.00 (0.72, 1.38)	104/322	0.94 (0.60, 1.48)	0.94 (0.61, 1.45)	68/320	1.07 (0.64, 1.79)	1.06 (0.66, 1.73)
C:C	14/90	0.58 (0.24, 1.38)	0.69 (0.34, 1.41)	6/49	**0.17 (0.04, 0.79)**	0.41 (0.16, 1.05)	6/39	1.10 (0.33, 3.67)	1.06 (0.43, 2.64)
Log-Add		0.90 (0.69, 1.19)	0.91 (0.69, 1.18)		0.74 (0.50, 1.09)	0.73 (0.50, 1.07)		1.06 (0.70, 1.61)	1.06 (0.71, 1.58)
Dominant		0.94 (0.69, 1.30)	0.94 (0.69, 1.29)		0.82 (0.52, 1.27)	0.81 (0.53, 1.23)		1.07 (0.65, 1.75)	1.07 (0.67, 1.71)
Recessive		0.58 (0.25, 1.37)	0.69 (0.34, 1.40)		**0.18 (0.04, 0.80)**	0.42 (0.16, 1.06)		1.08 (0.33, 3.57)	1.05 (0.43, 2.60)
rs2274223									
A:A	263/1402	1.00 (Ref)	1.00 (Ref)	145/704	1.00 (Ref)	1.00 (Ref)	108/671	1.00 (Ref)	1.00 (Ref)
A:G	116/705	0.89 (0.63, 1.26)	0.90 (0.64, 1.25)	61/348	0.90 (0.55, 1.45)	0.88 (0.56, 1.39)	48/349	0.83 (0.48, 1.41)	0.85 (0.52, 1.39)
G:G	21/97	1.19 (0.60, 2.34)	1.17 (0.63, 2.16)	13/48	1.21 (0.49, 2.98)	1.14 (0.53, 2.46)	7/44	1.10 (0.32, 3.84)	1.08 (0.43, 2.74)
Log-Add		0.98 (0.76, 1.28)	0.99 (0.76, 1.28)		1.00 (0.70, 1.42)	0.98 (0.69, 1.39)		0.91 (0.59, 1.41)	0.92 (0.61, 1.40)
Dominant		0.93 (0.67, 1.29)	0.94 (0.68, 1.29)		0.94 (0.60, 1.48)	0.93 (0.60, 1.42)		0.85 (0.51, 1.42)	0.88 (0.54, 1.41)
Recessive		1.23 (0.63, 2.41)	1.20 (0.65, 2.20)		1.25 (0.51, 3.05)	1.17 (0.55, 2.51)		1.17 (0.34, 4.03)	1.11 (0.44, 2.82)
rs2292305									
T:T	181/1014	1.00 (Ref)	1.00 (Ref)	101/499	1.00 (Ref)	1.00 (Ref)	71/498	1.00 (Ref)	1.00 (Ref)
C:T	180/935	1.15 (0.83, 1.59)	1.14 (0.83, 1.57)	95/472	1.47 (0.92, 2.35)	1.43 (0.92, 2.21)	77/446	1.01 (0.62, 1.66)	1.03 (0.65, 1.64)
C:C	35/268	0.83 (0.48, 1.44)	0.85 (0.51, 1.41)	17/143	1.03 (0.48, 2.22)	1.03 (0.53, 2.02)	17/120	0.65 (0.28, 1.49)	0.72 (0.36, 1.46)

dbSNP no.	All			Low Flavonoid Intake			High Flavonoid Intake		
	ca/co	aOR[a]	sbOR[a]	ca/co	aOR[a]	sbOR[a]	ca/co	aOR[a]	sbOR[a]
Log-Add		0.99 (0.78, 1.25)	0.99 (0.79, 1.25)		1.15 (0.83, 1.59)	1.15 (0.84, 1.59)		0.88 (0.62, 1.25)	0.88 (0.63, 1.24)
Dominant		1.08 (0.79, 1.48)	1.08 (0.79, 1.46)		1.38 (0.88, 2.16)	1.36 (0.88, 2.08)		0.93 (0.58, 1.49)	0.94 (0.60, 1.47)
Recessive		0.77 (0.46, 1.31)	0.80 (0.49, 1.30)		0.85 (0.41, 1.73)	0.89 (0.47, 1.68)		0.65 (0.29, 1.42)	0.71 (0.36, 1.41)
rs2352028									
C:C	277/1430	1.00 (Ref)	1.00 (Ref)	159/712	1.00 (Ref)	1.00 (Ref)	110/692	1.00 (Ref)	1.00 (Ref)
C:T	127/717	1.00 (0.72, 1.39)	1.02 (0.74, 1.40)	58/361	0.78 (0.49, 1.25)	0.81 (0.52, 1.26)	59/341	1.24 (0.76, 2.02)	1.22 (0.77, 1.93)
T:T	15/124	0.71 (0.32, 1.57)	0.77 (0.39, 1.51)	11/66	0.80 (0.30, 2.16)	0.87 (0.39, 1.92)	4/58	0.45 (0.10, 1.95)	0.64 (0.25, 1.67)
Log-Add		0.93 (0.72, 1.21)	0.94 (0.73, 1.22)		0.83 (0.58, 1.20)	0.85 (0.59, 1.20)		1.00 (0.67, 1.50)	0.98 (0.66, 1.45)
Dominant		0.96 (0.70, 1.31)	0.97 (0.71, 1.32)		0.78 (0.50, 1.22)	0.81 (0.53, 1.23)		1.13 (0.70, 1.82)	1.10 (0.70, 1.72)
Recessive		0.71 (0.33, 1.56)	0.77 (0.39, 1.50)		0.86 (0.32, 2.31)	0.90 (0.41, 2.00)		0.42 (0.10, 1.79)	0.62 (0.24, 1.60)
rs2910164									
C:C	131/826	1.00 (Ref)	1.00 (Ref)	69/420	1.00 (Ref)	1.00 (Ref)	52/393	1.00 (Ref)	1.00 (Ref)
G:C	202/1040	1.04 (0.74, 1.46)	1.05 (0.76, 1.45)	111/497	1.00 (0.63, 1.60)	1.05 (0.68, 1.63)	84/523	1.24 (0.74, 2.11)	1.21 (0.75, 1.96)
G:G	63/394	0.69 (0.43, 1.11)	0.71 (0.45, 1.11)	32/218	0.58 (0.30, 1.14)	0.66 (0.36, 1.20)	29/168	0.93 (0.46, 1.91)	0.92 (0.49, 1.73)
Log-Add		0.87 (0.70, 1.09)	0.87 (0.70, 1.08)		0.81 (0.59, 1.10)	0.83 (0.62, 1.13)		1.01 (0.72, 1.42)	1.00 (0.72, 1.39)
Dominant		0.94 (0.68, 1.29)	0.94 (0.69, 1.29)		0.88 (0.56, 1.37)	0.91 (0.60, 1.40)		1.16 (0.70, 1.90)	1.13 (0.71, 1.80)
Recessive		0.67 (0.43, 1.04)	0.69 (0.46, 1.05)		0.58 (0.31, 1.07)	0.64 (0.37, 1.12)		0.82 (0.43, 1.57)	0.84 (0.47, 1.51)
rs2953									
T:T	222/1267	1.00 (Ref)	1.00 (Ref)	118/636	1.00 (Ref)	1.00 (Ref)	92/609	1.00 (Ref)	1.00 (Ref)
G:T	157/836	0.88 (0.64, 1.22)	0.88 (0.64, 1.20)	87/415	1.01 (0.64, 1.58)	1.00 (0.66, 1.54)	63/408	0.80 (0.48, 1.34)	0.80 (0.50, 1.29)
G:G	27/164	1.02 (0.55, 1.88)	1.02 (0.58, 1.79)	16/86	1.14 (0.49, 2.63)	1.07 (0.52, 2.20)	11/73	0.97 (0.38, 2.48)	1.01 (0.46, 2.21)
Log-Add		0.95 (0.74, 1.21)	0.94 (0.74, 1.20)		1.04 (0.74, 1.46)	1.03 (0.74, 1.43)		0.90 (0.61, 1.32)	0.90 (0.62, 1.30)
Dominant		0.90 (0.66, 1.23)	0.90 (0.66, 1.21)		1.03 (0.67, 1.57)	1.02 (0.68, 1.53)		0.83 (0.51, 1.34)	0.83 (0.53, 1.31)
Recessive		1.07 (0.58, 1.95)	1.06 (0.61, 1.85)		1.13 (0.50, 2.57)	1.07 (0.52, 2.17)		1.05 (0.42, 2.65)	1.07 (0.50, 2.33)
rs3130932									
T:T	200/1043	1.00 (Ref)	1.00 (Ref)	109/531	1.00 (Ref)	1.00 (Ref)	80/500	1.00 (Ref)	1.00 (Ref)
G:T	161/957	0.84 (0.61, 1.16)	0.85 (0.62, 1.16)	97/471	0.83 (0.53, 1.29)	0.87 (0.57, 1.32)	60/462	0.94 (0.56, 1.57)	0.92 (0.57, 1.48)
G:G	48/256	0.92 (0.57, 1.50)	0.94 (0.59, 1.48)	19/125	0.48 (0.23, 1.02)	0.59 (0.31, 1.12)	27/126	**2.05 (1.04, 4.05)**	1.77 (0.96, 3.27)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		0.92 (0.74, 1.15)	0.92 (0.74, 1.15)		0.74 (0.54, 1.02)	0.76 (0.56, 1.04)		1.30 (0.93, 1.82)	1.27 (0.92, 1.76)
Dominant		0.86 (0.64, 1.16)	0.86 (0.64, 1.16)		0.74 (0.49, 1.12)	0.77 (0.52, 1.15)		1.16 (0.72, 1.85)	1.14 (0.73, 1.77)
Recessive		1.00 (0.63, 1.59)	1.00 (0.64, 1.56)		0.53 (0.26, 1.08)	0.62 (0.33, 1.16)		**2.11 (1.12, 4.00)**	**1.82 (1.01, 3.29)**
rs3204145									
T:T	181/1054	1.00 (Ref)	1.00 (Ref)	93/507	1.00 (Ref)	1.00 (Ref)	76/526	1.00 (Ref)	1.00 (Ref)
A:T	182/959	1.28 (0.93, 1.77)	1.26 (0.92, 1.72)	105/505	1.48 (0.94, 2.31)	1.45 (0.95, 2.22)	72/437	1.06 (0.65, 1.74)	1.04 (0.66, 1.66)
A:A	38/250	0.92 (0.55, 1.54)	0.91 (0.56, 1.48)	20/133	0.89 (0.44, 1.80)	0.87 (0.46, 1.63)	18/114	1.09 (0.49, 2.39)	1.04 (0.52, 2.07)
Log-Add		1.05 (0.84, 1.32)	1.04 (0.84, 1.30)		1.08 (0.79, 1.47)	1.07 (0.79, 1.44)		1.05 (0.74, 1.49)	1.03 (0.73, 1.46)
Dominant		1.20 (0.88, 1.63)	1.18 (0.87, 1.59)		1.33 (0.87, 2.05)	1.31 (0.87, 1.97)		1.07 (0.67, 1.71)	1.05 (0.67, 1.64)
Recessive		0.81 (0.50, 1.32)	0.82 (0.52, 1.30)		0.72 (0.37, 1.40)	0.74 (0.40, 1.35)		1.05 (0.50, 2.23)	1.02 (0.53, 1.98)
rs3729629									
G:G	210/1019	1.00 (Ref)	1.00 (Ref)	120/478	1.00 (Ref)	1.00 (Ref)	82/522	1.00 (Ref)	1.00 (Ref)
C:G	172/987	0.93 (0.68, 1.28)	0.95 (0.70, 1.28)	92/517	**0.62 (0.40, 0.97)**	0.67 (0.44, 1.02)	73/455	1.29 (0.80, 2.10)	1.28 (0.81, 2.01)
C:C	39/248	0.69 (0.39, 1.21)	0.74 (0.44, 1.23)	15/132	0.43 (0.19, 1.01)	0.55 (0.28, 1.10)	20/111	1.06 (0.47, 2.40)	1.03 (0.51, 2.08)
Log-Add		0.87 (0.69, 1.10)	0.88 (0.70, 1.11)		**0.64 (0.46, 0.90)**	**0.66 (0.48, 0.92)**		1.12 (0.79, 1.58)	1.12 (0.80, 1.56)
Dominant		0.89 (0.66, 1.20)	0.90 (0.67, 1.20)		**0.59 (0.39, 0.90)**	**0.62 (0.41, 0.93)**		1.25 (0.79, 1.98)	1.24 (0.80, 1.91)
Recessive		0.71 (0.42, 1.23)	0.75 (0.46, 1.24)		0.54 (0.24, 1.23)	0.64 (0.32, 1.26)		0.94 (0.43, 2.04)	0.94 (0.48, 1.86)
rs3734637									
A:A	271/1339	1.00 (Ref)	1.00 (Ref)	157/669	1.00 (Ref)	1.00 (Ref)	103/652	1.00 (Ref)	1.00 (Ref)
A:C	118/756	**0.71 (0.50, 1.00)**	0.73 (0.53, 1.02)	57/381	0.65 (0.40, 1.05)	0.69 (0.44, 1.08)	55/356	0.94 (0.56, 1.57)	0.98 (0.61, 1.59)
C:C	21/156	0.51 (0.25, 1.01)	0.58 (0.32, 1.05)	11/76	0.57 (0.22, 1.45)	0.67 (0.32, 1.43)	9/78	0.47 (0.17, 1.29)	0.60 (0.27, 1.31)
Log-Add		**0.71 (0.55, 0.92)**	**0.72 (0.56, 0.93)**		0.70 (0.49, 1.01)	0.71 (0.50, 1.01)		0.80 (0.55, 1.16)	0.81 (0.56, 1.16)
Dominant		**0.67 (0.48, 0.92)**	**0.69 (0.50, 0.94)**		**0.64 (0.41, 1.00)**	0.66 (0.43, 1.01)		0.83 (0.51, 1.34)	0.85 (0.54, 1.34)
Recessive		0.56 (0.29, 1.11)	0.62 (0.34, 1.13)		0.65 (0.25, 1.64)	0.73 (0.34, 1.55)		0.48 (0.18, 1.30)	0.60 (0.27, 1.31)
rs3740535									
G:G	226/1233	1.00 (Ref)	1.00 (Ref)	118/636	1.00 (Ref)	1.00 (Ref)	96/574	1.00 (Ref)	1.00 (Ref)
A:G	153/844	0.90 (0.65, 1.24)	0.90 (0.66, 1.24)	85/418	1.14 (0.73, 1.78)	1.11 (0.73, 1.69)	62/411	0.69 (0.42, 1.14)	0.74 (0.46, 1.18)
A:A	34/175	0.92 (0.52, 1.61)	0.92 (0.55, 1.55)	20/77	1.74 (0.83, 3.66)	1.51 (0.77, 2.95)	14/97	0.45 (0.18, 1.12)	0.59 (0.28, 1.22)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		0.93 (0.74, 1.18)	0.93 (0.74, 1.18)		1.25 (0.91, 1.72)	1.23 (0.89, 1.68)		**0.68 (0.47, 0.99)**	0.70 (0.49, 1.01)
Dominant		0.90 (0.66, 1.22)	0.90 (0.67, 1.22)		1.24 (0.81, 1.88)	1.21 (0.81, 1.80)		0.64 (0.40, 1.03)	0.67 (0.43, 1.05)
Recessive		0.96 (0.55, 1.65)	0.96 (0.58, 1.59)		1.65 (0.81, 3.38)	1.46 (0.76, 2.81)		0.53 (0.22, 1.28)	0.65 (0.31, 1.33)
rs3801790									
A:A	153/856	1.00 (Ref)	1.00 (Ref)	83/445	1.00 (Ref)	1.00 (Ref)	66/393	1.00 (Ref)	1.00 (Ref)
A:G	192/994	1.15 (0.82, 1.61)	1.16 (0.84, 1.60)	105/487	1.40 (0.88, 2.22)	1.38 (0.89, 2.14)	76/495	0.81 (0.48, 1.36)	0.82 (0.51, 1.33)
G:G	61/368	0.80 (0.49, 1.28)	0.81 (0.52, 1.27)	32/186	0.74 (0.38, 1.45)	0.80 (0.44, 1.44)	26/170	0.81 (0.39, 1.66)	0.85 (0.45, 1.59)
Log-Add		0.94 (0.76, 1.18)	0.95 (0.76, 1.18)		0.96 (0.71, 1.29)	0.97 (0.73, 1.31)		0.88 (0.62, 1.24)	0.88 (0.63, 1.23)
Dominant		1.05 (0.77, 1.45)	1.05 (0.77, 1.44)		1.20 (0.77, 1.86)	1.20 (0.78, 1.82)		0.81 (0.50, 1.32)	0.81 (0.51, 1.29)
Recessive		0.73 (0.47, 1.14)	0.75 (0.50, 1.14)		0.62 (0.33, 1.14)	0.68 (0.39, 1.19)		0.91 (0.47, 1.76)	0.93 (0.51, 1.68)
rs3929									
G:G	263/1531	1.00 (Ref)	1.00 (Ref)	135/749	1.00 (Ref)	1.00 (Ref)	115/749	1.00 (Ref)	1.00 (Ref)
C:G	128/673	1.00 (0.72, 1.40)	1.00 (0.73, 1.38)	77/362	0.87 (0.55, 1.37)	0.89 (0.58, 1.37)	47/304	1.16 (0.70, 1.93)	1.13 (0.70, 1.82)
C:C	16/92	1.06 (0.47, 2.38)	1.05 (0.52, 2.11)	10/37	1.14 (0.36, 3.62)	1.10 (0.45, 2.69)	5/54	1.00 (0.29, 3.41)	1.00 (0.40, 2.49)
Log-Add		1.01 (0.77, 1.33)	1.01 (0.78, 1.33)		0.93 (0.64, 1.37)	0.95 (0.66, 1.38)		1.09 (0.73, 1.64)	1.08 (0.73, 1.60)
Dominant		1.01 (0.74, 1.39)	1.01 (0.74, 1.38)		0.89 (0.57, 1.38)	0.92 (0.60, 1.39)		1.14 (0.70, 1.86)	1.11 (0.70, 1.77)
Recessive		1.06 (0.48, 2.36)	1.05 (0.52, 2.10)		1.19 (0.38, 3.75)	1.12 (0.46, 2.74)		0.96 (0.28, 3.22)	0.98 (0.39, 2.43)
rs4072391									
C:C	332/1870	1.00 (Ref)	1.00 (Ref)	179/935	1.00 (Ref)	1.00 (Ref)	136/902	1.00 (Ref)	1.00 (Ref)
C:T	66/364	1.06 (0.70, 1.60)	1.04 (0.70, 1.55)	34/186	1.00 (0.56, 1.77)	0.97 (0.57, 1.65)	30/170	1.15 (0.61, 2.15)	1.11 (0.62, 1.98)
T:T	7/32	0.57 (0.17, 1.88)	0.74 (0.30, 1.79)	3/13	0.34 (0.05, 2.28)	0.72 (0.24, 2.13)	4/19	0.75 (0.15, 3.66)	0.91 (0.32, 2.57)
Log-Add		0.95 (0.67, 1.34)	0.95 (0.67, 1.32)		0.86 (0.52, 1.42)	0.87 (0.54, 1.39)		1.03 (0.62, 1.71)	1.03 (0.64, 1.66)
Dominant		1.00 (0.67, 1.48)	0.99 (0.67, 1.45)		0.92 (0.52, 1.60)	0.90 (0.54, 1.52)		1.09 (0.60, 1.98)	1.07 (0.61, 1.86)
Recessive		0.57 (0.17, 1.86)	0.73 (0.30, 1.78)		0.34 (0.05, 2.27)	0.72 (0.24, 2.13)		0.73 (0.15, 3.58)	0.90 (0.32, 2.55)
rs42031									
A:A	365/2061	1.00 (Ref)	1.00 (Ref)	196/1027	1.00 (Ref)	1.00 (Ref)	152/1000	1.00 (Ref)	1.00 (Ref)
A:T	51/200	**1.78 (1.11, 2.86)**	**1.70 (1.08, 2.66)**	28/102	**2.01 (1.05, 3.85)**	1.72 (0.94, 3.14)	21/93	1.78 (0.87, 3.64)	1.58 (0.83, 3.01)
T:T	2/13	2.05 (0.37, 11.37)	1.30 (0.42, 4.06)	2/7	3.70 (0.59, 23.02)	1.57 (0.47, 5.21)	/6	0.00 (0.00, .0)	0.91 (0.24, 3.40)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		**1.69 (1.12, 2.55)**	**1.64 (1.10, 2.45)**		**1.98 (1.15, 3.40)**	**1.83 (1.09, 3.09)**		1.57 (0.81, 3.04)	1.44 (0.78, 2.65)
Dominant		**1.80 (1.14, 2.85)**	**1.72 (1.11, 2.67)**		**2.12 (1.14, 3.95)**	**1.86 (1.04, 3.32)**		1.71 (0.84, 3.47)	1.53 (0.80, 2.90)
Recessive		1.92 (0.35, 10.63)	1.28 (0.41, 3.96)		3.43 (0.56, 21.11)	1.55 (0.47, 5.12)		0.00 (0.00, .0)	0.90 (0.24, 3.38)
rs4678680									
T:T	360/2046	1.00 (Ref)	1.00 (Ref)	194/1031	1.00 (Ref)	1.00 (Ref)	150/976	1.00 (Ref)	1.00 (Ref)
G:T	46/249	1.00 (0.60, 1.64)	0.99 (0.62, 1.59)	25/118	1.35 (0.70, 2.62)	1.21 (0.66, 2.23)	19/129	0.68 (0.31, 1.50)	0.74 (0.38, 1.47)
G:G	4/11	0.84 (0.15, 4.63)	0.93 (0.32, 2.72)	4/4	1.61 (0.20, 12.80)	1.19 (0.37, 3.86)	/7	0.00 (0.00, .0)	0.79 (0.22, 2.85)
Log-Add		0.98 (0.63, 1.51)	0.97 (0.64, 1.48)		1.33 (0.75, 2.34)	1.25 (0.73, 2.13)		0.63 (0.30, 1.34)	0.69 (0.36, 1.32)
Dominant		0.98 (0.61, 1.60)	0.98 (0.62, 1.55)		1.37 (0.73, 2.59)	1.25 (0.70, 2.25)		0.65 (0.30, 1.41)	0.71 (0.36, 1.38)
Recessive		0.84 (0.15, 4.63)	0.93 (0.32, 2.73)		1.57 (0.20, 12.40)	1.19 (0.37, 3.85)		0.00 (0.00, .0)	0.80 (0.22, 2.87)
rs4730775									
C:C	258/1282	1.00 (Ref)	1.00 (Ref)	145/641	1.00 (Ref)	1.00 (Ref)	105/618	1.00 (Ref)	1.00 (Ref)
C:T	124/794	0.77 (0.55, 1.08)	0.79 (0.57, 1.09)	63/396	0.71 (0.45, 1.14)	0.75 (0.48, 1.17)	53/383	0.73 (0.43, 1.22)	0.77 (0.47, 1.25)
T:T	23/152	0.67 (0.36, 1.25)	0.72 (0.41, 1.27)	12/80	0.68 (0.28, 1.62)	0.80 (0.39, 1.67)	10/70	0.73 (0.28, 1.88)	0.81 (0.38, 1.76)
Log-Add		0.79 (0.62, 1.02)	0.80 (0.63, 1.03)		0.77 (0.54, 1.09)	0.80 (0.57, 1.12)		0.79 (0.54, 1.17)	0.81 (0.56, 1.17)
Dominant		0.75 (0.55, 1.03)	0.76 (0.56, 1.04)		0.71 (0.46, 1.09)	0.75 (0.49, 1.13)		0.73 (0.45, 1.18)	0.76 (0.48, 1.20)
Recessive		0.73 (0.39, 1.36)	0.77 (0.44, 1.35)		0.75 (0.32, 1.78)	0.86 (0.42, 1.77)		0.82 (0.32, 2.07)	0.87 (0.40, 1.86)
rs4975616									
A:A	285/1606	1.00 (Ref)	1.00 (Ref)	156/789	1.00 (Ref)	1.00 (Ref)	118/792	1.00 (Ref)	1.00 (Ref)
A:G	104/570	1.12 (0.79, 1.59)	1.11 (0.79, 1.56)	53/292	1.22 (0.75, 1.98)	1.14 (0.72, 1.80)	44/263	1.13 (0.65, 1.95)	1.10 (0.66, 1.83)
G:G	13/67	1.16 (0.48, 2.83)	1.10 (0.52, 2.34)	10/37	1.36 (0.45, 4.10)	1.17 (0.49, 2.82)	3/30	1.17 (0.26, 5.19)	1.07 (0.38, 2.98)
Log-Add		1.10 (0.83, 1.47)	1.10 (0.83, 1.46)		1.19 (0.81, 1.76)	1.14 (0.78, 1.66)		1.11 (0.70, 1.76)	1.10 (0.71, 1.70)
Dominant		1.12 (0.80, 1.57)	1.12 (0.80, 1.55)		1.23 (0.77, 1.96)	1.16 (0.74, 1.81)		1.13 (0.67, 1.92)	1.11 (0.68, 1.82)
Recessive		1.13 (0.46, 2.73)	1.08 (0.51, 2.29)		1.29 (0.43, 3.84)	1.14 (0.48, 2.74)		1.14 (0.26, 5.01)	1.06 (0.38, 2.95)
rs520692									
A:A	314/1724	1.00 (Ref)	1.00 (Ref)	169/877	1.00 (Ref)	1.00 (Ref)	130/822	1.00 (Ref)	1.00 (Ref)
A:G	97/504	1.13 (0.78, 1.62)	1.12 (0.79, 1.59)	51/244	1.31 (0.79, 2.18)	1.29 (0.80, 2.09)	42/247	1.07 (0.62, 1.83)	1.07 (0.65, 1.78)
G:G	3/42	0.59 (0.12, 2.82)	0.79 (0.29, 2.13)	1/14	0.65 (0.07, 6.12)	0.93 (0.29, 2.93)	2/25	0.60 (0.06, 6.32)	0.85 (0.27, 2.70)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		1.04 (0.75, 1.45)	1.04 (0.76, 1.43)		1.19 (0.75, 1.88)	1.20 (0.78, 1.86)		1.00 (0.61, 1.64)	1.01 (0.63, 1.60)
Dominant		1.09 (0.76, 1.56)	1.08 (0.77, 1.53)		1.27 (0.77, 2.09)	1.26 (0.78, 2.02)		1.04 (0.61, 1.77)	1.04 (0.63, 1.71)
Recessive		0.58 (0.12, 2.74)	0.78 (0.29, 2.10)		0.62 (0.07, 5.78)	0.91 (0.29, 2.87)		0.59 (0.06, 6.21)	0.85 (0.27, 2.68)
rs7372209									
C:C	213/1131	1.00 (Ref)	1.00 (Ref)	123/565	1.00 (Ref)	1.00 (Ref)	81/545	1.00 (Ref)	1.00 (Ref)
C:T	145/908	0.85 (0.61, 1.18)	0.86 (0.63, 1.18)	76/457	0.69 (0.44, 1.08)	0.73 (0.47, 1.11)	63/435	0.99 (0.60, 1.65)	0.97 (0.60, 1.56)
T:T	41/215	0.82 (0.48, 1.40)	0.84 (0.51, 1.38)	18/117	0.58 (0.26, 1.26)	0.66 (0.34, 1.30)	21/93	1.11 (0.51, 2.40)	1.09 (0.55, 2.14)
Log-Add		0.88 (0.70, 1.12)	0.89 (0.70, 1.11)		0.73 (0.52, 1.01)	0.74 (0.54, 1.02)		1.03 (0.73, 1.46)	1.02 (0.73, 1.44)
Dominant		0.85 (0.62, 1.15)	0.85 (0.63, 1.15)		0.66 (0.43, 1.02)	0.69 (0.46, 1.04)		1.02 (0.63, 1.63)	1.00 (0.64, 1.57)
Recessive		0.87 (0.52, 1.47)	0.89 (0.55, 1.44)		0.67 (0.31, 1.44)	0.74 (0.38, 1.43)		1.11 (0.53, 2.34)	1.10 (0.57, 2.12)
rs738722									
C:C	226/1220	1.00 (Ref)	1.00 (Ref)	128/613	1.00 (Ref)	1.00 (Ref)	91/586	1.00 (Ref)	1.00 (Ref)
C:T	146/806	0.90 (0.65, 1.26)	0.92 (0.67, 1.26)	73/407	**0.62 (0.38, 0.99)**	**0.64 (0.41, 0.99)**	63/383	1.34 (0.81, 2.23)	1.31 (0.81, 2.10)
T:T	28/179	0.98 (0.52, 1.85)	0.99 (0.55, 1.75)	15/87	0.83 (0.34, 2.02)	0.88 (0.42, 1.86)	13/90	1.47 (0.59, 3.69)	1.29 (0.59, 2.82)
Log-Add		0.95 (0.74, 1.22)	0.95 (0.74, 1.22)		0.75 (0.52, 1.08)	0.75 (0.53, 1.07)		1.27 (0.87, 1.84)	1.26 (0.88, 1.81)
Dominant		0.92 (0.67, 1.25)	0.93 (0.68, 1.26)		0.65 (0.41, 1.01)	0.66 (0.43, 1.01)		1.36 (0.84, 2.21)	1.34 (0.85, 2.12)
Recessive		1.02 (0.55, 1.90)	1.01 (0.57, 1.79)		1.00 (0.42, 2.37)	1.00 (0.48, 2.09)		1.31 (0.54, 3.20)	1.20 (0.56, 2.57)
rs748404									
T:T	362/2027	1.00 (Ref)	1.00 (Ref)	194/1023	1.00 (Ref)	1.00 (Ref)	151/968	1.00 (Ref)	1.00 (Ref)
C:T	45/215	1.16 (0.69, 1.94)	1.15 (0.71, 1.86)	24/99	1.73 (0.87, 3.41)	1.51 (0.80, 2.83)	19/110	0.79 (0.35, 1.76)	0.85 (0.43, 1.70)
C:C	/12	0.00 (0.00, .0)	0.67 (0.19, 2.30)	/5	0.00 (0.00, .0)	0.94 (0.24, 3.63)	/7	0.00 (0.00, .0)	0.76 (0.21, 2.72)
Log-Add		1.01 (0.62, 1.64)	1.01 (0.63, 1.60)		1.59 (0.83, 3.04)	1.43 (0.78, 2.63)		0.69 (0.32, 1.46)	0.76 (0.39, 1.46)
Dominant		1.08 (0.65, 1.81)	1.07 (0.66, 1.74)		1.68 (0.85, 3.31)	1.48 (0.79, 2.77)		0.72 (0.32, 1.60)	0.79 (0.40, 1.57)
Recessive		0.00 (0.00, .0)	0.67 (0.19, 2.29)		0.00 (0.00, .0)	0.94 (0.24, 3.62)		0.00 (0.00, .0)	0.76 (0.21, 2.72)
rs7626795									
A:A	267/1481	1.00 (Ref)	1.00 (Ref)	147/747	1.00 (Ref)	1.00 (Ref)	113/710	1.00 (Ref)	1.00 (Ref)
A:G	125/666	1.07 (0.76, 1.49)	1.07 (0.78, 1.48)	65/325	1.30 (0.82, 2.07)	1.21 (0.78, 1.89)	50/326	0.84 (0.50, 1.40)	0.86 (0.53, 1.39)
G:G	19/101	1.19 (0.54, 2.63)	1.17 (0.58, 2.35)	11/52	1.05 (0.33, 3.41)	1.10 (0.44, 2.71)	7/47	1.30 (0.38, 4.42)	1.14 (0.45, 2.92)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		1.08 (0.82, 1.41)	1.09 (0.83, 1.43)		1.18 (0.81, 1.73)	1.17 (0.81, 1.69)		0.94 (0.61, 1.44)	0.95 (0.63, 1.43)
Dominant		1.08 (0.78, 1.49)	1.09 (0.80, 1.49)		1.27 (0.81, 1.99)	1.21 (0.79, 1.86)		0.88 (0.54, 1.44)	0.90 (0.56, 1.43)
Recessive		1.16 (0.53, 2.56)	1.15 (0.58, 2.30)		0.97 (0.30, 3.10)	1.06 (0.43, 2.60)		1.37 (0.41, 4.62)	1.17 (0.46, 2.99)
rs8708									
A:A	276/1515	1.00 (Ref)	1.00 (Ref)	150/741	1.00 (Ref)	1.00 (Ref)	115/743	1.00 (Ref)	1.00 (Ref)
A:G	101/625	1.06 (0.75, 1.51)	1.05 (0.75, 1.47)	56/333	1.09 (0.68, 1.76)	1.04 (0.66, 1.64)	40/284	1.01 (0.59, 1.73)	1.02 (0.62, 1.68)
G:G	20/92	1.22 (0.58, 2.57)	1.16 (0.60, 2.25)	9/44	1.37 (0.48, 3.96)	1.24 (0.53, 2.91)	10/45	1.16 (0.36, 3.77)	1.06 (0.43, 2.63)
Log-Add		1.08 (0.82, 1.42)	1.07 (0.82, 1.40)		1.12 (0.77, 1.64)	1.10 (0.76, 1.59)		1.04 (0.68, 1.59)	1.03 (0.69, 1.55)
Dominant		1.08 (0.78, 1.51)	1.07 (0.78, 1.48)		1.12 (0.71, 1.77)	1.08 (0.70, 1.67)		1.03 (0.62, 1.71)	1.03 (0.64, 1.67)
Recessive		1.20 (0.57, 2.51)	1.14 (0.59, 2.21)		1.34 (0.47, 3.82)	1.23 (0.52, 2.88)		1.16 (0.36, 3.72)	1.06 (0.43, 2.62)
rs915894									
C:C	125/661	1.00 (Ref)	1.00 (Ref)	61/317	1.00 (Ref)	1.00 (Ref)	59/330	1.00 (Ref)	1.00 (Ref)
A:C	195/1055	0.98 (0.69, 1.40)	0.99 (0.70, 1.39)	109/529	1.12 (0.68, 1.86)	1.17 (0.73, 1.88)	75/512	0.84 (0.49, 1.43)	0.85 (0.52, 1.38)
A:A	84/506	1.03 (0.67, 1.60)	1.03 (0.68, 1.56)	47/263	0.94 (0.51, 1.75)	1.01 (0.57, 1.76)	35/231	1.16 (0.60, 2.25)	1.13 (0.63, 2.04)
Log-Add		1.01 (0.82, 1.26)	1.02 (0.82, 1.26)		0.98 (0.72, 1.33)	1.02 (0.76, 1.37)		1.05 (0.75, 1.46)	1.04 (0.75, 1.44)
Dominant		1.00 (0.71, 1.39)	1.00 (0.72, 1.39)		1.06 (0.66, 1.72)	1.13 (0.71, 1.78)		0.92 (0.56, 1.52)	0.93 (0.58, 1.48)
Recessive		1.05 (0.72, 1.53)	1.04 (0.72, 1.50)		0.88 (0.52, 1.48)	0.92 (0.56, 1.50)		1.29 (0.72, 2.31)	1.23 (0.72, 2.11)
rs9266									
C:C	254/1428	1.00 (Ref)	1.00 (Ref)	140/728	1.00 (Ref)	1.00 (Ref)	103/674	1.00 (Ref)	1.00 (Ref)
C:T	139/710	1.27 (0.91, 1.76)	1.25 (0.91, 1.72)	77/359	1.12 (0.71, 1.76)	1.11 (0.72, 1.72)	58/338	1.40 (0.85, 2.31)	1.34 (0.84, 2.14)
T:T	17/116	0.92 (0.45, 1.90)	0.93 (0.49, 1.77)	6/49	0.69 (0.23, 2.09)	0.85 (0.36, 2.01)	9/65	1.56 (0.61, 4.04)	1.33 (0.60, 2.94)
Log-Add		1.12 (0.86, 1.44)	1.11 (0.86, 1.43)		0.99 (0.68, 1.43)	1.01 (0.71, 1.45)		1.32 (0.91, 1.91)	1.29 (0.90, 1.85)
Dominant		1.22 (0.89, 1.66)	1.20 (0.88, 1.63)		1.06 (0.68, 1.64)	1.07 (0.70, 1.63)		1.42 (0.88, 2.29)	1.38 (0.88, 2.16)
Recessive		0.85 (0.42, 1.74)	0.88 (0.47, 1.65)		0.66 (0.22, 1.99)	0.83 (0.35, 1.95)		1.39 (0.55, 3.52)	1.24 (0.57, 2.71)
rs9267673									
C:C	278/1610	1.00 (Ref)	1.00 (Ref)	152/807	1.00 (Ref)	1.00 (Ref)	114/774	1.00 (Ref)	1.00 (Ref)
C:T	108/568	1.16 (0.82, 1.66)	1.15 (0.81, 1.61)	57/294	1.29 (0.78, 2.14)	1.20 (0.74, 1.92)	46/266	1.02 (0.59, 1.74)	1.02 (0.61, 1.68)
T:T	15/70	1.84 (0.78, 4.34)	1.55 (0.73, 3.28)	9/24	**4.53 (1.57, 13.03)**	2.44 (0.97, 6.15)	6/43	0.93 (0.24, 3.60)	0.95 (0.36, 2.51)

	All			Low Flavonoid Intake			High Flavonoid Intake		
dbSNP no.	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**	**ca/co**	**aOR[a]**	**sbOR[a]**
Log-Add		1.23 (0.92, 1.65)	1.22 (0.92, 1.63)		**1.59 (1.05, 2.40)**	**1.51 (1.02, 2.26)**		1.00 (0.64, 1.55)	0.99 (0.65, 1.52)
Dominant		1.22 (0.87, 1.71)	1.21 (0.87, 1.68)		1.47 (0.91, 2.38)	1.39 (0.88, 2.20)		1.01 (0.60, 1.69)	1.00 (0.61, 1.64)
Recessive		1.77 (0.75, 4.13)	1.51 (0.71, 3.18)		**4.21 (1.48, 11.99)**	2.37 (0.95, 5.94)		0.92 (0.24, 3.55)	0.95 (0.36, 2.50)
rs9275572									
G:G	240/1186	1.00 (Ref)	1.00 (Ref)	134/580	1.00 (Ref)	1.00 (Ref)	96/579	1.00 (Ref)	1.00 (Ref)
A:G	140/851	0.96 (0.69, 1.34)	0.96 (0.70, 1.32)	74/438	0.67 (0.42, 1.06)	0.69 (0.44, 1.07)	58/403	1.34 (0.81, 2.22)	1.29 (0.80, 2.07)
A:A	23/210	1.02 (0.57, 1.81)	1.01 (0.59, 1.72)	11/107	0.98 (0.44, 2.15)	0.99 (0.50, 1.97)	12/99	1.15 (0.50, 2.68)	1.07 (0.52, 2.21)
Log-Add		0.99 (0.78, 1.26)	0.99 (0.78, 1.25)		0.83 (0.59, 1.18)	0.83 (0.59, 1.17)		1.17 (0.82, 1.66)	1.14 (0.81, 1.61)
Dominant		0.97 (0.71, 1.33)	0.97 (0.72, 1.31)		0.72 (0.46, 1.10)	0.73 (0.48, 1.10)		1.30 (0.81, 2.08)	1.25 (0.80, 1.96)
Recessive		1.04 (0.59, 1.81)	1.02 (0.61, 1.72)		1.14 (0.53, 2.47)	1.10 (0.56, 2.19)		1.04 (0.46, 2.35)	1.00 (0.49, 2.03)
rs9868873									
G:G	282/1509	1.00 (Ref)	1.00 (Ref)	148/747	1.00 (Ref)	1.00 (Ref)	121/733	1.00 (Ref)	1.00 (Ref)
A:G	114/661	1.14 (0.81, 1.60)	1.13 (0.81, 1.56)	64/347	1.20 (0.76, 1.92)	1.18 (0.76, 1.83)	45/304	1.13 (0.67, 1.90)	1.11 (0.68, 1.80)
A:A	16/92	1.25 (0.60, 2.58)	1.23 (0.64, 2.35)	11/37	2.19 (0.87, 5.51)	1.79 (0.81, 3.98)	4/54	0.59 (0.16, 2.21)	0.75 (0.29, 1.90)
Log-Add		1.13 (0.87, 1.47)	1.13 (0.88, 1.47)		1.33 (0.93, 1.91)	1.34 (0.94, 1.91)		0.97 (0.64, 1.47)	0.96 (0.64, 1.43)
Dominant		1.15 (0.84, 1.59)	1.15 (0.84, 1.57)		1.31 (0.84, 2.03)	1.31 (0.86, 1.99)		1.05 (0.63, 1.73)	1.03 (0.64, 1.64)
Recessive		1.20 (0.58, 2.47)	1.20 (0.63, 2.28)		2.06 (0.83, 5.12)	1.73 (0.78, 3.81)		0.57 (0.15, 2.12)	0.73 (0.29, 1.86)

ca/co, cases/controls; aOR, adjusted odds ratios; sbOR, semi-Bayes adjusted odds ratio; Log-Add, log-additive model

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-year of smoking (continuous), and HBsAg status (positive, negative)

Table 5-3. Joint associations between selected SNPs and flavonoid intake on liver cancer in Jiangsu case-control study

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	**aOR**[a]	**sbOR**[a]	**aOR**[a]	**sbOR**[a]
rs1046472				
AC+AA	1.00 (Ref)	1.00 (Ref)	1.48 (0.86, 2.56)	1.45 (0.85, 2.47)
CC	1.13 (0.70, 1.82)	1.11 (0.69, 1.77)	1.34 (0.82, 2.18)	1.30 (0.82, 2.06)
Interaction	RERI: -0.28 (-1.15, 0.6)	sbRERI: -0.26 (-1.11, 0.59)	ROR: 0.8 (0.41, 1.54)	sbROR: 0.83 (0.46, 1.51)
rs10519613				
CC	1.00 (Ref)	1.00 (Ref)	1.64 (0.94, 2.85)	1.56 (0.91, 2.67)
CA+AA	1.47 (0.89, 2.42)	1.41 (0.87, 2.28)	1.61 (0.97, 2.67)	1.51 (0.94, 2.43)
Interaction	RERI: -0.48 (-1.51, 0.54)	sbRERI: -0.45 (-1.44, 0.53)	ROR: 0.67 (0.35, 1.31)	sbROR: 0.73 (0.4, 1.32)
rs12828				
AG+AA	1.00 (Ref)	1.00 (Ref)	1.27 (0.83, 1.95)	1.25 (0.82, 1.91)
GG	1.03 (0.64, 1.64)	1.01 (0.64, 1.61)	1.32 (0.84, 2.08)	1.29 (0.84, 1.98)
Interaction	RERI: 0.03 (-0.69, 0.76)	sbRERI: 0.03 (-0.69, 0.74)	ROR: 1.02 (0.54, 1.92)	sbROR: 1.02 (0.57, 1.8)
rs12894467				
TT	1.00 (Ref)	1.00 (Ref)	**1.61 (1.04, 2.47)**	**1.59 (1.04, 2.42)**
CT+CC	1.35 (0.84, 2.18)	1.33 (0.83, 2.14)	1.31 (0.80, 2.16)	1.27 (0.80, 2.03)
Interaction	RERI: -0.65 (-1.61, 0.31)	sbRERI: -0.65 (-1.60, 0.30)	ROR: 0.6 (0.31, 1.17)	sbROR: 0.66 (0.37, 1.2)
rs12934922				
AT+TT	1.00 (Ref)	1.00 (Ref)	**2.27 (1.24, 4.19)**	**2.23 (1.24, 4.04)**
AA	1.19 (0.71, 2.00)	1.17 (0.71, 1.93)	1.25 (0.73, 2.13)	1.21 (0.74, 1.99)
Interaction	RERI: -1.23 (-2.65, 0.2)	sbRERI: -1.19 (-2.56, 0.18)	**ROR: 0.46 (0.23, 0.93)**	sbROR: 0.54 (0.29, 1.00)
rs13409				
CT+TT	1.00 (Ref)	1.00 (Ref)	**1.58 (1.03, 2.41)**	**1.55 (1.02, 2.36)**
CC	1.38 (0.86, 2.21)	1.36 (0.86, 2.17)	1.40 (0.86, 2.27)	1.35 (0.85, 2.13)
Interaction	RERI: -0.56 (-1.51, 0.39)	sbRERI: -0.57 (-1.50, 0.37)	ROR: 0.64 (0.33, 1.23)	sbROR: 0.69 (0.39, 1.25)
rs1538660				
CC	1.00 (Ref)	1.00 (Ref)	1.15 (0.69, 1.90)	1.12 (0.68, 1.83)

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	**aOR**[a]	**sbOR**[a]	**aOR**[a]	**sbOR**[a]
CT+TT	1.14 (0.72, 1.80)	1.11 (0.71, 1.75)	1.47 (0.93, 2.32)	1.42 (0.92, 2.19)
Interaction	RERI: 0.19 (-0.53, 0.9)	sbRERI: 0.19 (-0.51, 0.88)	ROR: 1.13 (0.6, 2.13)	sbROR: 1.11 (0.62, 1.97)
rs1804429				
GT+GG	1.00 (Ref)	1.00 (Ref)	1.76 (0.72, 4.34)	1.65 (0.71, 3.81)
TT	1.10 (0.53, 2.28)	1.03 (0.53, 1.99)	1.39 (0.67, 2.92)	1.29 (0.68, 2.47)
Interaction	RERI: -0.47 (-1.94, 1.01)	sbRERI: -0.38 (-1.71, 0.94)	ROR: 0.72 (0.28, 1.86)	sbROR: 0.8 (0.37, 1.75)
rs197412				
TC+CC	1.00 (Ref)	1.00 (Ref)	1.38 (0.89, 2.14)	1.36 (0.88, 2.10)
TT	1.06 (0.67, 1.69)	1.05 (0.66, 1.67)	1.23 (0.77, 1.95)	1.20 (0.77, 1.87)
Interaction	RERI: -0.21 (-0.98, 0.55)	sbRERI: -0.21 (-0.97, 0.54)	ROR: 0.84 (0.45, 1.58)	sbROR: 0.86 (0.49, 1.54)
rs1981492				
GG	1.00 (Ref)	1.00 (Ref)	1.26 (0.80, 2.00)	1.24 (0.79, 1.95)
AA+AG	1.09 (0.69, 1.71)	1.07 (0.68, 1.67)	1.39 (0.87, 2.21)	1.34 (0.87, 2.08)
Interaction	RERI: 0.04 (-0.69, 0.77)	sbRERI: 0.04 (-0.68, 0.75)	ROR: 1.01 (0.54, 1.89)	sbROR: 1.01 (0.57, 1.78)
rs2014300				
AG+AA	1.00 (Ref)	1.00 (Ref)	1.26 (0.65, 2.45)	1.21 (0.64, 2.30)
GG	1.07 (0.63, 1.83)	1.04 (0.62, 1.74)	1.44 (0.83, 2.49)	1.37 (0.83, 2.28)
Interaction	RERI: 0.11 (-0.72, 0.94)	sbRERI: 0.13 (-0.67, 0.93)	ROR: 1.07 (0.51, 2.23)	sbROR: 1.05 (0.55, 2.02)
rs2057482				
CC	1.00 (Ref)	1.00 (Ref)	1.37 (0.91, 2.07)	1.37 (0.91, 2.04)
TC+TT	1.13 (0.70, 1.83)	1.12 (0.70, 1.81)	1.16 (0.73, 1.85)	1.14 (0.73, 1.78)
Interaction	RERI: -0.35 (-1.15, 0.45)	sbRERI: -0.35 (-1.14, 0.45)	ROR: 0.75 (0.39, 1.43)	sbROR: 0.79 (0.44, 1.42)
rs222851				
AA	1.00 (Ref)	1.00 (Ref)	1.35 (0.78, 2.31)	1.29 (0.76, 2.19)
AG+GG	1.31 (0.81, 2.11)	1.26 (0.79, 2.02)	**1.74 (1.07, 2.82)**	**1.64 (1.04, 2.58)**
Interaction	RERI: 0.08 (-0.77, 0.93)	sbRERI: 0.08 (-0.73, 0.90)	ROR: 0.99 (0.51, 1.9)	sbROR: 0.99 (0.55, 1.79)
rs2230793				
AA	1.00 (Ref)	1.00 (Ref)	1.15 (0.71, 1.84)	1.13 (0.71, 1.80)

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	**aOR**[a]	**sbOR**[a]	**aOR**[a]	**sbOR**[a]
AC+CC	1.00 (0.64, 1.58)	0.99 (0.63, 1.55)	1.30 (0.82, 2.07)	1.27 (0.82, 1.96)
Interaction	RERI: 0.15 (-0.52, 0.82)	sbRERI: 0.15 (-0.51, 0.81)	ROR: 1.13 (0.61, 2.11)	sbROR: 1.11 (0.63, 1.95)
rs2269700				
TT	1.00 (Ref)	1.00 (Ref)	1.45 (0.98, 2.15)	1.44 (0.98, 2.13)
CT+CC	1.05 (0.65, 1.70)	1.05 (0.65, 1.69)	1.16 (0.72, 1.86)	1.14 (0.72, 1.79)
Interaction	RERI: -0.35 (-1.14, 0.45)	sbRERI: -0.35 (-1.14, 0.44)	ROR: 0.76 (0.39, 1.46)	sbROR: 0.8 (0.44, 1.45)
rs2274223				
AG+GG	1.00 (Ref)	1.00 (Ref)	1.40 (0.80, 2.46)	1.36 (0.79, 2.34)
AA	1.10 (0.67, 1.79)	1.07 (0.66, 1.72)	1.46 (0.88, 2.41)	1.40 (0.87, 2.24)
Interaction	RERI: -0.04 (-0.86, 0.78)	sbRERI: -0.03 (-0.82, 0.77)	ROR: 0.95 (0.49, 1.84)	sbROR: 0.96 (0.53, 1.74)
rs2292305				
CT+CC	1.00 (Ref)	1.00 (Ref)	1.42 (0.91, 2.22)	1.41 (0.91, 2.20)
TT	1.07 (0.68, 1.70)	1.07 (0.68, 1.70)	1.09 (0.68, 1.75)	1.08 (0.69, 1.68)
Interaction	RERI: -0.41 (-1.21, 0.38)	sbRERI: -0.41 (-1.20, 0.38)	ROR: 0.71 (0.37, 1.35)	sbROR: 0.75 (0.42, 1.35)
rs2352028				
CC	1.00 (Ref)	1.00 (Ref)	1.48 (0.99, 2.22)	1.47 (0.99, 2.18)
CT+TT	1.13 (0.71, 1.79)	1.12 (0.71, 1.77)	1.17 (0.72, 1.92)	1.15 (0.73, 1.83)
Interaction	RERI: -0.43 (-1.25, 0.39)	sbRERI: -0.43 (-1.24, 0.38)	ROR: 0.71 (0.37, 1.34)	sbROR: 0.75 (0.42, 1.35)
rs2910164				
CC	1.00 (Ref)	1.00 (Ref)	1.56 (0.90, 2.70)	1.52 (0.89, 2.60)
GC+GG	1.17 (0.72, 1.91)	1.15 (0.71, 1.84)	1.35 (0.82, 2.22)	1.31 (0.82, 2.08)
Interaction	RERI: -0.38 (-1.3, 0.54)	sbRERI: -0.36 (-1.25, 0.53)	ROR: 0.74 (0.38, 1.43)	sbROR: 0.78 (0.43, 1.42)
rs2953				
GT+GG	1.00 (Ref)	1.00 (Ref)	1.46 (0.88, 2.40)	1.42 (0.87, 2.32)
TT	1.20 (0.75, 1.91)	1.17 (0.74, 1.85)	1.41 (0.88, 2.27)	1.36 (0.87, 2.13)
Interaction	RERI: -0.24 (-1.08, 0.6)	sbRERI: -0.23 (-1.05, 0.59)	ROR: 0.81 (0.43, 1.53)	sbROR: 0.84 (0.47, 1.5)
rs3130932				
TT	1.00 (Ref)	1.00 (Ref)	**1.63 (1.03, 2.58)**	**1.61 (1.02, 2.53)**

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	**aOR[a]**	**sbOR[a]**	**aOR[a]**	**sbOR[a]**
GT+GG	1.06 (0.67, 1.67)	1.05 (0.67, 1.65)	1.21 (0.76, 1.92)	1.18 (0.76, 1.84)
Interaction	RERI: -0.48 (-1.32, 0.37)	sbRERI: -0.47 (-1.31, 0.36)	ROR: 0.7 (0.38, 1.3)	sbROR: 0.74 (0.42, 1.31)
rs3204145				
TT	1.00 (Ref)	1.00 (Ref)	1.11 (0.67, 1.82)	1.08 (0.66, 1.76)
AT+AA	1.08 (0.68, 1.71)	1.06 (0.68, 1.67)	1.46 (0.93, 2.31)	1.41 (0.91, 2.17)
Interaction	RERI: 0.27 (-0.41, 0.96)	sbRERI: 0.27 (-0.40, 0.94)	ROR: 1.22 (0.65, 2.3)	sbROR: 1.18 (0.66, 2.1)
rs3729629				
GG	1.00 (Ref)	1.00 (Ref)	**1.98 (1.25, 3.12)**	**1.96 (1.25, 3.08)**
CG+CC	1.35 (0.86, 2.12)	1.34 (0.86, 2.09)	1.14 (0.72, 1.81)	1.13 (0.73, 1.74)
Interaction	**RERI: -1.19 (-2.26, -0.11)**	**sbRERI: -1.18 (-2.24, -0.11)**	**ROR: 0.43 (0.23, 0.79)**	**sbROR: 0.49 (0.28, 0.86)**
rs3734637				
AC+CC	1.00 (Ref)	1.00 (Ref)	1.12 (0.65, 1.92)	1.07 (0.63, 1.82)
AA	1.20 (0.75, 1.93)	1.16 (0.73, 1.84)	**1.76 (1.10, 2.83)**	**1.66 (1.07, 2.59)**
Interaction	RERI: 0.44 (-0.3, 1.18)	sbRERI: 0.43 (-0.28, 1.14)	ROR: 1.31 (0.68, 2.51)	sbROR: 1.25 (0.69, 2.25)
rs3740535				
AG+AA	1.00 (Ref)	1.00 (Ref)	**1.81 (1.12, 2.93)**	**1.76 (1.10, 2.83)**
GG	1.52 (0.96, 2.41)	1.49 (0.95, 2.34)	1.45 (0.91, 2.33)	1.40 (0.89, 2.18)
Interaction	RERI: -0.87 (-1.93, 0.19)	sbRERI: -0.85 (-1.89, 0.18)	**ROR: 0.53 (0.28, 0.99)**	sbROR: 0.59 (0.33, 1.04)
rs3801790				
AG+GG	1.00 (Ref)	1.00 (Ref)	**1.58 (1.04, 2.40)**	**1.56 (1.04, 2.35)**
AA	1.33 (0.83, 2.13)	1.31 (0.82, 2.10)	1.24 (0.77, 2.01)	1.21 (0.77, 1.91)
Interaction	RERI: -0.66 (-1.59, 0.26)	sbRERI: -0.66 (-1.58, 0.25)	ROR: 0.59 (0.31, 1.14)	sbROR: 0.65 (0.36, 1.17)
rs3929				
GG	1.00 (Ref)	1.00 (Ref)	1.40 (0.93, 2.10)	1.38 (0.93, 2.06)
CG+CC	1.10 (0.68, 1.78)	1.09 (0.68, 1.76)	1.29 (0.81, 2.07)	1.26 (0.81, 1.97)
Interaction	RERI: -0.21 (-1.01, 0.59)	sbRERI: -0.22 (-1.01, 0.57)	ROR: 0.84 (0.44, 1.6)	sbROR: 0.86 (0.48, 1.56)
rs4072391				
CC	1.00 (Ref)	1.00 (Ref)	1.31 (0.90, 1.89)	1.29 (0.90, 1.86)

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	aOR[a]	sbOR[a]	aOR[a]	sbOR[a]
CT+TT	1.08 (0.60, 1.94)	1.07 (0.60, 1.92)	1.20 (0.67, 2.16)	1.17 (0.68, 2.01)
Interaction	RERI: -0.17 (-1.11, 0.77)	sbRERI: -0.19 (-1.11, 0.72)	ROR: 0.86 (0.38, 1.94)	sbROR: 0.89 (0.44, 1.8)
rs42031				
AA	1.00 (Ref)	1.00 (Ref)	1.25 (0.88, 1.79)	1.21 (0.86, 1.72)
AT+TT	1.66 (0.83, 3.33)	1.62 (0.81, 3.24)	**2.58 (1.34, 4.95)**	**2.16 (1.18, 3.95)**
Interaction	RERI: 0.66 (-1.23, 2.56)	sbRERI: 0.33 (-1.32, 1.97)	ROR: 1.24 (0.48, 3.16)	sbROR: 1.16 (0.53, 2.52)
rs4678680				
GT+GG	1.00 (Ref)	1.00 (Ref)	2.44 (0.93, 6.40)	2.13 (0.88, 5.17)
TT	1.63 (0.75, 3.51)	1.42 (0.72, 2.79)	1.90 (0.87, 4.12)	1.63 (0.84, 3.16)
Interaction	RERI: -1.17 (-3.42, 1.08)	sbRERI: -0.92 (-2.78, 0.94)	ROR: 0.48 (0.17, 1.31)	sbROR: 0.62 (0.27, 1.38)
rs4730775				
CT+TT	1.00 (Ref)	1.00 (Ref)	1.22 (0.72, 2.07)	1.17 (0.70, 1.96)
CC	1.34 (0.83, 2.16)	1.30 (0.81, 2.06)	**1.74 (1.07, 2.83)**	**1.64 (1.03, 2.59)**
Interaction	RERI: 0.18 (-0.63, 0.98)	sbRERI: 0.17 (-0.60, 0.95)	ROR: 1.06 (0.56, 2.03)	sbROR: 1.05 (0.58, 1.89)
rs4975616				
AA	1.00 (Ref)	1.00 (Ref)	1.32 (0.88, 1.96)	1.29 (0.87, 1.91)
AG+GG	1.06 (0.63, 1.78)	1.04 (0.62, 1.74)	1.58 (0.96, 2.60)	1.50 (0.94, 2.40)
Interaction	RERI: 0.21 (-0.66, 1.08)	sbRERI: 0.17 (-0.67, 1.01)	ROR: 1.13 (0.56, 2.28)	sbROR: 1.11 (0.59, 2.06)
rs520692				
AA	1.00 (Ref)	1.00 (Ref)	1.21 (0.83, 1.76)	1.18 (0.81, 1.72)
AG+GG	1.04 (0.62, 1.75)	1.03 (0.62, 1.72)	1.54 (0.91, 2.62)	1.46 (0.89, 2.39)
Interaction	RERI: 0.3 (-0.6, 1.19)	sbRERI: 0.25 (-0.61, 1.10)	ROR: 1.23 (0.6, 2.53)	sbROR: 1.18 (0.62, 2.23)
rs7372209				
CC	1.00 (Ref)	1.00 (Ref)	1.54 (0.97, 2.44)	1.54 (0.98, 2.41)
CT+TT	1.00 (0.63, 1.58)	1.00 (0.63, 1.57)	1.05 (0.65, 1.70)	1.04 (0.67, 1.64)
Interaction	RERI: -0.49 (-1.3, 0.32)	sbRERI: -0.49 (-1.30, 0.32)	ROR: 0.68 (0.36, 1.28)	sbROR: 0.73 (0.41, 1.29)
rs738722				
CC	1.00 (Ref)	1.00 (Ref)	**1.93 (1.24, 3.01)**	**1.91 (1.24, 2.96)**

	High Flavonoid Intake		Low Flavonoid Intake	
dbsnp no.	**aOR[a]**	**sbOR[a]**	**aOR[a]**	**sbOR[a]**
CT+TT	1.43 (0.89, 2.29)	1.42 (0.89, 2.26)	1.17 (0.72, 1.90)	1.15 (0.73, 1.82)
Interaction	**RERI: -1.19 (-2.28, -0.09)**	**sbRERI: -1.18 (-2.27, -0.09)**	**ROR: 0.43 (0.22, 0.82)**	**sbROR: 0.5 (0.28, 0.89)**
rs748404				
CT+CC	1.00 (Ref)	1.00 (Ref)	2.57 (0.94, 7.03)	2.30 (0.91, 5.81)
TT	1.32 (0.60, 2.90)	1.19 (0.59, 2.37)	1.59 (0.72, 3.54)	1.41 (0.71, 2.79)
Interaction	RERI: -1.28 (-3.71, 1.16)	sbRERI: -1.07 (-3.14, 1.00)	ROR: 0.47 (0.17, 1.35)	sbROR: 0.62 (0.27, 1.43)
rs7626795				
AG+GG	1.00 (Ref)	1.00 (Ref)	1.61 (0.92, 2.81)	1.57 (0.91, 2.71)
AA	1.15 (0.71, 1.86)	1.13 (0.71, 1.81)	1.32 (0.81, 2.16)	1.28 (0.81, 2.03)
Interaction	RERI: -0.44 (-1.39, 0.51)	sbRERI: -0.42 (-1.34, 0.50)	ROR: 0.71 (0.37, 1.38)	sbROR: 0.76 (0.42, 1.38)
rs8708				
AA	1.00 (Ref)	1.00 (Ref)	1.30 (0.87, 1.95)	1.28 (0.86, 1.90)
AG+GG	1.08 (0.65, 1.78)	1.07 (0.65, 1.75)	1.46 (0.89, 2.37)	1.40 (0.88, 2.21)
Interaction	RERI: 0.07 (-0.75, 0.9)	sbRERI: 0.05 (-0.75, 0.85)	ROR: 1.04 (0.53, 2.03)	sbROR: 1.03 (0.56, 1.89)
rs915894				
AC+AA	1.00 (Ref)	1.00 (Ref)	1.30 (0.87, 1.93)	1.29 (0.87, 1.90)
CC	1.06 (0.65, 1.73)	1.06 (0.65, 1.72)	1.20 (0.71, 2.01)	1.17 (0.72, 1.91)
Interaction	RERI: -0.16 (-0.96, 0.64)	sbRERI: -0.17 (-0.96, 0.61)	ROR: 0.87 (0.44, 1.73)	sbROR: 0.89 (0.48, 1.65)
rs9266				
CC	1.00 (Ref)	1.00 (Ref)	1.48 (0.97, 2.25)	1.45 (0.96, 2.19)
CT+TT	1.47 (0.93, 2.35)	1.45 (0.91, 2.30)	1.55 (0.96, 2.49)	1.48 (0.94, 2.32)
Interaction	RERI: -0.41 (-1.35, 0.54)	sbRERI: -0.42 (-1.35, 0.51)	ROR: 0.71 (0.37, 1.34)	sbROR: 0.75 (0.42, 1.35)
rs9267673				
CC	1.00 (Ref)	1.00 (Ref)	1.16 (0.78, 1.73)	1.14 (0.77, 1.68)
CT+TT	1.00 (0.60, 1.66)	0.98 (0.59, 1.62)	**1.72 (1.03, 2.85)**	1.61 (1.00, 2.59)
Interaction	RERI: 0.55 (-0.32, 1.43)	sbRERI: 0.49 (-0.34, 1.32)	ROR: 1.48 (0.73, 2.96)	sbROR: 1.36 (0.73, 2.54)
rs9275572				
GG	1.00 (Ref)	1.00 (Ref)	1.54 (1.00, 2.38)	1.53 (1.00, 2.34)

dbsnp no.	High Flavonoid Intake		Low Flavonoid Intake	
	aOR[a]	**sbOR**[a]	**aOR**[a]	**sbOR**[a]
AG+AA	1.24 (0.78, 1.96)	1.23 (0.78, 1.94)	1.17 (0.73, 1.87)	1.15 (0.73, 1.79)
Interaction	RERI: -0.61 (-1.49, 0.26)	sbRERI: -0.61 (-1.48, 0.25)	ROR: 0.61 (0.32, 1.15)	sbROR: 0.66 (0.37, 1.18)
rs9868873				
GG	1.00 (Ref)	1.00 (Ref)	1.19 (0.80, 1.78)	1.17 (0.78, 1.73)
AG+AA	1.02 (0.63, 1.66)	1.00 (0.62, 1.62)	1.55 (0.97, 2.48)	1.48 (0.95, 2.31)
Interaction	RERI: 0.35 (-0.43, 1.12)	sbRERI: 0.32 (-0.43, 1.06)	ROR: 1.28 (0.67, 2.48)	sbROR: 1.23 (0.68, 2.22)

aOR, adjusted odds ratios; sb, Semi-Bayes; OR, odds ratio; RERI, relative excess risk due to interaction; ROR, ratio of odds ratios

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day, when not included in interaction term), pack-year of

Table 5-4. Associations between genetic scores and liver cancer in Jiangsu case-control study by flavonoid intake

Variable		Tertile	All			Low Flavonoid Intake			High Flavonoid Intake		
			ca/co	aOR[a]	p[b]	ca/co	aOR[a]	p[b]	ca/co	aOR[a]	p[b]
PRS	T1	0-0.80	132/879	1.00 (Ref)	**<0.001**	65/443	1.00 (Ref)	**0.001**	61/417	1.00 (Ref)	0.071
	T2	0.80-1.15	217/1,117	**1.60 (1.14, 2.25)**		124/555	1.56 (0.97, 2.50)		83/547	1.29 (0.77, 2.16)	
	T3	1.15+	47/165	**2.89 (1.68, 4.95)**		29/86	**3.50 (1.70, 7.24)**		17/76	2.27 (0.98, 5.27)	
PRS	T1	0-0.80	137/917	1.00 (Ref)	**<0.001**	67/463	1.00 (Ref)	**0.001**	64/434	1.00 (Ref)	**0.009**
(imputed)	T2	0.80-1.15	300/1,306	**1.96 (1.42, 2.69)**		162/642	**1.89 (1.22, 2.94)**		126/643	**1.76 (1.09, 2.83)**	
	T3	1.15+	48/175	**2.67 (1.58, 4.52)**		29/91	**2.84 (1.40, 5.78)**		18/81	**2.34 (1.04, 5.30)**	
MGI	T1	0-0.56	141/977	1.00 (Ref)	**<0.001**	71/482	1.00 (Ref)	**0.001**	63/474	1.00 (Ref)	0.092
	T2	0.56-0.69	97/562	1.06 (0.70, 1.60)		56/289	0.88 (0.50, 1.56)		38/267	1.20 (0.64, 2.24)	
	T3	0.69+	148/582	**2.09 (1.45, 3.02)**		88/291	**2.33 (1.40, 3.87)**		54/281	1.65 (0.93, 2.94)	
MGI	T1	0-0.56	149/1,023	1.00 (Ref)	**<0.001**	75/508	1.00 (Ref)	**<0.001**	67/493	1.00 (Ref)	**0.001**
(imputed)	T2	0.56-0.69	107/603	1.16 (0.79, 1.71)		58/305	0.94 (0.55, 1.61)		45/289	1.39 (0.77, 2.50)	
	T3	0.69+	229/772	**2.41 (1.75, 3.34)**		125/383	**2.36 (1.51, 3.69)**		96/376	**2.39 (1.46, 3.92)**	

ca/co, case/control; aOR, adjusted odds ratio; PRS, polygenic risk score; MGI, multigenetic index

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day), pack-year of smoking (continuous), and HBsAg status (positive, negative)

[b]p for trend

Table 5-5. Joint associations between genetic risk scores and novel dietary factors as well as established risk factors on liver cancer in Jiangsu case-control study

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Flavonoid Intake				
High Flavonoid and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: 0.59 (-0.52, 1.7)	ROR: 1.11 (0.59, 2.1)
Low Flavonoid and Low PRS	1.50 (0.96, 2.35)	1.38 (0.89, 2.14)	sbRERI: 0.49 (-0.54, 1.52)	sbROR:1.09 (0.61, 1.94)
High Flavonoid and High PRS	**1.72 (1.08, 2.74)**	**1.60 (1.01, 2.54)**		
Low Flavonoid and High PRS	**2.77 (1.76, 4.36)**	**2.47 (1.60, 3.81)**		
High Flavonoid and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: 0.26 (-0.78, 1.3)	ROR: 0.97 (0.5, 1.87)
Low Flavonoid and Low MGI	1.67 (1.00, 2.81)	1.52 (0.92, 2.53)	sbRERI: 0.23 (-0.75, 1.20)	sbROR:0.97 (0.54, 1.77)
High Flavonoid and High MGI	1.62 (1.00, 2.63)	1.47 (0.91, 2.36)		
Low Flavonoid and High MGI	**2.57 (1.60, 4.12)**	**2.22 (1.42, 3.46)**		
Glycemic Index				
Low GI and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: 0.92 (-0.39, 2.23)	ROR: 1.15 (0.54, 2.48)
High GI and Low PRS	1.58 (0.88, 2.86)	1.51 (0.86, 2.66)	sbRERI: 0.77 (-0.33, 1.87)	sbROR:1.12 (0.57, 2.18)
Low GI and High PRS	1.54 (0.81, 2.95)	1.44 (0.75, 2.74)		
High GI and High PRS	**2.99 (1.65, 5.44)**	**2.72 (1.56, 4.74)**		
Low GI and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: 0.97 (-0.13, 2.07)	ROR: 1.35 (0.6, 3.03)
High GI and Low MGI	1.68 (0.85, 3.33)	1.48 (0.78, 2.78)	sbRERI: 0.86 (-0.04, 1.77)	sbROR:1.25 (0.62, 2.52)
Low GI and High MGI	1.35 (0.68, 2.71)	1.08 (0.55, 2.12)		
High GI and High MGI	**2.89 (1.49, 5.61)**	**2.42 (1.34, 4.40)**		
Chronic HBV Infection				
HBsAg- and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: 12.13 (-6.04, 30.3)	ROR: 0.71 (0.38, 1.32)
HBsAg+ and Low PRS	**29.35 (18.68, 46.13)**	**24.90 (16.13, 38.43)**	sbRERI: 3.46 (-9.26, 16.18)	sbROR:0.75 (0.42, 1.33)
HBsAg- and High PRS	**2.06 (1.37, 3.10)**	**1.77 (1.20, 2.61)**		
HBsAg+ and High PRS	**42.52 (26.41, 68.43)**	**29.13 (18.86, 44.98)**		
HBsAg- and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: 18.27 (1.65, 34.88)	ROR: 1.3 (0.67, 2.49)

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
HBsAg+ and Low MGI	**21.83 (13.12, 36.33)**	**18.11 (11.12, 29.50)**	sbRERI: 9.84 (-1.47, 21.15)	sbROR:1.24 (0.68, 2.23)
HBsAg- and High MGI	1.43 (0.94, 2.19)	1.20 (0.80, 1.79)		
HBsAg+ and High MGI	**40.53 (25.27, 65.02)**	**28.15 (18.34, 43.20)**		
Mildew/Aflatoxin Exposure				
No Mildew and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: 0.72 (-1.73, 3.16)	ROR: 1.42 (0.31, 6.46)
Mildew and Low PRS	1.00 (0.29, 3.42)	0.98 (0.29, 3.36)	sbRERI: 0.19 (-1.72, 2.10)	sbROR:1.17 (0.43, 3.24)
No Mildew and High PRS	**1.72 (1.24, 2.37)**	**1.69 (1.23, 2.33)**		
Mildew and Higher PRS	**2.44 (1.00, 5.92)**	1.86 (0.86, 4.04)		
No Mildew and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: 0.51 (-2.1, 3.12)	ROR: 1.16 (0.25, 5.42)
Mildew and Low MGI	1.33 (0.36, 4.85)	1.29 (0.35, 4.71)	sbRERI: 0.04 (-2.15, 2.22)	sbROR:1.07 (0.38, 2.98)
No Mildew and High MGI	**1.57 (1.12, 2.19)**	**1.53 (1.10, 2.13)**		
Mildew and Higher MGI	**2.40 (1.01, 5.71)**	1.86 (0.87, 3.98)		
Alcohol Drinking				
Never Drinker and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: -0.97 (-2.4, 0.47)	ROR: 0.52 (0.27, 0.99)
Drinker and Low PRS	**1.79 (1.11, 2.91)**	**1.68 (1.05, 2.68)**	sbRERI: -0.95 (-2.31, 0.40)	sbROR:0.58 (0.33, 1.04)
Never Drinker and High PRS	**2.62 (1.60, 4.30)**	**2.48 (1.53, 4.02)**		
Drinker and High PRS	**2.45 (1.49, 4.02)**	**2.21 (1.39, 3.52)**		
Never Drinker and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: -0.64 (-1.91, 0.64)	ROR: 0.6 (0.31, 1.17)
Drinker and Low MGI	**1.78 (1.02, 3.11)**	1.65 (0.97, 2.81)	sbRERI: -0.60 (-1.78, 0.59)	sbROR:0.66 (0.36, 1.2)
Never Drinker and High MGI	**2.17 (1.29, 3.64)**	**2.03 (1.23, 3.34)**		
Drinker and High MGI	**2.31 (1.36, 3.91)**	**2.08 (1.28, 3.38)**		
Smoking				
Never Smoker and Low PRS	1.00 (Ref)	1.00 (Ref)	RERI: -0.45 (-1.74, 0.84)	ROR: 0.66 (0.35, 1.27)
Smoker and Low PRS	1.62 (1.00, 2.62)	1.51 (0.95, 2.41)	sbRERI: -0.45 (-1.66, 0.76)	sbROR:0.71 (0.4, 1.28)
Never Smoker and High PRS	**2.31 (1.38, 3.86)**	**2.18 (1.32, 3.60)**		
Smoker and High PRS	**2.48 (1.51, 4.06)**	**2.24 (1.41, 3.55)**		

	aOR[a]	sbOR[a]	RERI[a]	ROR[a]
Never Smoker and Low MGI	1.00 (Ref)	1.00 (Ref)	RERI: -0.37 (-1.59, 0.85)	ROR: 0.68 (0.34, 1.35)
Smoker and Low MGI	1.69 (0.96, 2.99)	1.55 (0.90, 2.66)	sbRERI: -0.33 (-1.46, 0.79)	sbROR:0.74 (0.4, 1.36)
Never Smoker and High MGI	**2.06 (1.19, 3.57)**	**1.90 (1.12, 3.23)**		
Smoker and High MGI	**2.38 (1.39, 4.10)**	**2.12 (1.29, 3.50)**		

aOR, adjusted odds ratios; sb, semi-Bayes; OR, odds ratio; RERI, relative excess risk due to interaction; ROR, ratio of odds ratios

[a]Adjusted for study area (Dafeng, Ganyu, Chuzhou), age (continuous), gender (male, female), education level (illiteracy, primary school, middle school, high school and college), family history of liver cancer (yes, no), alcohol consumption (0, <500g/day, >500g/day, when not included in interaction term), pack-year of smoking (continuous, when not included in interaction term), daily kcal, and HBsAg status (positive, negative, when not included in interaction term)

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