The relation between green tea and risk of gastric cancer, liver cancer, esophagus cancer and pancreatic cancer-a meta analysis

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Abstract: Purpose: To investigate the relation between green tea and risk of tumor of digestive system such as gastric cancer, liver cancer, esophagus cancer and pancreatic cancer. **Methods**: A meta analysis was conducted to estimate the risk of digestive system cancer from the case-control and prospective cohort studied, which were identified through electronic search of PubMed, MEDLINE, EMBASE,CNKI and CBM from January 1980 to January 2012. Results from individual studies were combined synthetically using R software and its Meta package. **Results**: A total of 98 articles were included in the meta analysis. In total, the pooled relative risk(RA) for highest versus non/lowest tea consumption levels of digestive system cancer was 0.87(95%CL:0.80-0.94). The results showed that green tea was inversely associated with the risk of stomach cancer with a pooled RR of 0.75(95%CL:0.61-0.97). We also observed a moderate reduction in risks for the common cancer sites such as cancer of esophagus, colon and pancreas with the pooled RRs of 0.89 (95% CL:0.77-1.15), 0.96 (95% CL:0.80-1.05), 0.77 (95% CL:0.45-1.12), respectively. In which, the RR,0.78 (95% CL:0.60-1.09) of liver cancer was in the borderline statistical significance. Furthermore, sub-group analysis indicated that the protective role of green tea was associated with cancer of esophagus among women with a pooled RR of 0.34 (95% CL:0.18-0.57). In this study, a pooled RR of 1.08 (95% CL:1.00-1.26) was also estimated for green tea and the risk of rectum cancer, but there was no statistic significance. **Conclusion**: Green tea was possibly associated with the decreased risk of digestive system cancer, and maybe one of the protective factors for cancers of stomach.
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Keywords: green tea, gastric cancer, liver cancer, esophagus cancer, pancreatic cancer, meta analysis

1. Introduction

Tea is one of the main beverages, the relationship between tea drinking and cancer has been well studied. International Agency for Research on Cancer had reviewed all literatures prior to 1989, and pointed out that the evidence of tea being the protective factors in human and experimental animals is not sufficient [Intemational Agency for Reseaeh on Cancer, 1989]. In recent years, there are lots of researches, however, the results of relationship between tea and digestive malignancies are confusion in different countries or regions. In this study, we systematically collected and arranged the literatures about the relationship between green tea and digestive malignant tumor, including esophagus tumor, stomach tumor, colon tumor, rectum tumor, liver tumor and pancreas tumor from January, 1979 to January, 2010, and a Meta-analysis was performed. The results provided more evidence for exploring the relationship between green tea and digestive malignancy.

2.Materials and methods

2.1 Literature search

We searched PubMed, MEDLINE, EMBASE, CNKI and CBM for randomized controlled trials (from January 1980 to January 2012).The terms used for research words included “green tea”, "gastric cancer", "liver cancer", "esophagus cancer", "pancreatic cancer" and "randomized controlled trial". The references of the retrieved articles were also checked. Language restriction was not imposed in our search. The inclusion criteria of this meta-analysis was met all of the following inclusion criterias: randomized controlled trials and observational studies of gastric cancer,liver cancer, esophagus cancer and pancreatic cancer; interventional factors was green tea; Objective of study was to perfored perspectiveness randomized controlled trials. The major reasons for exclusion from the study were that the outcomes were too less.

2.2 Data extraction and main endpoints

Two review authors extracted the data independently to a self-developed data extraction form. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. We would write to study authors for further

information if necessary. Disagreements would be resolved by majority vote, if necessary, of a third review author. One author entered data into Review Manager software(RevMan 5.0.20), and a second author independently checked the data entry. Confirmation of the extracted information was sought by correspondence with investigators.

2.3 Statistical analysis

For dichotomous data, results will be summarised as risk ratios(RR), with 95% confidence intervals (CI). For continuous out-comes we will use weighted mean difference (WMD) (when measures are in the same unit), or standardisedmean difference (SMD) (when different scales are used to evaluate the same outcome) with 95% CI as well, for example, if the confidence interval include 0, it shows there are no statistics significance. The pooled ORs and 95%CI were performed on the progress ratio of disease and incidence of side effect. If CI include 1, it shows there are no statistics significance. I2 will be used to assess heterogeneity among studies. I2 > 50% will be considered considerable heterogeneity.

Based on the details loss follow-up represention of literatures,the data of perprotocol analysis were translated into available-case analysis or intention-to-treat (ITT) analysis. we will make every attempt to analysis our data by this principal. Reporting biases adopted funnel plot analysis.

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among studies will be estimated by the I2 statistic. Typically, values above 50% are deemed to suggest significant heterogeneity. Values of 25% to 50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity.

We will perform a sensitivity analysis if there is a significant heterogeneity (I^2> 50%).

3.Results

3.1 Literatures

A total of 83 qualified literatures[Ui et al.,2009; Inoue et al.,2009; Wang et al.,2008; Wang et al.,2008; Montella et al.,2007; Yu et al.,2006; Shimazu et al., 2005; Mu et al.,2003a; Mu et al.,2003b;Han et al., 2002; Nagano et al.,2001; Nakachi et al.,2000; Sidong et al.,1999; Kono et al.,1988; Kato et al.,1990; Yu and Hsieh 1991;Hoshiyama and Sasaba 1992;Yu et al., 1995; Ji et al.,1996;Inoue et al.,1998;Galanis et al., 1998; Huang et al.,1999; Nakachi et al., 2000; Setiawan et al.,2001;Nagano et al.,2001;Tsubono et al., 2001; Hoshiyama et al.,2002;Hoshiyama et al., 2004; Sasazuki et al.,2004; Mu et al., 2005;Kuriyama et al., 2006;Deandrea et al., 2010;Wouters et al., 2011; Baron et al., 1994; Zheng et al., 1996;Tavani et al., 1997; Ji et al., 1997;Muñoz et al.,1998;Inoue et al., 1998; Slattery et al.,1999;Nakachi et al., 2000; Nagano et al., 2001;Su et al.,2002;Woolcott et al., 2002; Zhang et al.,2002;Il'yasova et al., 2003;Suzuki et al., 2005;Michels et al.,2005;Kuriyama et al., 2006; Yang et al., 2007;Sun et al., 2007;Ishikawa et al., 2006; Sun et al., 2002;Wang et al.,2007;Wu et al., 2009; Islami et al., 2009; Gao et al., 1994;Hu et al., 1994; Inoue et al., 1998;Zhang et al.,2001;Tavani et al., 2003; Hung et al.,2004;Ganesh et al., 2009;Gao et al., 2009;Chen et al.,2009;Wang et al.,2003;Yang et al., 1999;Liu et al., 2001;Pen et al., 2005; Xie et al., 2005; Zhao et al., 2005;Wang et al., 2008;Li et al., 2008; Li et al., 2008;Yang et al.,2009;Whittemore et al., 1994;Harnack et al.,1997;Luo et al., 2007;Lin et al., 2008;Zatonski et al.,1993;Ji et al., 1997;Qi et al., 1995] were collected, including 26 studies of esophageal cancer (2 cohort studies and 24 case-control studies, 16 Chinese and 10 English articles), 19 studies of gastric cancer (8 cohort studies and 11 case-control studies, 19 articles are all English), 19 studies of colorectal cancer (8 cohort studies and 11 case-control studies, 19 articles are all English), 13 studies of liver cancer (7 cohort studies and 6 case-control studies, 6 Chinese and 7 English articles), 9 studies of pancreatic cancer (6 cohort studies and 3 case-control studies, 1 Chinese and 8 English articles). One article reported pancreatic cancer and colorectal cancer together, two articles reported esophageal cancer and liver cancer at the same time.

3.2 Meta-analysis of the relationship of green tea and digestive malignancies

80 study results including male and female were performed heterogeneity test, Q=328.630, P<0.001, indicating heterogeneity existed between studies; therefore, random effect model was used to combined analyze the effect value, the pooled RR was 0.88 (95%CI: 0.81-0.95), suggesting there is a certain relationship between green tea and digestive malignancies, tea is the protective factor for digestive malignancies. We conducted heterogeneity test of 35 studies only including male and 32 studies only including female, and found that heterogeneity existed between studies; therefore, random effect model was used to combined analyze the effect value, the pooled RR for male and female were 1.01 (95%CI: 0.89-1.14) and 0.71 (95%CI: 0.61-0.84), respectively (Table 1), suggesting the green tea has a protective effect on digestive system tumors for female, not male.

Table 1. The relationship between green tea and malignant tumor of digestive system.

	Total population			male			female		
	number	mRR(95% CI)	P	number	mRR(95%CI)	P	number	mRR(95%CI)	P
esophagus cancer	22	0.89(0.71–1.13)	(0.001	4	1.22(0.76–1.98)	0.009	2	0.32(0.17–0.59)	0.710
case control study	22	0.89(0.71–1.13)	(0.001	2	1.15(0.55–2.41)	0.003	2	0.32(0.17–0.59)	0.710
cohort study	—	—	—	2	1.41(0.85–2.34)	0.153	—	—	—
country									
Japanese	1	1.14(0.05–2.35)	—	1	1.87(0.99–3.52)	—	—	—	—
Chinese	18	0.81(0.62–1.06)	(0.001	3	1.08(0.61–1.91)	0.009	2	0.32(0.17–0.59)	0.710
Other	3	1.45(0.56–0.73)	(0.001	—	—	—	—	—	—
（300	17	0.810.61–1.07)	(0.001	2	1.41(0.85–2.34)	0.153	—	—	—
≥300	5	1.23(0.69–2.17)	(0.001	2	1.15(0.55–2.41)	0.003	2	0.32(0.17–0.59)	0.710
Publication year									
1979–1995	1	3.90(1.69–9.02)	—	1	0.79(0.56–1.12)	—	1	0.34(0.17–0.69)	—
1996–2010	21	0.85(0.67–1.07)	(0.001	3	1.59(1.19–2.12)	0.309	1	0.26(0.07–0.94)	—
tea water temperature									
adjustment	2	1.25(0.95–1.65)	0.410	—	—	—	—	—	—
unadjustment	20	0.87(0.67–1.12)	(0.001	4	1.22(0.76–1.98)	0.010	2	0.32(0.17–0.59)	0.710
gastric carcinoma	15	0.73(0.57–0.93)	(0.001	10	0.97(0.78–1.21)	0.005	8	0.85(0.68–1.05)	0.783
case control study	9	0.49(0.35–0.69)	0.003	5	0.75(0.62–0.90)	0.075	3	0.79(0.56–1.12)	0.822
cohort study	6	1.13(.97–1.32)	0.284	5	1.14(0.95–1.36)	0.327	5	0.88(0.67–1.16)	0.500
country									
Japanese	9	0.93(.72–1.12)	0.004	7	1.13(0.96–1.32)	0.467	6	0.86(0.68–1.09)	0.630
Chinese	6	0.44(.26–0.75)	0.001	3	0.64(0.52–0.80)	0.566	2	0.77(0.45–1.32)	0.541
other	—	—	—	—	—	—	—		—
（300	9	0.70(.48–1.02)	(0.001	5	1.07(0.70–1.65)	0.013	3	1.05(0.66–1.67)	0.597
≥300	6	0.73(.51–1.05)	0.001	5	0.93(0.71–1.22)	0.033	5	0.80(0.63–1.02)	0.755
Publication									

year									
1979–1995	3	0.39(.25–0.63)	0.571	2	1.09(0.77–1.53)	0.335	1	0.81(0.51–1.28)	
1996–2010	12	0.83 (0.65–1.05)	(0.001	8	0.94(0.73–1.22)	0.003	7	0.86(0.67–1.09)	0.687
colorectal	12	0.96 (0.84–1.10)	0.016	6	1.05(0.68–1.02)	0.001	6	0.90(0.75–1.07)	0.213
carcinoma									
case	7	0.99 (0.61–1.20)	0.018	2	1.18(0.87–1.60)	0.261	2	0.66(0.49–0.89)	0.675
control									
study									
cohort	5	0.94 (0.82–1.09)	0.270	4	0.89(0.42–1.89)	(0.001	4	0.97(0.80–1.18)	0.285
study									
country									
Japanese	4	0.82 (0.68–0.99)	0.284	—	—	—	—	—	—
Chinese	8	1.11 (1.11–1.21)	0.109	1	1.01(0.67–1.52)	—	2	0.67(0.48–0.93)	0.691
other	—	—	—	5	1.02(0.59–1.78)	(0.001	4	1.00(0.82–1.23)	0427
(300	1	0.61 (0.41–0.91)	—	—	—	—	1	0.71(0.45–1.12)	—
≥300	11	1.07 (0.98–1.16)	1.102	6	1.05(0.68–1.62)	0.001	5	0.93(0.77–1.13)	0.208
Publication									
year									
1979–1995	2	0.78 (0.60–1.02)	0.097	—	—	—	—	—	—
1996–2010	10	1.08 (0.99–1.17)	0.077	6	1.05(0.68–1.62)	0.001	6	0.90(0.75–1.07)	0.213
rectal	7	1.10 (0.97–1.24)	0.144	3	1.36(0.98–1.88)	0.968	4	0.66(0.49–0.89)	0.410
carcinoma									
case	5	1.10 (0.97–1.26)	0.080	1	1.30(0.78–2.17)	—	2	0.70(0.48–1.03)	0.125
control									
study									
cohort	2	1.06 (0.76–1.47)	0.280	2	1.40(0.91–2.14)	0.885	2	0.60(0.38–0.96)	0.593
study									
country									
Japanese	4	1.14 (0.88–1.48)	0.629	—	—	—	—	—	—
Chinese									
other	3	0.96 (0.66–1.39)	0.021	3	1.36(0.98–1.88)	0.968	2	0.74(0.49–1.11)	0.178
(300	3	1.13 (0.85–1.49)	0.436	—	—	—	1	0.70(0.34–1.45)	—
≥300	4	1.00 (0.74–1.36)	0.049	3	1.36(0.98–1.88)	0.968	3	0.65(0.47–0.90)	0.240
Publication									
year									
1979–1995	2	0.85 (0.37–1.98)	0.019	—	—	—	—	—	—
1996–2010	5	1.14 (1.00–1.30)	0.836	3	1.36(0.98–1.88)	0.968	4	0.66(0.49–0.89)	0.410
hepatocell	12	0.77 (0.57–1.03)	(0.001	4	0.86(0.77–0.95)	0.248	4	0.54(0.37–0.79)	0.102
ular									
carcinoma									
case	7	0.70 (0.44–1.14)	(0.001	—	—	—	—	—	—
control									
study									
cohort	5	0.84(0.69–1.02)	0.051	4	0.86(0.77–0.95)	0.248	—	—	—

study country									
Japanese	5	0.84(0.69–1.02)	0.051	2	0.77(0.54–1.11)	0.107	2	0.66(0.40–1.11)	0.071
Chinese	6	0.63(0.37–1.08)	<0.001	2	0.86(0.76–0.98)	0.275	2	0.42(0.24–0.75)	0.200
other	1	1.43(0.76–2.68)	—	—	—	—	—	—	—
<300	11	0.75 (0.54–1.04)	<0.001	2	0.77(0.54–1.11)	0.107	2	0.66(0.40–1.11)	0.071
≥300	1	0.95(0.69–1.30)	—	2	0.86(0.77–0.97)	0.275	2	0.42(0.24–0.75)	0.200
Publication year									
1979–1995	—	—	—	—	—	—	—		
1996–2010	12	0.77(0.57–1.03)	<0.001	4	0.86(0.77–0.95)	0.248	4	0.54(0.37–0.80)	0.102
pancreatic carcinoma	6	0.73(0.45–1.19)	0.001	5	0.81(0.65–1.02)	0.131	4	0.74(0.56–0.97)	0.002
case control study	1	0.20(0.09–0.45)		2	0.81(0.60–1.09)	0.234	2	0.47(0.32–0.68)	0.536
cohort study	5	1.02(0.81–1.30)	0.264	3	0.82(0.58–1.15)	0.059	2	1.32(0.87–2.00)	0.330
study country									
Japanese	4	1.05(0.81–1.36)	0.166	2	1.10(0.72–1.70)	0.390	2	1.32(0.87–2.00)	0.330
Chinese	—	—	—	2	0.81(0.60–1.09)	0.234	2	0.47(0.32–0.68)	0.536
other	2	0.44(1.01–1.97)	0.002	1	0.50(0.29–0.87)	—	2	—	—
<300	6	0.73(0.45–1.19)	0.001	3	0.82(0.58–1.15)	0.059	2	1.32(0.87–2.00)	0.330
≥300	—	—	—	2	0.81(0.60–1.09)	0.234	2	0.47(0.32–0.68)	0.536
Publication year									
1979–1995	2	0.25(0.13–0.47)	0.390	1	0.50(0.29–0.87)	—	—	—	—
1996–2010	4	1.07(0.84–1.36)	0.555	4	0.90(0.70–1.15)	0.324	4	0.74(0.39–1.41)	0.002
Total	80	0.88(0.81–0.95)	<0.001	35	1.01(0.89–1.14)	<0.001	32	0.71(0.61–0.84)	<0.001

3.3 Meta-analysis of the relationship of green tea and esophageal cancer

22 study results including male and female were performed heterogeneity test, Q=137.790, P<0.001, indicating heterogeneity existed between studies; therefore, random effect model was used to combined analyze the effect value, the pooled RR was 0.89 (95%CI: 0.71-1.13); the result of fixed effect model was 1.05 (95%CI: 1.00-1.09), which was similar with the result of random effect model, indicating the result is reliable. Publication bias Begg test Z=-0.903, P=0.367, there was no statistically significant, suggesting the publication bias was not significant. Subgroup analysis revealed that there was significant heterogeneity between each subgroup; green tea had a certain protective effect on esophageal in the subgroup (n<300) of 1996-2010 in China, in cohort study of male population, the consistency between each subgroup (n<300) of 1996-2010 was good, and the consistency between each subgroup of all literatures was good in female population. In addition, some literatures provided the effect value of adjusting the temperature of boiled water; therefore, we conducted the subgroup analysis of whether to adjust the temperature, the pooled RR of adjusting temperature was 1.25 (95%CI: 0.95-1.65), the pooled RR of unadjusting temperature was 0.87 (95%CI: 0.67-1.12), P>0.05.

3.4 Meta-analysis of the relationship of green tea and gastric cancer

15 study results including male and female were performed heterogeneity test, Q=50.060, P<0.001, indicating there was heterogeneity between studies; therefore, random effect model was used to combined analyze the effect value, the pooled RR was 0.73 (95%CI: 0.57-0.93), the result of fixed effect model was 0.85 (95%CI: 0.77-0.95), which was similar with the result of random effect model, P<0.05, indicating the result is reliable. The results

showed that green tea has protective effect on gastric cancer. Publication bias Begg test Z=-1.945, P=0.052, suggesting the publication bias was not significant. We also performed subgroup analysis for the literatures, the subgroup of cohort study, 1979-1995 had good consistency. The consistency of literatures in the same region was good in male subgroup, while the consistency of all literatures was good in female subgroup.

3.5 Meta-analysis of the relationship of green tea and colon cancer

12 colon cancer results including male and female were performed heterogeneity test, Q=23.240, P=0.016, indicating there was heterogeneity between studies; therefore, random effect model was used to combined analyze the effect value, the pooled RR was 0.96 (95%CI: 0.84-1.10), the result of fixed effect model was 1.05 (95%CI: 0.96-1.13), the results of two models were close, indicating the result is reliable. Publication bias Begg test Z=-1.359, P=0.174, suggesting the publication bias was not significant. The consistency of each subgroup was good by subgroup analysis, and the consistency was also good in female subgroup.

3.6 Meta-analysis of the relationship of green tea and rectal cancer

7 rectal cancer results including male and female were performed heterogeneity test, Q=9.580, P=0.144, indicating there was no heterogeneity between studies; therefore, fixed effect model was used to perform effect value combined analysis, the pooled RR was 1.10 (95%CI: 0.97-1.24), the result of random effect model was 1.06 (95%CI: 0.88-1.28), the results of two models were close, indicating the result is reliable. Publication bias Begg test Z=-1.150, P=0.881, suggesting the publication bias was not significant. The consistency of each subgroup was good in male and female subgroups.

3.7 Meta-analysis of the relationship of green tea and liver cancer

12 studies including male and female were performed heterogeneity test, Q=56.630, P<0.001, indicating there was heterogeneity between studies; therefore, random effect model was used to perform effect value combined analysis, the pooled RR was 0.77 (95%CI: 0.57-1.03), the result of fixed effect model was 0.90 (95%CI: 0.80-1.00), the results of two models were close, indicating the result is reliable. Publication bias Begg test Z=-0.960, P=0.337, suggesting the publication bias was not significant. The consistency of each subgroup was good in male and female subgroups.

3.8 Meta-analysis of the relationship of green tea and pancreatic cancer

6 studies including male and female were performed heterogeneity test, Q=19.790, P=0.001, indicating there was heterogeneity between studies; therefore, random effect model was used to perform effect value combined analysis, the pooled RR was 0.73 (95%CI: 0.45-1.19), the result of fixed effect model was 0.90 (95%CI: 0.72-1.13), the results of two models were close, indicating the result is reliable. Publication bias Begg test Z=-2.066, P=0.039, suggesting there might be publication bias. The consistency of each subgroup was good in cohort studies, the same regions and the same publication year subgroup; the consistency of each subgroup was also good in male and female subgroups.

4.Discussion

Tea polyphenol is main active ingredient in green tea, which composes of epigallocatechin gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epicatechol (EC), and its target organs are digestive tract, liver and lung [Jankun et al .,1997]. EGCG is considered to have the strongest protective effect in the four forms; it can suppress tumorigenesis by inhibiting urokinase activity [Mukhtar and Ahmad 1999]. It has been proved that green tea extract had effects of antioxidant and anti-gene mutation, and it could promote the activity of two-phase detoxification enzyme glutathione S-transferase (GSTs) to enhance detoxification for carcinogens [Uesato et al.,2001]. Tea polyphenol also can inhibit the generation of endogenous nitroso compounds, tumor and cell proliferation [Yang and Wang 1993].

In this Meta-analysis, the sensitivity analysis was compare of random effect model and fixed effect model, and the results of two models were similar, suggesting the results of Meta-analysis were reliable. The analysis showed that drinking green tea could reduce the risk of gastrointestinal malignancies, in which, there was statistically significant between green tea and gastric cancer, the pooled RR was 0.73 (95%CI: 0.57-0.93), indicating green tea and gastric cancer were closely related. The RR, 0.77 (95%CI: 0.57-1.03) of liver cancer was in the borderline statistical significance, it seems green tea could reduce the risk of liver cancer. However, there were no statistically significant between green tea and esophageal cancer with a pooled RR of 0.89 (95%CI: 0.71-1.13), colon cancer with a pooled RR of 0.96 (95%CI: 0.84-1.10), rectal cancer with a pooled RR of 1.10 (95%CI: 0.97-1.24) and pancreatic cancer with a pooled RR of 0.73 (95%CI: 0.45-1.19), respectively. Subgroup analysis indicated that the protective effect of green tea drinking was associated

with esophageal cancer, especially for women.

Heterogeneity analysis showed that heterogeneity existed between subgroups, and its source might be related to the types and number of confounding factors in each study. In the esophageal cancer subgroup analysis, the results were different with the main results and the robustness was poor, which might be related to the etiology difference of different population, and lower test power caused by less number of cases. Hobby of hot food is one of the risk factors of esophageal cancer; the different temperature of tea may conceal the real effects on esophageal cancer [Islami et al.,2009]. In this study, we conducted a subgroup analysis for adjusting and unadjusting boiled water temperature, the results showed that the green tea had no protective effect in adjusting temperature subgroup, and the reason might be a small number of literatures. In gastric cancer subgroup analysis, the green tea had stronger protective effect in China than that in Japan, which might be related to the dietary habits of different countries. In the type of research subgroup analysis, the green tea had stronger protective effect in case-control studies than that in cohort studies, and cohort studies were carried out mainly in Japan, and most case-control studies were carried out in China. In the publication year subgroup analysis, the results of esophageal cancer, gastric cancer subgroups were significant different with the main results, it might be there were less confounding factor in earlier literatures. The literatures about colon cancer and rectal cancer were published late, and there was only one colon cancer article in which the case number is less than 300, and it had good robustness. Recently, there are a large number of epidemiological and laboratory research data suggest that HBV, HCV and aflatoxin are important risk factors for primary liver cancer [Yu and Yuan 2004]. A part of liver cancer literatures adjusted HBV and HCB infection, not aflatoxin. Only a small number of pancreatic cancer literatures were included in this study, and some of the literatures were published earlier, most of the literatures adjusted less confounding factors and had poor robustness.

Meta-analysis is observational study, there must be bias in the process of design, data collection, statistical analysis, data quality evaluation and trade-offs, and especially publication [Thornton and Lee 2000]. In general, the publication of positive results with “statistically significant” is easier than that of invalid results with “no statistically significance”, which produce publication bias, and affect the authenticity and reliability of results. To control bias, the only way is to collect all research data, and the blinded evaluation is carried out by different people to trade-offs data, at last all the qualified data are combined analyzed. In this study, we collected a variety of studies of relationship of green tea and digestive malignancies, including case-control study (based on hospital and population), cohort study (nested case-control study and case-cohort study), which reduce the selection bias as much as possible; we also comprehensively analyzed the effect value of confounding factors, and reduced the impact on results. In addition, the literatures were collected independently by two authors, and verified and supplemented by the third author, the contradictions and inconsistencies were discussed together; the publication bias was also an important aspect of analysis. The results showed that publication bias only existed in pancreatic cancer, not other cancers; however, the publication bias can’t be excluded completely. Due to language differences, the included literatures are only in English or Chinese, which could lead to language selection bias. When there are too many tumor sites and research regions in Meta-analysis, difficulties will appear, such as, different sample sizes, different subgroup data, and different confounding factors. Because each study is independent, without uniform standards and formats, we have to analyze the effect indicators according to the actual situation. Therefore, we summarized the data in accordance with international standards.

In summary, our results suggested that green tea might be the protective factor for most of the digestive system malignancies, especially gastric cancer(women); however, this conclusion still needs to be verified by large-sample prospective studies and intervention studies.

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References

1 Intemational Agency for Reseaeh on Cancer Coffee, tea,mate, methylxanthines,and methylgloxyal. IARC mongur aph on the evaluation of the carcinogenic risks to humans--lARC monographs v.511991

2 Ui A, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, Hozawa A, Nishino Y, Tsuji I. Green tea consumption and the risk of liver cancer in Japan:the Ohsaki Cohort study. Cancer Causes Control. 2009;20:1939-45.

3 Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, Tsugane S; Japan Public Health Center-Based Prospective Study Group.

Effect of coffee and green tea consumption on the risk of liver eancer:Cohort analysis by hepatitis virus infection status.Cancer Epidemiol Biomarkers Prev. 2009;18:1746-53.

4 Jingyuan Wang, Li,Zhu,Delin Wu.An Analysis on Death Cause of Cancer in High and Low Incidence Areas of Jiangsu Province.Chinese Journal of Cancer Prevention and Treatment 2008;8:1-4.

5 Wang N, Zheng Y, Jiang Q, Yu X, Chen Y. Tea and reduced liver cancer mortality.Epidemiology. 2008;19:761.

6 Montella M, Polesel J, La Vecchia C, Dal Maso L, Crispo A, Crovatto M, Casarin P, Izzo F, Tommasi LG, Talamini R, Franceschi S. Coffee and tea consumption and risk of hepatoeellular carcinoma in Italy. Int J Cancer. 2007;120:1555-9.

7 Xinsen Yu,Peixin Huang,Jiang Qin.A Cohort Study on Risk Factors of Hepatocellular Carcinoma in Haimen City.CHINA PREVENTIVE MEDICINE 2006;7:23-5.

8 Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, Shibuya D, Tsuji I. Coffee consumption and the risk of primary liver cancen pooled analysis of two prospective studies in Japan.Int J Cancer. 2005;116:150-4.

9 Mu LN, Zhou XF, Ding BG, Wang RH, Zhang ZF, Chen CW, Wei GR, Zhou XM, Jiang QW, Yu SZ. A case-contral study on drinking green tea and decreasing risk of cancers in the alimentary canal among cigarette smokers and alcohol drinkers. CHINESE JOURNAL OF EPIDEMIOLOGY 2003;24:23-6.

10 Mu LN, Zhou XF, Ding BG, Wang RH, Zhang ZF, Jiang QW, Yu SZ. Study on the protective effect of green tea on gastric,liver and esophageal cancers.CHINESE JOURNAL OF EPIDEMIOLOGY. 2003;37:1-5.

11 Han X, Xing Q, Li Y, Sun J, Ji H, Huazheng P, Jun L. The case control study for the risk factors of HCC in Luoyang. Modern Preventive Medicine 2002;29:723-5.

12 Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence,Hiroshima and Nagasaki (Japan). Cancer Causes Control. 2001;12:501-8.

13 Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention.Biofactors. 2000;13:49-54.

14 Sidong Chen,Guanqun Zhang,Jianhua Lian. Case control study of primary hepatic carcinoma in Guangdong. Chinese journal of public health. 1999;18:231-2.

15 Kono S, Ikeda M, Tokudome S, Kuratsune M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. Jpn J Cancer Res. 1988;79:1067-74.

16 Kato I, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, Kameya A, Kano T. A comparative case-control analysis of stomach cancer and atrophic gastritis. Cancer Res. 1990;50:6559-64.

17 Yu GP. Hsieh CC. Risk factors for stomach cancer.a population-based case-control study in Shanghai. Cancer Causes Control. 1991;2:169-74.

18 Hoshiyama Y.Sasaba T. A casecontrol study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. Cancer Causes Control. 1992;3:441-8.

19 Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, Jin TH. Green-tea consumption and risk of stomach cancer.a population-based case-controlstudy in Shanghai, China.Cancer Causes Control. 1995; 6:532-8.

20 Ji BT,Chow WH,Yang G, et al. The influence of cigarette smoking.altohol,and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China.Cancer 1996;77:2449-2457.

21 Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Tea and coffee consumption and the risk of digestive tract cancers:data from a comparative case-referent study in Japan.Cancer Causes Control. 1998;9:209-16.

22 Galanis DJ, Kolonel LN, Lee J, Nomura A. Intakes of selected foods and bey.erages and the incidence of gastric cancer among the Japanese residents of Hawaii:a prospective study.Int J Epidemiol. 1998;27:173-80.

23 Huang X, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, Hirose K, Tominaga S, Xiang J, Tokudome S. Effect of life styles on the risk of subsite-spocific gastric cancer in those with and without family history.J Epidemiol. 1999;9:40-5.

24 Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. Biofactors. 2000;13:49-54.

25 Setiawan VW, Zhang ZF, Yu GP, Lu QY, Li YL, Lu ML, Wang MR, Guo CH, Yu SZ, Kurtz RC, Hsieh CC. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. Int J Cancer. 2001;92:600-4.

26 Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control. 2001;12:501-8.

27 Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Green tea and the risk of gastric cancer in Japan.Cancer Causes Control. 2001;12:501-8.

28 Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Tamakoshi A, Ohno Y, Yoshimura T; Japan Collaborative Cohort Study Group. A prospective study of atomach cancer death in relation to green tea consumption in Japan.Br J Cancer. 2002;87:309-13.

29 Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Tamakoshi A, Ohno Y, Yoshimura T; Japan Collaborative Cohort Study Group. A nested case-control study of stomach cancer in relation to green tea consumption in Japan.Br J Cancer. 2004;90:135-8.

30 Sasazuki S, Inoue M, Hanaoka T, Yamamoto S, Sobue T, Tsugane S. Green tea consumption and subsequent risk of gastric cancer by subsite:the JPHC Study. Cancer Causes Control. 2004;15:483-91.

31 Mu LN, Lu QY, Yu SZ, Jiang QW, Cao W, You NC, Setiawan VW, Zhou XF, Ding BG, Wang RH, Zhao J, Cai L, Rao JY, Heber D, Zhang ZF. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. Int J Cancer. 2005;116:972-83.

32 Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease,cancer,and all causes in Japan: the Ohsaki study. JAMA. 2006;296:1255-65.

33 Deandrea S, Foschi R, Galeone C, La Vecchia C, Negri E, Hu J. Is temperature all effect moditier of the association between green tea intake and gastric cancer risk.Eur J Cancer Prev. 2010;19:18-22.

34 Wouters EG, Buishand FO, Kik M, Kirpensteijn J. A comparative ease-control study of coiorectal cancer and adenoma.J Small Anim Pract. 2011;52:139-45.

35 Baron JA, Gerhardsson de Verdier M, Ekbom A. Coffee, tea,tobacco,and cancer of the large bowel. Cancer Epidemiol Biomarkers Prev. 1994;3:565-70.

36 Zheng W, Doyle TJ, Kushi LH, Sellers TA, Hong CP, Folsom AR. Tea consumption and cancer incidence in a prospective cohoa study of postmenopausal women.Am J Epidemiol. 1996;144:175-82.

37 Tavani A, Pregnolato A, La Vecchia C, Negri E, Talamini R, Franceschi S. Coffee and tea intake and risk of cancer of the colon and rectum:a study of 3,530 cases and 7,057 controis.Int J Cancer. 1997;73:193-7.

38 Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorects/cancers.Int J Cancer. 1997;70:255-8.

39 Muñoz SE, Navarro A, Lantieri MJ, Fabro ME, Peyrano MG, Ferraroni M, Decarli A, La Vecchia C, Eynard AR. Alcohol. methyhanthine-conmining beverages,and colorectal cancer in Cordoba,Argentina.Eur J Cancer Prev. 1998;7:207-13.

40 Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan.Cancer Causes Control. 1998;9:209-16.

41 Slattery ML, Caan BJ, Anderson KE, Potter JD.Intake of fluids and methylx-anthine-containing beverages: association with colon cancer. Int J Cancer. 1999;81:199-204.

42 Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention.Biofactors. 2000;13:49-54.

43 Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence,Hiroshim and Nagasaki Oapan). Cancer Causes Control. 2001;12:501-8.

44 Su U,Arab L. Tea consumption and the reduced risk of colon carlcerresults from a national prospective cohoa study. Public Health Nutr. 2002;5:419-25.

45 Woolcott CG, King WD, Marrett LD. Coffee and tea consumption and cancers of the bladder, colon and rectum.Eur J Cancer Prev. 2002;11:137-45.

46 Zhang B, Li X, Nakama H, Zhang X, Wei N, Zhang X, Zhang L. A case-control study on risk of changing food consumption for colorectal cancer. Cancer Invest. 2002;20:458-63.

47 Il'yasova D, Martin C, Sandler RS. Tea intake and risk of colon cancer in African-Americans and whites: North Carolina colon cancer study. Cancer Causes Control. 2003;14:767-72.

48 Suzuki Y, Tsubono Y, Nakaya N, Koizumi Y, Suzuki Y, Shibuya D, Tsuji I. Green tea and the risk of eolorectal cancer.pooled analysis of two prospective studies in Japan. J Epidemiol. 2005;15:118-24.

49 Michels KB, Willett WC, Fuchs CS, Giovannucci E. Coffee, tea, and caffeine

consumption and incidence of colon and rectal cancer. J Natl Cancer Inst. 2005;97:282-92.

50 Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. 2006;296:1255-65.

51 Yang G, Shu XO, Li H, Chow WH, Ji BT, Zhang X, Gao YT, Zheng W. Prospective cohoa study of green tea consumption and colorectal cancer risk inwomen.Cancer Epidemiol Biomarkers Prev. 2007;16:1219-23.

52 Sun CL, Yuan JM, Koh WP, Lee HP, Yu MC. Green tea and black tea consumption in relation to colorectal cancer risk:the Singapore Chinese Health Study. Carcinogenesis.2007;28: 2143-8.

53 Ishikawa A, Kuriyama S, Tsubono Y, Fukao A, Takahashi H, Tachiya H, Tsuji I. Smoking, alcohol drinking,green tea consumption and the risk of esophageal cancer in Japanese men.J Epidemiol. 2006;16:185-92.

54 Sun CL, Yuan JM, Lee MJ, Yang CS, Gao YT, Ross RK, Yu MC. Urinary tea polyphenols in relation to gastric and esophageal cancers:a prospective study of men in Shanghai, China. Carcinogenesis. 2002;23:1497-503.

55 Wang JM, Xu B, Rao JY, Shen HB, Xue HC, Jiang QW. Diet habits,alcohol drinkin9,tobacco smoking, green tea drinking,and the risk of esophageal squamous cell carcinoma in the Chinese population.Eur J Gastroenterol Hepatol. 2007;19:171-6.

56 Wu M, Liu AM, Kampman E, Zhang ZF, Van't Veer P, Wu DL, Wang PH, Yang J, Qin Y, Mu LN, Kok FJ, Zhao JK. Green tea drinking,high tea temperature and esophageal cancer in high-and lowrisk areas of Jiangsu Province, China:a population-based ease-control study.Int J Cancer. 2009;124:1907-13.

57 Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, Abedi-Ardekani B, Merat S, Vahedi H, Semnani S, Abnet CC, Brennan P, Møller H, Saidi F, Dawsey SM, Malekzadeh R, Boffetta P. Tea drinking habits and oesophageal cancer in a high risk area in northern Lran:population based case-control study.BMJ. 2009;338:b929.

58 Gao YT, McLaughlin JK, Blot WJ, Ji BT, Dai Q, Fraumeni JF Jr. Reduced risk of esophageal cancer associated with green tea consumption.J Natl Cancer Inst. 1994;86:855-8.

59 Hu J, Nyrén O, Wolk A, Bergström R, Yuen J, Adami HO, Guo L, Li H, Huang G, Xu X Risk factors for oesophageal cancer in northeast China.Int J Cancer. 1994;57:38-46.

60 Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Tea and coffee consumption and the risk of digestive lract cancer$: data from a comparative case-referent study in Japan.Cancer Causes Control. 1998;9:209-16.

61 Wending Zhang,Fengshan An,Hansheng Lin.A case-control study on the risk factors of esophageal cancer in Jieyang city of Guangdong in China. CHINESE JOURNAL OF EPIDEMIOLOGY 2001;22:712-4.

62 Tavani A, Bertuzzi M, Talamini R, Gallus S, Parpinel M, Franceschi S, Levi F, La Vecchia C. Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. Oral Oncol. 2003;39:695-700.

63 Hung HC, Huang MC, Lee JM, Wu DC, Hsu HK, Wu MT. Association between diet and esophageal cancer in Taiwan.J Gastroenterol Hepatol. 2004;19:632-7.

64 Ganesh B, Talole SD, Dikshit R. Tobacco, alcohol and tea drinking as riskfactors for esophageal cancee a casecontrol study from Mumbai, India. Cancer Epidemiol. 2009;33:431-4.

65 Gao Y, Hu N, Han X, Giffen C, Ding T, Goldstein AM, Taylor PR. Jasnine tea consumption and upper gastrointestinal cancer in China. Cancer Causes Control. 2009;20:1997-2007.

66 Chen YK, Lee CH, Wu IC, Liu JS, Wu DC, Lee JM, Goan YG, Chou SH, Huang CT, Lee CY, Hung HC, Yang JF, Wu MT. Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwaneso men. Nutrition. 2009;25:753-61.

67 Mingrong Wang, Chunhua Guo,Maosheng Li. A case-control study on the dietary risk factors of upper digestive tract cancer.1999;CHINESE JOURNAL OF EPIDEMIOLOGY 2003;20:24-6.

68 Hongkang Yang, Ailing Xu,Jinao Zhou. The relationship betweeen life-style,gastric carcinoma and esophagus cancer. Chinese Primary Health Care 1999;12:30-1.

69 Xinmin Liu,Qingsheng Wang,Yali Zhang. A case- control study on the association between esophageal cancer and dietary factors. JOURNAL OF TIANJIN MEDICAL UNIVERSITY 2001;7:312-4.

70 Xiane Pen, Zijin Zhou,Xishun Shi. case on control study on risk factors of esophageal cancer in Anxi country.Chinese Journal of Public Health 2005;21:10-2.

71 Ying Xie, Guiju Sun,Xu Hu. Case control study for between residents' dietary,behavial factor and esophagus cancer in Huaian.Journal of Hygiene Research 2005;34:479-80.

72 Jinkou Zhao, Ming Wu,Aimin Liu. Case

control study of esophagus cancer in Jiangsu province. Chinese Journal of Prevention and Control of Chronic Non-Communicable Diseases 2005;21:13-5.

73 Xushan Wang, Delin Wu,Xiaofeng Zhang. Case control study of esophagus cancer in Ganyu country. Chinese Journal of Health Statistics 2008;7:26-8.

74 Wei Li, Xiaolei Guo,Zhentao Fu.Case-control study on risk factors of esophageal cancer. Chinese Journal of Public Health 2008;24:43-6.

75 Hong Li,Chengyi Qu,Lixia Bai.case control study on the risk factors in behavior and life style of esophageal carcinoma.Chin J Dis Control Prev 2008;12:211-4.

76 Juan Yang,Ying Shao, Shujuan Yang. Non Conditional Logistic Regression Analysis On The Risk Factors Of Esophageal Cancer In Linzhou Modern Preventive Medicine. 2009;36:34-7.

77 Whittemore AS, Paffenbarger RS Jr, Anderson K, Halpern J. Early precursors of pancreatic cancer in college men.J Chronic Dis. 1983;36:251-6.

78 Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly.Int J Cancer. 1994;58:46-9.

79 Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking,alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas:the Iowa women's health study. Cancer Epidemiol Biomarkers Prev. 1997;6:1081-6.

80 Luo J, Inoue M, Iwasaki M, Sasazuki S, Otani T, Ye W, Tsugane S; JPHC Study Group. Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population -based cohort study in Japan (JPHC study).Eur J Cancer Prev. 2007;16:542-8.

81 Lin Y,Kikuchi S,Tamakoshi A. Green tea consumption and the risk of pancreatic cancer in Japanese adults. Pancreas. 2008;37:25-30.

82 Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM. Cigarette smoking, alcohol,tea and coffee consumption and pancreas cancer risk:a case-control study from Opole, Poland.Int J Cancer. 1993;53:601-7.

83 Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorectal cancers.Int J Cancer. 1997;70:255-8.

84 Qi Dai,Butian Ji,Fan Jin. The relationship between pancreatic carcinoma and smoking, driking and green tea in Shanghai.Chinese journal of tumor 1995;5:23-5.

85 Jankun J, Selman SH, Swiercz R, Skrzypczak-Jankun E. Why drinking green tea could prevent cance.Nature. 1997;387:561.

86 Mukhtar H. Ahmad N. Green Tea in Chemoprevention of Cancer.Toxicol Sci. 1999;52:111-7.

87 Uesato S, Kitagawa Y, Kamishimoto M, Kumagai A, Hori H, Nagasawa H. Inhibition of green tea catechins against the growth of cancerous human colon and hepatic epithelial teNs. Cancer Lett. 2001;170:41-4.

88 Yang CS,Wang ZY. Tea and Cancer.J Natl Cancer Inst. 1993 Jul 7;85:1038-49.

89 Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk-a systematic review.Int J Cancer. 2009;125:491-524.

90 Yu MC,Yuan JM. Environmental factors and risk for hepatecellular carcinoma. Gastroenterology. 2004;127:S72-8.

91 Thornton A, Lee P.Publication bias in meta-analysis: its causes and consequences.J Clin Epidemiol. 2000;53:207-16.

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