REVIEW

Green and black tea in relation to gynecologic cancers

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Scope: Observational studies have evaluated the relationship between green tea intake and cancers of the ovary and endometrium, but we are not aware of the published studies on green tea intake and risk of human papillomavirus (HPV)-related cancers of the cervix, vagina, or vulva.

Methods and results: A critical review of the published literature on tea intake and risk of ovarian and endometrial cancers was conducted. In meta-analyses, we report inverse associations for green tea intake and risk of ovarian cancer (odds ratio [OR] = 0.66; 95% confidence interval [CI]: 0.54, 0.80), and for green tea and risk of endometrial cancer (OR = 0.78, 95% CI: 0.62, 0.98). There was no association for black tea and ovarian cancer risk (OR = 0.94, 95% CI: 0.87, 1.02) and a positive association with endometrial cancer risk (OR = 1.20, 95% CI: 1.05, 1.38). We summarized the experimental evidence supporting the antiviral and immunomodulatory activities of green tea catechins, and results from randomized clinical trials that demonstrated green tea catechin efficacy on treatment of cervical lesions and external genital warts.

Conclusion: Observational data support a protective role of green tea on risk of ovarian and endometrial cancers. Observational data are needed to evaluate whether green tea reduces risk of human papillomavirus-related cancers.

Keywords:
Cervical cancer / Endometrial cancer / Genital warts / Green tea / Ovarian cancer

1 Introduction

Gynecologic cancers include those of the ovary, endometrium, cervix, vagina, and vulva. Ovary and endometrial cancers are the seventh and eighth most common cancers among women worldwide, whereas cervical cancer is the second most common [1]. Incidence of ovarian and endometrial cancers is highest among developed western countries and has been increasing among developing countries in various parts of Asia. Cervical cancer incidence is highest in developing countries in Asia and South America and is associated with relatively poor survival in the populations with the highest incidence.

In general, dietary factors are not thought to play major roles in the etiology of gynecologic cancers. There is limited suggestive evidence for the protective effect of nonstarchy vegetable intake and risk of ovarian and endometrial cancers, and of carrots and risk of cervical cancer [2]. There is also a suggestive adverse effect of red meat intake on endometrial cancer risk [2]. While dietary factors may not have a direct role for the other gynecologic cancers, diet may be related to susceptibility to and/or persistence of human papillomavirus (HPV) infection, a necessary cause of cervical, vaginal, and vulval cancers [3, 4].

Tea is made from the leaves of *Camellia sinensis* and contains polyphenols with chemopreventive properties. For example, epigallocatechin-3-gallate (EGCG), the major catechins found in green tea, has been shown to inhibit cyclooxygenase-dependent promotion effects in ovarian carcinoma cell lines [5]. Anticarcinogenic effects of green tea have also been demonstrated in animal models of ovarian

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Abbreviations: **CI,** confidence interval; **EGCG,** epigallocatechin-3-gallate; **EGW,** external genital warts; **HPV,** human papillomavirus; **OR,** odds ratio; **RR,** relative risk; **SHBG,** sex hormone-binding globulin

cancer [6] and endometriosis [7, 8]. Green tea catechins also have antiviral and immunomodulating properties that may protect against HPV-related cancers [9, 10].

Previously conducted reviews of tea and cancers of the ovary [11–14] and endometrium [15] did not consistently present summary associations separately for green tea and black tea intake, or for case–control and prospective cohort studies. We present updated meta-analyses results on green tea and black tea intake and risk of ovarian and endometrial cancers, and a summary of the experimental evidence for the antiviral activities of green tea catechins and randomized clinical trial data evaluating the efficacy of green tea catechins on treatment of cervical lesions and external genital warts (EGWs). To identify relevant articles, we searched PubMed (from 1962 to December 2010) using the following search terms ''beverages,'' ''black tea,'' ''cancer,'' ''diet,'' ''green tea,'' and ''tea'' combined with ''cancer,'' ''cervical cancer,'' ''endometrial cancer,'' ''ovarian cancer,'' ''human papilloma virus,'' ''vaginal cancer,'' and ''vulval cancer.'' We restricted our search to English-language articles, with one exception. We included a Chinese-language article, because relevant information was available in an English-language abstract [16]. We included all human, epidemiologic studies that evaluated tea intake and cancers of the ovary, endometrium, cervix, vagina, and/or vulva. To calculate combined odds ratios (ORs) and corresponding 95% confidence intervals (CIs), we used the ORs or relative risks (RRs) from each article and pooled them according to tea type, cancer site, study design, and/or population (e.g. western). If the study was conducted among a western population and tea type was not specified, we assumed that black tea was the primary type consumed. On the contrary, if the study was conducted among an Asian population, we assumed that green tea was the primary type consumed. For each pooled estimate, we tested the heterogeneity of results across the studies using the Q-statistic. If statistically significant heterogeneity was observed (e.g. $p \geq 0.05$), then a random effect model was used to calculate the combined OR. Otherwise, a fixed effects model was used.

2 Ovarian cancer

Of the gynecologic cancers, ovarian cancer risk has been evaluated most often in relation to tea intake. During the past three decades, at least 17 epidemiologic studies have evaluated tea and ovarian cancer risk [12, 14] but only four case–control studies have published results specifically for green tea intake and ovarian cancer risk [14, 17–19]. We are not aware of any prospective cohort results on green tea intake and risk of ovarian cancer. Three of the four case–control studies were conducted in western populations: Australia [14] and the US [17, 19]. The fourth study was conducted in Hangzhou, China [18]. The combined ORs from these four studies show a significant inverse association between green tea intake and risk of ovarian cancer (OR = 0.66, 96% CI: 0.54, 0.80) (Table 1). This association should be interpreted cautiously, given that the prevalence of green tea intake differed substantially across study populations; daily intake ranged from 2.7% in the US (Seattle) to 37% in China, and there were no prospective results available.

In a separate survival analysis, Zhang et al. followed 244 women diagnosed with ovarian cancer from the case–control study for a minimum of 3 years. Green tea drinkers experienced lower risk of death due to ovarian cancer, compared with nondrinkers (hazard ratio [HR] = 0.55; 95% CI: 0.34, 0.90). The mean survival time among green tea drinkers was 5.39 years (95% CI: 4.94, 5.85), and 4.19 years (95% CI: 3.66, 4.72) among nondrinkers. When restricted to

Table 1. Characteristics of studies on green tea and ovarian cancer

Study	Location	Cases/ controls (n)	Number of levels	Lowest versus highest exposure	Percent in lowest versus highest exposure among controls	OR (95% CI)[a)]
Nagle [14]	Australia	1368/1416	6	Never vs. $\geq$1 cups/day	63 vs. 9%	0.84 (0.64, 1.12)[b)]
Song [19]	US	781/1262	3	Never or $<$monthly vs. $\geq$1 cup/day	71 vs. 4%	0.46 (0.26, 0.84)
Goodman [17]	US	194/164	3	Nondrinkers vs. $\geq$1 cups/week	63 vs. 19%	0.9 (0.5, 1.6)
Zhang [18]	China	237/569	4	Never or seldom vs. $\geq$1 times/day	29 vs. 43%	0.43 (0.30, 0.63)

Case-control studies Combined OR = 0.66 (95% CI: 0.54, 0.80)[c),d)]
Western population case–control studies Combined OR = 0.74 (95% CI: 0.51, 1.06)[e)]

a) All ORs were adjusted for age and hormone use. Some ORs were additionally adjusted for menstrual and/or reproductive factors [14, 18, 19], smoking [18, 19], body mass index [18, 19], coffee intake [14, 18], and/or alcohol use [18].
b) The OR was calculated as a weighted average using the adjusted ORs presented by Nagle et al. for 1/day, 2–3/day, and $\geq$4/day so that the ''highest'' exposure group was comparable with the other studies [14].
c) Combined OR = 0.63 (95% CI: 0.51, 0.78) when the study by Goodman et al. [17] was excluded. Test for heterogeneity, $p = 0.010$.
d) Test for heterogeneity, $p = 0.015$.
e) Test for heterogeneity, $p = 0.164$.

Table 2. Characteristics of studies on black tea and ovarian cancer

Study	Location	Cases/controls or cohort (*n*)	Number of levels	Lowest vs. highest exposure	Percent in lowest vs. highest exposure among controls or noncases	OR or RR (95% CI)[a]
Nagle [14][b]	Australia	1368/1416	6	Never vs. ≥4 cups/day	16.9 vs. 14.7%	0.88 (0.66, 1.18)
Song [19][b]	USA	781/1263	3	Nondrinkers vs. ≥1 cups/day	49.3 vs. 10.4%	0.91 (0.65, 1.27)
Silvera [55][c]	Canada	264/46 613	4	None vs. ≥4 cups/day	22.4 vs. 6.3%[c]	1.07 (0.64, 1.79)
Gates [56][c]	USA	347/66 940	4	1 servings/wk vs. ≥2 servings/day	45.2 vs. 10.4%	0.63 (0.40, 0.99)
Steevens [12][c]	Netherlands	280/2083	4	1 to <3 vs. ≥5 cups/day[d]	38 vs. 12.9%[c]	0.65 (0.41, 1.03)[e]
Baker [57][b]	USA	414/868	4	None vs. ≥2 cups/day	27.7 vs. 27.2%	0.70 (0.51, 0.97)
Larsson [58][c]	Sweden	301/61 057	4	Never or seldom vs. ≥4 cups/day	31.5 vs. 8.3%[c]	0.54 (0.31, 0.91)
Jordan [59][b]	Australia	696/786	5	None vs. ≥4 cups/day	14.4 vs. 23.5%	1.10 (0.76, 1.61)
Zheng [31][c]	USA	107/27 305	4	Never or monthly vs. ≥2 cups/day	58.3 vs. 8.6%	0.98 (0.50, 1.90)
Goodman [17][b]	USA	164/194	3	Nondrinker vs. ≥2.5 cups/week	40.7 vs. 19.6%	1.1 (0.6, 2.0)
Zhang [18][b]	China	454/652	4	Never or seldom vs. ≥1 times/day	81 vs. 6.8%	0.06 (0.01, 0.50)
Tavani [60][b]	Italy	1031/2411	2	Nondrinkers vs. ≥1 cups/month	49.5 vs. 50.0%	0.90 (0.75, 1.08)
Kuper [61][b]	USA	549/516	2	Rarely vs. ≥1 times/wk	61.8 vs. 38.2%	1.06 (0.83, 1.36)
La Vecchia [35][b]	Italy	742/6147	2	None vs. any	82.9 vs. 17.0%	1.2 (1.0, 1.4)
Miller [62][b]	USA	290/376 with cancer; 480 noncancer	4	0 vs. ≥5 cups/day	58 vs. 5% among cancer controls; 54 vs. 6% among noncancer controls[e]	0.7 (0.3, 1.6) with cancer controls; 0.5 (0.2, 1.0) with noncancer controls[f]
Byers [63][b]	USA	274/1034	3	None vs. ≥3 cups/day	14 vs. 13%	0.84 (not available)

All studies Combined OR = 0.94 (95% CI:0.87, 1.02)[g),h),i)]
Prospective cohort studies Combined OR = 0.73 (95% CI: 0.57, 0.93)[j)]
Case–control studies Combined OR = 0.98 (95% CI: 0.90, 1.07)[g),k)]

a) All ORs or RRs were adjusted for age. Some ORs were additionally adjusted for menstrual and/or reproductive factors [14, 18, 19, 31, 55, 56, 58–60, 62], hormone use [14, 17–19, 56, 58–60, 62], smoking [12, 14, 18, 19, 31, 55, 56, 59, 62], body size [18–19, 31, 55, 58–60, 62], coffee intake [12, 14, 18, 58], and/or alcohol use [18, 58, 59, 62].
b) Case–control studies.
c) Prospective cohort studies.
d) Percentage of total person–years.
e) The reference group was 1 to <3 cups/day, compared with 0 to <1, 3 to <5, and ≥5 cups/day.
f) There was no difference in the combined ORs and 95% CIs whether we used the OR and 95% CI calculated with the cancer controls or noncancer controls.
g) Results from Byers [63] were excluded, because the 95% CIs were not available in the article.
h) Test for heterogeneity, $p = 0.003$.
i) Combined OR = 0.78 (95% CI: 0.65, 0.93) when the following studies were excluded due to relatively low [17, 60, 61] or broad [35] levels of intake. Test for heterogeneity, $p = 0.083$.
j) Test for heterogeneity, $p = 0.317$.
k) Test for heterogeneity, $p = 0.007$.

tea-drinking status during post-diagnosis only, there was an almost 2 year greater mean survival among green tea drinkers compared with nondrinkers [20].

There is observational evidence for a protective effect of black tea on ovarian cancer risk. A meta-analysis from Steevens et al. showed a statistically significant 29% decrease in risk for highest versus lowest tea intake using data from five prospective cohorts conducted among western populations (RR = 0.71, 95% CI: 0.55, 0.93) [12]. On the contrary, a meta-analysis using data from six case–control studies conducted among western populations showed no association (OR = 1.04, 95% CI: 0.93, 1.15) [13].

Consistent with the previous retrospective studies, two recent population-based case–control studies reported no association between black tea intake and ovarian cancer risk [14, 19]. The first was conducted in a US population where 49% of controls were nondrinkers of black tea [19]. The second study was conducted in an Australian population with a wide variation of black tea intake (e.g. among controls 17% were never drinkers and 15% drank four or more cups per day). The OR comparing highest intake to never drinkers was 0.88 (95% CI: 0.66, 1.18, p for trend = 0.7) [14]. The updated meta-analysis shows no association between black tea and ovarian cancer from case–control study data (combined OR = 0.94, 95% CI: 0.87, 1.02) (Table 2).

3 Endometrial cancer

In a 2009 meta-analysis on tea and endometrial cancer, Tang et al. reported a summary RR of 0.81 (95% CI: 0.71, 0.93) using data from five studies conducted among Asian populations [15]. Of these studies, three were conducted in Japan [21–23] and two in China [16, 24]. It can be presumed that green tea was the main tea type consumed in these populations. The supportive evidence for green tea from Tang et al.'s meta-analysis [15] includes results from the only prospective cohort study [21] and a large population-based case–control study [24].

The prospective cohort study was conducted in Japan among a cohort of 53 724 women who were followed for up to 15 years with minimal (0.3%) loss to followup [21]. Risk of endometrial cancer was inversely associated with green tea intake; the hazard ratio was 0.75 (95% CI: 0.44, 1.30) for ≥ 5 cups/day versus ≤ 4 cups/wk. The high prevalence of green tea intake in Japanese populations does not provide a wide variation of intake, particularly at the lower levels. This may explain the lack of a statistically significant finding in these data.

In the large population-based case–control study (1199 cases and 1212 controls) in Shanghai, China, ever green tea intake was inversely associated with endometrial cancer risk (OR = 0.78; 95% CI: 0.64, 0.94) [24]. In a separate analysis of the same data, statistically significant dose-dependent trends were observed for greater amount of tea consumed (p for trend = 0.03) and greater frequency of tea intake (p for trend = 0.006) [25]. A dose-dependent trend, however, was not observed for more years of green tea intake and endometrial cancer risk (p for trend = 0.13).

A population-based case–control study among the US population was published since the meta-analysis by Tang et al. [15]. Using data collected from 417 cases and 395 controls, a statistically nonsignificant inverse association was reported for green tea intake and endometrial cancer risk, comparing one or more cups/wk to nondrinkers (OR = 0.76, 95% CI: 0.48, 1.21, p for trend = 0.2) [26]. Green tea is not a frequently consumed beverage in the US, for example, only 20% of controls consumed green tea at least once per week [26]. With the addition of this study, for a total of six studies, the updated combined OR continues to support a protective effect of green tea on endometrial cancer risk (combined OR = 0.78, 95% CI: 0.62, 0.98) (Table 3).

Sex steroid hormones and the sex hormone-binding globulin (SHBG) are important in the etiology of endometrial cancer. For example, higher blood levels of SHBG are related to lower risk of endometrial cancer in postmenopausal women [27, 28]. A missense mutation in SHBG (rs6259) is associated with lower circulating levels of the molecule in postmenopausal women [29, 30]. Xu et al. report interaction between the SHBG genotype and the green tea intake on the association with endometrial cancer (p for interaction = 0.03), where a stronger inverse association was observed among those with the Asp327Asp genotype (OR = 0.67; 95% CI: 0.52, 0.86, comparing ever versus never green tea intake) [24].

In contrast to the overall protective effect found for green tea, black tea intake appears to be positively associated with risk of endometrial cancer. Tea intake and risk of endometrial cancer has been evaluated in several western populations including the US [26, 31, 32], Canada [33], and Europe [34, 35]. Although an inverse association was reported in one hospital-based case–control study [32], the remaining studies reported either positive or no associations. The combined OR for black tea and endometrial cancer was 1.20 (95% CI: 1.05, 1.38) (Table 4).

4 HPV-related conditions

Persistent HPV infection is a prerequisite for the development of invasive genital cancers [3], as well as premalignant and nonmalignant lesions, including EGWs [36, 37]. To our knowledge, there are no published data from epidemiologic studies of green tea intake and risk of cervical, vaginal, or vulval cancers. There are a total of four randomized clinical trials published to date that evaluated green tea catechin efficacy for the treatment of premalignant cervical lesions [38] and EGWs [39–41]. The design and results of these trials are summarized in Table 5.

Ahn et al. conducted an intervention study to evaluate the efficacy of green tea extracts on the treatment of cervical

Table 3. Characteristics of studies on green tea and endometrial cancer

Study	Location	Cases/controls or cohort (*n*)	Number of levels	Lowest vs. highest exposure	Percent in lowest vs. highest exposure among controls or noncases	OR or RR (95% CI)[a]
Bandera [26][b]	USA	397/373	3	0 cups/wk vs. ≥1 cups/wk	38 vs. 20%	0.76 (0.48, 1.21)
Kakuta [23][b]	Japan	152/285	4	4 cups/wk vs. ≥4 cups/day	25 vs. 26%	0.33 (0.15, 0.75)
Shimazu [21]	Japan	117/53 724	4	4 cups/wk vs. ≥5 cups/day	–	0.75 (0.44, 1.30)
Hirose [22][b]	Japan	229/12 425	–	Never/occasional vs. ≥7 cups/day	–	1.33 (0.75, 2.35)
Xu [25][b]	China	1204/1212	4	Never vs. primarily green tea	69 vs. 28%	0.8 (0.6, 0.9)[c]
Gao [16][b]	China	995/1087	3	Never vs. ≥7cups/day	–	0.76 (0.60, 0.95)

All studies Combined OR = 0.78 (95% CI: 0.64, 0.95)[c]
Case–control studies Combined OR = 0.78 (95% CI: 0.62, 0.98)[d]

a) ORs or RRs were adjusted for age [21, 22, 24–26], menstrual and/or reproductive factors [21–26], hormone use [21, 23, 26], smoking [21–23, 26], body mass index [21–26], coffee intake [23], and/or alcohol use [22–25].
b) Case–control studies.
c) Test for heterogeneity, $p = 0.163$.
d) Test for heterogeneity, $p = 0.097$.

lesions along the carcinogenesis pathway from chronic cervicitis to severe dysplasia [38]. Fifty-one patients received one of the following four treatments for 8–12 wk: poly E ointment, poly E oral capsule, poly E ointment+capsule, or EGCG capsule. The poly E capsule was given daily and contained 200 mg EGCG, 37 mg epigallocatechin, and 31 mg epicatechin. The EGCG capsule was also given daily and contained 200 mg EGCG. The ointment was applied twice weekly. The treatment groups were compared to 39 untreated controls in terms of three outcomes defined by changes in Papanicolaou cytology, HPV DNA titers, and degree of dysplasia. The overall response rates for treated and untreated subjects were 69 and 10%, respectively. The response rates by treatment group were 50% for poly E capsule, 60% for EGCG capsule, 74% for poly E ointment, and 75% for poly E ointment and capsule [38].

The following three trials randomized subjects with EGWs to green tea catechin ointment (Polyphenone E or sinecatechin) at 10 or 15% or matching vehicle (placebo). In a trial of 242 subjects, complete EGW clearance was observed in 59% of those who received the 15% catechin ointment, compared with 37.3% in the placebo group (p for difference = 0.007) [39]. In the two other trials of ≈500 subjects, complete EGW clearance was statistically significant at both the 10 and 15% catechin ointment levels. Complete EGW clearance was reported at 53, 51, and 37% for the 10 and 15% and placebo groups (p for difference was 0.01 for 15% versus placebo and 0.03 for 10% versus placebo) [40]. Similar results were reported in the final trial that applied the ointments three times daily for up to 16 wk [41].

5 Antiviral and immunomodulatory effects of green tea catechins

Green tea catechins have antiviral and immunomodulating properties, in addition to their antitumor affects. It is hypothesized that green tea catechins may protect against HPV-related cancers via mechanisms related to all three properties. Summarized below is the experimental evidence for the antiviral and antitumor affects of the green tea catechin, EGCG on HPV-positive cells and tumors, and for EGCG's immunomodulatory effects in humans.

The antiviral effects of EGCG are demonstrated in vitro by downregulation of the HPV oncoproteins E6 and E7 [10]. These oncogenes are essential for cervical carcinogenesis [42]. Qiao et al. demonstrated that in HPV-positive cervical cancer cells, EGCG treatment resulted in a 30–60% reduction of E6 and E7 mRNA expression in a time- and dose-dependent manner, compared with untreated control cells [43]. The downregulation of E6/E7 may be a mechanism by which green tea catechins inhibit HPV-infected cancer cell growth.

There is ample in vitro evidence for the affect of the green tea catechin, EGCG on inhibiting growth and simulating apoptosis in HPV-infected cervical cells and cervical cancer cell lines in a dose-dependent manner [10, 43–45]. Singh et al. demonstrated that green tea polyphenols inhibited proliferation of HPV16 cervical cancer cells by inducing apoptosis in a dose-dependent manner [44]. Cells treated with green tea polyphenols at concentrations of 0.30, 0.35, and 0.40% resulted in 14.8, 17.4, and 21.9% cells in the G2/M phase, respectively, compared with 2.3% in untreated control cells ($p < 0.05$) [44].

Table 4. Characteristics of studies on black tea and endometrial cancer

Study	Location	Cases/ controls or cohort (*n*)	Number of levels	Lowest vs. highest exposure	Percent in lowest vs. highest exposure among controls or noncases	OR or RR (95% CI)[a)]
Zheng [31]	USA	249/21 019	4	Never or monthly vs. $\geq$2 cups/day	58.3 vs. 8.6%	0.76 (0.45, 1.27)
McCann [32][b)]	USA	513/512	4	None vs. >2 cups/day	28.1 vs. 13.3%	0.56 (0.35, 0.90)
Bandera [26][b)]	USA	417/395	3	None vs. >1 cups/day	14.8 vs. 23.1%	1.93 (1.08, 3.34)
Jain [33][b)]	Canada	552/562	4	0 vs. >500 g/day	25 vs. 25%	0.99 (0.68, 1.45)
Levi [34][b)]	Switzerland and Italy	274/572	2	None vs. any	59.8 vs. 40.2%	1.84 (not available)
La Vecchia [35][b)]	Italy	657/6147	2	None vs. any	82.9 vs. 17.0%	1.4 (1.2, 1.7)
Goodman [64][b)]	USA	332/511	4	0 vs. >118 g/day	25 vs. 25%	0.9 (not available)

All studies Combined OR = 1.20 (95% CI: 1.05, 1.38)[c), d), e)]
Case-control studies Combined OR = 1.25 (95% CI: 1.08, 1.44)[c), f)]

a) ORs or RRs were adjusted for age [26, 31, 32, 34, 35], menstrual and/or reproductive factors [26, 31–33, 64], hormone use [26, 32, 33, 64], smoking [26, 31–33, 35], body size [26, 31–33, 64], and/or coffee intake [32, 35].
b) Case–control studies.
c) Results from Levi [34] and Goodman [64] were excluded, because the 95% CIs were not available in the articles.
d) Test for heterogeneity, $p = 0.001$.
e) Combined OR = 0.92 (95% CI: 0.72, 1.16) when the study by La Vecchia [35] was excluded because of the relatively broad level of intake. Test for heterogeneity, $p = 0.009$.
f) Test for heterogeneity, $p = 0.001$.

In vivo evidence for EGCG's antitumor immunity effect on HPV infected tumors has been recently provided [9, 46]. Using an E7-expressing tumor mouse model, Kang et al. demonstrated that EGCG was effective in combination with a DNA vaccine at inhibiting tumor growth [9]. There was a statistically significant, dose-dependent increase in E7-specific $CD8^+$ T cells with EGCG drinking water concentrations from 0 to 0.5 mg/mL. In addition, in mice that received both the DNA vaccine and the EGCG (at 0.5 mg/mL) for 14 days, a 6.5-fold increase in the number of IFN-γ-secreting E7-specific $CD8^+$ T-cell precursors, compared with either vaccine or EGCG alone was observed. In conclusion, the combination treatment led to a higher cure rate than either treatment alone, perhaps due to the enhanced tumor-specific T-cell immune response observed in the mice with both EGCG and vaccine treatments [9]. Together, the experimental evidence shown here suggests that green tea catechins have the ability to enhance cell-mediated immunity that is important in considering it as a chemopreventive agent for HPV-associated gynecologic cancers.

Green tea catechins may modulate the immune system by disrupting the proinflammatory cascade via antioxidant effects, altering cell signaling (e.g. nuclear factor-κB) [47, 48], cytokines, and/or proinflammatory mediators (e.g. C-reactive protein [CRP]) [49, 50]. The few clinical trial data available do not support a direct effect of green tea intake on circulating inflammatory markers. In a 4-wk randomized placebo-controlled trial among current smokers ($N = 64$), no changes in plasma levels of the cytokines IL6, IL1β, and tumor necrosis factor (TNF)-α or C-reactive protein were observed following daily intake of black or green tea or a green tea polyphenol capsule equivalent to 240 mg, 852 mg, and 2.1 g total catechins, respectively [51]. Similar null results were observed in two trials, one among 20 adult male smokers who ingested 600 mL of green tea for 4 wk [52] and another among 66 male and female subjects with borderline diabetes or diabetes who were treated with $\approx$500 mg tea catechins per day for 2 months [53].

A randomized double-blind placebo-controlled trial among 124 men and women was conducted to compare a 12-wk treatment with a proprietary formulation containing EGCG versus placebo [54]. Subjects kept an illness log including daily cold and flu symptoms, and provided a blood sample at days 0 and 21. Fewer subjects (43.2%) in the treatment than the placebo arm (63.6%) reported at least one cold or flu symptom during the study period. Peripheral blood mononuclear cells were isolated from the subjects and cultured them for 24 h in media alone or media containing ethylamine, a γδ T-cell antigen. In the ethylamine media, the γδ T cells from the subjects who received the EGCG supplement expanded to 28% of $CD3^+$ cells, compared with 20.3% from the subjects who received placebo [54]. These data imply that EGCG intake was associated with fewer cold and flu symptoms and with an increase in the capacity of γδ T cells to proliferate in response to antigenic challenge.

Table 5. Characteristics of randomized placebo-controlled trials that tested the efficacy of green tea catechins for the treatment of cervical lesions and EGWs

Study	Subjects	Outcome	Treatment (duration)	Results
Ahn [38]	90 women with HPV-positive precancerous cervical lesions	Changes in Papanicolaou cytology, HPV DNA titers, and degree of dysplasia	Four arms: poly E ointment, poly E oral capsule, poly E ointment+capsule, or EGCG capsule (8–12 wk)	Overall response rates: 10% for untreated, and 69% for treated. Response rates by foue treatment arms: 50% for poly E capsule, 60% for EGCG capsule, 74% for poly E ointment, and 75% for poly E ointment+capsule
Gross [39]	242 (125 men, 117 women) with 2–30 EGWs (double-blinded study)	Complete clearance of baseline warts	Two arms: Polyphenon E 10% cream, or Polyphenon E 15% ointment (up to 12 wk)	Percentage of patients with complete clearance (group): 59% (15% ointment), 47% (10% cream), 37% (placebo). $p = 0.23$ for 10% versus placebo $p = 0.007$ for 15% versus placebo
Stockfleth [40]	503 (277 men, 226 women) with 2–30 EGWs (double-blinded study)	Complete clearance of baseline and new warts	Two arms: Polyphenon E ointment 10 or 15% (up to 16 wk)	Percentage of patients with complete clearance (group): 53% (15% ointment) 51% (10% ointment) 37% (placebo). $p = 0.01$ for 15% versus placebo; $p = 0.03$ for 10% versus placebo
Tatti [41]	502 (258 men, 244 women) with 2–30 EGWs (double-blinded study)	Complete clearance of baseline and new warts	Two arms: sincatechins ointment 10 or 15% (up to 16 wk)	Percentage of patients with complete clearance (group): 56% (10% ointment) 57% (15% ointment) 34% (placebo). $p < 0.001$ for 15% versus placebo; $p < 0.001$ for 10% versus placebo

6 Concluding remarks

In our critical review and meta-analyses of the published results from observational data, we report that green tea intake is associated with decreases of 32% for ovarian cancer risk, and 23% for endometrial cancer risk. The lack of any prospective cohort results on green tea intake and risk of ovarian cancer suggests a cautious interpretation of the inverse association. Both prospective and retrospective observational data supported an inverse association for green tea and endometrial cancer risk. On the contrary, black tea was positively associated with endometrial cancer risk. These opposing effects for black and green tea on risk of endometrial cancer are also found for breast cancer and may be due to their opposing effects on circulating hormones [11].

Limitations of our meta-analyses include the different classifications of tea intake that were used across the individual studies that we included in the combined OR. Our meta-analyses by tea type may also be subjected to a small degree of nondifferential exposure misclassification. For example, if the tea type was not specified in the individual article, we made the assumption that the tea consumed was black if the study was conducted among the western population, and conversely, that green tea was consumed if the study was conducted among an Asian population. While our assumption is generally supported, it is also true that both black and green tea are consumed in western and Asian populations. Our meta-analyses may also be confounded by age, body size, coffee intake, or alcohol use, because these factors were not consistently adjusted for in the individual studies (see footnotes in Tables 1–4).

There was no observational data available that explored the relationship between green tea intake and cancers of the cervix, vagina, and vulva. Persistent HPV infection is a prerequisite for the development of these cancers, thus providing a long premalignant phase ideal for chemoprevention [3]. The strong experimental evidence for the antitumor, antiviral, and immunomodulatory effects of green tea catechins on HPV-positive cells and tumors supports an underlying mechanism for green tea and protection against genital cancers. Results from the randomized, placebo-controlled clinical trials demonstrating EGCG efficacy for the treatment of premalignant cervical lesions and EGWs further supports the immunomodulatory benefits of green tea catechins. Together, the experimental and human evidence support the dedication of resources toward future observational investigations of green tea in relation to risk of cervical, vaginal, and vulval cancers.

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