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The Effect of Green Tea Consumption on Prostate Cancer Risk and Progression: A Systematic Review

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ABSTRACT
This systematic review aimed to assess the clinical benefits of green tea consumption on the progression and prevention of prostate cancer (PCa). A systematic search was performed across the following databases: PubMed, Excerpta Medica database, Database of Abstracts of Reviews of Effects, Current Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. We included studies from database inception to September 2015. Studies must report on the effect of green tea consumption on PCa. The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS), while randomized controlled trials (RCTs) were assessed for quality using the Jadad scale. A total of 15 articles were included, with 11 reporting on the effect of green tea consumption on PCa prevention, and four reporting on the effect of green tea on treatment. Mean NOS for observational studies was 7.4 (SD = 1.3), with a range from 6 to 9, while all three RCTs scored 5 on the Jadad scale. Findings demonstrate that green tea appears to be an effective chemopreventive agent, particularly in those with high-grade prostate intraepithelial neoplasia. However, evidence of efficacy in the treatment of PCa is currently lacking. Given the limitations in current studies, more well-designed RCTs should be undertaken to determine if green tea indeed has a role in the prevention and treatment of PCa.

Introduction
Prostate cancer (PCa) has the second highest incidence of all cancers in males worldwide (1), and is one of the leading causes of cancer death among men of different races (2). In 2009, it was estimated that PCa accounted for 25% (192,280) of cancer cases in the United States (3). Histological examination is currently the only method to diagnose PCa, although prostate-specific antigen (PSA) levels have now been widely adopted as a screening tool. There is much debate, however, with regard to the cut-off levels of PSA and the issue of overdiagnosis in men, leading to unnecessary radical prostatectomies (4). Nonetheless, more evidence supports the fact that PCa is underdiagnosed, especially in the early stages due to the fact that patients are asymptomatic at this stage (5). Although the prevalence of PCa differs across different regions, overall the rates are higher in Western countries (e.g., United States and Western Europe) as compared to Asian countries (e.g., China, Japan, and Korea) (6). Researchers thus pointed to the fact that given the differing diets between Western and Eastern populations, environmental factors such as dietary factors play a vital role in the risk and progression of PCa (7). Increasing attention has been paid particularly to the consumption of green tea.

Green tea is one of the most popular beverages worldwide, particularly in Asian countries such as China, Korea, and Japan. Indeed green tea, which is not fermented, accounts for approximately 20% of tea consumption worldwide. In traditional Chinese medicine, the use of green tea for medicinal purpose dates back to around 4700 yr ago. Green tea is produced from the leaves of the plant Camellia sinensis, an evergreen shrub of the Theaceae family. The main active ingredients of green tea include polyphenolic compounds such as epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate, all of which are responsible for the strong antioxidant and anticarcinogenic properties of green tea (8). In vitro and in vivo studies suggest that polyphenols from green tea exhibit anticarcinogenic properties by inducing...
apoptosis, and by inhibiting cell-growth, cyclin-dependent kinase inhibitors, and urokinase (an enzyme vital for cancer growth), thus affecting the progression of PCa (9).

The understanding of any potential chemopreventive dietary factors is important to decrease the impact of PCa, as this cancer is always diagnosed in men over the age of 50. It has also been noted that a delay in the progression of the disease could considerably reduce the risk of PCa (7). With the growing research findings on the anticarcinogenic properties of green tea, most studies thus far have focused on in vitro or animal models (10–12); however, there has been a paucity of studies involving humans. Previously conducted systematic reviews and meta-analyses either did not assess the quality of included studies that is an essential criterion to scrutinize the effectiveness of green tea, or paid scant attention to the effect of green tea consumption on prostate cancer (13). These reviews also did not focus specifically on green tea consumption and only included studies until 2012 (14); or only focused on observational studies (15). We therefore conducted a systematic review to study the current evidence for the effect of green tea consumption specifically on PCa risk and progression in humans.

Methods

Reporting for this systematic review was done according to the PRISMA guidelines (Appendix A) (16).

Data Sources and Search Strategy

Systematic searches were performed in the following databases: PubMed, Excerpta Medica dataBASE, Database of Abstracts of Reviews of Effects, Current Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. We included studies from database inception to September 30, 2015. Keywords used were a combination of clinical (prostate cancer) and therapeutic (green tea) search terms, as listed in Table 1. Additional studies were identified from references cited in retrieved articles. The bibliographic records obtained via the database search were imported into Endnote X7 (Thomson Reuters, New York, NY). Records from different databases were merged, and duplicates were removed. Two authors independently screened all titles and abstracts identified from the electronic database search. The bibliographies of relevant studies were also checked for additional publications. Full-text articles of potentially relevant studies were retrieved and independently assessed to confirm eligibility.

Study Selection

Studies were considered eligible if they fulfilled the following inclusion criteria: 1) studies that evaluate the effect of green tea consumption on PCa; 2) the outcome of interest should be an incidence of PCa or change in either PSA level, radiologic changes, prostate size, or any other objective measure of PCa; 3) studies involve human subjects; and 4) studies are randomized controlled trials (RCTs), case-control studies, cohort studies, and other epidemiological studies. We included both observational and experimental studies, as the purpose of this systematic review was to gather the overall evidence to answer the question under investigation or review. In this way, readers can assess for themselves the number of quality studies currently available, and hence assist them in making a final conclusion based on the evidence presented. Studies were excluded if abstracts were not available in English, if there was no proper assessment of outcomes, and if the intervention only involved green tea in combination with another drug or supplement. In vitro studies, studies involving only animals, case series, cross-sectional studies, systematic reviews, and meta-analyses were also excluded. There were no language restrictions imposed on full-text articles.

Data Extraction

The following data were extracted independently by two authors: 1) author, year of publication, 2) study characteristics including objectives, sample size, and treatment duration, 3) population characteristics including age, race, baseline disease stage, and PSA level, and 4) outcomes including PSA levels. For studies fulfilling the eligibility criteria but where full texts were not available, authors were contacted personally to request for full texts. Any discrepancies were discussed between both authors.

Quality Assessment

Risk of bias of all RCTs was done using Cochrane’s risk of bias assessment tool (17). Methodological quality of randomized controlled trials (RCTs) was further assessed using the Jadad scale (18). The Newcastle-Ottawa Scale (NOS) for cohort studies (19) was used to assess the

Table 1. Search terms.

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Green tea</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Camellia sinensis</td>
<td>Prostate neoplasm</td>
</tr>
<tr>
<td>Catechins</td>
<td>Chemoprevention</td>
</tr>
<tr>
<td>Epigallocatechin gallocate</td>
<td></td>
</tr>
</tbody>
</table>
quality of observational studies. The NOS awards stars for three categories: “Selection,” “Comparability,” and “Outcome,” each divided into further subcategories. Each study can be awarded a maximum of one star for each subcategory, while “Comparability” can be awarded a maximum of two stars. The maximum number of stars that can be achieved in a study is 9, which indicates complete absence of bias.

Protocol and Registration

The protocol for this study has been registered with PROSPERO (registration no. CRD42014015547) and can be accessed at http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42014015547

Results

Study Search

A total of 19 studies met the inclusion criteria; however, three studies did not assess PCa risk or progression as an outcome (20–22), while one study (23) was a duplicate of another study included in the final analysis (24). Therefore, only 15 articles were included for full analysis (24–38) (Fig. 1). Three studies were RCTs (35,35,37), three were single-arm Phase 2 open-label studies (26,26,38), four were case-control studies (24,28,30,34), and five were cohort studies (27,29,32,32,36). Of these, four looked at the effect of green tea on the progression of PCa (26,26,38), while 11 studied the effect of green tea consumption on PCa risk (33–35,37).

Study Characteristics

For the RCTs (n = 3) (35,35,37) and open-label studies (n = 3) (26,26,38), a total of 185 patients were administered green tea/polyphenol E (daily dose of 400–800 mg/day), and the effect on prostate cancer was compared versus control groups, which comprised of a total of 100 patients. The treatment duration varied from a minimum of 3 wk to a maximum of 12 mo, and the study population mainly comprised American men; with only two studies involving Canadians (38) and Italians (37). The majority of the patients participating in the RCTs and open-label studies

Figure 1. PRISMA flowchart of study selection.
were more than 55 yr of age, and were confirmed cases of high-grade prostate intraepithelial neoplasia (HGPIN), followed by androgen-independent metastatic prostate carcinoma (AIMPC) and hormone refractory prostate cancer (HRPC). Assessment of exposure in these studies was done using PSA levels. Details are shown in Tables 2 and 3.

For the case-control studies (n = 4), approximately 516 cases and 856 controls were analyzed, while for the cohort studies, there were approximately 1179 cases. Daily consumption of green tea ranged from <1 cup to a maximum of 10 or more cups, and most of these studies involved Chinese and Japanese populations. To ascertain exposure to green tea, three studies used interviews with structured questionnaires (24,27), two studies used a food frequency questionnaire with interview (30,32), and four studies used self-administered questionnaires (28,29,31,36). All four case-control studies were hospital based. Further details are shown in Table 4.

Quality Assessment

Risk of bias of the RCTs was assessed using the Cochrane risk of bias assessment tool. Overall, all three RCTs showed low risk of bias, except in two categories. Both studies by Nguyen (35) and Bettuzzi (37) did not state if there was concealment of allocation, while all three studies did not control for confounding factors such as either age or smoking (35,35,37). The risk of bias graph and summary are illustrated in Figs. 2 and 3, respectively. All three RCTs were awarded a maximum score of 5 using the Jadad scale, indicating they were of good quality (Table 2).

Appendices B and C present data on the quality assessment of cohort and case-control studies using the NOS. The mean NOS score was 7.4 (SD±1.3), with a range from 6 to 9. All four case-control studies used hospital controls, warranting a lower rating (24,28,30,34). The study by Li et al. (34) did not control for confounding factors, while the study by Berroukche et al. (28) only controlled for smoking. With regard to ascertainment of exposure, it was unclear if the interviewers were blinded to the case-control status of the subjects during the interview in all four case-control studies, yielding a lower rating. Subjects were also asked very specific questions with regard to green tea consumption; and it was unclear if subjects were blinded to the objective of the study. In the study by Jian et al. (24), the nonresponse rate between both the case and control groups differed by more than 5%, with no explanation provided, thus merit- ing the lowest rating for that section. This author had published a similar study using the same data and population in a different journal (23), and as such we deemed this author as having a high risk for bias in reporting.

With regard to the cohort studies, all studies demonstrated that subjects did not have PCa at the start of the study, and the follow-up period was considered adequate. Three studies involved subjects who were not representative of individuals in the community, where subjects were either restricted to two dialect groups in a study conducted in Singapore (27); subjects were from either Hiroshima or Nagasaki who were previously exposed to radiation (31); or subjects were those of Japanese ancestry living in Hawaii (32). Additionally, the study by Severson et al. (32) did not explain the missing subject numbers in the study, thereby yielding a low rating in terms of adequacy of follow-up of cohorts. This study also only controlled for age, but did not control for other confounding factors such as smoking or diet.

Green Tea for the Prevention of Prostate Cancer

Eleven studies assessed the effect of green tea consumption on the prevention of PCa (24,27–37). Five of the 11 studies supported a chemopreventive effect of green tea against PCa (24,33,36,36,37). In RCTs conducted by Bettuzzi et al. (37) and Kumar et al. (33), subjects with
Table 2. Characteristics of RCTs.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Objective—Intervention</th>
<th>Treatment duration</th>
<th>Study period N&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Age (mean ± SD)&lt;sup&gt;c&lt;/sup&gt;; Race (region)</th>
<th>Baseline disease stage</th>
<th>Baseline PSA&lt;sup&gt;k&lt;/sup&gt; level (ng/ml)</th>
<th>Prevalence of PCa</th>
<th>Others</th>
<th>PSA levels</th>
<th>JADAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bettuzzi et al. (2006)</td>
<td>Prevention—3 capsules/d (EGCG 600mg/d)</td>
<td>12 mo</td>
<td>30 (IG) vs. 30 (CG)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>64.4 ± 5.9 (IG) vs. 65.1 ± 6.8 (CG); Italians (Italy)</td>
<td>HGPIN&lt;sup&gt;h&lt;/sup&gt;</td>
<td>7.6 ± 3.8 (IG) vs. 7.9 ± 6.9 (CG)</td>
<td>3% (IG) vs. 30% (CG), P &lt; 0.01</td>
<td>No significant difference between groups, however level always lower in IG</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Kumar et al. (2015)</td>
<td>Prevention—Polyphenol E (EGCG 400mg/d)</td>
<td>12 mo</td>
<td>49 (IG) vs. 48 (CG)</td>
<td>62.0 ± 7.9 (IG) vs. 64.1 ± 7.9 (CG); Americans (US)</td>
<td>HGPIN and/or ASAP&lt;sup&gt;i&lt;/sup&gt;</td>
<td>4.5 ± 1.8 (IG) vs. 4.6 ± 2.1 (CG)</td>
<td>10.2% (IG) vs. 18.8% (CG), P = NS&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Greater reduction of serum PSA in IG (−0.87ng/ml; 95%CI, −1.66 to −0.09), P = 0.029</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Nguyen et al. (2012)</td>
<td>Treatment—Polyphenol E 4 capsules each morning with food (EGCG 800mg/d)</td>
<td>3–6 wk</td>
<td>24 (IG) vs. 22 (CG)</td>
<td>63.4 ± 5.9 (IG) vs. 61.3 ± 5.7 (CG); Americans (US)</td>
<td>Biopsy-confirmed PCA&lt;sup&gt;l&lt;/sup&gt;</td>
<td>5.63 ± 4.18 (IG) vs. 7.14 ± 6.70 (CG)</td>
<td>NA&lt;sup&gt;m&lt;/sup&gt;</td>
<td>58.3% in IG vs. 36.4% in CG showed decrease in PSA; P = NS</td>
<td>Tissue biomarkers of cell proliferation, apoptosis, and angiogenesis did not differ between treatment arms; Decrease in Gleason score greater in IG but not statistically significant</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>EGCG: Epigallocatechin gallate.<br><sup>b</sup>N: Number of subjects.<br><sup>c</sup>IG: Intervention group.<br><sup>d</sup>CG: Control group.<br><sup>e</sup>SD: Standard deviation.<br><sup>f</sup>US: United States.<br><sup>g</sup>Reflects mean age of 24 patients in CG at baseline.<br><sup>h</sup>HGPIN: High-grade prostate intraepithelial neoplasia.<br><sup>i</sup>ASAP: Atypical small acinar proliferation.<br><sup>j</sup>PCA: Prostate cancer.<br><sup>k</sup>PSA: Prostate-specific antigen.<br><sup>l</sup>NS: Not significant.<br><sup>m</sup>NA: Not available.
### Table 3. Characteristics of single-arm phase II, open-label studies.

<table>
<thead>
<tr>
<th>Author et al. (year)</th>
<th>Study characteristics</th>
<th>Population characteristics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Objective—Intervention</td>
<td>Age (mean ± SD(^d)); Baseline disease stage</td>
<td>Baseline PSA(^a) level (ng/ml)</td>
</tr>
<tr>
<td>Choan et al. (2005)</td>
<td>Treatment—250 mg bd capsule containing &gt;30% EGCG(^a)</td>
<td>Minimum 2 mo; HRPC(^f)</td>
<td>Median 161 (Range 8.53–588)</td>
</tr>
<tr>
<td>Jatoi et al. (2003)</td>
<td>Treatment—Green tea 6g/d (administered in canisters, 1 g to be diluted into water, amount not stated. 6 such doses to be ingested)</td>
<td>Median time on study 1 mo; Americans (US)</td>
<td>5.83 ± 2.165</td>
</tr>
<tr>
<td>McLarty et al. (2009)</td>
<td>Treatment—Polyphenol E 4 capsules with food (EGCG 800mg/d)</td>
<td>Average 6 wk (before surgery); Americans (US)</td>
<td>Men with a recent diagnosis of Stage I, II, or II scheduled for radical prostatectomy</td>
</tr>
</tbody>
</table>

\(^a\)EGCG: Epigallocatechin gallate.  
\(^b\)NA: Not available.  
\(^d\)SD: Standard deviation.  
\(^f\)HRPC: Hormone refractory prostate cancer.  
\(^g\)AIMPC: Androgen-independent metastatic prostate carcinoma.  
\(^h\)PSA: Prostate-specific antigen.  
\(^i\)PCA: Prostate cancer.  
\(^j\)Response defined as a decline of \(\geq 50\%\) in baseline PSA value.  
\(^k\)HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor; IGF: Insulin-like growth factor; IGFBP: IGF binding protein.
Table 4. Characteristics of cohort and case-control studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Objective</th>
<th>Study period</th>
<th>N</th>
<th>Age (mean ± SD)</th>
<th>Race (region)</th>
<th>Baseline disease stage</th>
<th>Lowest consumption level (cup/d)</th>
<th>Highest consumption level (cup/d)</th>
<th>OR/RR/HR (95% CI) for the highest vs. lowest level</th>
<th>Others</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berroukche et al. (2012)</td>
<td>Prevention 2007–2011</td>
<td>160 cases vs. 160 controls</td>
<td>N</td>
<td>71.6 ± 10 (Cases) vs. 68.3 ± 9.4 (Control); Algerian (Algeria)</td>
<td>Confirmed histological PCA; Localized (22%), regional (74%), disseminated (4%)</td>
<td>≤ 1</td>
<td>&gt; 6</td>
<td>OR = 0.66 (0.31–1.40), P = NS</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Li et al. (2014)</td>
<td>Prevention 2007–2013</td>
<td>144 cases vs. 337 controls</td>
<td>Median 70.3 (Range 33–90); Chinese (China)</td>
<td>Newly diagnosed with histopathological verification</td>
<td>NA</td>
<td>NA</td>
<td>OR = 0.66 (0.48–0.90), P = 0.008</td>
<td>Risk declined with increasing duration of tea drinking—40 yr 0.12 (0.06–0.26), P &lt; 0.01; Increasing number of batches brewed per day to ≥ 2 associated with 76% reduced risk, P &lt; 0.01</td>
<td>6</td>
<td></td>
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</tr>
<tr>
<td>Jian et al. (2004)</td>
<td>Prevention 2001–2002</td>
<td>72 case vs. 219 controls</td>
<td>Range 59–73; Chinese (China)</td>
<td>Confirmed histopath report; A (12%), B (28%), C (37%), D (52%)</td>
<td>&lt; 1</td>
<td>&gt; 3</td>
<td>OR = 0.27 (0.15–0.48), P &lt; 0.01</td>
<td></td>
<td>6</td>
<td></td>
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<tr>
<td>Sonoda et al. (2004)</td>
<td>Prevention 1996–2002</td>
<td>140 cases vs. 140 controls</td>
<td>Stage 1 (&lt;2%) cases; stage 2 (61%); stage 3 (26%); stage 4 (11%)</td>
<td></td>
<td>≤ 1</td>
<td>≥ 10</td>
<td>OR = 0.67 (0.27–1.64), P = NS</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen et al. (2004)</td>
<td>Prevention 1963–1996</td>
<td>193 cases among 18115 men</td>
<td>Japanese (Japan)</td>
<td>No PCA</td>
<td>&lt; 1</td>
<td>≥ 5</td>
<td>RR = 1.29 (0.84–1.98), P = NS</td>
<td></td>
<td>8</td>
<td></td>
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</tr>
<tr>
<td>Kikuchi et al. (2006)</td>
<td>Prevention 1994–2001</td>
<td>110 cases among 19561 men</td>
<td>Japanese (Japan)</td>
<td>No PCA</td>
<td>&lt; 1</td>
<td>≥ 5</td>
<td>HR = 0.85 (0.50–1.43), P = NS</td>
<td></td>
<td>9</td>
<td></td>
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<tr>
<td>Kurahashi et al. (2008)</td>
<td>Prevention 1990–2004</td>
<td>404 cases among 49920 men</td>
<td>Japanese (Japan)</td>
<td>No PCA</td>
<td>&lt; 1</td>
<td>≥ 5</td>
<td>All cases RR = 0.89 (0.65–1.21), P = 0.43; Localized cases RR = 1.04 (0.72–1.52), P = NS; Advanced cases RR = 0.52 (0.28–0.96), P = 0.01</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montague et al. (2012)</td>
<td>Prevention 1993–2007</td>
<td>298 cases from 27293 men</td>
<td>Chinese (Singapore)</td>
<td>No PCA</td>
<td>None</td>
<td>≥ 2</td>
<td>HR = 0.95 (0.62–1.45), P = NS</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: Number of subjects.
b: Standard deviation.
c: PCa: Prostate cancer.
d: NA: Not available.
e: OR: Odds ratio; RR: Relative risk; HR: Hazard ratio.
f: CI: Confidence interval.
g: NS: Not significant.
h: NOS: Newcastle-Ottawa scale.
HGPIN consumed 600 and 400 mg/d of EGCG, respectively. After 1 yr, the incidence of cancer in the study by Bettuzzi et al. (37) was 3% in the intervention group compared to 30% in the control group ($P < 0.01$), suggesting a 90% chemopreventive effect of green tea. There was, however, no significant difference in PSA levels between both groups, and no significant adverse effects.

The study by Kumar et al. (33) found no significant difference in the incidence of PCa at the end of 1 yr between both treatment arms ($P > 0.25$). There was, however, a significant difference in the rate of PCa plus atypical small acinar proliferation (ASAP), observed in 11.5% of patients in the intervention group versus 40% in the control group ($P = 0.024$). ASAP has been associated with the risk of PCa. There was also a significantly greater reduction in serum PSA levels in the intervention group compared to the control group ($P = 0.029$). Adverse events did not differ significantly between both groups.

In the study by Kurahashi et al. (36) involving a cohort of 49,920 Japanese men, 404 men developed PCa. Green tea consumption of more than 5 cups/day was associated with a significant decline in the risk of advanced PCa ($P = 0.01$). There was, however, no significant association with localized PCa. Li et al. (34) and Jian et al. (24) conducted case-control studies involving 144 and 72 Chinese patients with PCa, respectively. The study by Jian et al. (24) found that increasing the amount of green tea consumption to more than 3 cups/day was associated with a 73% reduction in the risk of PCa (95% CI = 0.15–0.48), while drinking for more than 40 yr was associated with an 88% risk reduction (95% CI = 0.06–0.26). The risk also declined with the increased quantity of green tea leaves per day, with adjusted odds ratio (OR) = 0.10 [95% confidence interval (CI) = 0.04–0.23] when 5 or more grams were used. There was a significant reduction in risk when 2 or more new batches were brewed per day, with adjusted OR = 0.24 (95% CI = 0.11–0.51). All findings were significant at a $P$-value of $<0.01$. In the study by Li et al. (34), it was found that those who consumed green tea had a significantly reduced risk of PCa, with OR = 0.66 (95% CI = 0.48–0.90, $P = 0.008$).

Two case-control studies found no role for green tea in the prevention of PCa (28,30). In the study by Berroucke et al. (28) involving 160 patients from Western Algeria, consumption of up to more than 6 cups of green tea per day showed no significant effect on the prevention of PCa, while the study by Sonoda et al. (30) involving 140 Japanese men found no significant effect when 10 or more cups were consumed daily. Four cohort studies, 2 involving Japanese men (29,31), one involving

**Figure 3.** Risk of bias summary: review authors’ judgments about each risk of bias item for each included RCT.
Singaporean Chinese (27), and one involving Hawaiian men of Japanese ancestry (32), did not support the chemopreventive role of green tea in PCa. The study by Allen et al. (31) involving 193 cases found that consumption of 5 or more cups of green tea a day was associated with a 29% increase in the risk of PCa; however, this was not significant ($P = 0.16$).

**Green Tea for the Treatment of Prostate Cancer**

Four studies looked at the role of green tea in the treatment of PCa (25,26,35,38). Only one study showed a significant decrease in PSA levels, which was observed in 69% of patients. In this Phase II study involving 26 patients scheduled for radical prostatectomy, 40% of patients also had a significant decline in hepatocyte growth factor levels, while 24% had a significant decline in serum levels of vascular endothelial growth factor (25). However, the RCT by Nguyen et al. (35) involving 50 PCa patients scheduled for prostatectomy, as well as the single-arm study by Choan et al. (38) involving 19 patients with HRPC, revealed no significant effect of green tea on the treatment of PCa.

In a Phase II trial by Jatoi et al. (26), 42 patients with AIMPc consumed 6 g of green tea per day. Only one patient demonstrated a significant decline in PSA levels, but this was not sustained beyond 2 mo. At the end of the first month, median change in PSA values from baseline for the cohort increased by 43%. Additionally, approximately 69% of patients experienced Grade 1 or 2 toxicity as a result of green tea consumption, which involved vomiting, nausea, and abdominal pain, while 12% of patients experienced Grade 3 toxicity, which manifested as insomnia, diarrhea, abdominal pain, confusion, and fatigue.

**Discussion**

The findings from this systematic review did not support the role of green tea in the treatment of PCa, where 3 out of the 4 studies did not find a significant decline in PSA levels at the end of the study. Two were single-arm studies, while one was an RCT. All four studies involved non-Asians. Similar results were found for lung cancer from a systematic review of 84 studies, where green tea had no effect on the treatment of lung cancer (39).

While only 5 (24,33,34,36,37) out of the 11 studies found a significant role for green tea in the prevention of PCa, these included two RCTs (33,37) each with a Jadad score of 5 and with an overall low risk of bias. These two studies supported the role of green tea involving patients with HGPIN. The two case-control studies (24,34) had a moderate NOS rating of 6 each, while the cohort study by Kurahashi (36), which had a maximum NOS score of 9, showed a significant role in patients with advanced PCa. These findings correspond with the meta-analysis of observational studies conducted by Zheng et al. (15), where green tea consumption involving Asian populations decreased the risk of PCa by 38%. It has been suggested that even a modest delay in disease progression could significantly decrease the risk of PCa (15). This will then translate to reduced morbidity associated with radical PCa therapy (40).

It has been postulated that by the year 2030, the number of new cases of PCa could increase to close to 2 million annually, which would translate to half a million deaths (41). While it has been suggested that the lower rates of PCa in Asians are due to the inadequate practice of PSA testing in those regions (42,43), the role of dietary factors like green tea certainly cannot be discounted. The catechins contained in green tea, in particular EGCG, have demonstrated strong antioxidant properties in vitro and in animal studies (44), which inhibit tumor growth as well as damage to DNA (15).

Having said that, the currently available RCTs have all involved small sample sizes, different doses of green tea, as well as different treatment periods and study durations. Thus keeping in view these limitations, along with others which will be expounded upon in detail later, readers should approach these findings with caution. This is similar with the case of beta-carotene, which was strongly supported in the 1980s as a chemopreventive agent, by epidemiological and experimental studies. However, recent well-designed RCTs proved the contrary, finding instead that beta-carotene potentially contains co-carcinogenic properties (45). Similar issues have been noted with other dietary antioxidants, where the lack of well-designed RCTs involving standardized dosages and formulations has led to ambiguity with regard to their true role and effectiveness in PCa (46).

As more people are turning to the use of herbs and other complementary and alternative medicines (CAMs) mainly due to the perception that they are natural and thus free from side effects, it is important as well for more trials to focus on obtaining these data as part of the outcome. Green tea, especially in high doses, is indeed not without its risk of side effects. This is mainly due to its caffeine and aluminum content, as well as its effect on decreasing the bioavailability of iron. In the study by Jatoi et al. (26), approximately 70% of patients reported Grade 1 and Grade 2 toxicity, while more than 10% experienced Grade 3 toxicity. Thus, consumption should be cautioned in those with cardiovascular disorders, and pregnant and breast feeding women due to the effect of caffeine on heart rhythm. Those with renal failure should also be vigilant due to the risk of accumulation of...
aluminum, which could subsequently lead to neurologic complications (47). There is also a concern regarding the interaction of green tea with other drugs, especially chemotherapy agents, due to its diuretic as well as antioxidant properties (39,47). Given that PCa is a disease of the aged who are already on multiple medications especially those for cardiovascular disorders, this is a cause for concern. As such if we are to advocate the use of green tea in the prevention of PCa, proper guidelines and instructions should be drawn up with regard to its administration schedule to prevent potential drug interactions.

**Limitations and Considerations**

Several limitations and considerations need to be addressed in this systematic review. First, a less stringent inclusion criteria related to the design of the studies included in the review was adopted. Thus, a wide variety of studies were included that resulted in heterogeneity among studies, which then made it difficult to synthesize quantitative results and perform a meta-analysis. There were three potential abstracts that were not available in full-text format, and attempts to obtain it from the authors were unsuccessful (48–50). Thus, conclusions drawn here should consider this fact. Secondly, RCTs and single-arm studies included in this systematic review had very small sample sizes, ranging from 15 to 49 patients per arm. Some studies also involved patients at different stages of PCa, with no discernment as to the effect of green tea on different stages of the disease during analysis (24,27,28,30,32). Different types of PCa were also assessed in different studies, that is, Bettuzzi et al. (37) and Kumar et al. (33) looked at patients with HGPIN, Choan et al. (38) involved patients with HRPC, while Jatoi et al. (26) focused on patients with AIMPC. Some studies did not even present information on the type or stage of PCa altogether (31,31,34).

The cohort studies reported that control patients did not have PCa at the start of the study; however, this relied on self-reports by patients, which might not be very accurate, given that patients are usually asymptomatic in the early stages. With regard to ethnicity, studies involved both Asians and Westerners, introducing differences in the genetic and epigenetic makeup of the populations being studied. This might also have some bearing on the outcomes observed as genetic polymorphism has been noted to play a role in the effect of tea polyphenols (51,52). This is similar with the case of beta-carotene, which was strongly supported in the 1980s as a chemopreventive agent, by epidemiological and experimental studies. It has been suggested that the number of batches brewed has an effect on the amount of EGCG, where the first 2 cups brewed from a new batch contain almost equal amounts of EGCG but this declines substantially in the third cup (24). Thus, it is important to assess this as this gives a more accurate picture of the amount of EGCG actually consumed. In the same vein, no standard container was used to measure the amount of green tea consumed in case-control and cohort studies (27,29–32,34,36). Thus, the effective dose cannot be determined. This is similar with RCTs and single-arm studies, where different doses and quantities of green tea were prescribed, ranging from 400 mg/d (33) to 6 g/d (26).

Dosing period was also different, ranging from 3 wk (35) to 12 mo (33,37). The type of formulation used was also different with some studies using capsules, while some administered the green tea in powdered form (26). With observational studies, there is the issue of recall bias as well as differences in recall periods, ranging from 1 yr prior to diagnosis (34), 1 yr prior to diagnosis or 1 yr prior to onset of symptoms (28), 5 yr before diagnosis (24,30). Finally for cohort studies, four studies (28,29,31,36) used self-administered questionnaires to assess dietary intake, which might not be as precise as in-person interviews.

**Conclusions**

Clinical data screened from the included studies demonstrate that green tea appears to be an effective chemopreventive agent, especially in those with HGPIN. However, evidence of efficacy in the treatment of PCa is currently lacking. Assessing the evidence based on the quality of studies, most of the studies included in this systematic review were of moderate to high quality. Nonetheless, there were several limitations within the design of a number of the studies, as illustrated above. Most pertinent of all was the fact that the amount of green tea consumed varied from study to study. Given the numerous limitations in the studies included, despite the high quality and low risk of bias, findings should however be interpreted with caution. In view of the increasing use of CAMs for chemoprevention, there is thus an urgent need for well-structured RCTs involving larger sample sizes, standardized doses, and according to specific disease stages, in order to be able to make a definitive conclusion as to the chemoprotective effect of green tea, as well as the amount that needs to be consumed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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