Primo Simposio Nazionale sulla Nutraceutica in Urologia

Tè verde e polifenoli

Cibo e apparato urogenitale: leggende e realtà

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Polyphenols

Polyphenols are the most abundant antioxidants in diet.

Phenolic compounds can be distinguished in:

- **Flavonoids** (base structure: 2 phenolic rings bound to a pyranosic ring)
- **Non-flavonoid compounds**: phenolic acids (as hydroxycinnamates, in coffee) and stilbenoid (as resveratrol, in red wine)

Flavonoid family:

- **Flavanols** or **catechins** (tea, cocoa, apples…);
- Flavanones (hesperidin in citrus fruit);
- Flavonols (quercetin in onions, apples and tea);
- Anthocyanins (in berries, like cranberry);
- Isoflavones (in soy).

Williamson G, Nutr Bull. 2017

Polyphenols (2)

Studies on animals or cultured human cell lines support a role of polyphenols in the:

- Prevention of cardiovascular diseases;
- Cancer prevention and treatment;
- Neurodegenerative diseases;
- Diabetes;
- Osteoporosis.

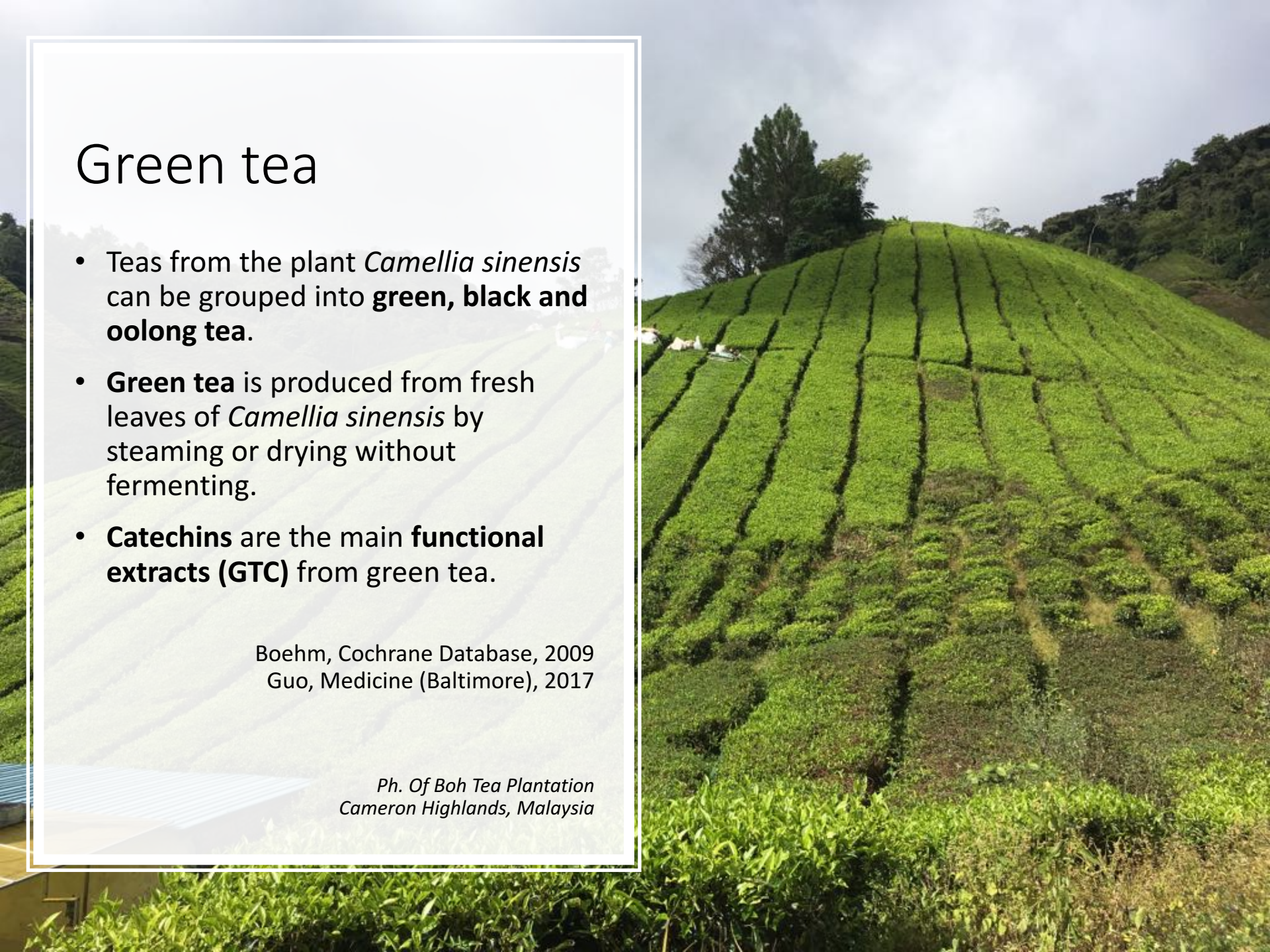
Applicability of these findings to human health **is still questioned.**

Scalbert et al., Crit Rev Food Sci Nutr. 2005

Green tea

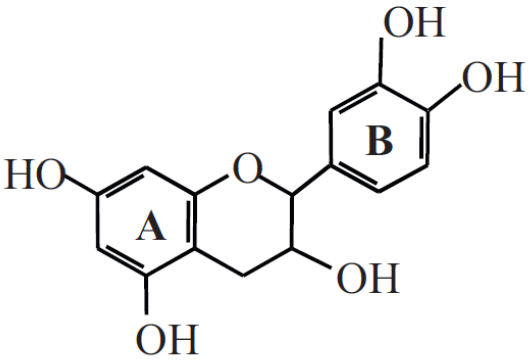
- Teas from the plant *Camellia sinensis* can be grouped into **green, black and oolong tea**.
- **Green tea** is produced from fresh leaves of *Camellia sinensis* by steaming or drying without fermenting.
- **Catechins** are the main **functional extracts (GTC)** from green tea.

Boehm, Cochrane Database, 2009
Guo, Medicine (Baltimore), 2017

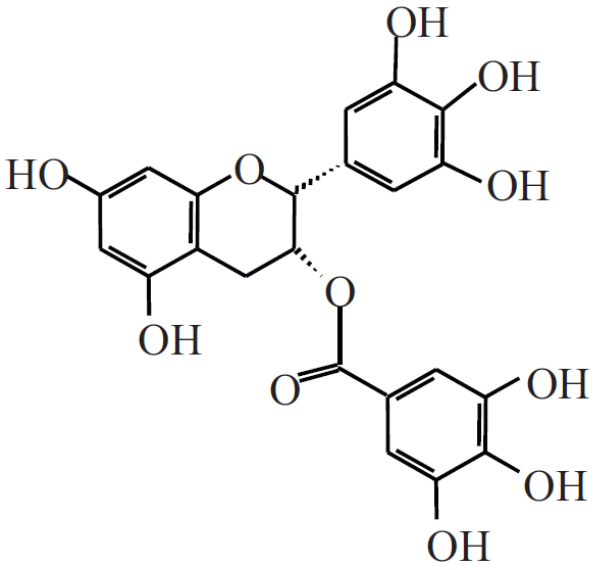


Ph. Of Boh Tea Plantation
Cameron Highlands, Malaysia

Epigallocatechin-3-gallate (EGCG)



Catechin backbone



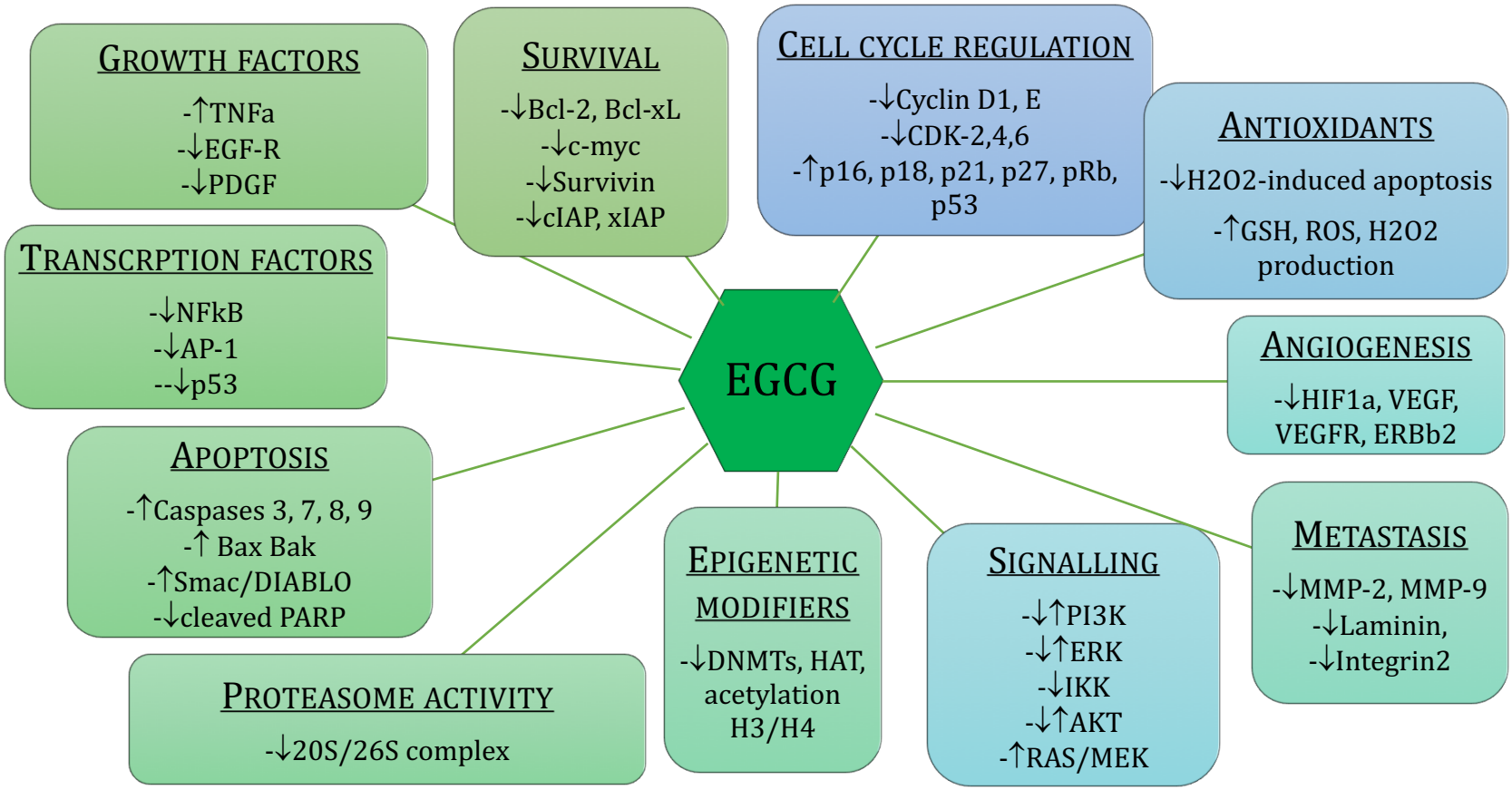
(-)-Epigallocatechin-3-gallate

- **Three to five cups of green tea** per day provide at least **250 mg of catechins;**
- The major green tea polyphenol is **epigallocatechin- 3-gallate (EGCG)** accounting for more than 50% of total polyphenols.

(Boehm, 2009)
(Guo, 2017)

Potential *in vitro* actions of EGCG

The list of potential *in vitro* targets of EGCG for prevention and treatment of cancer is vast. Definitive data on most significant *in vivo* mechanisms are lacking.



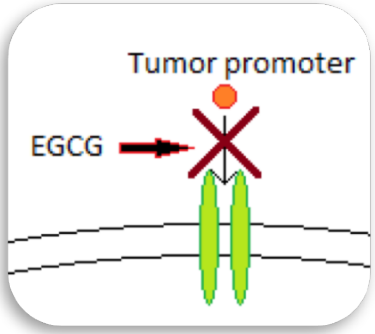
Adapted from: *Singh et al., Biochemical Pharmacology, 2011*

Mechanisms of EGCG (2)

Three principal mechanisms are hypothesized:

- **Anticarcinogenic effect**: by modulating signalling pathways of tumour apoptosis, survival, invasion, metastasis (gap junctions).

- **Sealing effect on receptors:** by inhibiting the interaction of various growth factors with their receptors.



- **Antioxidant and anti-inflammatory effect:** involving lipid peroxidation, free radicals, LOX, COX2, nitric oxide synthase, telomerase, TNFa & IL-1.

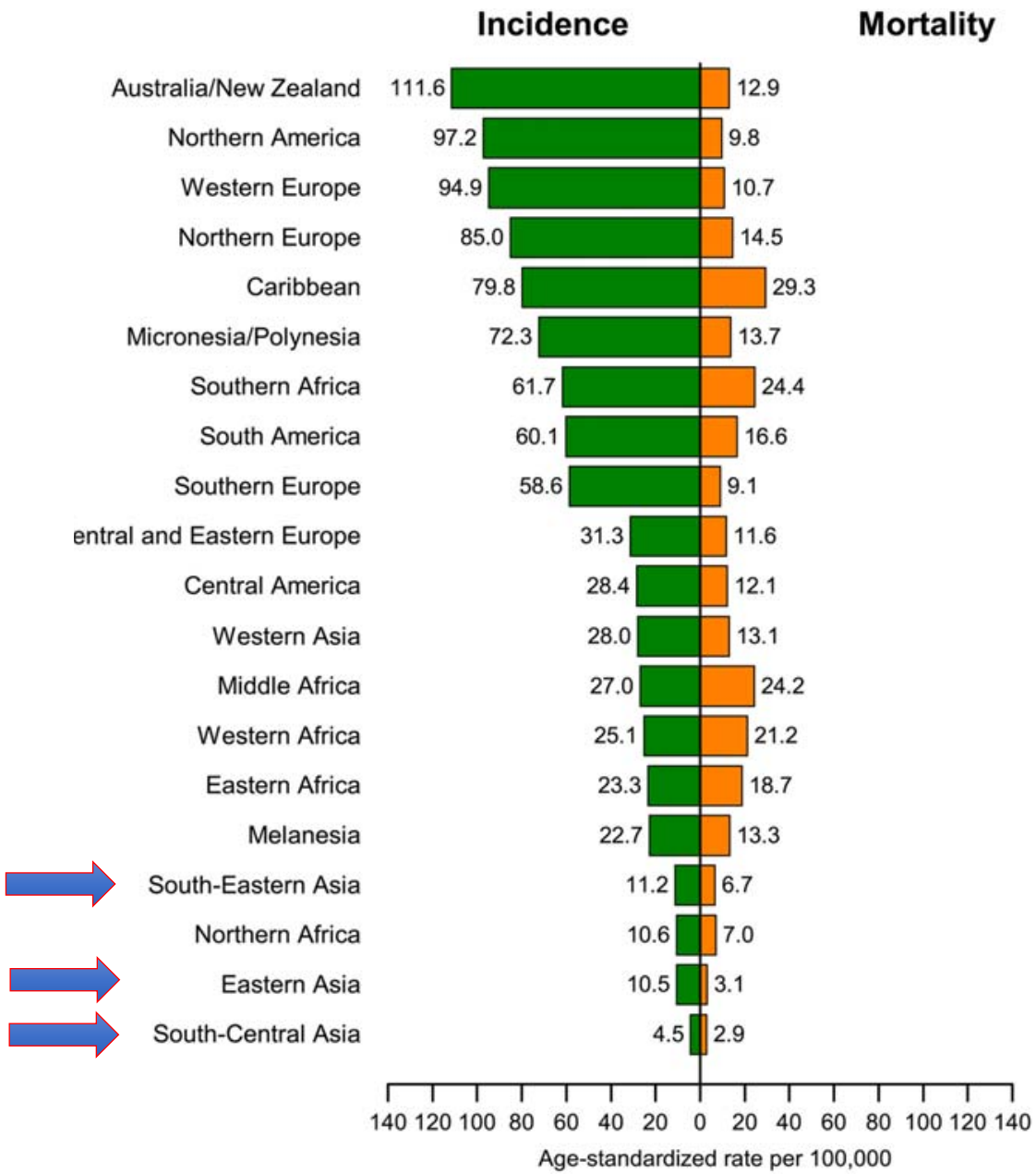
(Boehm, 2009)

Who drinks green tea?

- Brewed **tea is the second most common beverage** consumed worldwide next to water, **particularly in Asian countries** such as China, Korea, and Japan. Green tea accounts for 20% of world consumption.

- **PCa prevalence** is higher in Western countries and **lower in Asian countries** (e.g., China, Japan, and Korea). Environmental factors, such as diet, could play a vital role: increasing interest towards green tea.

Boehm, 2009
Jacob, 2017



Global cancer statistics 2012, CA Cancer J Clin 2015

Who drinks green tea? (2)

A wide market:

- **30% of men having a brother with PCa** take vitamins or supplements, including green tea, magnesium, male hormones, saw palmetto, selenium, soy, vitamins A, C, E, and zinc.

  Bauer CM et al., Integr Cancer Ther, 2012.

- **25% with PCa uses a complementary therapy**. The most frequently used CTs are vitamins, low-fat diets, lycopene and green tea.

  Wilkinson S. et al., Eur J of Cancer Care, 2008

Safety of EGCG

- Randomized, placebo-controlled trial evaluating the safety of one-year administration of green tea catechins in 97 ASAP/HGPIN patients.
- 400 mg/die of **EGCG vs placebo**: **no significant differences in toxicities** and IPSS were observed.

Kumar et al., Oncotarget, 2016

Interactions

- Sub-apoptotic doses of EGCG (1.5-7.5 µM) significantly **reduced radiation therapy-induced apoptosis** (3,5 Gy) in DU145 prostate cancer cells, *in vitro*.

  Thomas, Urology, 2011.

- Very high doses of EGCG (>200 µM) can **impair antitumour activity of Bortezomib** (a proteasome inhibitor used in multiple myeloma treatment). This is not observed when doses 4-fold greater than normal range are administered, in mice.

  Bannerman, Can Chemother Pharmacol, 2011.

- EGCG **reduced the bioavailability of Sunitinib** (TYR-K inhibitor, used for mRCC and GIST) by forming insoluble complexes, both *in vivo and in vitro*.

  Ge, J Mol Med, 2011.

Bioavailability

- After oral administration, tea catechins can be detected in blood, urine and faeces.
- Most catechins **are sufficiently absorbed** to have the potential to exert biological effects, reaching concentrations in the blood stream that have been shown to exert effects in-vitro.
- However, dietary polyphenols **are rapidly metabolized** in tissues and by colonic microbiota: in the short term (1st hour), blood levels of natural polyphenol can vary greatly.

Polyphenol	Source	polyphenol ingested	concentration in plasma
		mg	*μM*
Catechins			
Epigallocatechin gallate	Green tea infusion, *1.2 g*	88	0.33
Epigallocatechin		82	0.67
Epicatechin gallate		33	ND
Epicatechin		32	0.27
Epigallocatechin gallate	Green tea infusion, *5 g*	105	0.13–0.31
Epigallocatechin gallate	Green tea infusion, *6 g*		5.0
Epigallocatechin gallate	Green tea extract	525	4.4

Table from: Scalbert, J Nutr. 2000
Boehm, Cochrane Sys Rev, 2009
Estrela, J Med Chem. 2017

Off-topic

Green tea and cardiovascular risk

A favourable impact on CVD risk factors is suggested by limited evidence:

- Reduction in LDL cholesterol (-0,48 mmol/l CI -0,61;-0,35)
- Blood pressure reduction (circa 2 mmHg of SBP and 3 mmHg of DBP).
- Further high-quality studies are needed

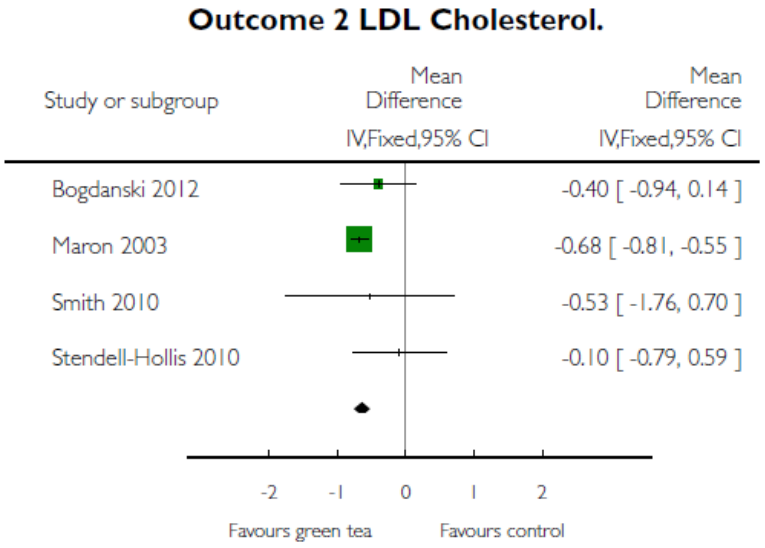
Hartley, Cochrane Database Syst Rev, 2013

Cochrane Library

Cochrane Database of Systematic Reviews

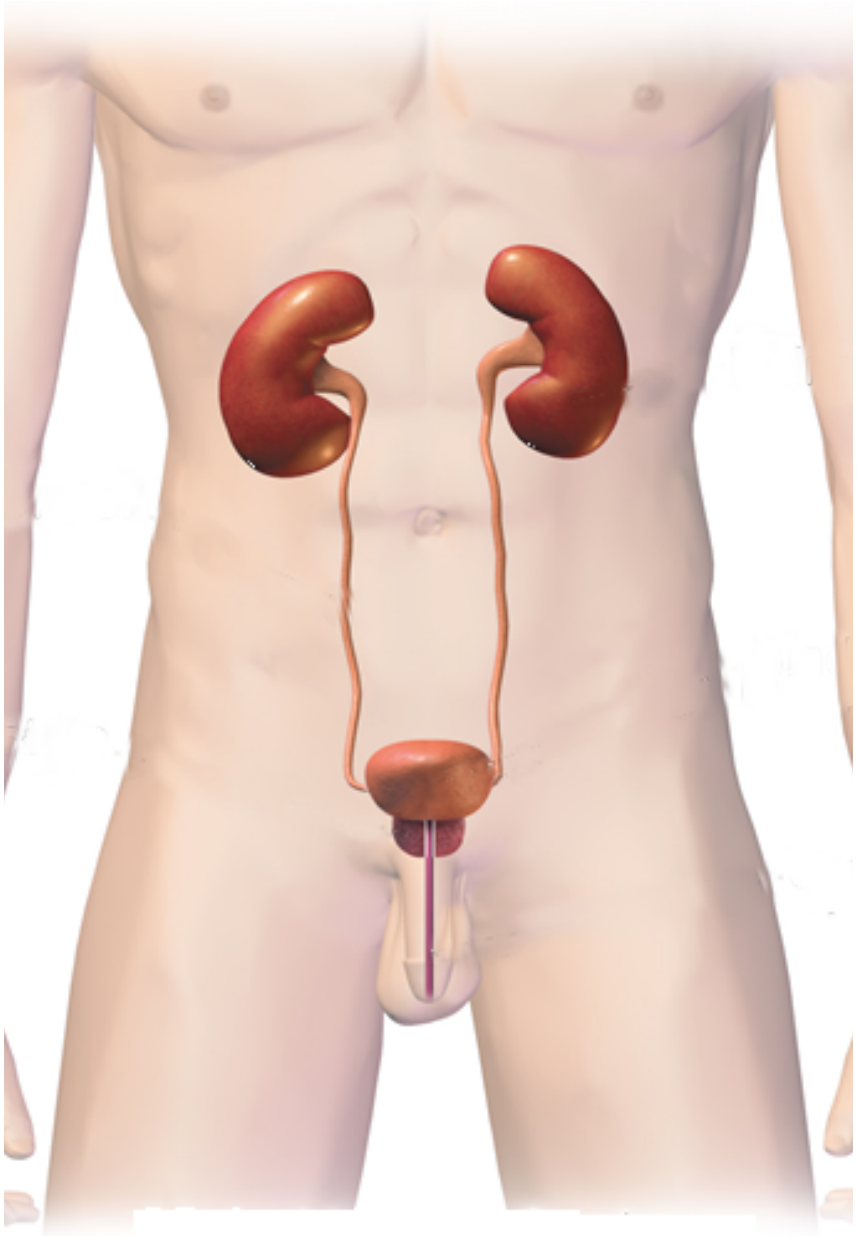
Green and black tea for the primary prevention of cardiovascular disease (Review)

Hartley L, Flowers N, Holmes J, Clarke A, Stranges S, Hooper L, Rees K



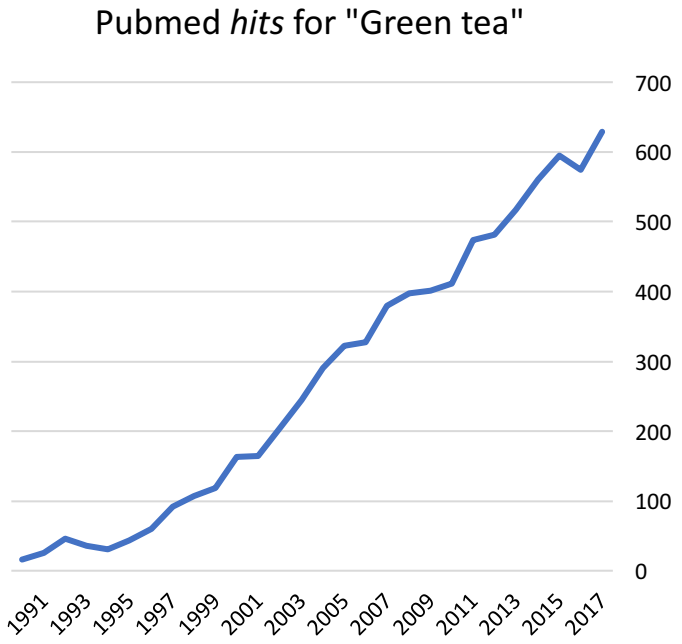
Green tea in Urology

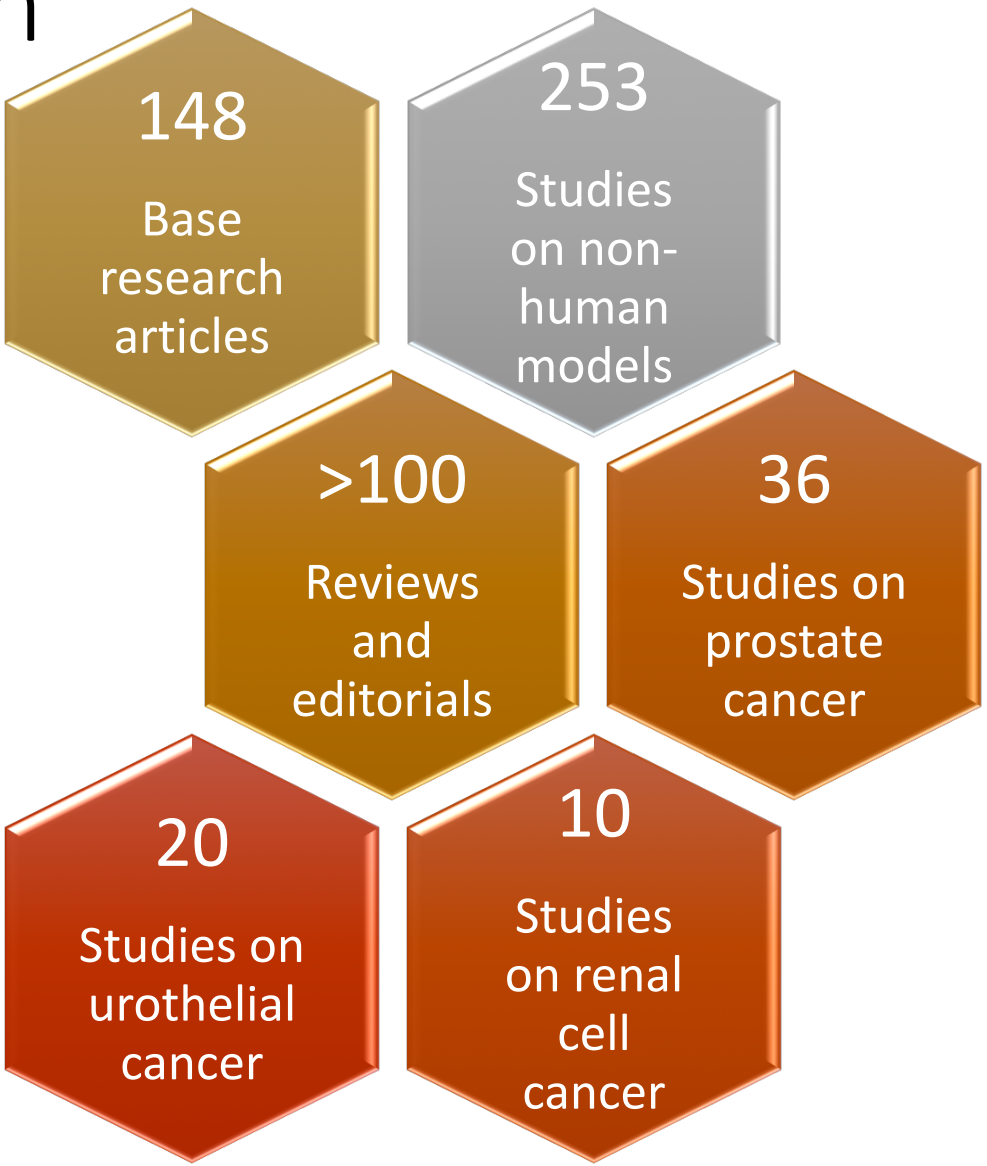
Evidence on cancer prevention and treatment, BPH, IVUs and other applications



Literature search

A wide and heterogeneous literature on **green tea** and **prostate**, bladder and kidney **cancer** is available on PubMed.



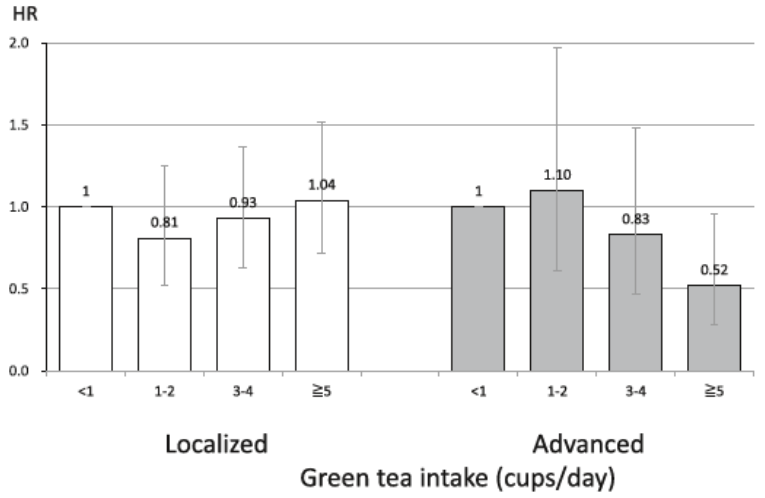


Evidence from observational studies on PCa prevention

Author (year)	Study design	PCa risk
Kikuchi (2006)	Epidemiologic (19,561 Japanese men)	PCa unchanged
Kurahashi (2007)	Epidemiologic (49,920 Japanese men)	Advanced PCa reduced
Jian (2007)	Case-control (404 men)	Reduced
Sonoda (2004)	Case-control (280 men)	Unchanged

Sawada (2016), *Japan Public Health Center-based prospective study (JPHC) on 49.920 men:*

- **Decreased risk of advanced PCa**
  HR was 0.52 (95% CI: 0.28-0.96) for men drinking 5 cups/day
- **Unchanged risk of localized PCa.**



Evidence from systematic reviews and meta-analyses on PCa prevention

Author, year	Journal	Type	Main findings
Boehm, 2009	Cochrane Database of Syst Rev	SR	In **prostate cancer**, observational studies with higher quality and the only included RCT **suggested a decreased risk** in men consuming higher quantities green tea or green tea extracts.
Cui, 2017	Oncotarget	MA	Trend towards reduced PCa risk for GTC, in overall analysis. **In subgroup analysis, reduction of PCa risk** (RR = 0.39; 95% CI: 0.16-10.97, P = 0.044).
Guo, 2017	Medicine	MA	Green tea intake might reduce the incidence of PCa with a linear dose–response effect and **decrease PCa risk significantly with over 7cups/day.**
Jacob, 2017	Nutrition and Cancer	MA	Green tea appears to be an effective chemopreventive agent, particularly in those with high-grade prostate intraepithelial neoplasia.

A **trend towards PCa risk reduction** by GTC is generally observed in systematic reviews and meta-analyses, which include mostly observational studies. However, **strength of evidence is insufficient to give any recommendation**. Well-designed, large RCT are required.

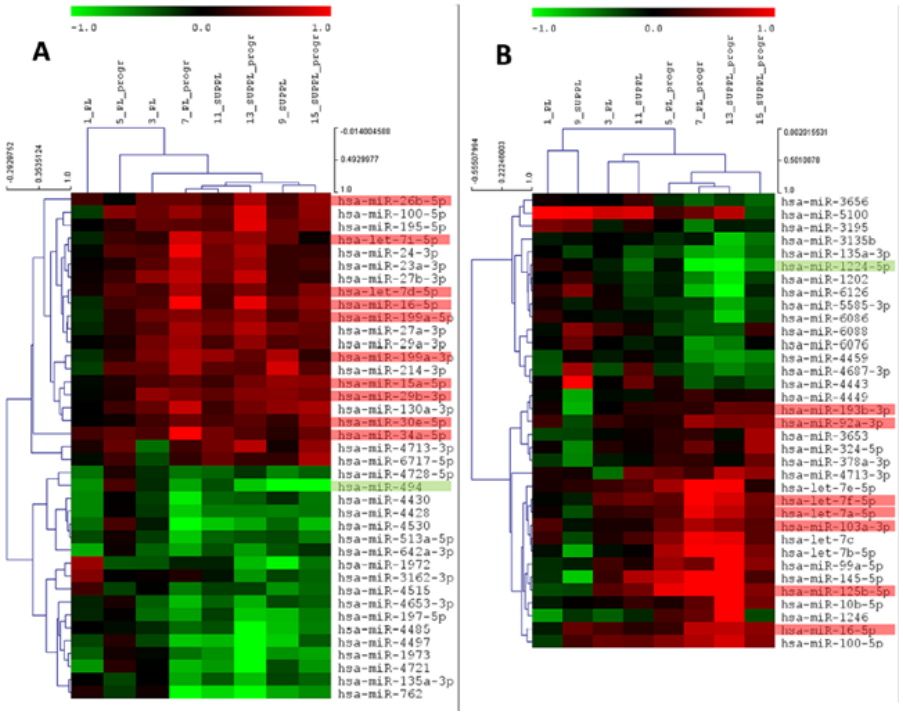
Evidence from RCT on PCa prevention

Author (year)	N	Pts	Treatment	PCa risk	Notes
Bettuzzi (2006), *Cancer res.*	60	HG-PIN	600 mg GTC; 1 year	10-fold reduction (p<0,01)	IPSS reduction (small but ss). PSA unchanged. No adverse effects.
Brausi (2008) *Update on Bettuzzi, Eur Urol.*	22	HG-PIN	600 mg GTC; 20 months circa	5-fold reduction	P<0,01
Kumar (2015) *Oncotarget*	97	HG-PIN /ASAP	400 mg GTC; 1 year	No reduction *Not primary outcome*	No adverse effects. IPSS unchanged. PSA reduction (ss).
Gontero (2015) *The Prostate*	60	HG-PIN /ASAP	Lycopene 35 μg; Selenium 55 μg; GTCs 600 mg; 6 months	3-fold increase (p=0,052)	IPSS unchanged PSA unchanged. Upregulation of tumour-like miRNA.
Micali (2017) *Arch Ital Urol Androl.*	60	HG-PIN	600 mg GTC; 1 year	No reduction	PSA reduction (ss). IPSS unchanged.

A focus on miRNA modulation

A composite supplementation of Lycopene 35 μg, Selenium 55 μg and GTCs 600 mg, **in hgPIN/ASAP patients**, led to:

- Overexpression of miRNAs present in PCa versus non-cancer tissue;
- Underexpression of miRNAs suppressing PCa proliferation;
- Detection of 35 miRNAs in PCa patients versus disease-free men, including androgen-regulated miR-125b-5p and PTEN-targeting miR-92a-3p.



Gontero, The Prostate, 2015

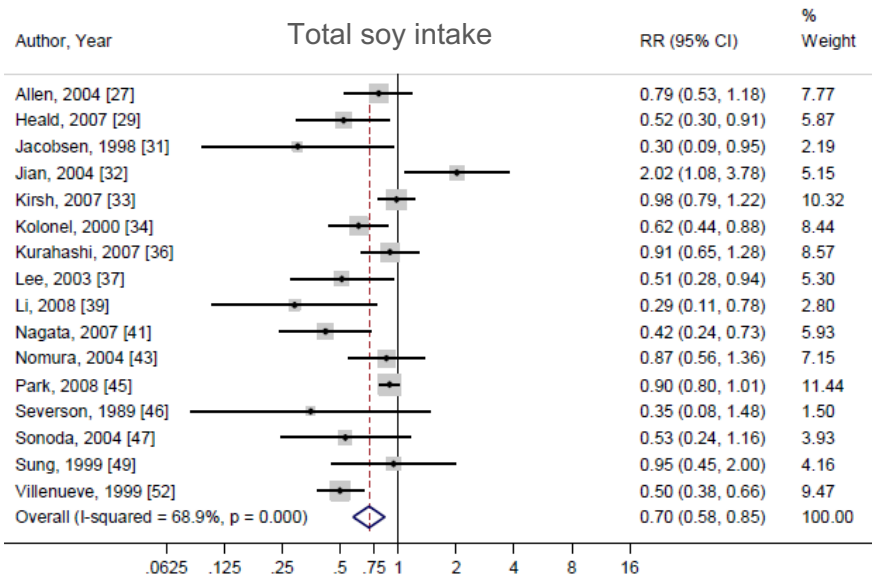
Off-topic

Other polyphenols in PCa prevention

- **Curcumin** (Turmeric) and **Resveratrol** (wine): *in vitro* studies showing mechanism of action **similar to EGCG**. High quality evidence on humans lacking.

Castelli, 2016

- **Soy isoflavones**:
  A recent meta-analysis included 30 **observational studies** (no RCTs) and documented a **decreased PCa risk** for overall soy intake (**RR=0,70**; p<0,01) and for both **genistein** (p=0,01) and **daidzein** (p=0,02).



Applegate, Nutrients, 2018

Evidence in PCa treatment (BCR)

Author (year)	N	pts	Intervention	Outcome
Van Die (2017) RCT, *The Prostate*	22	BCR	Turmeric, Resveratrol, Green tea, broccoli sprouts vs placebo (12 wks)	No efficacy on PSA-DT.
Thomas (2014) RCT, *Prost Canc Prost Dis.*	199	BCR	Pomegranate, green tea, broccoli sprouts and turmeric – all 300 mg/day (PomiT) vs placebo (6 months)	Significant difference in % PSA rise.

Systematic reviews:

- «High-quality studies in this area are lacking. Sulphoraphane, lycopene, soy isoflavones, POMx, and Pomi-T are **safe and well tolerated**. There is **limited evidence that they can affect PSA dynamics»**.

  Van Die, BJUI, 2016

- **« Green tea** […] **efficacy in the treatment of PCa is currently lacking**».

  Jacob, Nutr Cancer, 2017

Bladder and Kidney cancer

- Inconclusive evidence from observational studies on GTC-associated risk reduction of both kidney cancer (RCC) and bladder cancer (BC).

- In a recent meta-analysis, **no significant association** was observed between tea consumption (green or black) and risk of **bladder cancer**. Dose-response *odds ratio* for 1 cup/day was 1,01 (95%CI: 0.97–1.05).

Weng, Front Physiol, 2017

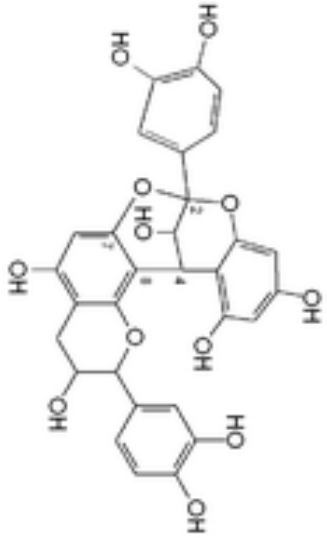
- A meta-analysis of 12 retrospective studies has found **no evidence to support a decreased RCC risk in tea drinkers** (RR=1.03; 95%CI: 0.89-1.21).

Hu et al., Asian Pac J Cancer Prev. 2013

UTIs and polyphenoles

- **Cranberry proanthocyanidins:**
  - Have a **well-established use for UTI prevention**, especially for recurrent cystitis, due to anti-adhesion effect on *E. coli*.
  - However, a recent Cochrane review has pointed out that **benefits could be smaller** than previously thought (RR=0.86; CI: 0.71-1.04 for ≥1 UTI at follow-up vs placebo).

Jepson, Cochrane Database Syst Rev, 2012



- **Green tea**:
  - Controversial evidence of EGCG **antimicrobial activity** on *E. coli* exists *in vitro.*

(Reygaert, Front Microbiol, 2013)

  - Intravesical green tea extracts can **attenuate inflammation** during bacterial cystitis in mice.

(Rosenberg, BJU Int, 2014)

Other applications

Benign prostatic hyperplasia (BPH)

- Evidence on polyphenols and BPH is still very limited.
- **Anti-proliferative** activity of green tea antioxidant activity combined with the action on **5a-reductase** could have a protective role on both BPH onset and progression.
- A RCT enrolling 176 patients, comparing 40 mg isoflavones vs placebo for 12 months has documented a slight significant increase in Qmax (but not in IPSS score).

Castelli, Int Braz J Urol, 2016
Ranjan, Urology, 2006
Wong, Altern Complement Med, 2012

Sexual Function

- A moderate intake of red wine in healthy women is associated with **higher** FSFI scores for both sexual desire, lubrication, and **overall sexual function**.
- Red wine polyphenols are probably involved in a **better endothelial function**, by promoting NO synthesis.

Mondaini, J Sex Med, 2009

Methodological issues

Examining the impact of GTCs on cancer incidence and mortality, attention must be paid to:

- **Selection** bias and **publication bias** on observational studies;
- Choice of **control group** (hospital- or population-controlled);
- **Genetic factors** of involved populations (Asian cultures mostly);
- **Scarce homogeneity** of quality, quantity and duration of administration, as well as different environmental factors;
- Safety (*eg.* caffeine content of green tea, with related gastrointestinal problems, insomnia, tachicardia…)

(Boehm, 2009)

Conclusions on GTCs

- GTCs are safe and well-tolerated.
- Associated with a ↓ PCa risk in observational studies.
- Evidence from RCT in PCa prevention for hgPIN/ASAP patients is insufficient to give any firm recommendation. Larger, well-designed RCTs are needed.
- Associations of GTC with other potential chemo-preventive agents deserve careful risk-benefit evaluation (Selenium, vitamin E…).
- Bladder and renal cancer: no association.
- BPH and UTIs: insufficient evidence.