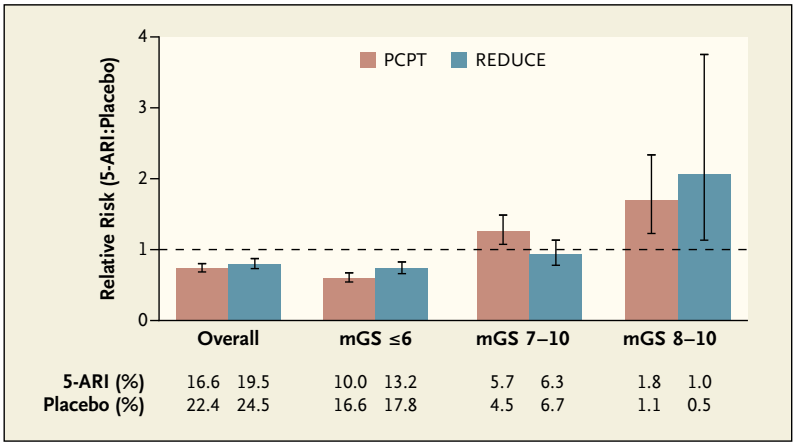
Risks and benefits of 5α-reductase inhibitors for prostate-cancer prevention

In two large randomized, placebo control trials (Prostate Cancer Prevention Trial – PCPT and Reduction by dutasteride of prostate Cancer Events – REDUCE) it was proved that finasteride and dutasteride impact relative reduction of 23% to 25% in prostate cancer diagnosis.

The FDA analysis of the trials confirmed that there was a relative reduction of approximately 25% in the overall incidence of prostate cancer and a significantly increased incidence of high-grade prostate cancers.



Relative and Absolute Risk of Prostate Cancer According to Modified Gleason Score (mGS), PCPT and REDUCE Trial.

The abbreviation 5-ARI denotes 5α-reductase inhibitors. I bars indicate 95% confidence intervals.

Taken from: Theoret MR et al. The Risks and Benefits of 5α-Reductase Inhibitors for Prostate-Cancer Prevention. NEJM. 2011;365:97-9.

These results suggest that one additional man would receive a diagnosis of high-grade prostate cancer (modified Gleason score, 8 to 10) for every 150 to 200 men treated for a long time with a 5α-reductase inhibitor. The 5α-reductase inhibitors reduce serum levels of prostate-specific antigen (PSA) and prostate volume, which leads to an increase in detection of high-grade prostate cancer in the finasteride group of the PCPT.

Approximately 56% of all prostate cancers in the PCPT and 90% of those in the REDUCE trial were diagnosed by means of scheduled biopsies.

Exploratory Analyses of Prostate Volume and Detection Bias for Tumors with a Modified Gleason Score of 7 to 10 versus 8 to 10 in the Prostate Cancer Prevention Trial (PCPT).*

Variable	Method	Result	Modified Gleason Score, 7–10	Modified Gleason Score, 8–10
Prostate volume	Logistic regression	Odds ratio (95% CI)	1.03 (0.84–1.26)	1.51 (1.01–2.26)
	Peters–Belson method	No. observed	243	73
		No. predicted	239	47
Prostatectomy	Weighted imputation estimation	Relative risk (95% CI)	0.73 (0.56–0.96)	1.25
			0.82 (0.64–1.06)	1.40 (0.71–2.76)
			0.84 (0.68–1.05)	1.39 (0.78–2.50)

* The logistic regression in the analysis of prostate volume was adjusted for treatment group, baseline covariates (age, baseline PSA level, family history of prostate cancer, and race), prostate volume, and number of biopsy cores. The Peters–Belson method was used to predict the number of high-grade prostate cancers in the finasteride group on the basis of a regression model developed using patients in the placebo group, with adjustment for all covariates listed above except treatment group; significant differences between the number of predicted and observed high-grade cancers in the finasteride group suggest that detection bias due to prostate volume does not explain the higher incidence of high-grade cancers seen with finasteride. In the prostatectomy analysis, weighted imputation was used to estimate the relative risk of high-grade prostate cancer using information from the subgroup of patients who had a prostatectomy specimen submitted to the PCPT Core Pathology Laboratory to impute the outcome for all other patients. Results shown are from three publications using similar analytic methods. Data are from the Oncologic Drugs Advisory Committee briefing information.[5]

Taken from: Theoret MR et al. The Risks and Benefits of 5α-Reductase Inhibitors for Prostate-Cancer Prevention. NEJM. 2011;365:97-9.

The conclusion drawn by the advisory committee in December was that finasteride and dutasteride do not have a favorable risk-benefit profile for the proposed use of chemoprevention of prostate cancer in healthy men. The FDA agrees with this assessment. The effects of finasteride or dutasteride on the incidence of metastatic prostate cancer and prostate-cancer–specific morbidity and mortality have not been evaluated.

The labels of approved 5α-reductase inhibitors, which are currently indicated for the treatment of symptomatic benign prostatic hyperplasia and male-pattern hair loss, have been modified to include the observation of high-grade prostate cancers in the relevant trials.

REFERENCE

1 Theoret MR, Ning Y-M, Zhang JJ, Justice R, Keegan P, Pazdur R. The Risks and Benefits of 5α-Reductase Inhibitors for Prostate-Cancer Prevention. *NEJM*. 2011;365:97-9.

New strategies in Barrett's esophagus: integrating clonal evolutionary theory with clinical management

Barrett's esophagus is a condition in which the normal stratified squamous epithelium of the distal esophagus is replaced by intestinal metaplasia. For more than three decades, the prevailing clinical paradigm has been that Barrett's esophagus is a complication of symptomatic reflux disease that predisposes to esophageal adenocarcinoma. However, no clinical strategy for cancer prevention or early detection based on this paradigm has been proven to reduce esophageal adenocarcinoma mortality in a randomized clinical trial in part because only about 5% to 10% of individuals with Barrett's esophagus develop esophageal adenocarcinoma. Recent research indicates that Barrett's metaplasia is an adaptation for mucosal defense in response to chronic reflux in most individuals. The risk of progressing to esophageal adenocarcinoma is determined by development of genomic instability and dynamic clonal evolution in the distal esophagus modulated by host and environmental risk and protective factors, including inherited genotype. The challenge for investigators of Barrett's esophagus lies in integrating knowledge about genomic instability and clonal evolution into clinical management to increase the lifespan and quality of life of individuals with this condition.

Taken from: Reid BJ, et al. New strategies in Barrett's esophagus: integrating clonal evolutionary theory with clinical management. Clin Cancer Res; 2011;17(11):3512–9.

Memory type 2 helper T cells induce long-lasting antitumor immunity by activating natural killer cells

Functionally polarized helper T cells (Th cells) play crucial roles in the induction of tumor immunity. There is considerable knowledge about the contributions of IFN-producing Th1 cells that supports the role of cytotoxic cluster of differentiation (CD8) T cells and natural killer (NK) cells, but much less is known about how IL-4–producing Th2 cells contribute to tumor immunity. In this study, we investigated the cellular and molecular

mechanisms employed by memory Th2 cells in sustaining tumor immunity by using a mouse model system wherein ovalbumin (OVA) is used as a specific tumor antigen. In this model, we found that OVA-specific memory Th2 cells exerted potent and long-lasting antitumor effects against NK-sensitive OVA-expressing tumor cells, wherein antitumor effects were mediated by NK cells. Specifically, NK cell cytotoxic activity and expression of perforin and granzyme B were dramatically enhanced by the activation of memory Th2 cells. Interleukin 4 (IL-4) produced by memory Th2 cells in vivo was critical for the antitumor effects of the NK cells, which IL-4 directly stimulated to induce their perforin- and granzyme-B–dependent cytotoxic activity. Our findings show that memory Th2 cells can induce potent antitumor immunity through IL-4–induced activation of NK cells, suggesting potential applications in cellular therapy for cancer patients.

Taken from: Kitayima M, et al. Memory type 2 helper T cells induce long-lasting antitumor immunity by activating natural killer cells. Cancer Res. 2011;71(14):4790–8.

FoxM1: a master regulator of tumor metastasis

The *FoxM1* transcription factor gene is overexpressed in cancer. Its expression is stimulated by oncogenic signaling pathways and reactive oxygen species. It is also a target of regulation by the tumor suppressor genes. The transcriptional activity of FoxM1 depends upon activation by cyclin and cyclin-dependent kinases as well as Plk1. FoxM1 stimulates expression of several genes involved in the cell cycle progression. Moreover, it supports proliferation of tumor cells by stimulating expression of the antioxidant genes and reducing oxidative stress. A new study provides evidence that FoxM1, in the absence of its inhibitor, the tumor suppressor Arf, drives metastasis of hepatocellular carcinoma (HCC). It induces an epithelial–mesenchymal–like transition phenotype in HCC cells, increases cell migration, and induces premetastatic niche at the distal organ of metastasis. FoxM1 directly activates genes involved in multiple steps of metastasis. In this review, we discuss the evidence for a master regulatory role of FoxM1 in tumor metastasis.

Taken from: Raychaudhuri P, et al. Cancer Res. 2011; 71(13):4329–33.

Report on the 16TH Academy of Studenica

This year, the 16th Academy of Studenica was held on July 1-3, in Novi Sad not in the Serbian orthodox monastery Studenica as it has been the case for many years before. The main topic of this year's Academy was *Cyanobacteria and human health*.

The Meeting was organized by the Oncology Institute of Vojvodina and two Departments of the Faculty of Sciences: Department for Biology and Ecology and Department of Geography and Hotel Management.

Participants from the United Kingdom, France, the Czech Republic, the Republic of Macedonia, Slovenia, Bulgaria, the USA, and from Serbia attended the Conference.

Prof. Zorica Svirčev (fourth from the left) with participants of the 16th Academy of Studenica

Prof. Dr. Vladimir Baltić, president of the Academy of Studenica

Participants of the 16th Academy of Studenica (The Palić Lake)

Participants had the opportunity to listen to more than 40 lectures that were presented in several sessions. Two main parts of the Meeting were biological/ecological and medical aspects of the topic.

Biological and ecological aspects covered biology and the role of cyanobacteria in the environment of different countries, toxicological aspects of cyanotoxins, their detection and removal methods. Inspiring, interesting, and very informative introductory lecture on risk management of cyanobacterial blooms and cyanotoxins for the protection of health and water resources was given by G.A Cood (UK). Participants also learned about good and bad sides of cyanobacteria and their metabolic products (R. Rippka , France; M. Gantar, USA) as well as about new trends in the field of phylogeny of toxic and nontoxic cyanobacteria (M. Herdman, France). Experiences on different aspects relating to cyanobacteria and their toxins were reported by lecturers from the USA (Yin-tak Woo), the Czech Republic (L. Blaha), and from the surrounding countries (Bulgaria, Macedonia and Slovenia). During the second day of the Meeting, mostly Serbian participants reported experiences and results on cyanobacterial blooms, mechanisms of cyantoxin activity, hazard for human exposure, and on methods of detection and removal of cyanotoxins from water resources.

During the Conference, a special workshop took place on perspectives and expectations in relation to colorectal cancer.

Medicinal aspects of the cyanotoxins covered molecular pathogenesis of hepatocellular carcinoma induced by microtoxins, other toxic manifestation of exposure to different cyanotoxins in humans, and contemporary imaging methods in diagnosis of the disease that might be caused by cyanotoxins.

Proposal of cyanotoxin legislative was also presented with hope that the filed of cyanobacteria and cyanotoxins will be regulated in Serbia.

A book and brochures relating to ecological and toxicological aspects of cyanobacteria and their toxins, and Serbian guidance of cyanobacterial blooms were promoted at the end of the Meeting.

On the third day of the Meeting, all participants got an opportunity to visit important water resources, lakes Palić and Ludas, and a pond Kapetanski rit. They were introduced with the problems these places are coping with in the management of water quality. The 16th Studenica meeting was a very successful scientific meeting and was very well organized.

Conference details can be found on website www.onk.ns.ac.rs.

Gordana Bogdanović