



"Sipylus"



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Niobe daughter of Tantalus attempting to shield her children from Artemis and Apollo in Greek mithology





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OMICS International
conferenceseries.com

4th International Conference and Exhibition on
Nutrition
October 26-28, 2015 Chicago, Illinois, USA

TRACE ELEMENTS in PROSTATE CANCER: CLINICAL SURVEY

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PROSTATE CANCER PREVALENCE AND MORTALITY

- 1 in 6 men in the U.S. may develop prostate cancer in their lifetime; 1/6= %18 lifetime risk
- 29% of all cancer diagnoses
- 11% of all cancer deaths in men
- incidence of prostate cancer is increasing, mostly due to increased awareness and screening.
- Overalert—dr&population
- Widespread use PSA = enhance early PCa

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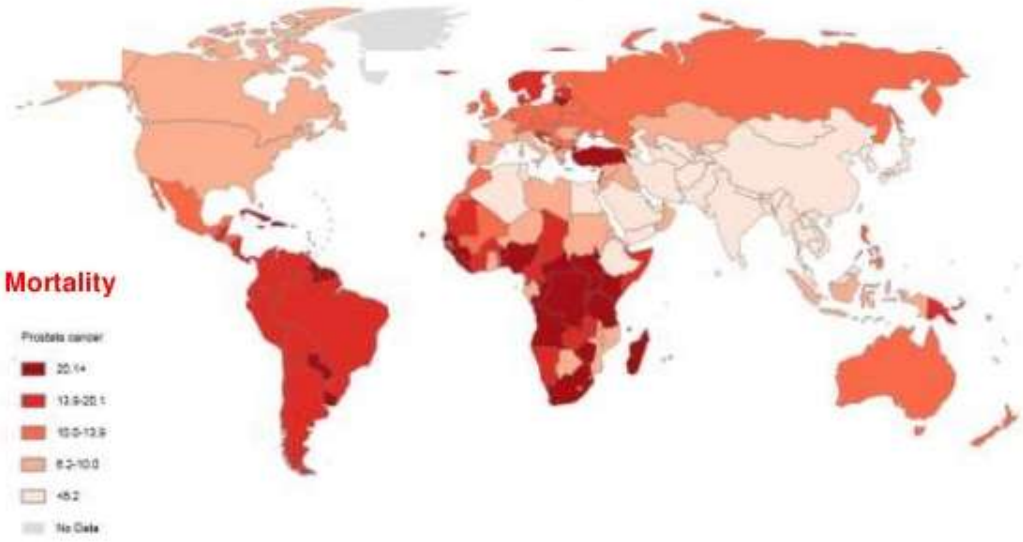
World Cancer Research Fund International

Prostate cancer incidence and mortality

CUP Continuous Update Project

Analysing research on cancer prevention and survival





GLOBOCAN 2012 (IARC)
http://globocan.iarc.fr

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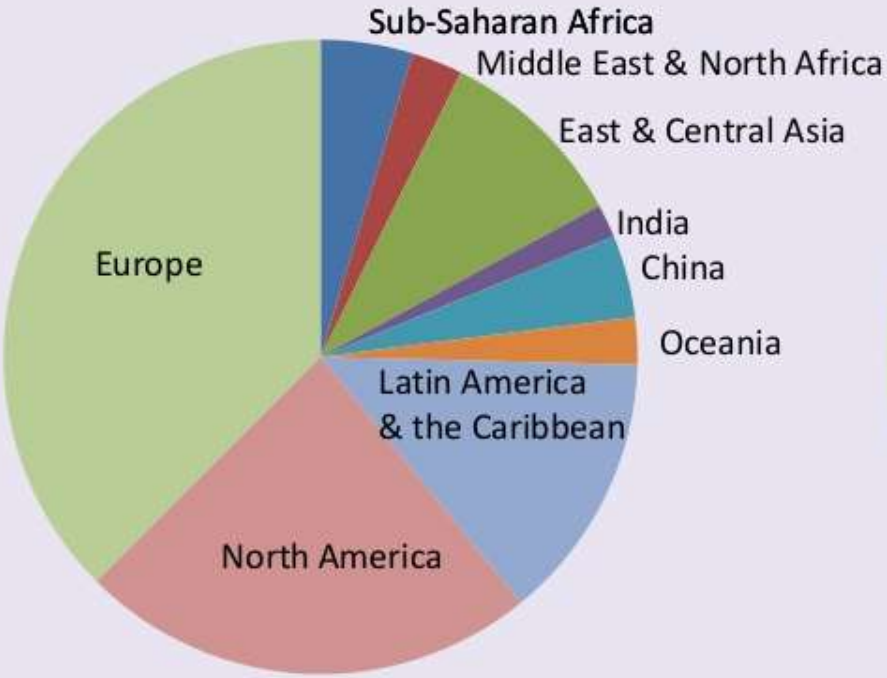
www.wcrf.org

World Cancer Research Fund International

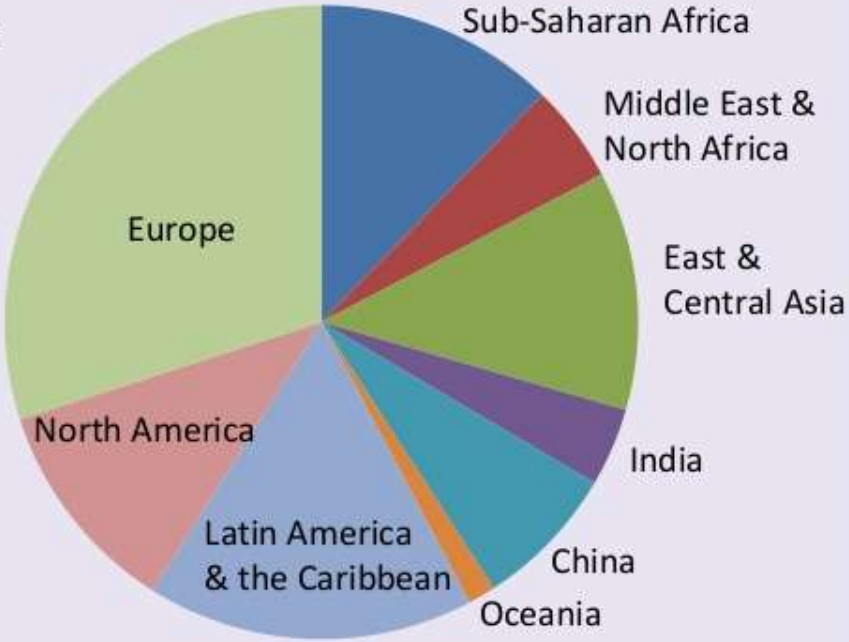
CUP Continuous Update Project

Analysing research on cancer prevention and survival

Prostate cancer incidence



Prostate cancer mortality



World Cancer Report (IARC 2014)

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www.wcrf.org



Int J Cancer 2000; **85**: 60–7

Important health problem for all communities !!

Study

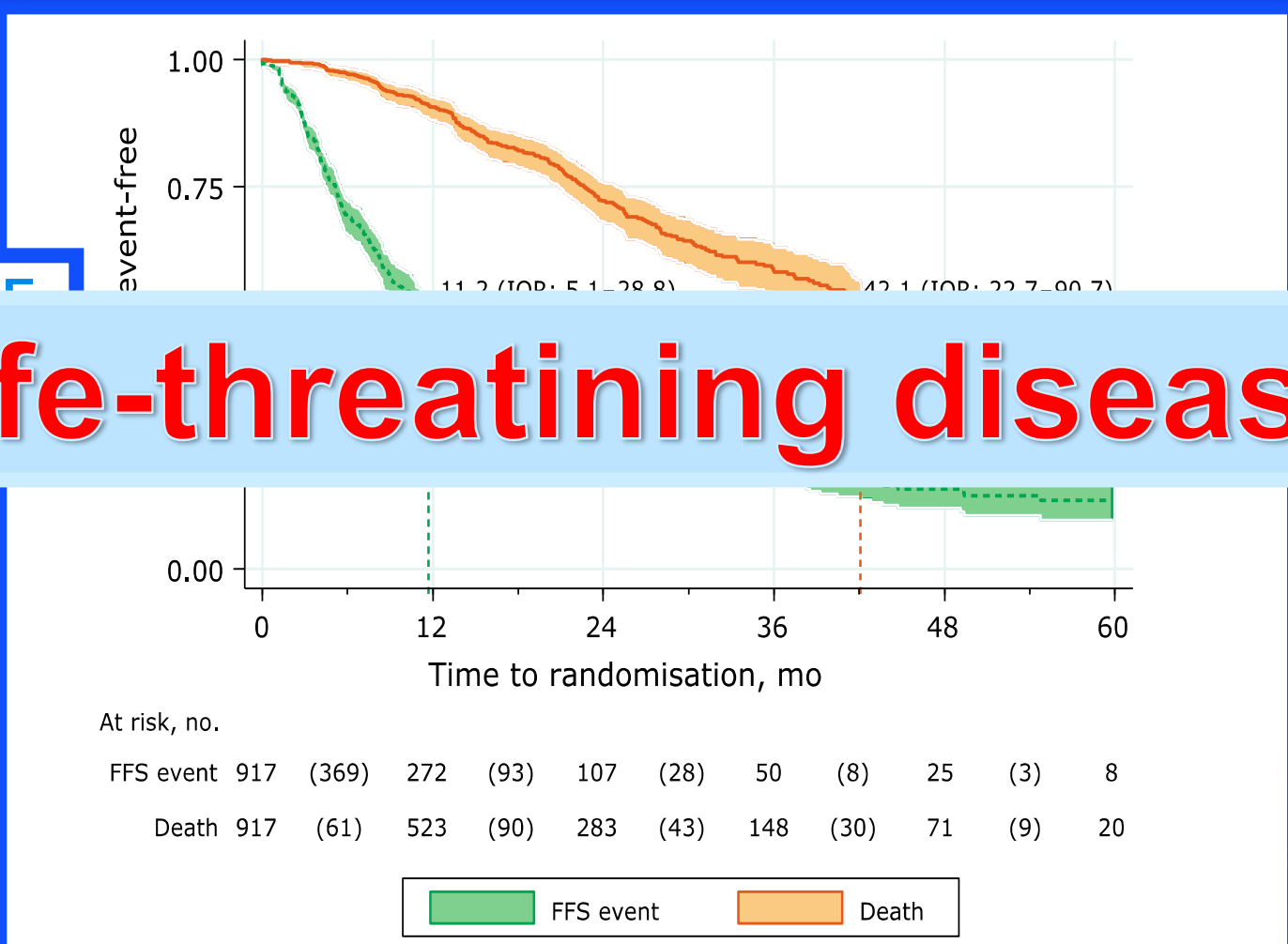
Ferruh Zorlu[1], Rauf Taner Divrik[2], Sultan Eser[3]*, Kutsal Yorukoglu[4]

Age-adjusted prostate cancer incidence rate was 35 cases per 100,000 in Turkey

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014

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MPCA - Prognosis



Life-threatining disease !!

Conclusions: Survival remains disappointing in men presenting with M1 disease who are started on only long-term ADT, despite active treatments being available at first failure

James ND et al. Eur Urol, 2014, http:// dx.doi.org/10.1016/j.eururo.2014.09.032

Definition; trace elments…

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Definitions

- **Element**: An element is a chemical substance that is made up of a particular kind of atoms and can not be broken down or transformed by a chemical reaction into a different element

- **Trace element**: Those elements which occur or function in living tissues in concentrations most conveniently expressed in µg/l

Trace elements in human nutrition, WHO, 1973

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Trace Elements

- Definition
  - Trace elements have a concentration of less than 0.0001 g/g or 0.1 g/L.
- Significance:
  - 14 elements are essential for bacteria, plants and animals (including humans);
    - the transition elements V, Cr, Mn, Fe, Co, Ni, Cu, Mo and Zn
    - the metalloids B, Si Silicon and Se
    - the halogen elements F Fluoride and I Iron
- Why?:
  - There are two main reasons for their measurement in a clinical-nutritional setting:
    - to determine deficiency or toxicity

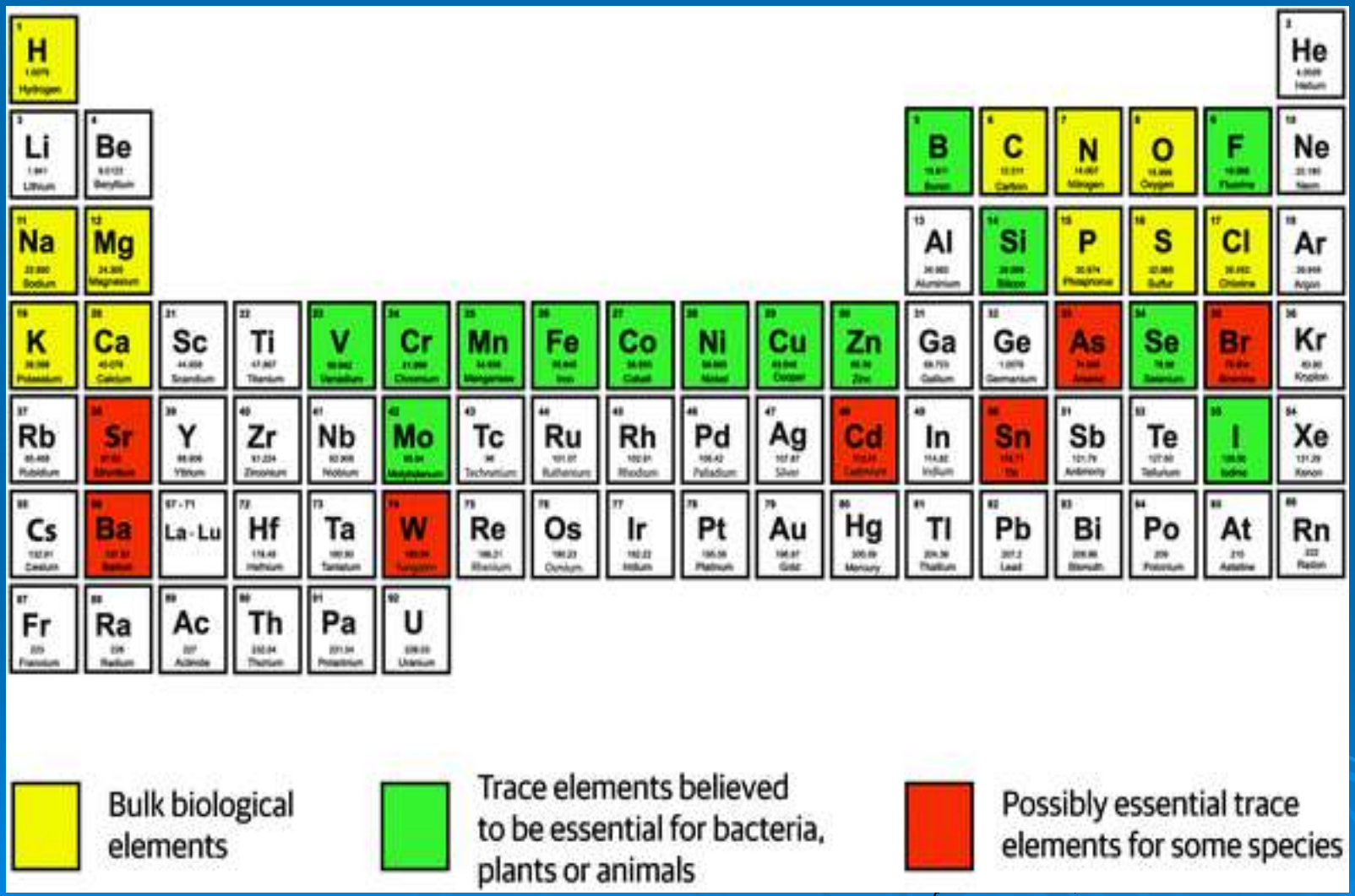
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Classification (WHO, 1996)

- **Essential trace elements**
  - Iodine, Zinc, Selenium, Copper, Molybdenum, Chromium, Cobalt, Iron
- **Trace elements that are probably essential**
  - Manganese, Nickel, Silicon, Boron, Vanadium
- **Potentially toxic elements with possible essential functions in low doses**
  - Fluoride, Lead, Cadmium, Mercury, Arsenic, Lithium, Tin, Aluminium

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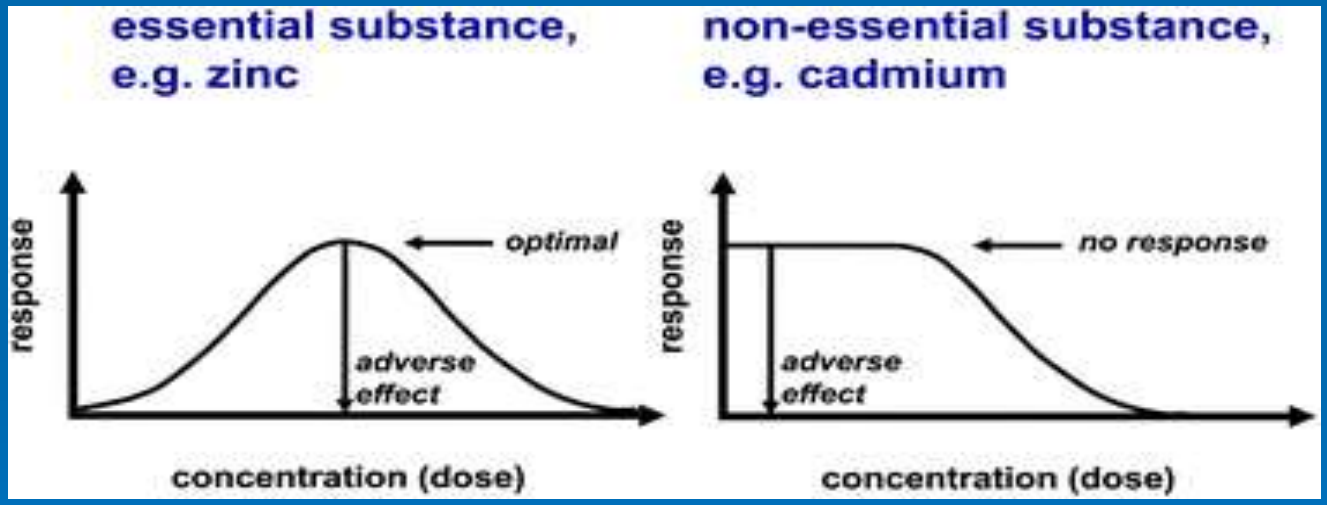
Elemental Classification



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Overload and Deficiency

- Metals act as nutrients
  - Macronutrients (K) and Micronutrients (Mo, Zn etc).
- Metals act as toxic agents:
  - (Fluoride, Lead, Cadmium, Mercury, Arsenic, Lithium, Tin, Aluminium).



- The toxicity depends on the concentration and the target organism.
- Toxicity also depends on the chemical form of e.g. Cr (III) essential, Cr (VI) toxic.

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Analytical Methods





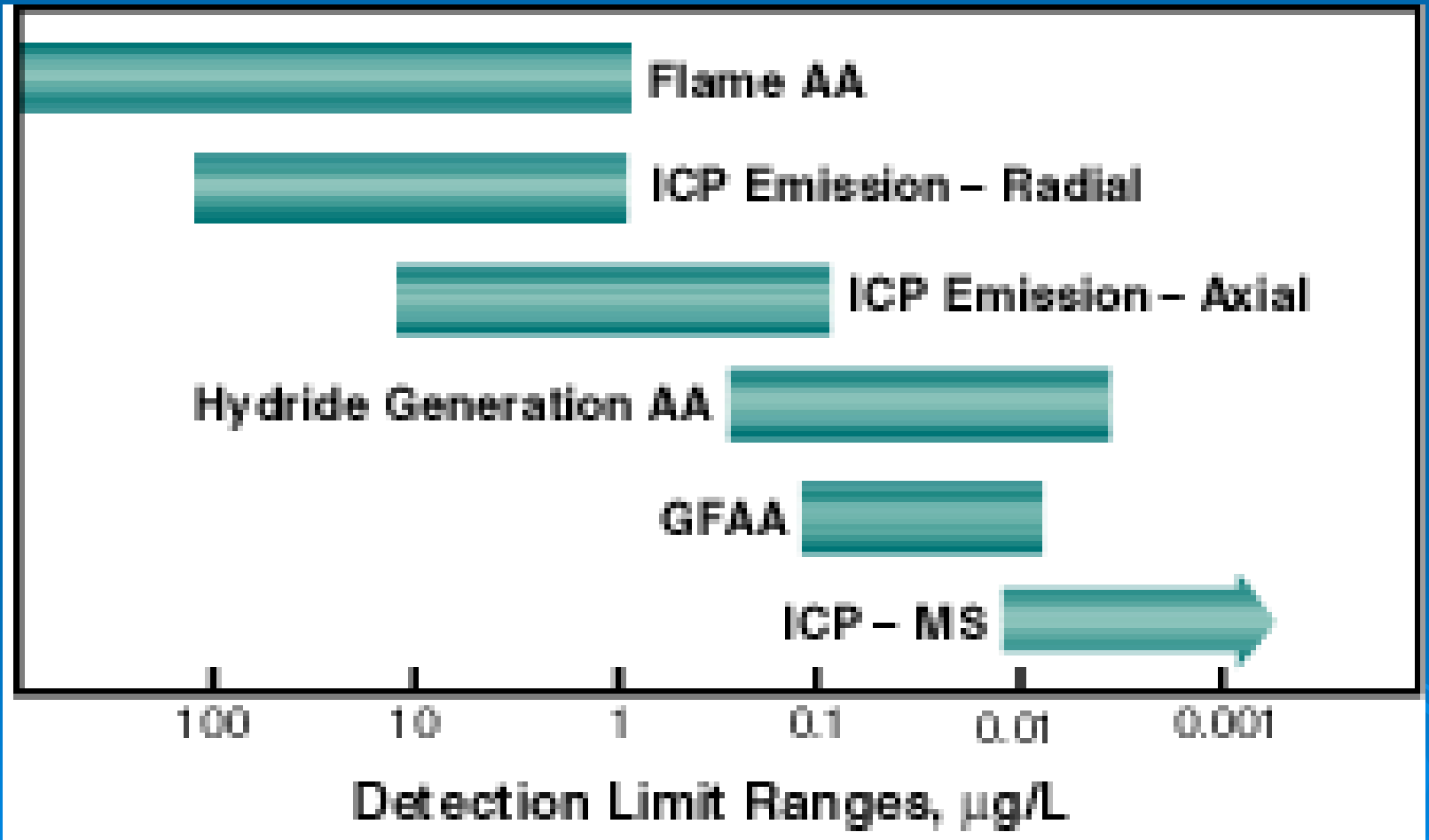
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Analytical Chemistry to the Rescue

- Qualitative - identification of trace metals
- Quantitative – concentration (amount) present eg ug/L, mol/L, %
- Requirements of method –
  - Liquid form required so solid samples have to be dissolved or digested using an acid;
  - Specific for the trace metal of interest;
  - Accurate, not affected by other components, in agreement with other methods;
  - Precise, stable over short and long term;
  - Able to detect low concentrations as well as high;
  - Automated and multi-elemental.

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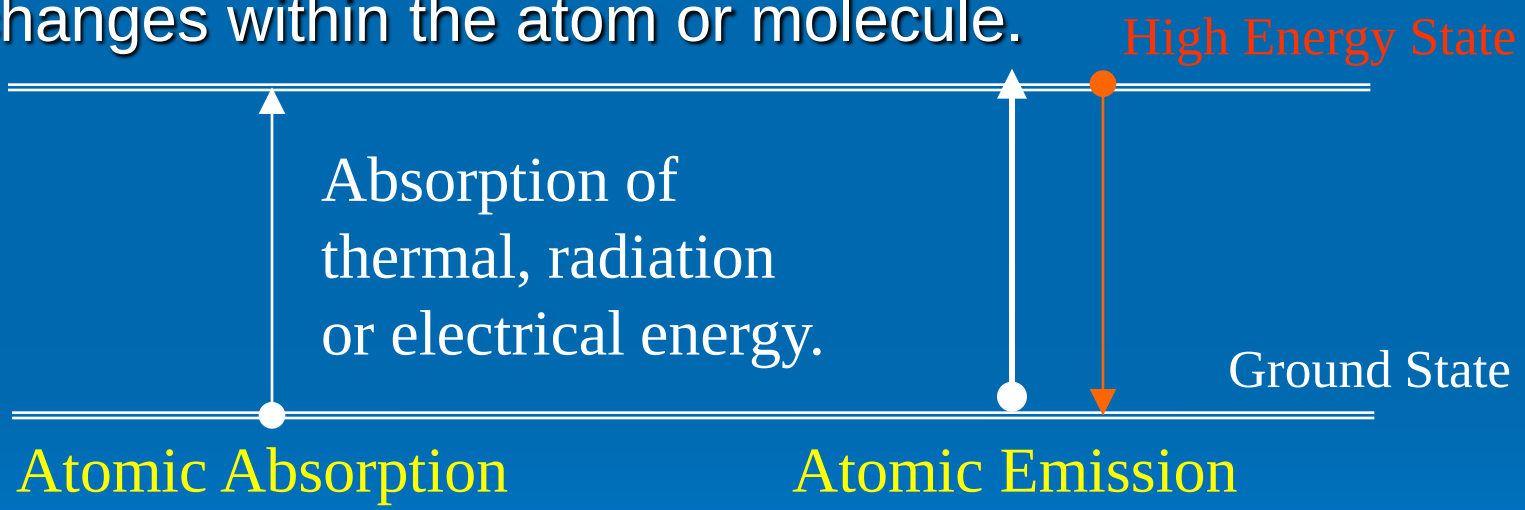
Instrument Detection Limits



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Absorption or Emission ?

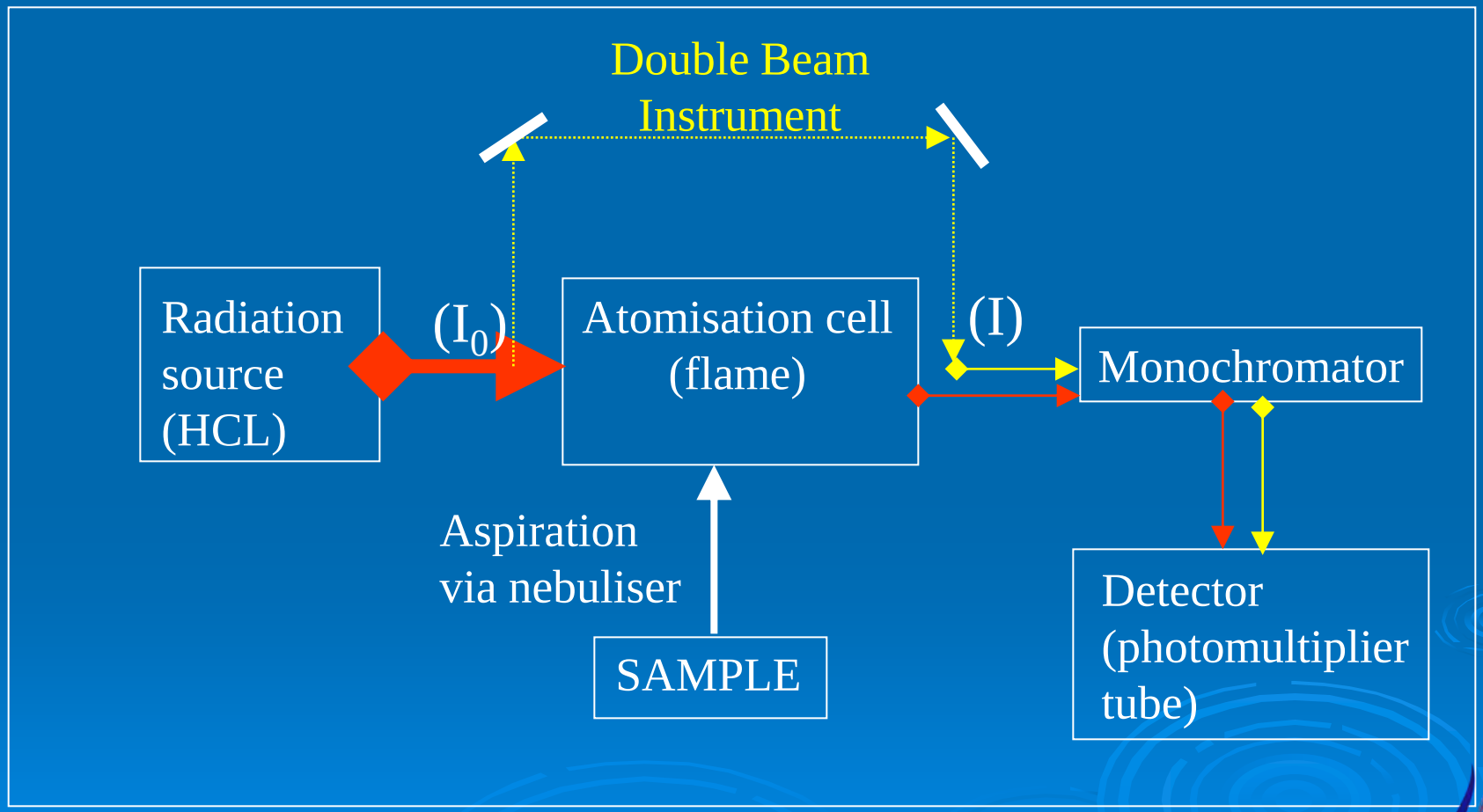
- All spectroscopic techniques depend on the absorption or emission of electromagnetic radiation.
- Absorption or emission arise from quantized energy changes within the atom or molecule.



$E = h \times f = h \times c/\lambda$ (h Planck constant and c speed of light)

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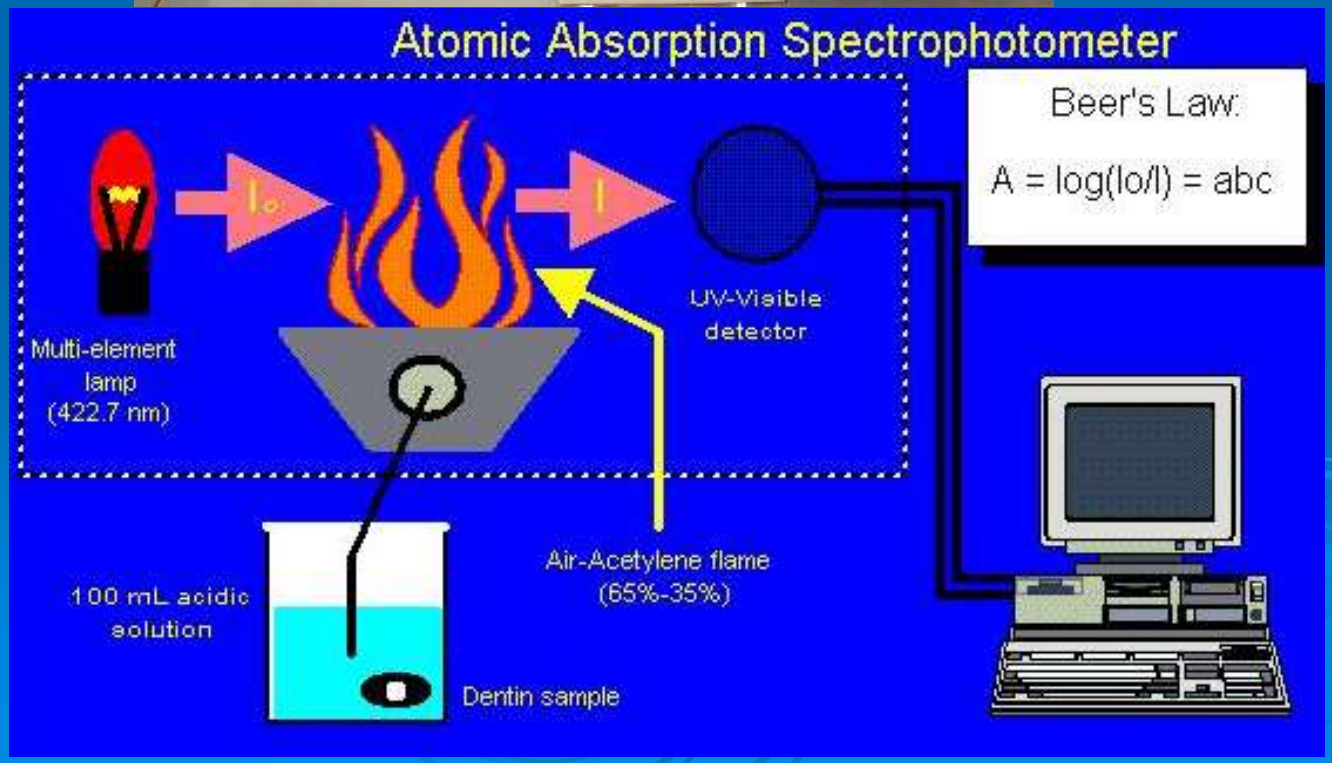
Atomic Absorption Spectroscopy



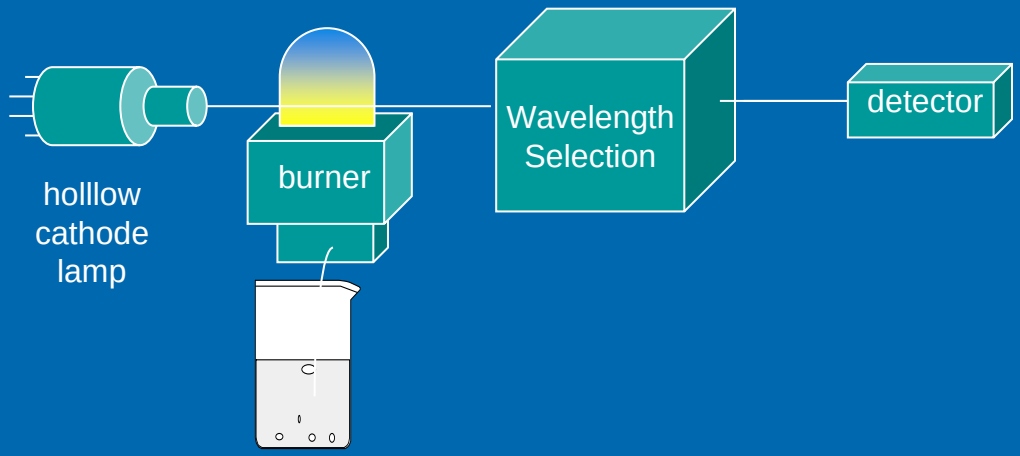
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Atomic Absorption Spectroscopy

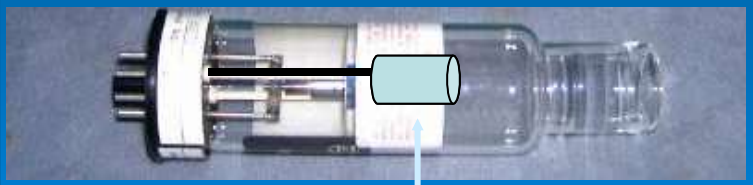




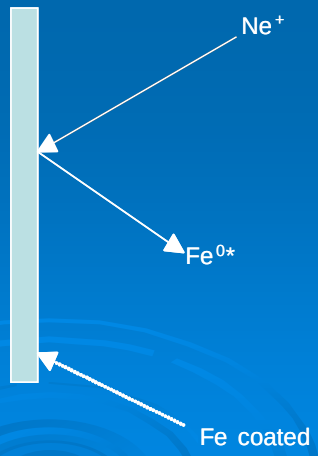
Atomic Absorption Spectroscopy



- Hollow cathode lamp – special light source.



Hollow cathode



~300 V potential in the lamp causes ionization of the fill gas

$Ne \rightarrow Ne^{+} + e^{-}$

The Ne^{+} hits the surface (cathodes attract positive charge)

$Fe^{0}*$ (Excited state Fe^{0}) is ejected .

$Fe^{0}* \rightarrow Fe^{0} + h\nu$.

Atomic Emission Spectroscopy

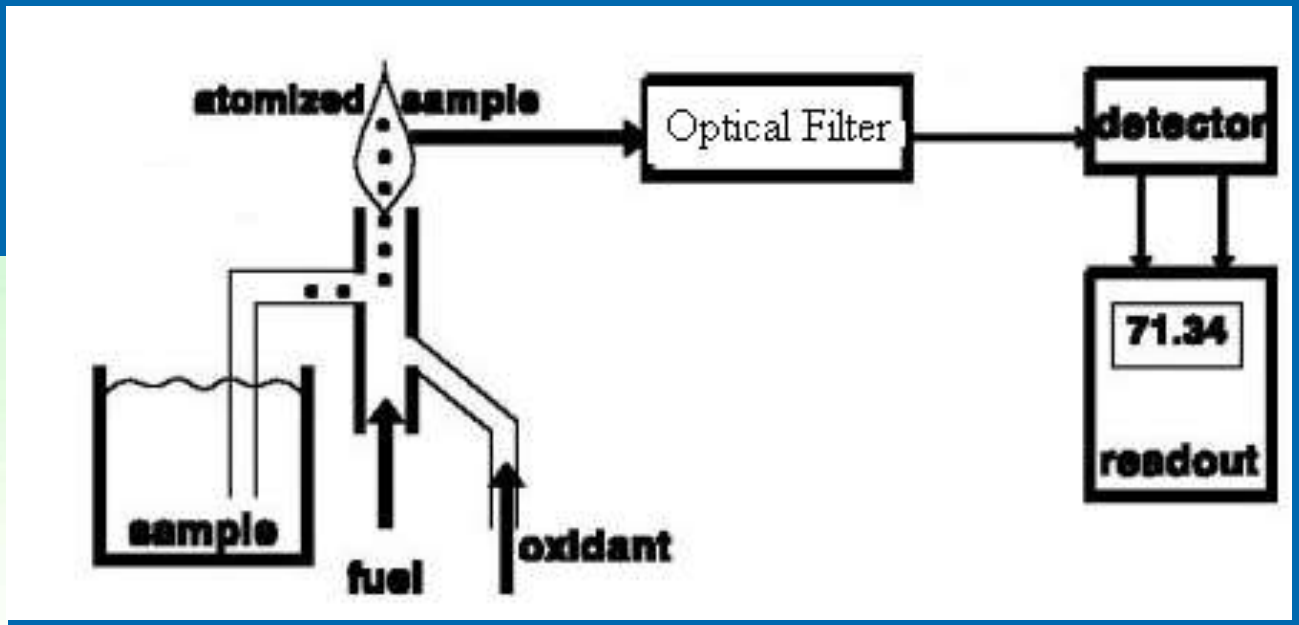
Atomic Emission Spectroscopy

- Flame emission is the oldest spectroscopic technique
- In contrast to AAS where specificity is generated by HCL this is not the case in FES
  - Spectral interferences cannot be resolved by monochromator
- Flame photometry only applicable to specific elements in simple matrices. Group I and Group II
- Uses cooler flame (air-propane/butane/natural gas)
- No other metals are excited so monochromator is not needed. An Interference filter is used
- Cheap

Flame (Emission) Photometry

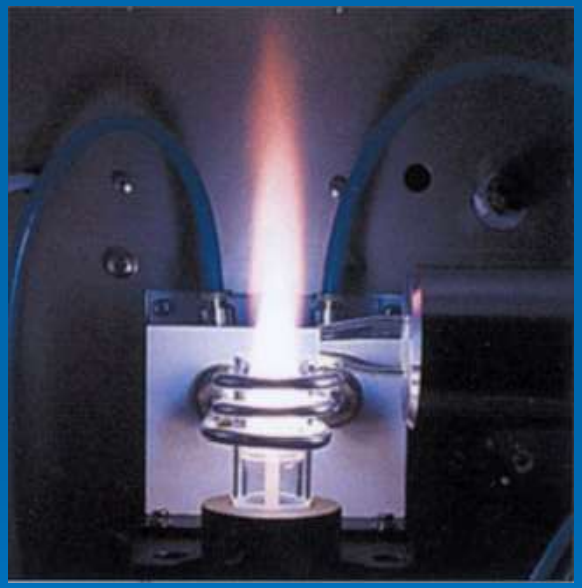
Corning 410



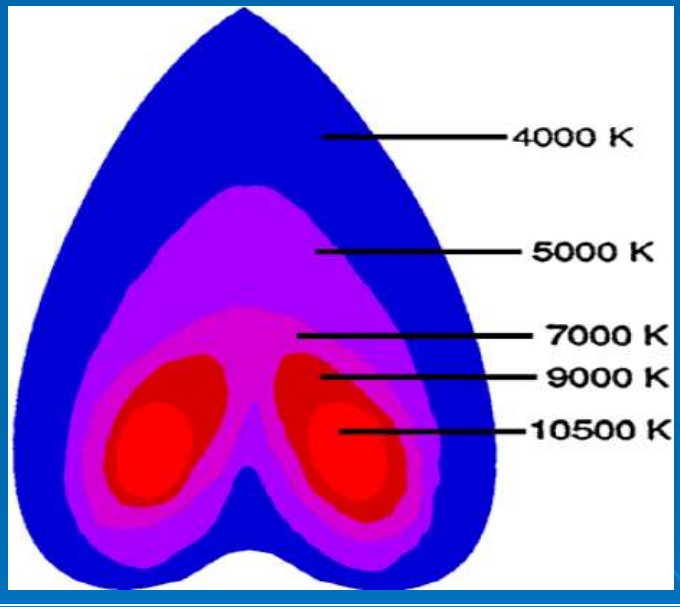


Inductively Coupled Plasma

- Use a hotter flame eg ICP Temperature is between 7000 and 10 000 K (same temp. as surface of sun).
- Can do multi-elemental analysis

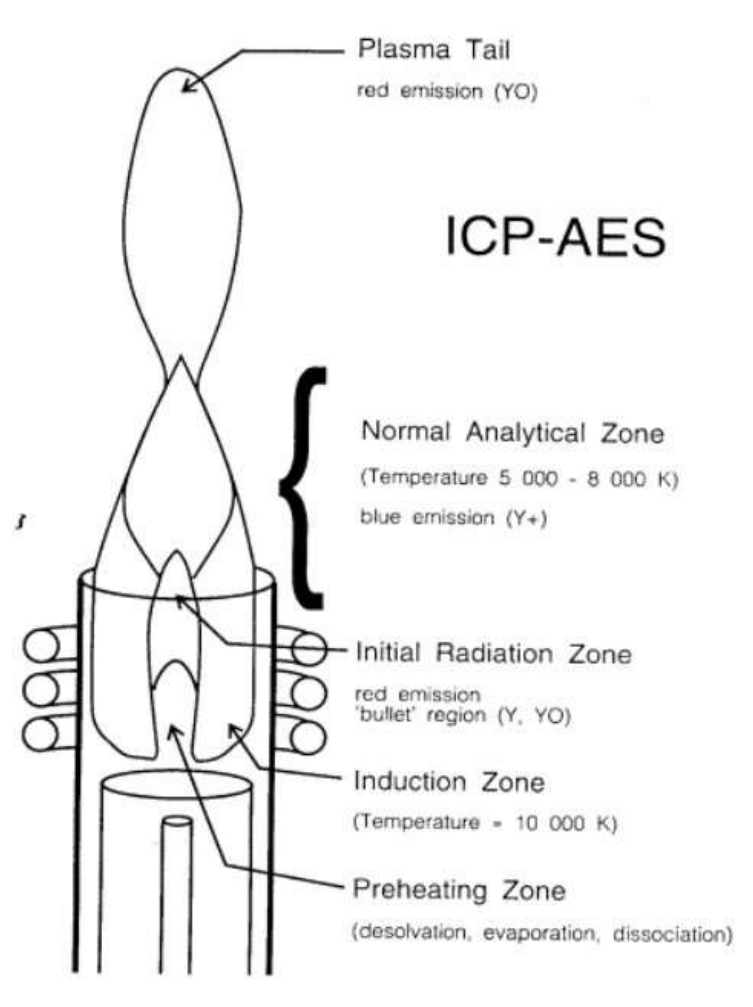


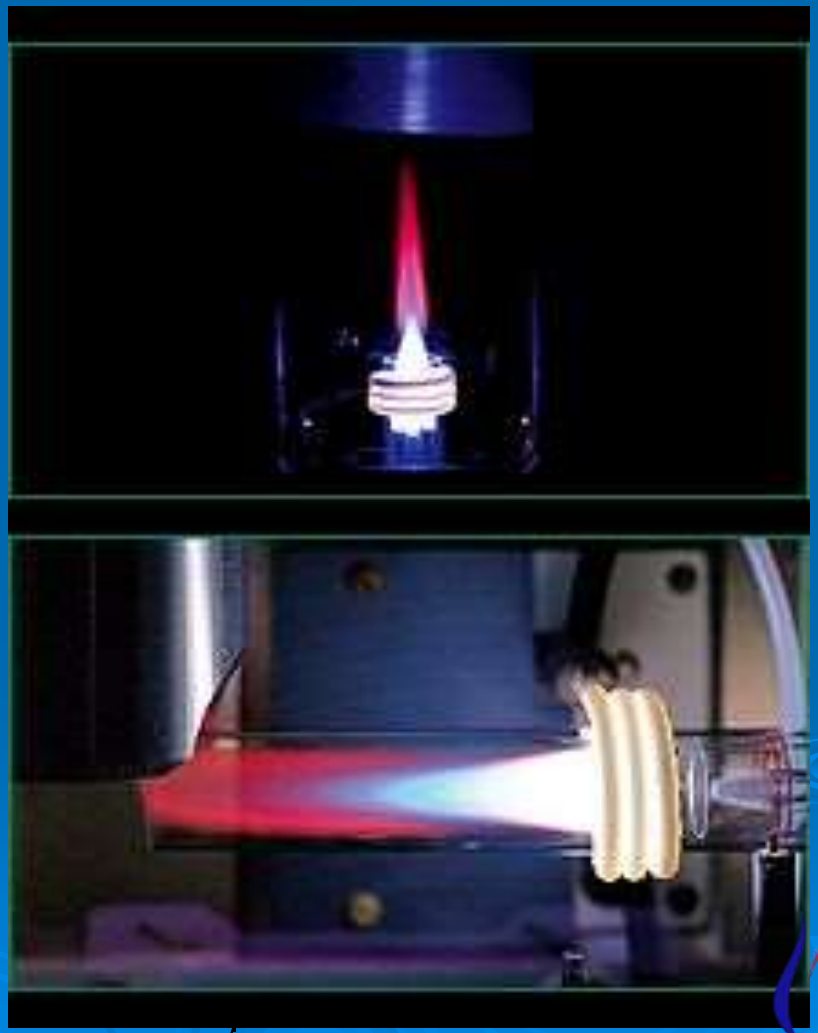
ICP-OES Plasma



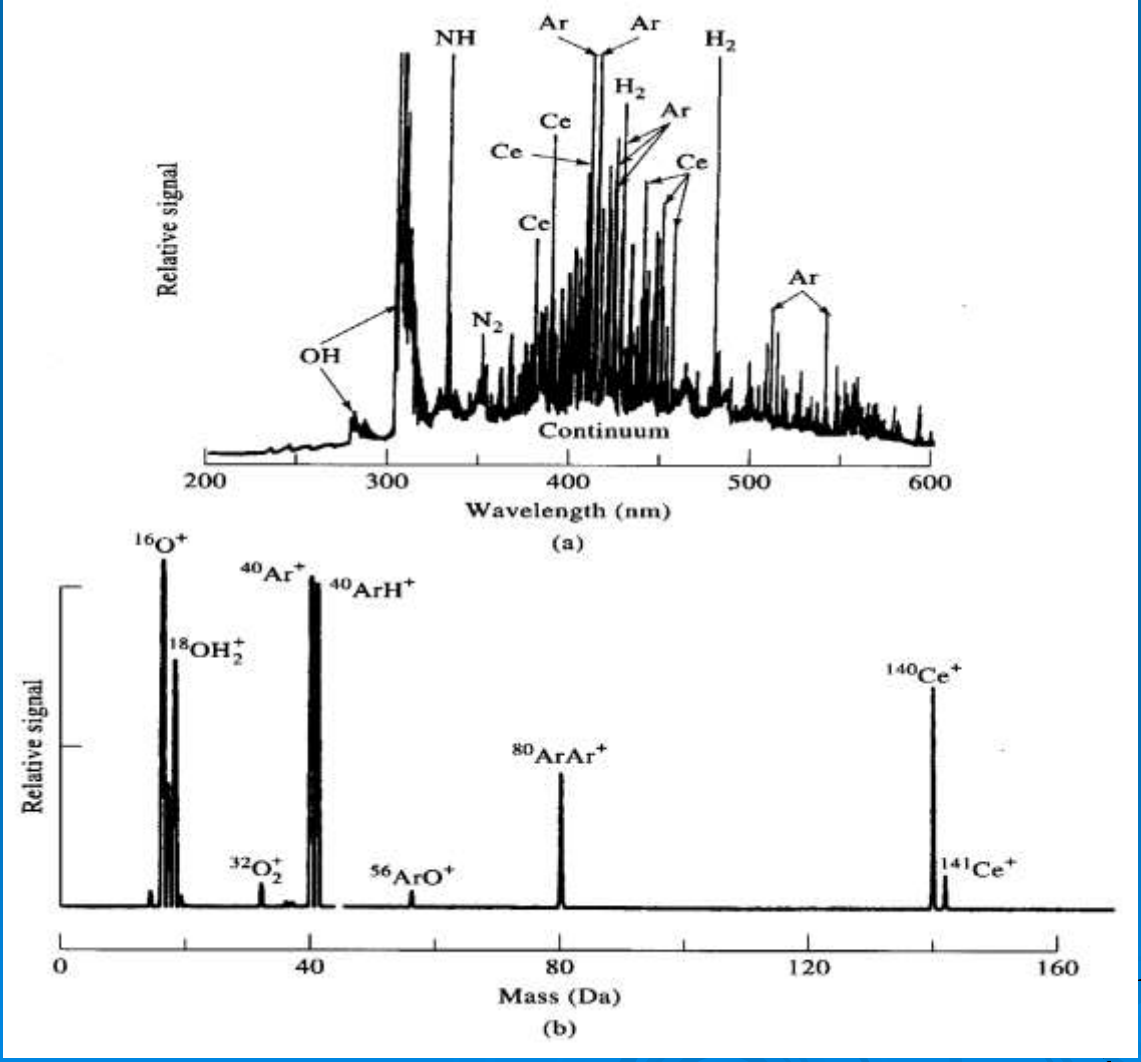
Cross Section of Plasma

ICP-OES or ICP-AES





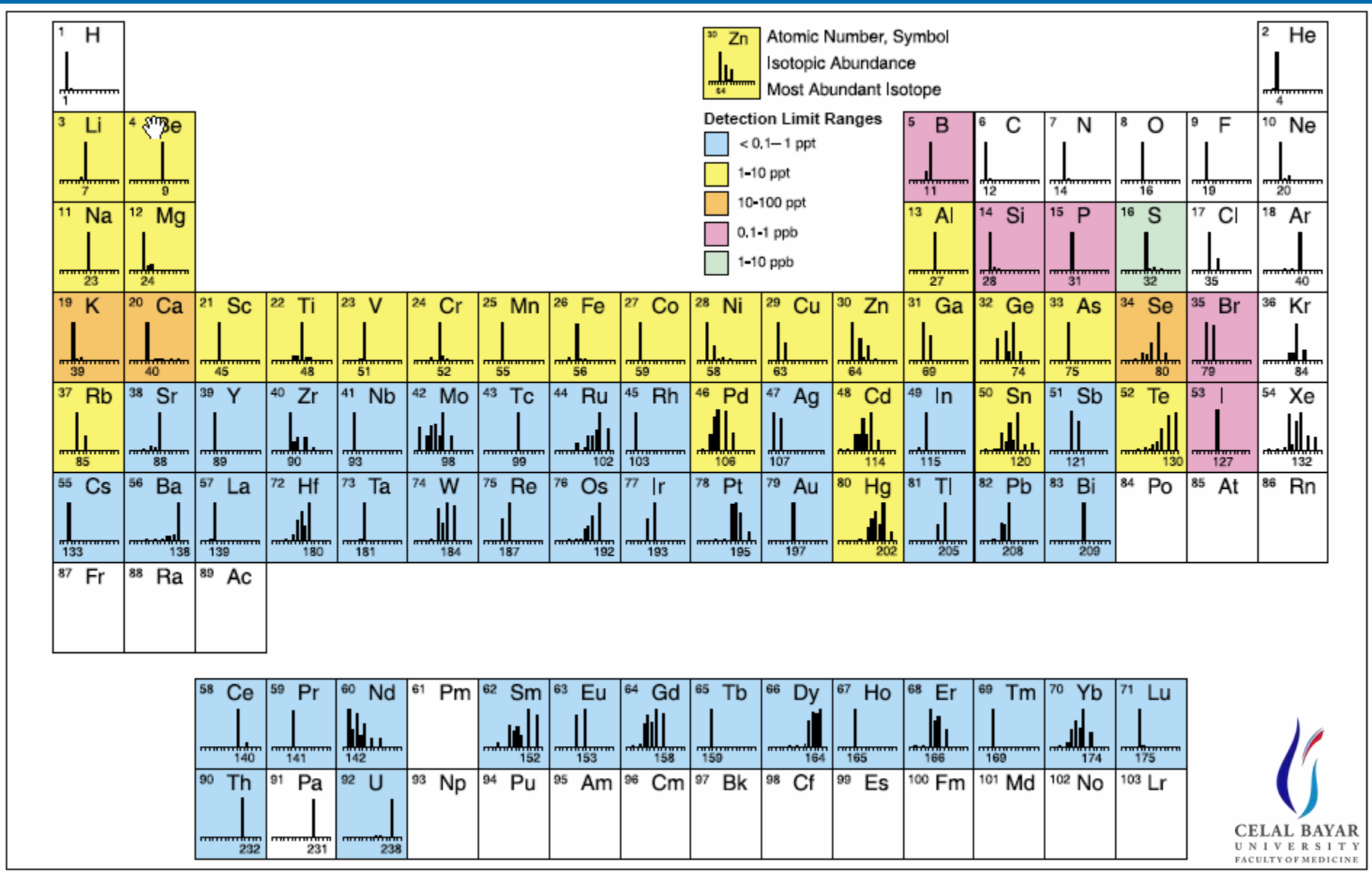
ICP-OES vs ICP-MS



Comparison of (a) ICP-optical spectrum for 100 ppm cerium and

(b) ICP-MS spectrum for 10ppm cerium.

Detection Limits



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Environ Sci Pollut Res (2015) 22:13070–13076
DOI 10.1007/s11356-015-4555-y

RESEARCH ARTICLE

Selenium, nickel, and calcium levels in cancerous and non-cancerous prostate tissue samples and their relation with some parameters

İlker Çelen[1] · Talha Müezzinoğlu[2] · O. Yavuz Ataman[3] · Sezgin Bakırdere[4] · Mehmet Korkmaz[5] · Nalan Neşe[6] · Feriye Şenol[3] · Murat Lekili[7]

Abstract In the present study, tissue samples of patients with cancerous and non-cancerous prostate were analyzed for their Se, Ni, and Ca contents. Possible relationship between Se, Ni, and Ca concentrations and some parameters including preoperative prostate-specific antigen (PSA) levels, histopathological neurovascular invasion, extra-capsular extension, seminal vesicle invasion, positive surgical margins, PSA relapse after radical prostatectomy, and total Gleason scores were obtained. Inductively coupled plasma (ICP) optical emission spectrometry and ICP-mass spectrometry instruments were used for the determination of analytes interested. All the system parameters in digestion and measurement steps were optimized to obtain efficient digestion and sensitive measurements. There was no statistically meaningful difference observed in the concentration of selenium in cancerous and benign prostatic tissues ($p=0.347$) while nickel levels in cancerous tissues were observed as significantly lower than benign tissues ($p<0.001$). In addition, calcium concentration in cancerous tissue samples were found to be statistically lower than those in benign tissues ($p<0.001$) with mean values of 657 and 1,431 mg/kg, respectively.

Keywords Selenium · Nickel · Calcium · Prostate cancer

Introduction

Number of the new cancer cases per year is more than 10 million over the world, and approximately 12 % of all the deaths result from cancer. Hence, there is a great attention to

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Introduction

- There is no information of mecanism

Banas 2010

- Selenium is known to be both an essential and toxic element.
  - Selenoproteins ---- defense mechanism

Goldhaber 2003

- Toxicity= Selenosis !
- Daily dose 0.005 mg/kg-day (USEPA)

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Selenium

- It is present in all body tissues except fat.
- **Sources : Meat, fish, nuts and eggs are good sources. v**egetarians and vegans may be at risk of deficiency.

Functions :

- Selenium is an integral part of over 30 selenoproteins; the most important of which are **glutathione peroxidases** and **iodothyronine deiodinases.**

Table 1. *In vivo* animal studies that assessed prostate cancer prevention by selenium.

Animal Model [Ref.]	Agent and Dose	Results
	Studies relevant to SELECT trial design	
N-Nitroso-*N*-methylurea (MNU) + testosterone-treated Wistar-Unilever rats [42]	L-selenomethionine (1.5 or 3 mg/kg diet) DL-α-tocopherol (4000 or 2000 mg/kg diet) L-selenomethionine (3 mg/kg diet) + DL-α-tocopherol (2000 or 5000 mg/kg diet) Selenized yeast (target Se levels of 9 or 3 mg/kg diet) Control	No effect on prostate cancer incidence in any group
Testosterone + estradiol-treated NBL rat [43]	L-selenomethionine (1.5 or 3.0 mg/kg diet) DL-α-tocopherol (4000 or 2000 mg/kg diet) Control	No effect on prostate tumor incidence, multiplicity, or death in any group
	Studies on selenium in combination with other agents only	
Lady transgenic mice [44]	α-tocopherol succinate (800 IU) + L-selenomethionine (200 µg) + lycopene (50 mg) α-tocopherol succinate (800 IU) + L-selenomethionine (200 µg) Control	Increased survival ($p < 0.0001$) in both treatment groups compared to control, no effect on prostate tumor incidence in any group
Lady transgenic mice [45]	α-tocopherol succinate (800 IU) + L-selenomethionine (200 µg) + lycopene (50 mg) Control	Four-fold decrease in prostate cancer incidence in animals treated with 3 agents combined compared to control animals ($p < 0.0001$)
	Studies on other forms of selenium	
Transgenic adenocarcinoma mouse prostate (TRAMP) model [46]	Methylseleninic acid (3 mg selenium/kg body weight) for 10 weeks Methylseleninic acid (3 mg selenium/kg body weight) for 16 weeks Control	Decreased cancer-specific mortality in methylseleninic acid groups compared to control group ($p_{10\ weeks} = 0.0078$, $p_{16\ weeks} = 0.0385$)
MNU + testosterone-treated Wistar rats [47]	Sodium selenite (4 mg/L in drinking water/day) Control	No effect on prostate intraepithelial neoplasia, decreased prostate cancer multiplicity by 44.6% in sodium selenite group compared to control group

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TABLE 1
Characteristics of the identified studies included in the meta-analyses on selenium status and prostate cancer[1]

Study	Country	Study population	Study design	Age	Follow-up	No. of participants	Outcome(s)	Outcome assessment	Study description, size cohort
				y					
Plasma/serum selenium studies									
Allen et al, 2008 (11)	Europe		Nested case-control	43–76		959 cases; 1059 controls	Prostate cancer incidence (total)	Cancer registry, medical records, pathology	EPIC, 127,811
						203 cases; 216 controls	Advanced prostate cancer incidence	Cancer registry, medical records, pathology	
Brooks et al, 2001 (38)	USA	White	Nested case-control			52 cases; 96 controls	Prostate cancer incidence	Tissue analysis	Baltimore Longitudinal Study of Aging, 1535
Gill et al, 2009 (37)	USA	Multi-ethnic	Nested case-control	45–75		490 cases; 936 controls	Prostate cancer incidence	Cancer registry	Hawaii–Los Angeles MEC Study, 215,251
						123 cases; 344 controls	Advanced prostate cancer incidence	Cancer registry	
Goodman et al, 2001 (35)	USA	Multiethnic (smoker or asbestos-exposed worker	Nested case-control	45–74		235 cases; 456 controls	Prostate cancer incidence	Tissue analysis	CARET, 18,314
						37 cases; 36 controls	Advanced prostate cancer incidence	Tissue analysis	
Hardell et al, 1995 (34)	Sweden	Not stated	Case-control	44–87		164 cases; 121 controls	Prostate cancer incidence	Histology	Sweden 1987–1990
Li et al, 2004 (2)	USA	Multiethnic	Nested case-control	40–84		586 cases; 577 controls	Prostate cancer incidence	Tissue analysis	Physicians' Health Study, 22,071
						171cases; 577 controls	Advanced prostate cancer incidence	Tissue analysis	
Nomura et al, 2000 (3)	USA	Japanese	Nested case-control	44–85	12.4	249 cases; 249 controls	Prostate cancer incidence	Tissue analysis	Honolulu Heart Program, 9345
						64 cases; 64 controls	Advanced prostate cancer incidence	Tissue analysis	
Peters et al, 2007 (36)	USA	Black and white	Nested case-control	55–74	8	724 cases; 879 controls	Prostate cancer incidence (total)	Self reports, hospital records, death certificates	PLCO Cancer Screening trial, 26,935
						278 cases; 879 controls	Advanced prostate cancer incidence	Self reports, hospital records, death certificates	
Vogt et al, 2003 (33)	USA	Multi-ethnic	Case-control			212 cases; 233 controls	Prostate cancer incidence (total)	Histology	USA (Georgia, Michigan, New Jersey), 1986–1989
Toenail selenium studies									
Ghadirian et al, 2000 (39)	Canada	Not stated	Case-control study	35–84		83 cases; 82 controls	Prostate cancer incidence	Histology	Canada, 1989–1993
Helzlsouer et al, 2000 (40)	USA	White	Nested case-control			117 cases; 233 controls	Prostate cancer incidence	Tissue analysis	CLUE II study, 10,456
van den Brandt et al, 2003 (41)	Netherlands	Not stated	Nested case-control	55–69	6.3	300 cases; 1210 controls	Prostate cancer incidence	Tissue analysis	The Netherlands cohort study, 58,279

[1] CARET, Carotene and Retinol Efficacy Trial; CLUE II, Campaign Against Cancer and Heart Disease; EPIC, European Prospective Investigation into Cancer and Nutrition; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal and Ovarian.

Vinceti et al; 2015 May 22.

- No convincing evidence suggests that selenium supplements can prevent cancer in humans.



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Ni & PCa

- Not clear whether nickel-containing enzymes have the same functions in human mechanism as like plants and animals
- capability of promoting tumor:
  - induction of DNA aberration,
  - deletion, inhibition of intercellular transmission mechanism,
  - Formation ofDNA–protein crosslink,
  - inhibition of the maintenance of nucleotide excision, oxidative deformation,
  - Methylation of DNA

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Ca & PCa

- Dairy calcium may increase total prostate cancer risk
- Supplemental calcium was associated with increased risk of fatal prostate cancer

  Am J Clin Nutr, 2015 Jan;101(1):87-117

- Calcium may not have a strong independent effect on prostate cancer risk

  Am J Clin Nutr. 2015 Jan;101(1):173-83

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Materials

- PCa tissue from RRP 50 pts
- BPH tissue from TUR-P 50 pts
- TEs analysed at ICP-OES and ICP-MS

In the digestion of prostate tissue samples, a closed vessel microwave digestion system (ETHOS, Plus, Milestone) equipped with fiber optic temperature sensor and PTFE digestion bombs were used. BSB-939-IR Berghof subboiling acid distillation system was applied to purify the HNO_3 used throughout the digestion of samples and preparation of standard solutions. Thermo X Series inductively coupled plasma mass spectrometer was used in the determination of Se and Ni, and Leeman Labs. Inc. model DRE inductively coupled plasma optical emission spectrometer was used for Ca. In the quantitative measurement for Se and Ni using inductively coupled plasma-mass spectrometry (ICP-MS), $^{82}Se^{+}$ and $^{60}Ni^{+}$ were monitored, respectively. Although $^{78}Se^{+}$, $^{61}Ni^{+}$, $^{62}Ni^{+}$, and $^{64}Ni^{+}$ were also monitored throughout this study,

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M&M

- relationships between analyte concentrations and
  - preoperative PSA levels,
  - histopathological neurovascular invasion,
  - extracapsular extension,
  - seminal vesicle invasion,
  - positive surgical margins,
  - PSA relapse after radical prostatectomy
  - total Gleason scores

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Results

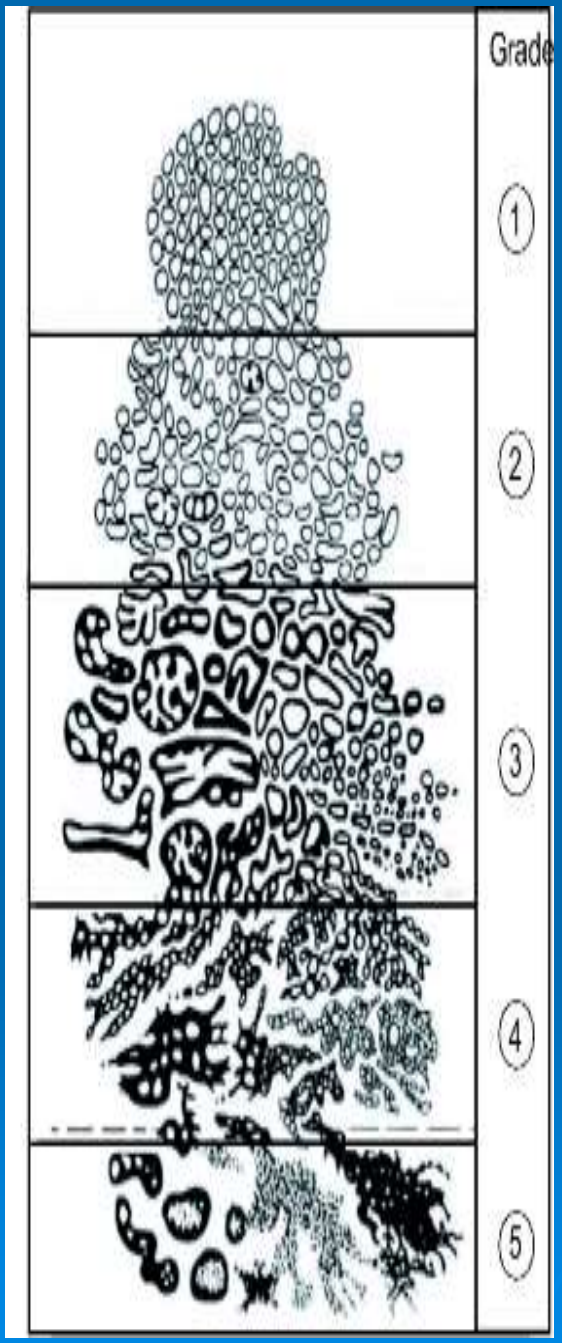
Table 2 Concentration of Se, Ni, and Ca in cancerous and BPH prostate tissues

Diagnosis		*n*	Average Ca (mg/kg), Se, Ni (μg/kg)	SE	*P* value[a]
Se	BPH, PCa	49, 49	191, 168	132, 112	0.347
Ni	BPH, PCa	47, 49	2,174, 784	1,996, 828	<0.001
Ca	BPH, PCa	49, 50	1,431, 657	1,143, 852	<0.001

PCa prostate cancer

[a] Student's *t* test *P* value

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Se; in BPH >PCa

- Se – Gleason Score pos correlation
- There was no statistically meaningful relationship between selenium levels and other clinical parameters.

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Ni; in BPH > PCa

- There is no other statistically meaningful relationship observed between nickel concentration and the other parameters.

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Ca; in BPH > PCa

- Mean calcium concentration was found to be significantly lower in patients with neurovascular invasion.

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Conclusions

- Se level was found to be significantly higher in patients with Gleason≥7 in cancerous group
- Correlation between selenium and preoperative PSA levels was observed (p>)
- no independent prognostic relationship observed between PSA relapse and TE
- little is known about the role of these elements in initiation and/or progression for different cancer types including prostate cancer.

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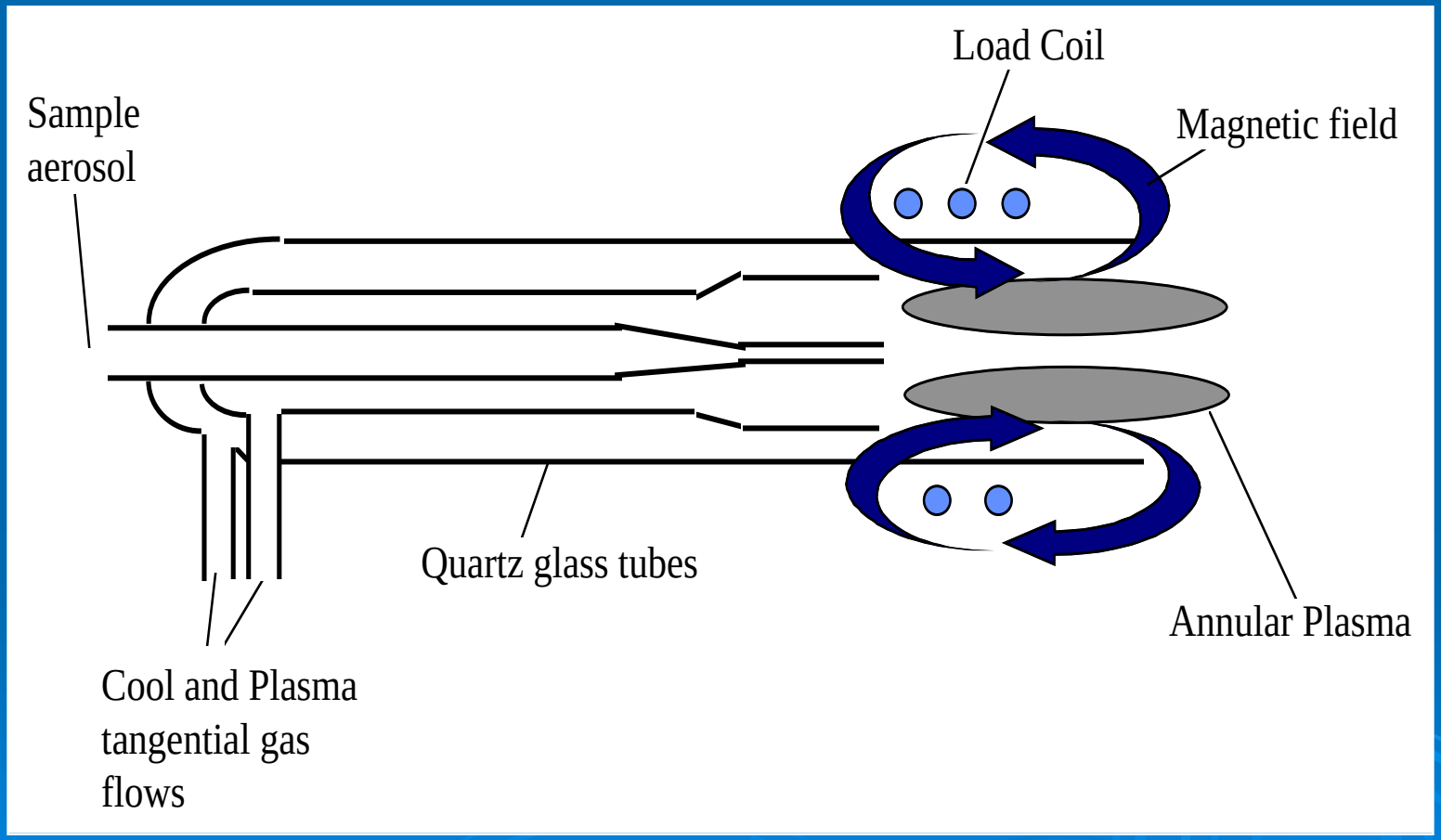
Prostate Fighters



Thank you…

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Inductively Coupled Plasma



Atomic Mass Spectrometry

Learning Outcomes

- At the end of this lecture you should:
- Appreciate the function and effect of trace elements
- Understand the basic concepts behind their measurement
- Appreciate the different types of atomic spectrocopy: AAS, FES, ICP-OES and ICP-MS
- Understand the main interferences associated with each technique

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Practical Session

- Thursday 20th November 2014
- Meet in SAS Trace Element Lab, 15 Frederick Sanger Road, Surrey Research Park
- Directions on the research park website http://www.surrey-research-park.com/location/
- Practical sheets will be handed out
- The practical involves a tour of the lab, a demonstration of ICP-MS and ICP-OES, followed by some problems to be solved.

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