Etiology and epidemiology of malignant tumours – Methods for cancer prevention and screening – Basic principles of complex oncotherapy

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Etiology of malignant tumours

- Multifactorial etiology
- Environmental factors – chemical and physical factors (80-90%)
- Infections – Viral, bacterial and wormal oncogenesis (5-10%)
- Hereditary tumours (< 5%)

Chemical and physical factors – Carcinogenic agents (n=984)

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

- Group 1: carcinogenic to humans (n=118; tobacco, asbest, alcohol, UV, solar and ionizing radiation, outdoor air pollution, oral contraceptives, processed meat)
- Group 2/A: probably carcinogenic to humans (n=75; bitumens, DDT, anabolic, steroids, red meat)
- Group 2/B: possibly carcinogenic to humans (n=288; phenobarbital, chloroform, coffee, glass fiber, gasoline, diesel fuel, carbon black, lead, chrome, nickel)
- Group 3: not classifiable as to its carcinogenicity to humans (n=503; caffeine, tea, PVC, printing ink, magnetic & electric fields, paracetamol, diazempam)
- Group 4: probably not carcinogenic to humans (n=1; caprolactam)

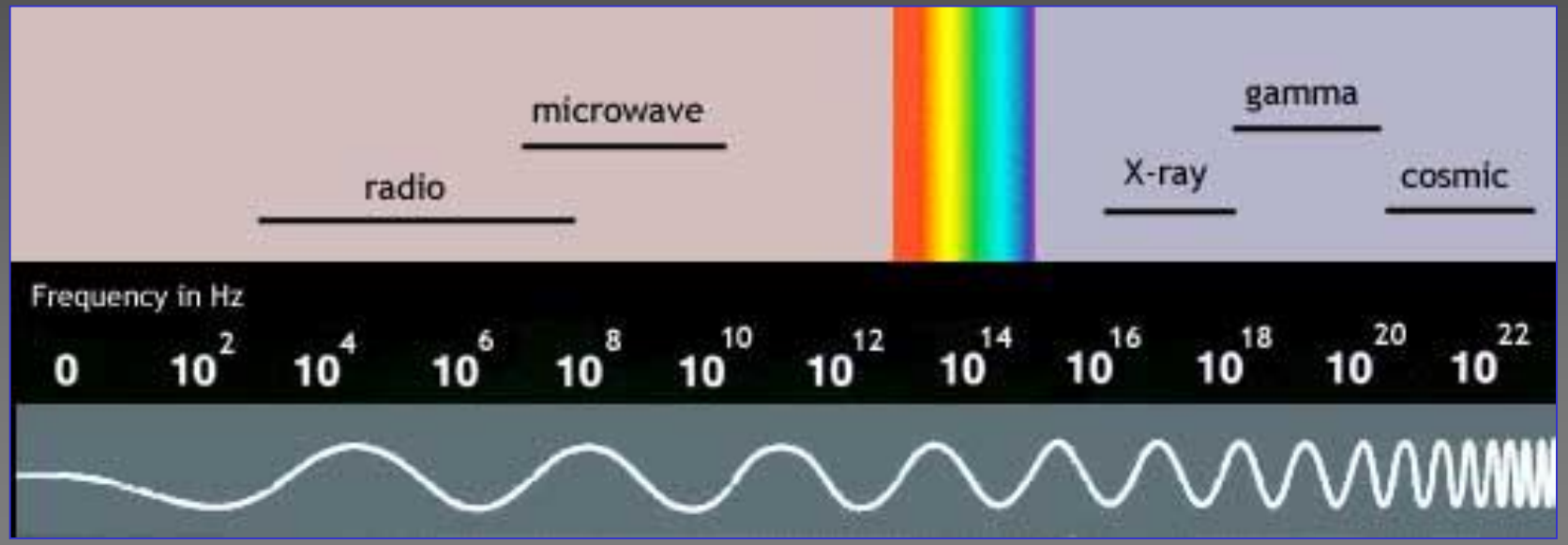
Group 1 carcinogenic chemical agents

- Policyclic aromatic carbohydrogens (combustion products)
  - tobacco smoke, smut, exhausted gas, urban outdoor air
- Aromatic amines
  - production of aniline-dye, plant-protecting agents, plastic materials
- Nitroze-amines
  - tobacco smoke, rubber and war industry
- Aflatoxines (mushroom toxine)
- Not classified, other agents
  - arsenic compounds, chrome, nickel, mustard gas, plant alkaloids etc.
  - processed meat (2015)

Carcinogenic physical factors

- Ionising radiation (physical-chemical-biologic phases → DNA-damage)

- Non-ionising radiations
  - UV (melanoma, skin squamous and basal cell cancers)
  - Microwave & radiofrequency radiation (Group 2/B, gliomas?)
  - Very low frequency electromagnetic field (0-300 Hz) (Group 2/B, leukemia?)



- Asbestos, quartz, talc (powders, fibres, crystals)

Carcinogenic viral, bacterial, and worm infections (5-10%)

Virus/Bacteria/Germ	Type	Increased cancer risk
Human papilloma virus (HPV)	16,18,6,11…31,33,35,39,45,51, 52,56,58,59,68,73,82	cervix, anal, bladder, head&neck ca.
Hepatitis B virus (HBV)	B, C (far-east)	hepatocellular ca.
Human polyoma virus	BK, JC	childhood neuroblastoma
Human herpes virus	EBV, CMV, KS	nasophyarynx, Burkitt-lymphoma. lethal midline granuloma, Kaposi sarcoma
Exogen retrovirus	HTLV-1, HTLV-2	T-cell leukemia
Hepatitis C virus	HCV	lymphoma, aplastic anaemia, cirrhosis, hepatocellular ca.
Human immunodeficiency virus	HIV-1	cancer risk increased indirectly by primary immunosuppresion
Helicobacter pylori	bacteria	gastric cc.
Schistosomas	worms: S. haematobium, S. japonicum,	bladder, liver, colorectal, gastric ca.

Hereditary tumours (< 5%)

Cancer is caused by DNA-mutations

↓

Cancer (at cellular level) is a genetic disease

- Aquired, sporadic tumours (> 95%):
  Mutations in somatic cells caused by cumulated environmental effects

- Hereditary tumours (< 5%):
  Hereditary germ-cell mutations + aquired somatic mutations

↓

- Cancer itself is NOT hereditary!
- There is only a hereditary higher propensity for developing cancer!

Hereditary cancer syndromes (< 5%)

Mainly based on the inactivation tumour supressor genes

Syndrome	Affected gene	Tumours
Hereditary breast cancer	BRCA1, BRCA2	breast, ovary, prostate, pancreas
Hereditary retinoblastoma	RB1	retinoblastoma, osteosarcoma
Wilms-tumour	WT1	Wilms-tumour
Fam. adenomatosus polyposis	APC	GI, brain, thyroid gland, retina
Lynch	MLH1; MSH2,6; PMS1-2 stb.	non polyposus colorectal ca.
Peutz-Jeghers	STK11/LKB1	GI, breast, ovary, endometrial, testicular, pancreatic ca.
Ataxia teleangiectasia	ATM	lymphoma, leukemia, breast, suprarenal gland
Li-Fraumeni	TP53	sarcoma, breast, leukemia
Multiplex Endokrin Neoplasia 1	MEN1	insulinoma, gastrinoma, hypophyseal & parathyroid glands
Xeroderma pigmentosum	XPA, XPB, XPC, XPD, XPE stb.	melanoma, basalioma
von Hippel-Lindau	VHL	clear cell renal ca., phaeochromo-cytoma, retinal angioma

Significance of cancer morbidity and mortality – Hungarian data

- ≈ 77.000 new cancer cases/year → 2030: ≈ 100.000 new cases/year
- 1 out of 3 men/women will develop cancer during his/her life-time
- 2nd. most frequent cause of death
- 1 out of 4 deaths (25%) is caused by cancer

↓

- Cancer burden is a global challenge for the public health systems

Cancer incidence in Hungary (2008-2015) (male & female)

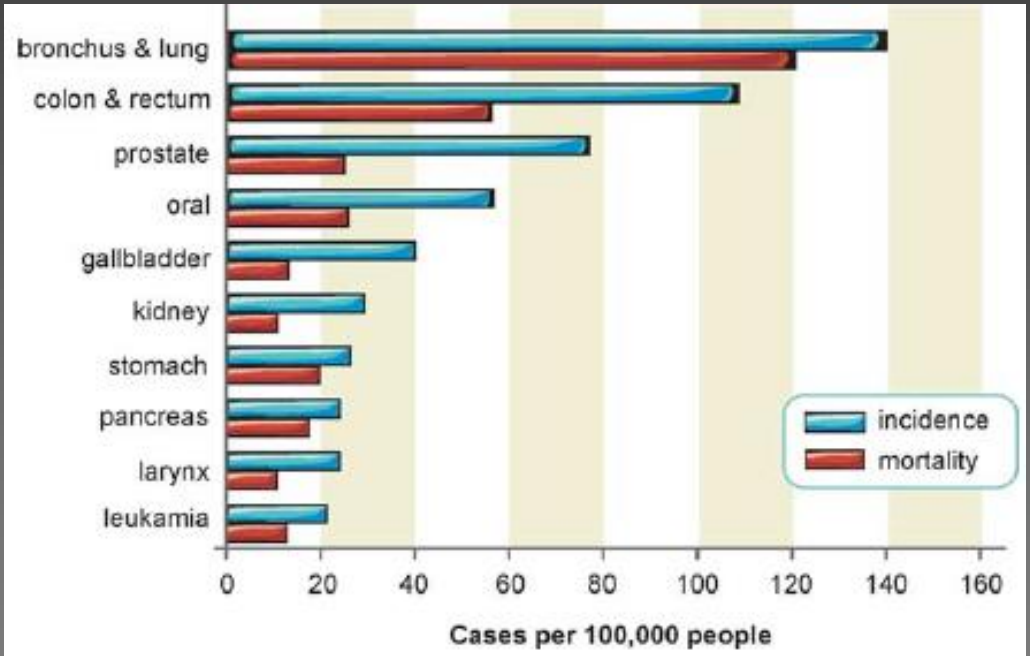
	Tumour site	Incidence by year								
		2008	2009	2010	2011	2012	2013	2014	2015	
	Skin (non-melanoma) (C44)	12011	12070	11319	14375	14079	14629	15983	15370	↑↑↑
1	Lung (C33-C34)	11892	11263	10564	11947	11333	11304	11470	11776	→
2	Colorectal (C18-C21)	10004	9543	9545	10673	10584	10664	10589	10567	↑
3	Breast (C50)	7070	6992	6711	7939	7927	7919	8075	8324	↑↑
4	Prostate (C61)	3790	3645	3635	4352	4028	4648	4576	4501	↑↑
5	Lymphoproliferative (C81-95)	3822	3812	3688	4046	4477	4287	4284	4318	↑
6	Oral cavity (C00-C14)	3950	3653	3599	3956	3742	3759	3765	3700	↓
7	Bladder (C67)	3064	2873	2789	3182	3315	3300	3518	3427	↑↑
8	Pancreas (C25)	2571	2396	2324	2260	2546	2738	2693	2885	↑
9	Kidney (C64-C66 és C68)	2492	2399	2402	2735	2728	2814	2831	2735	↑
10	Stomach (C16)	2672	2442	2243	2559	2437	2433	2260	2361	↓
	ALL :	84144	80745	78014	90879	89993	91089	92166	93043	↑
	ALL (wo C44):	72136	68676	66666	76504	75914	76460	76183	77673	

Cancer mortality in Hungary (2008-2015) (male & female)

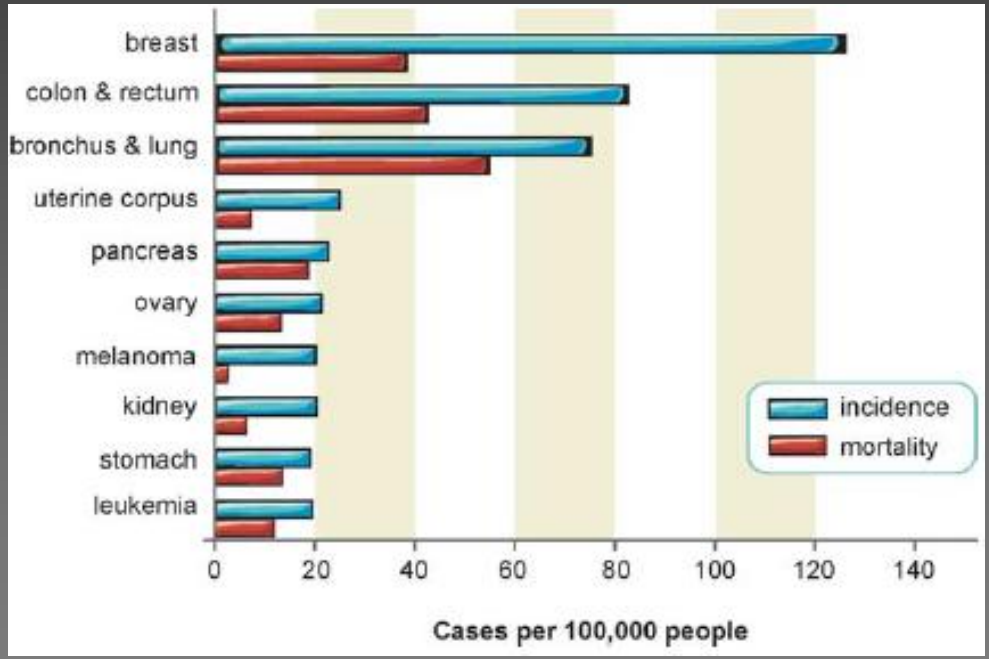
	Tumour site	Mortality by year								
		2008	2009	2010	2011	2012	2013	2014	2015	
1	Lung (C33-C34)	8330	8453	8648	8533	8896	8591	8733	8753	↑
2	Colorectal (C18-C21)	4753	4949	4965	5054	5084	5017	5050	5008	→
3	Breast (C50)	2141	2183	2040	2159	2123	2194	2133	2250	→
4	Pancreas (C25)	1794	1837	1848	1850	2003	1976	1999	1978	↑
6	Lymphoproliferative (C81-95)	1732	1665	1725	1734	1688	1700	1630	1791	→
5	Stomach (C16)	1725	1824	1626	1701	1732	1619	1602	1500	↓
7	Oral cavity (C00-14)	1651	1521	1524	1494	1536	1431	1460	1472	↓
8	Prostate (C61)	1186	1193	1209	1198	1125	1211	1280	1258	→
9	Bladder (C67)	831	831	904	923	983	899	906	959	↑
10	Kidney (C64-C66 és C68)	712	709	829	849	784	835	830	775	→
	ALL:	32111	32536	32460	33274	33224	32748	32748	33121	→

Incidence and mortality of the 10 most common types of cancer in Hungary

Males



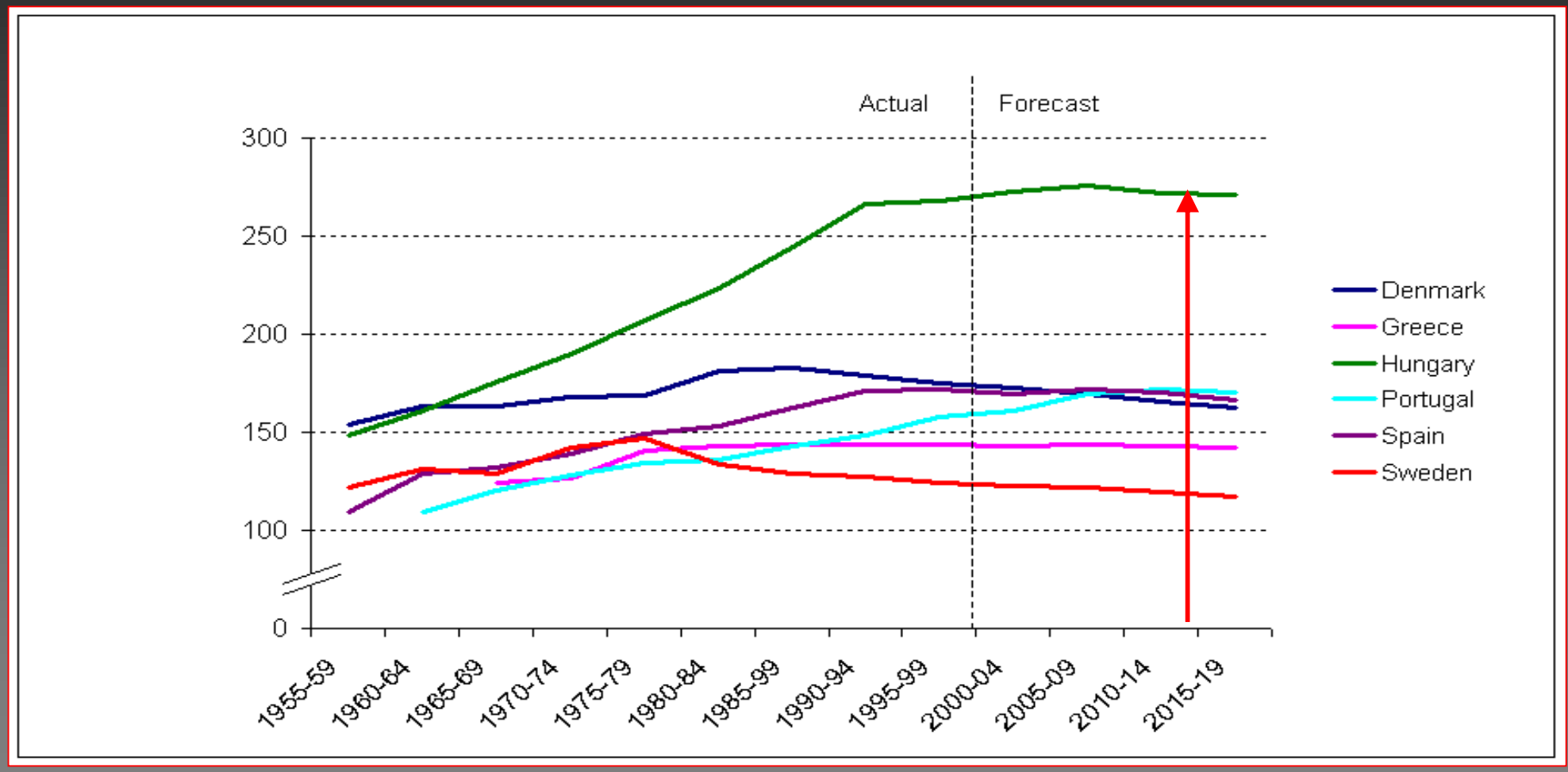
Females



Standardized cancer death rate in EU-28 member states

Country	Standardised death rate (per 100,000 people)			
	Total	Men	Women	Age less than 65
EU-28	**251.5**	**349.1**	**200.6**	**79.2**
Hungary	348.1 (1st)	478.7 (1st)	266.5 (1st)	140.4 (1st)
Croatia	336.4 (2nd)	474.3 (3rd)	247.0 (4th)	107.8 (3rd)
Slovakia	324.1 (3rd)	463.5 (5th)	239.0 (5th)	103.7 (5th)
Denmark	300.6 (4th)	363.1 (11th)	258.3 (2nd)	76.1 (14th)
Slovenia	299.9 (5th)	424.4 (7th)	223.7 (8th)	84.3 (10th)
Estonia	299.4 (6th)	456.7 (4th)	217.8 (11th)	88.3 (9th)
Latvia	299.3 (7th)	476.9 (2nd)	212.0 (12th)	105.2 (4th)
Poland	292.3 (8th)	405.9 (8th)	222.0 (9th)	100.7 (8th)
Ireland	288.3 (9th)	344.5 (16th)	249.1 (3rd)	69.5 (21th)
Czech Republic	284.6 (10th)	382.4 (9th)	219.8 (10th)	82.9 (11th)
The Netherlands	282.2 (11th)	356.5 (12th)	232.7 (7th)	75.3 (16th)
UK	278.4 (12th)	341.1 (17th)	234.7 (6th)	68.7 (22th)
Lithuania	276.2 (13th)	441.4 (6th)	188.8 (19th)	101.9 (7th)
Romania	273.2 (14th)	381.8 (10th)	194.3 (17th)	118.5 (2nd)
Luxembourg	260.7 (15th)	356.5 (13th)	194.0 (18th)	62.6 (25th)
Germany	253.2 (16th)	328.4 (23th)	202.1 (15th)	73.1 (17th)
Belgium	252.6 (17th)	333.9 (20th)	195.9 (16th)	72.2 (19th)
Austria	249.3 (18th)	320.7 (24th)	202.4 (13th)	72.3 (18th)
Greece	249.3 (18th)	344.7 (15th)	173.5 (25th)	75.7 (15th)
Italy	246.6 (20th)	332.0 (22th)	187.3 (20th)	65.3 (23th)
France	245.4 (21th)	339.9 (18th)	178.3 (22th)	80.5 (12th)
Bulgaria	242.4 (22th)	332.8 (21th)	178.7 (21th)	103.2 (6th)
Portugal	242.1 (23th)	350.3 (14th)	166.7 (26th)	79.3 (13th)
Sweden	234.8 (24th)	282.4 (27th)	203.3 (14th)	54.2 (26th)
Malta	233.5 (25th)	310.0 (25th)	177.4 (24th)	64.8 (24th)
Spain	232.7 (26th)	337.0 (19th)	155.9 (27th)	71.5 (20th)
Finland	218.6 (27th)	283.5 (26th)	178.3 (22th)	53.0 (28th)
Cyprus	201.0 (28th)	275.3 (28th)	140.8 (28th)	53.1 (27th)

Cancer mortality for male population in Europe 1955-2019



Definition of National Cancer Control Program (NCCP):

A national cancer control program is a public health program designed to reduce the incidence and mortality of cancer and improve the quality of life of cancer patients in a particular country or state, through the implementation of evidence-based strategies for prevention, early detection, treatment, and palliation, making the best use of available resources.

Hungarian NCCP (1993-2001-2006-2018)

Content (WHO recommendation):

- primary prevention
- secondary prevention (screening)
- early diagnosis
- therapy
- rehabilitation
- palliation – hospice
- education
- PR activity
- participants
- national oncological structure
- indicators, monitoring

Risk-Disease-Prevention –

Primary and secondary prevention opportunities

Primary prevention	
Lifestyle	– Smoking – Drinking alcohol – Eating habits – Personal hygiene
Environmental pollution	– Water – Pesticides – Fuels – Soil
Vaccination	– HBV vaccination – HPV vaccination
Secondary prevention	
Organised screening (secondary prevention)	– Cervical cancer – Breast cancer – Colorectal cancer

European Code against Cancer – 12 ways to reduce cancer risk

Primary prevention

1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet: Eat plenty of vegetables and fruits, high-fibre foods. Avoid high-calorie foods (foods high in sugar or fat) and sugary drinks. Avoid processed meat; limit red meat and salt consumption.
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is best for cancer prevention.
7. Avoid too much sun, be careful with sunburn. Use sun protection. Protect children from strong sunlight!
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions!
9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
10. For women: Breastfeeding reduces cancer risk for the mother. If you can, breastfeed your baby. Menopausal hormone replacement therapy increases the risk of certain cancers. Limit the use of hormone replacement therapy.
11. Ensure your children take part in vaccination programmes for: Hepatitis B (for newborns), Human papillomavirus (HPV) (for girls).

Secondary prevention

12. Take part in organised cancer screening programmes for: bowel cancer (men and women); breast cancer (women); cervical cancer (women).

Primary prevention

Elimination and minimalisation of carcinogenic factors

Smoking: **lung,** oral cavity, laryngeal, oesophageal, stomach, bladder, cervix

- legislation – new law against smoking (2012)
- public health program

Obesity: esophageal, colorectal, breast, endometrium, kidney

- diet: new tax – „chips tax" (2012)
- increasing tax on alcohol & tobacco (2013, 2015, 2016, 2018)

Physical activities: public health program – primary schools involved (2012-)

Occupational – environmental injuries

- physical: ionizing irradiation, solar irradiation
- chemical: several hundreds
- biological:
  - HPV – vaccination (supported by the government; 2014-)

Early detection and screening

Screening: in symptom- and complaint-free risk groups

Early diagnosis: patients with symptoms

Early detection:

- Possibility of an effective treatment
- Reality of effective treatment: breast, cervix, oral cavity, larynx, colorectal, prostate, skin

Screening:

- if effectiveness proven (specificity, sensitivity)
- if conditions provided (method, staff, equipment)
- if the target population can be screened (conditions given)
- if patients identified by screening can be treated/cured (conditions given)
- if financing provided
- localization:
  - breast, cervix, colorectal (US Task Force, European Code Against Cancer)
  - lung, oral cavity, prostate, skin, ovary (under investigation)

Recommendations for early detection and screening of selected cancers

Site of cancer	Early diagnosis	Screening in Hungary
Breast	Yes	Yes
Cervix	Yes	Yes
Colorectal	Yes	Yes (Sept 2018-)
Lung	Yes	Low-dose CT?
Oral cavity/Pharynx/Larynx	Yes	Physical exam.???
Ovary	Yes	CA-125 + TVUS???
Prostate	Yes	PSA + RDE???
Oesophagus	Yes	No
Stomach	Yes	No
Skin melanoma	Yes	No
Other skin cancers	Yes	No
Bladder	Yes	No
Retinoblastoma	Yes	No
Testis	Yes	No

European Code against Cancer, 4th Edition: Cancer screening☆

Cervical cancer screening:

- Either cytology (Pap) testing or human papillomavirus (HPV).
- If cytology is used for screening, women starting at age 25–30 years and from then on, every 3 or 5 years.
- If HPV testing is used for screening, women starting at age 35 years (usually not before age 30 years) and from then on, every 5 years.

Irrespective of the test used, women continue participating in screening until the age of 60 or 65 years, and continue beyond this age unless the most recent test results are normal.

Breast cancer screening:

- women starting at age 50 years and not before age of 40 years,
- and from then on, every 2 years until age 70–75 years.

Colorectal cancer screening:

- men and women starting at age 50–60 years,
- and from then on, every 2 years if the screening test is the guaiac-based faecal occult blood test (gFOBT) or the fecal immunochemical test (FIT),
- or every 10 years or more if the screening test is flexible sigmoidoscopy (FS) or colonoscopy (TC).

Most programs continue sending invitations to screening up to age 70–75 years.

Secondary prevention - Screening

Cervix :

- cytology (Kellner, NIO, 1950-)
- cytological network (Kellner, Döbrössy, NIO, 1960-)
- Cytological cervical screening (Döbrössy, Bodó, NIO, 1970-)
- Public Health Program (Kertai – 1994, 2001, 2002)

Breast:

- HNCCP (Kásler, NIO, 1993)
- Public Health Program, model screening (Kertai – 1994, 2001, 2002)
- Nationwide mammography screening program (2002-)
- Biannual mammography screening for women ageing 45 to 65 years

Colorectal:

- HNCCP (Kásler, NIO, 1993)
- Public Health Program (Kertai – 1994, 2001, 2002)
- Model Screenings
- Debate on methodology (occult bleeding vs colonoscopy)
- Occult bleeding fecal test will be implemented in 2018 for men and women ageing 50 to 70 years

Hungarian population based mammography screening – 3rd. screening cycle (2006-2007)

- Invited: 925.036
- Participated: 428.151
  - Participation rate: 46.3%
- Recalled (suspicious): 23.477 5.5%
- Returned: 21.743
  - Appearance rate: 92.6%
- Operated: 1.503
  - Bening: 379
  - Malignant: 1.124 74.8%
    - DCIS: 131 11.7%
    - < 15 mm: 545 48.5%

Boncz I. et al: Magyar Onkológia 2013;57:140-146.

Strategy for colorectal cancer screening

(1) Detection of occult colorectal bleeding

(2) Colonoscopy -

- tumour localisation
- biopsy
- polypectomy

Basic principles of complex oncotherapy – 3 methods for the managemant of malignant tumours

- Surgical treatment
- Radiotherapy
- Drug treatments
  - Chemotherapy
  - Hormonal therapy
  - Targeted biological therapy
  - Immunotherapy

Local/locoregional treatments

Systemic treatments

Multidisciplinary treatment of malignant tumours

- Surgery (S)
- Radiotherapy (RT)
- Systemic therapy
  - Chemo- , hormone-, immuno-therapy + targeted therapies

- Combined (multidisciplinary) management:
  - S + postop. RT
  - S + concomittant radio-chemotherapy (RCT)
  - Primary RCT
  - Preop. RT + S
  - Radio-biotherapy
  - Radio-immunotherapy

Anticancer therapies – Intention to treat

- Curative treatments
  - Goal: Complete eradication of all tumour cells
  - Intented to lead to the complete recovery of the patient

- Palliative treatments
  - Goals:
    - Mitigation of life-threatening conditions/symptoms caused by the tumor
    - Temporary improvement of quality of life
    - Prolongation of life and symptom-free interval

Types of surgical oncology interventions

- Prophylactic
- Diagnostic
- Therapeutic
  - Curative
  - Palliative

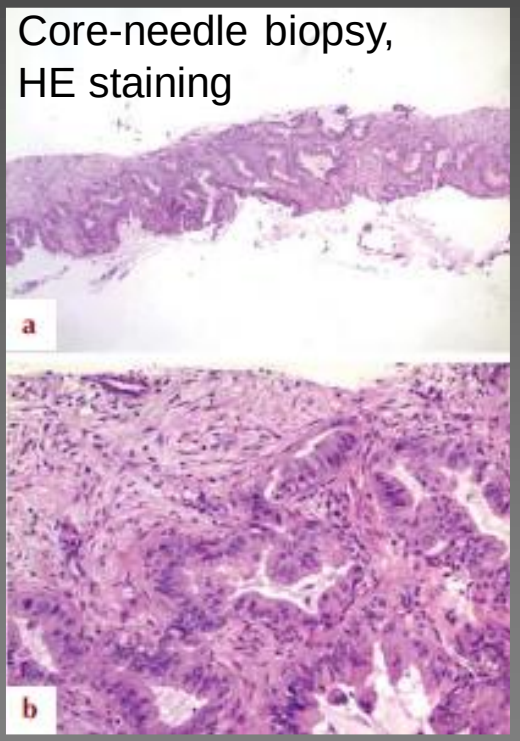
Profilactic surgical oncology:

- Endoscopic removal of colorectal polyps
- Prophylactic segmental colectomy (hereditary colon ca.)
- Prophylactic ovariectomy/mastectomy (BRCA mutation carriers)

Diagnostic surgical interventions

- Aspiration cytology (cervical smear sample or fine-needle aspiration)
- Core-needle biopsy
- Incisional biopsy
- Excisional biopsy

Goal: Cytological/Histological diagnosis



Therapeutic surgical interventions

- Curative operations = radical removal
  - Operability – refers to the patient
  - Resectability – refers to the tumour
  - Radicality = Clear surgical margins = R0 resection!
  - Reconstructive/oncoplastic surgery
  - Organ/function preserving surgery
  - Quality of Life (QoL)
  - Minimal invasive surgery – laparoscopic surgery, VATS
  - Robotic surgery (Da-Vinci robot)

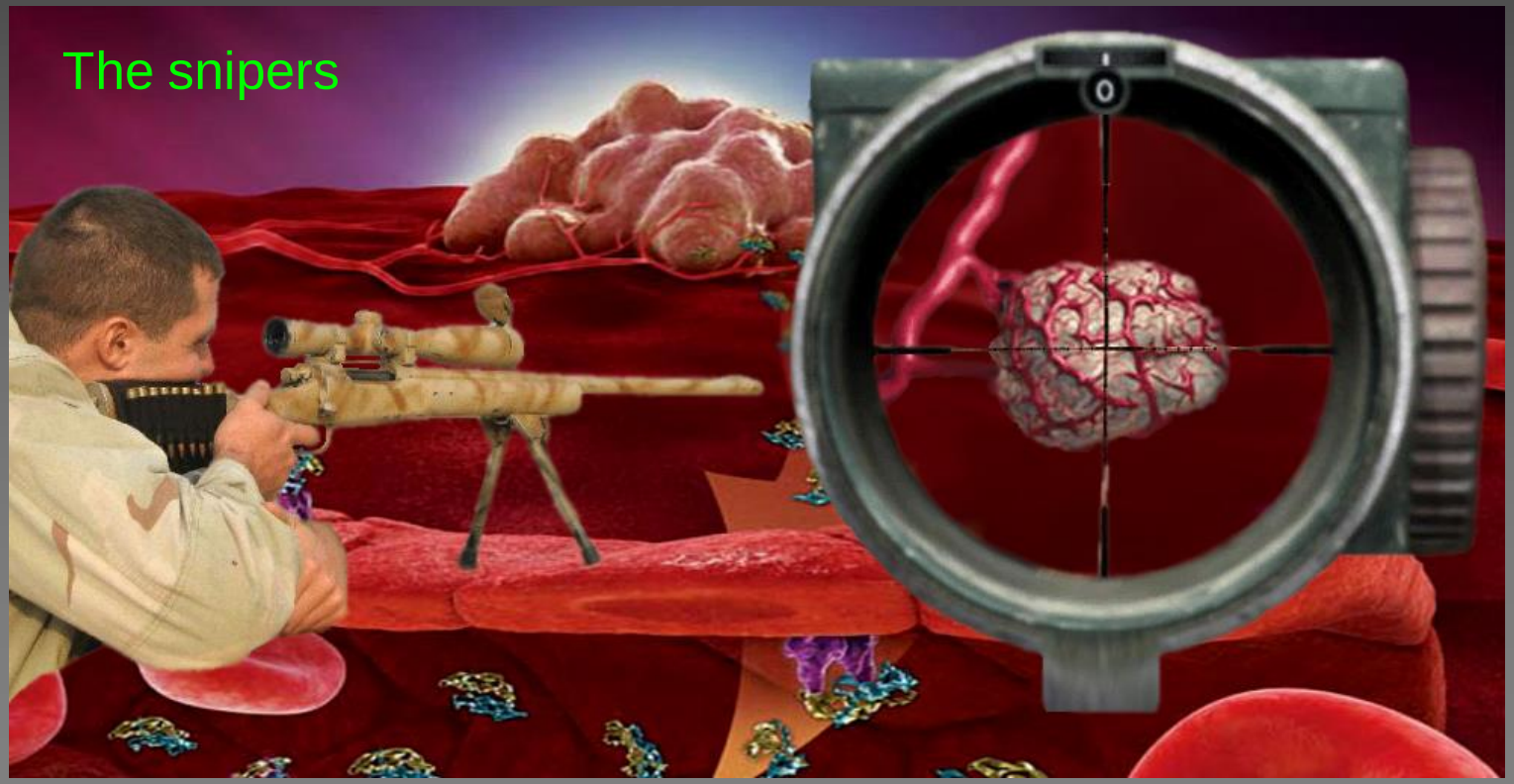
- Palliative operations
- - Stomas, stents, ligation of a. hypogastrica, tracheotomia, vertebral fixation etc.

Chemotherapy

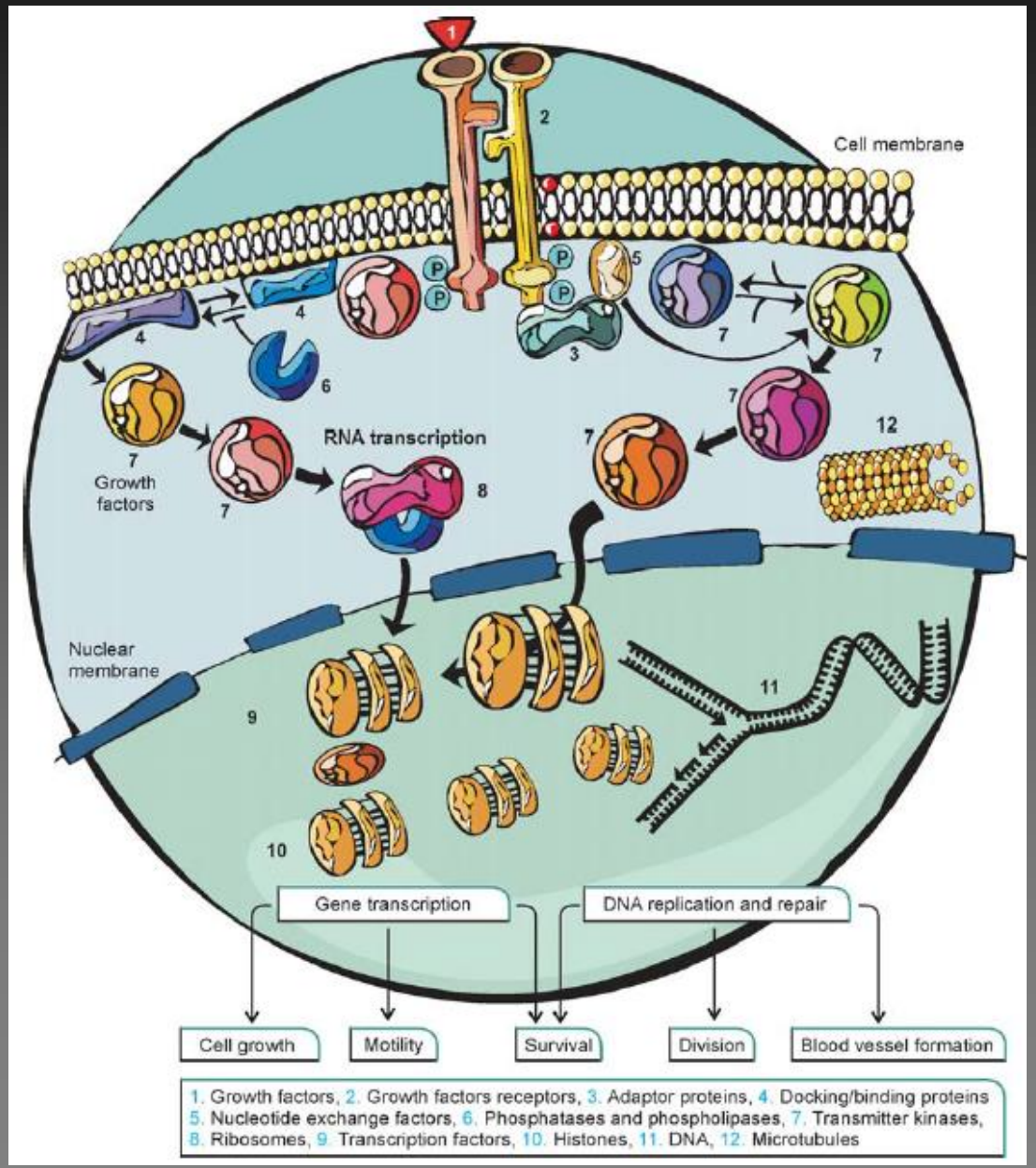
- Chemotherapy = Use of cytotoxic/cytostatic agents
- ”Selective” killing of all rapidly dividing cells (tumour + healthy tissues)
- Systemic treatments = general effect on the whole organism
- Specific side-effects (hair-loss, nausea/vomiting, deterioration of blood count, oral mucositis etc.)

Targeted biological therapies

- Specifically affect tumour cells with cell surface receptors of a given type of tumour (and only that type)
- Specific killing of targeted tumour cells
- Milder side effects



Cell division and metabolism control – Potential targets for oncotherapy



Immunotherapy

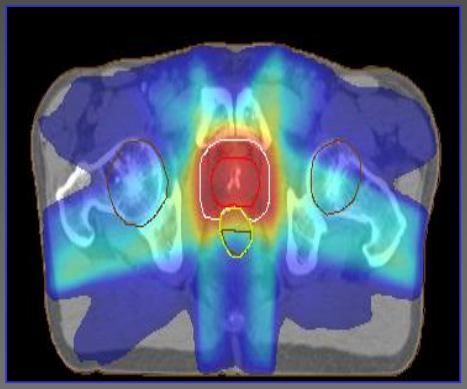
- Intended to enhance the natural, physiological anticancer immune response mechanisms of the body, and turn these against the tumour
- At immunotherapy check-points the administered drugs inhibit the immunosuppressive effects of tumours

Immunological characteristics of tumours, immunotherapy targets, and the immunological effects of radiotherapy

Immunological characteristics of tumours	Immunotherapy checkpoints	Immunological effects of radiotherapy
Decreasing tumour antigen expression		Inducing neoantigen production from necrotic tumour cells
Decreasing tumour antigen presentation (decreasing the expression of MHC class I and II molecules)		Stimulating tumour antigen presentation (increasing MHC class I expression)
Immunosuppressive cytokine (TGFβ) secretion		Releasing cytokines (IFNγ) to promote T-cell infiltration
Immunosuppressive cell (CTLA-4) secretion	Anti CTLA-4	
PD-L1 overexpression (T-cell inhibition)	Anti PD-1, Anti PD-L1	

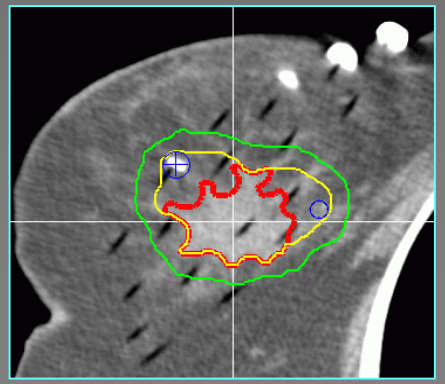
Radiotherapy

- Clinical modality dealing with the use of ionizing radiation in the treatment of patients with malignant tumours.
- Aim: To deliver precisely measured dose of irradiation to a defined tumour volume with as minimal damage as possible to the surrounding healthy tissues, resulting eradication of the tumour.
- Selective killing of malignant cells

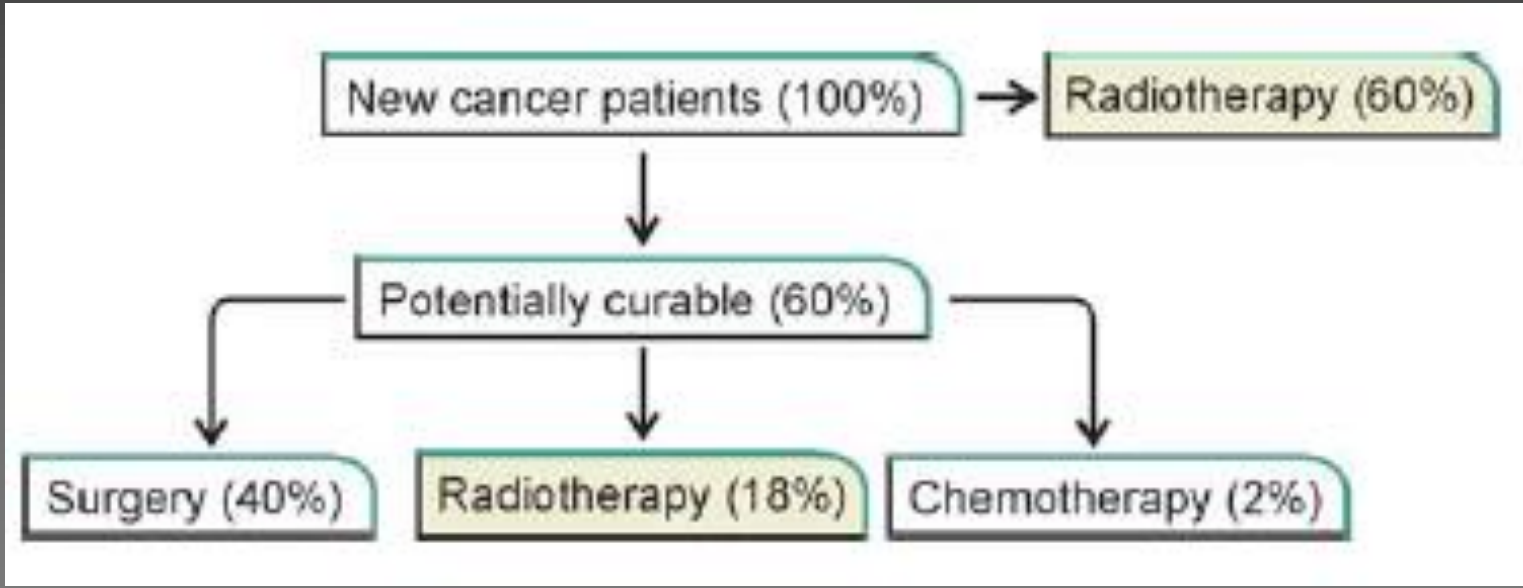


- Teletherapy = external beam irradiation

- Brachytherapy = irradiation with sealed radioactive sources placed close to or in contact with the tumour.



The role of radiotherapy as an anticancer treatment modality



Intention of radiation therapy

- Intention to treat:
  - Curative (total dose: 50-80 Gy)
  - Palliative (total dose: 20-60 Gy)

- Preoperative RT (down-staging & down-sizeing, devitalisation of tumour cells before surgery → organ preservation surgery)
- Postoperative RT (eradication of microscopic residual tumour cells)
- Definitive or primary RT

- RT alone
- Combined RCT (head & neck, cervical, bladder, anal canal, rectal, lung)
- Combined radio-biotherapy (head & neck: cetuximab + RT)
- Combined radio-immunotherapy (investigational)

Thank you for your kind attention!