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 **FRAUEN  
GESUNDHEITS  
ZENTRUM**

Onkologie:  
Welche Geschlechtsunterschiede  
sind wissenschaftlich dokumentiert?  
Welche Auswirkungen hat das auf  
unsere PatientInnen?

Univ.-Prof. Dr. Margarethe  
Hochleitner

 MEDIZINISCHE UNIVERSITÄT  
INNSBRUCK

**onkologie**


Ringvorlesung **GENDER MEDIZIN**  
Leitung: ao.Univ.-Prof.<sup>in</sup> Dr.<sup>in</sup> Margarethe Hochleitner

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Gibt es Geschlechtsunterschiede  
bei Krebserkrankungen?

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**Structure**


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1. Gender differences in Prävention
2. Gender differences in Epidemiologie
3. Gender differences in Symptomen und comorbidities
4. Gender difference in Pharmakokinetics
5. Gender differences in der Prognose
6. Gender differences in der Grundlagenforschung

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**GENDER DIFFERENCES IN DER  
PRÄVENTION**


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**CANCER PREVENTION**


**MEDLINE: MAY 3, 2011**

CANCER PREVENTION	84.026
BREAST CANCER PREVENTION	21.351
UTERUS CANCER PREVENTION	9.673
PROSTATE CANCER PREVENTION	7.471
OVARY CANCER PREVENTION	3.681
<b>CANCER AND GENDER MEDICINE</b>	<b>276</b>


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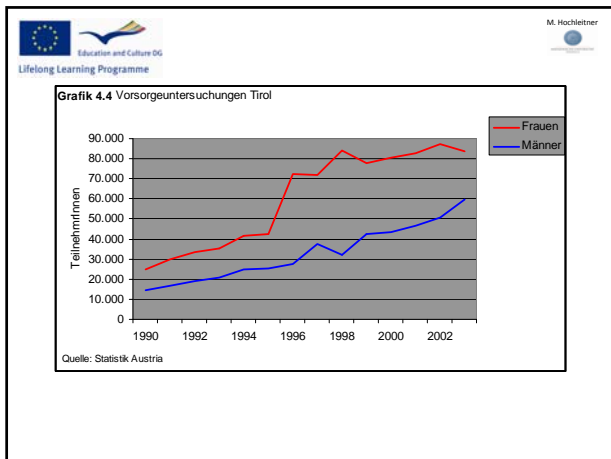
**Sex + Gender Differences  
in der Prävention**

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- Präventions**bedarf**? → Frauen/Männer?
- Präventions**empfehlungen** → Frauen/Männer?



Bilder: www.clipartconnection.com



**Früherkennung Prostatakrebs**

Gliederungsmerkmal	"Würde bei Ihnen jemals eine Vorsorgeuntersuchung zur Früherkennung von Prostatakrebs mittels PSA-Test durchgeführt?"		"Wenn wurde bei Ihnen das letzte Mal ein PSA-Test durchgeführt?"	
	in %		in %	
	Ja	Nein	Innerehalb der letzten 12 Monate	Nicht innerhalb der letzten 3 Jahre
<b>Integriert</b>	94,9	43,4	1.076,8	96,9
<b>Alter in vollständigen Jahren</b>				
40 bis unter 45	45,1	54,9	306,4	32,9
45 bis unter 50	28,0	71,9	190,0	48,4
50 bis unter 55	43,3	56,7	328,9	54,4
55 bis unter 60	53,5	46,5	442,0	62,4
60 und mehr	65,9	34,1	624,6	76,5
<b>60 und mehr</b>				
60 bis unter 65	69,4	30,6	524,4	65,4
65 bis unter 70	75,4	24,6	501,1	65,1
70 bis unter 75	88,6	11,4	401,1	76,9
75 und mehr	88,4	11,6	348,9	72,2
<b>Staatsangehörigkeit</b>				
Österreich	94,5	43,5	1.021,1	94,7
Ausland	32,6	67,4	30,8	28,1
<b>Geburtsland</b>				
Österreich	94,5	43,5	956,6	87,1
Ausland	32,6	67,4	114,2	27,8
<b>Bundesland</b>				
Burgenland	72,1	27,9	41,8	33,3
Kärnten	60,0	40,0	48,9	39,6
Niederösterreich	54,4	45,6	212,8	36,1
Oberösterreich	65,7	34,3	182,9	54,4
Salzburg	65,0	35,0	48,6	33,0
Steiermark	62,3	37,7	112,9	52,9
Tirol	82,0	18,0	102,0	31,0
Vorarlberg	84,0	16,0	44,9	40,0
Wien	91,3	8,7	193,6	58,5

**Krebsinzidenzen der Prostata und des äußeren Genitales (anspruchsberechtigt ab 45 Jahre, jährliche Untersuchung)**

Jahr	Prostata	äußeres Genital
1989	517.280	81.372
1990	508.858	82.214
2000	508.382	81.441
2001	508.312	80.552
2002	511.899	80.791
2003	518.822	81.818
2004	522.419	81.058
2005	530.710	80.638
2006	544.122	82.829
2007	558.139	82.442
2008	582.274	85.428

**Mammographie**

Gliederungsmerkmal	"Würde bei Ihnen jemals eine Vorsorgeuntersuchung zur Früherkennung von Brustkrebs mittels Mammographie durchgeführt?"		"Wenn wurde bei Ihnen das letzte Mal eine Mammographie durchgeführt?"	
	in %		in %	
	Ja	Nein	Innerehalb der letzten 12 Monate	Nicht innerhalb der letzten 3 Jahre
<b>Integriert</b>	83,9	17,9	1.881,4	41,8
<b>Alter in vollständigen Jahren</b>				
40 bis unter 45	69,9	30,1	1.026,0	42,7
45 bis unter 50	60,0	40,0	273,5	43,8
50 bis unter 55	67,7	32,3	342,3	51,7
55 bis unter 60	80,2	19,8	238,4	47,0
60 und mehr	92,0	8,0	326,6	57,7
<b>60 und mehr</b>				
60 bis unter 65	90,1	9,9	208,9	48,1
65 bis unter 70	88,6	11,4	207,6	44,3
70 bis unter 75	91,0	9,0	138,9	38,2
75 und mehr	95,0	5,0	202,0	33,0
<b>Staatsangehörigkeit</b>				
Österreich	84,1	15,9	1.763,9	41,0
Ausland	68,8	31,2	87,9	50,3
<b>Geburtsland</b>				
Österreich	84,2	15,8	1.623,7	41,4
Ausland	75,3	24,7	238,1	48,2
<b>Bundesland</b>				
Burgenland	83,9	16,1	37,6	42,4
Kärnten	67,1	32,9	128,6	37,1
Niederösterreich	84,4	15,6	385,5	45,3
Oberösterreich	61,8	38,2	301,9	41,1
Salzburg	78,8	21,2	111,2	48,5
Steiermark	86,2	13,8	287,6	43,1
Tirol	82,4	17,6	149,2	42,0
Vorarlberg	86,0	14,0	74,9	33,8
Wien	79,6	20,4	362,5	38,0

**Health Check-up**

**Teilnahme von GKV-Versicherten an Krebsfrüherkennungsuntersuchungen in Baden 1998 - 2008 nach Geschlecht**

Jahr	Krebsfrüherkennungsuntersuchungen			
	Frauen		Männer	
	Anspruchsberechtigt <sup>1)</sup>	teilnehmend <sup>2)</sup>	Anspruchsberechtigt <sup>1)</sup>	teilnehmend <sup>2)</sup>
1998	1.232.714	892.545	53,9	x
1999	1.239.265	874.260	54,4	x
2000	1.228.954	750.025	57,1	x
2001	1.217.749	708.841	58,3	x
2002	1.210.081	711.850	58,8	x
2003	1.212.122	729.428	60,2	x
2004	1.209.832	884.813	73,4	x
2005	1.224.138	883.837	72,3	x
2006	1.226.104	883.737	72,2	x
2007	1.241.418	883.709	71,2	x
2008	1.243.859	886.212	71,3	x

**The best protection is early detection**

Support Pink Ribbon Quick Donate October | Breast Cancer

**PINKRIBBON**

You can find us at [www.pinkribbon.org](http://www.pinkribbon.org) Enter >

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## Awareness

- Herztod ist **männlich besetzt!**



Bild: <http://www.br-online.de/umwelt-gesundheit/thema/herz/index.xml>

- Krebstod + Mammakarzinom ist **weiblich besetzt!**

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## Gender differences in epidemiology

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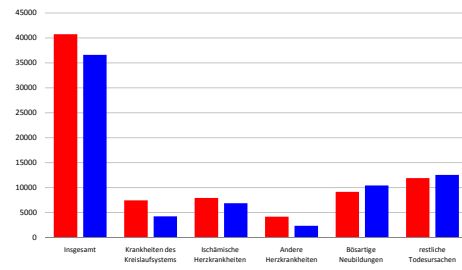
## Causes of Death worldwide

Causes of Death (WHO statistics 2008)	
CVD	30,4%
Cancer	14,1%
Communicable Diseases	27,0%

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## Todesursachen Tirol 2009

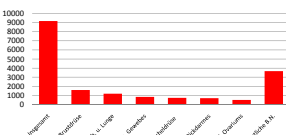


Quelle: Statistik Austria.

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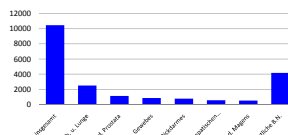
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### Krebstodesursachen FRAUEN Tirol 2009



Gestorbene weiblich 2009 - Bösartige Neubildungen	
Insgesamt	9172
B.N. der Brustdrüse	1659
B.N. d. Kehlk., Luftr., Bronch. u. Lunge	1198
B.N. d. lymphat.- u. hämatopoet. Gewebes	830
B.N. d. Bauchspeicheldrüse	721
B.N. d. Dickdarmes	681
B.N. d. Ovariums	489
restliche B.N.	3872

### Krebstodesursachen MÄNNER Tirol 2009



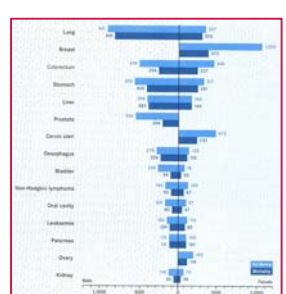
Gestorbene männlich 2009 - Bösartige Neubildungen	
Insgesamt	10469
B.N. d. Luftr., Bronch. u. Lunge	2455
B.N. d. Prostata	1129
B.N. d. lymphat.- u. hämatopoet. Gewebes	848
B.N. d. Dickdarmes	771
B.N. d. Leber u. d. intrahepatischen Gallengänge	554
B.N. d. Magens	517
restliche B.N.	4191

Quelle: Statistik Austria, Todesursachenstatistik.

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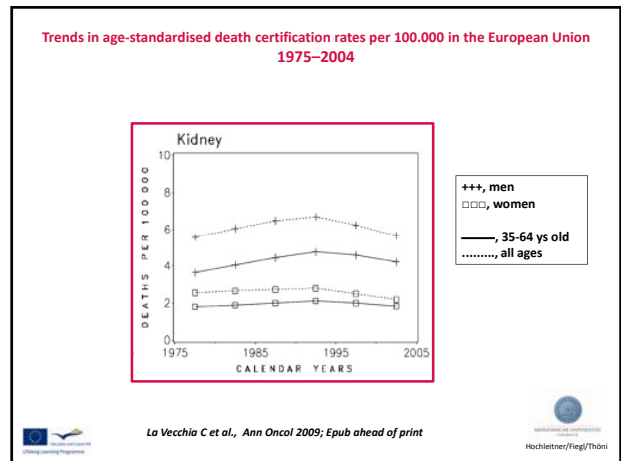
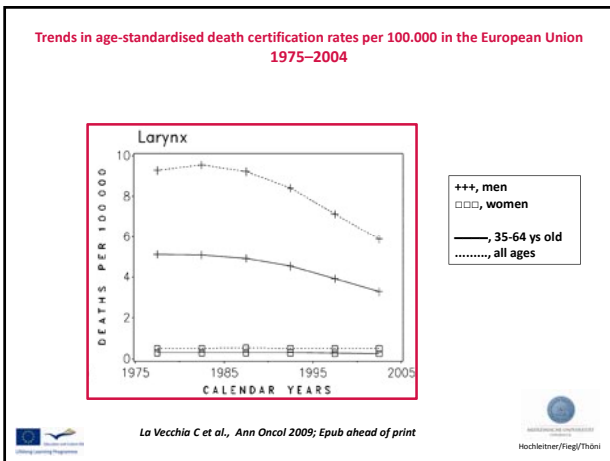
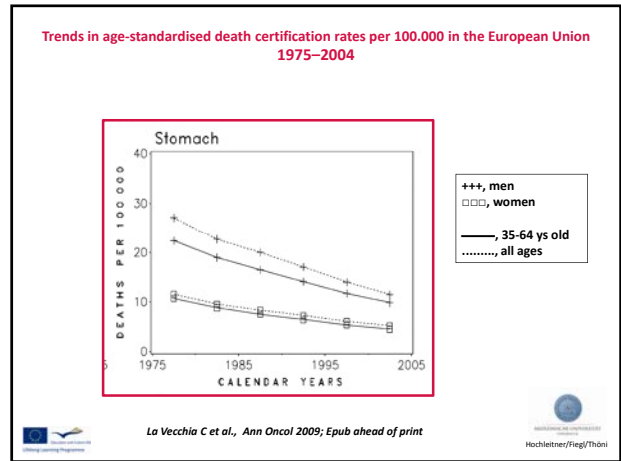
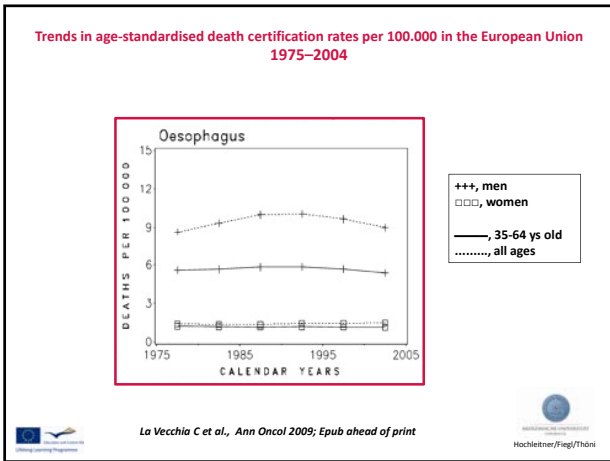
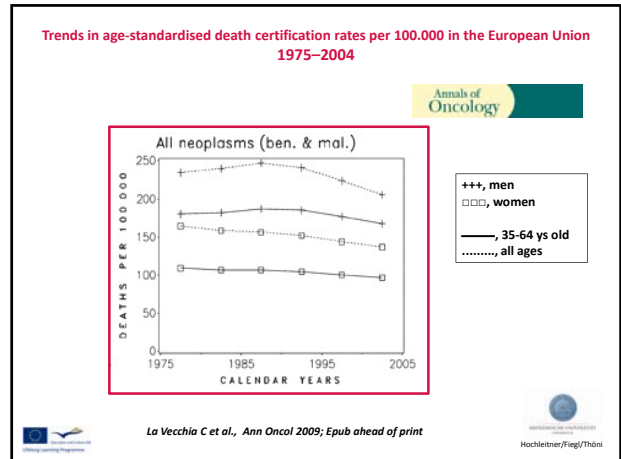
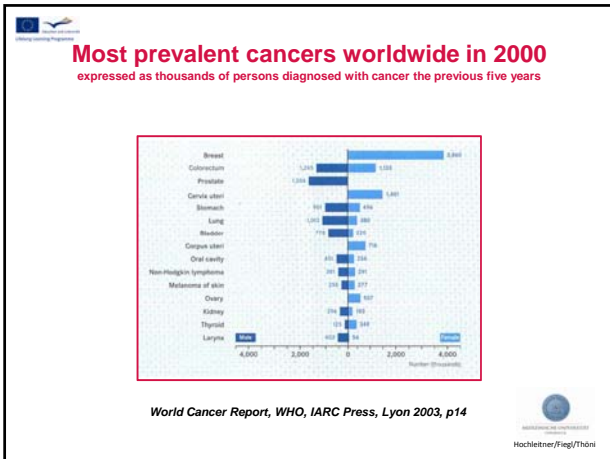
## Incidence and mortality of the most common cancers worldwide

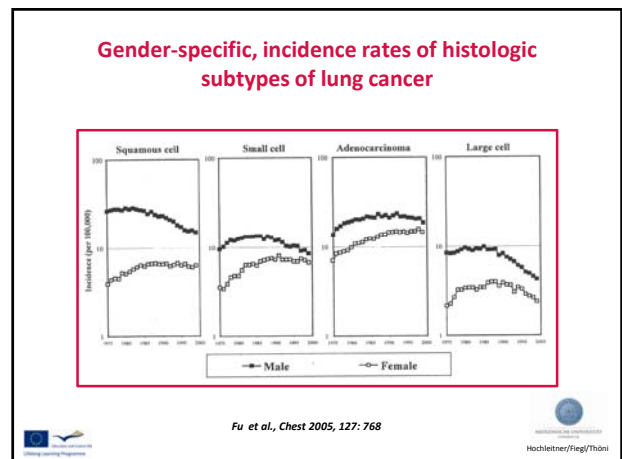
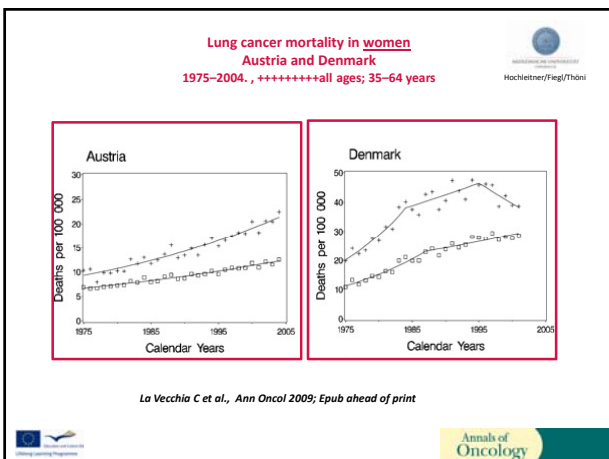
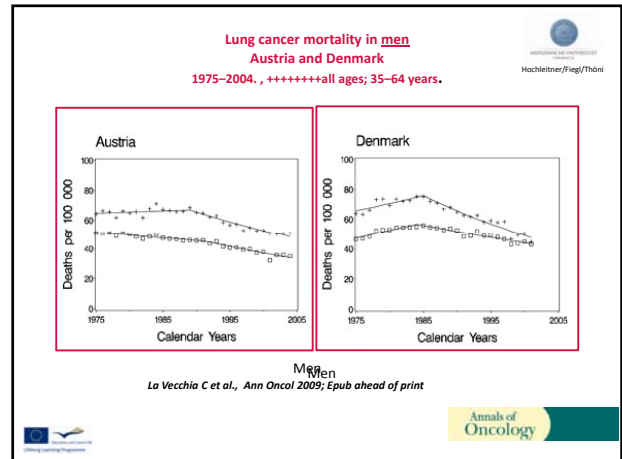
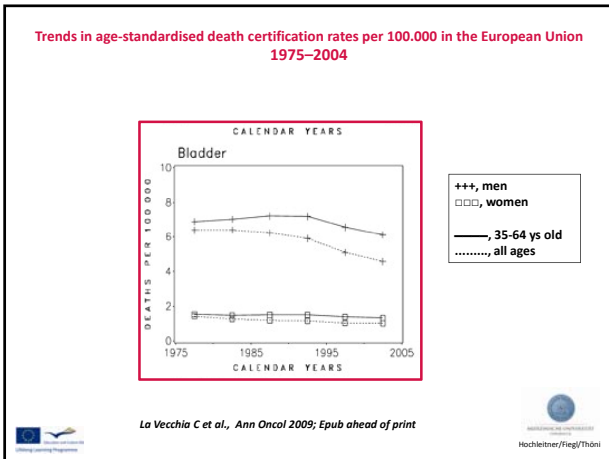
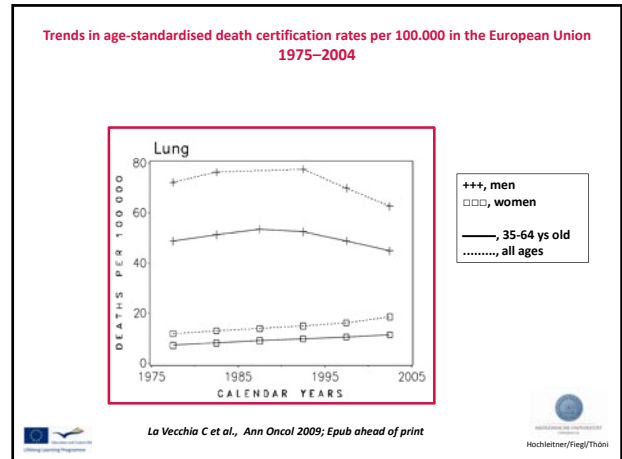
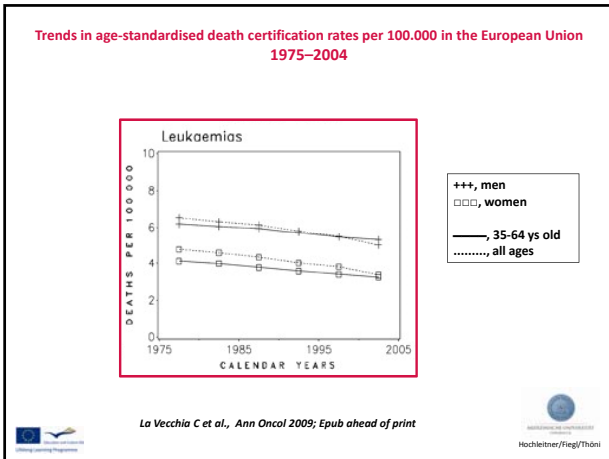


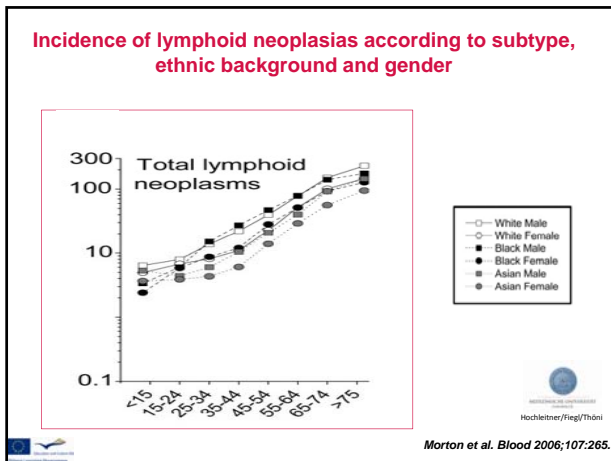
World Cancer Report, WHO, IARC Press, Lyon 2003, p13

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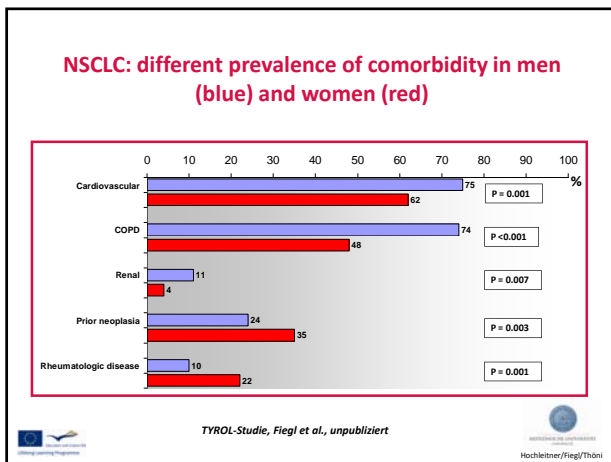






### Gender differences in symptomatology and comorbidities

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### Gender difference in pharmacokinetics

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## Medikamente

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- Geschlechtsunterschiede in Wirkung
- Geschlechtsunterschiede in Testung
- Geschlechtsunterschiede in Verordnung
- Geschlechtsunterschiede in Compliance

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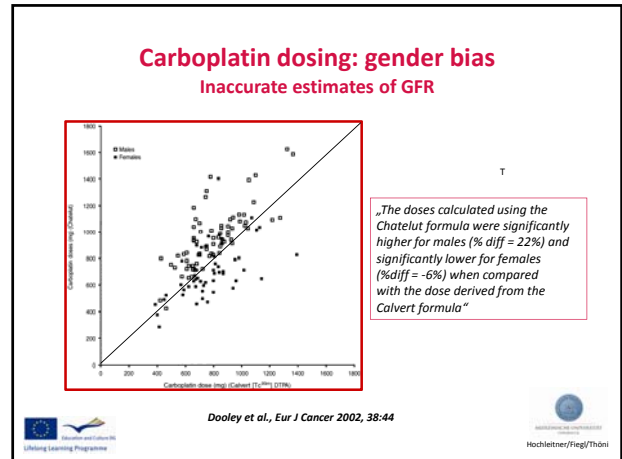
## Medikamente

- Körpergröße, Gewicht
- Fett-, Wasseranteil, Muskelmasse
- Enzymunterschiede: schnellerer Abbau
- Hormonschwankungen – Zyklus, Menopause
- Medikamentenresorption und Ausscheidung

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**Table 1. Gender differences in pharmacokinetics for cytostatics and novel biologic antitumoral drugs**

Substance	Measure	Outcome	Reference
S-FU	S-FU clearance	Lower in women	Milano et al., JCO 1992: 1171
S-FU (contin. infusion)	S-FU clearance	No sex difference	Elionne et al., Eur J Cancer 1996, 34:92
S-FU	Toxicity	Sex and age predictors	Stein et al., Cancer 1995, 75:11
Topotecan	Clearance	Lower in women	Loos, Anticancer Drugs 11: 673
Carboplatin	Dosing based on renal function-dependent formula	Women receive lower doses	Dooly et al., Eur J Cancer 2002, 38:44 (Slides)
Paclitaxel	Elimination capacity	Lower in women	Joergler, Clin Cancer Res 2006, 12:2150 (Slides)
Docetaxel, Paclitaxel, Etoposide, Topotecan	Hemato-toxicity, neutropenia	Increased risk in women	Klotz, Clin Cancer Res 2006, 12:5481
Sunitinib	Clearance	Decreased in women	Houk et al., CCR 2009, 24:97 (Slide)
Erlotinib	Maximum plasma concentration, AUC, terminal elimination half-life	Increased in women	Frohna, J Clin Pharmacol 2006, 46: 282
Oxaliplatin	Clearance	Decreased in women	Bestin, Anticancer Drugs 2003, 14:817
Cisplatin	Clearance	No sex difference	De Jongh, Cancer Chemother Pharmacol 2004, 54: 105-112
Cis/Etoposide	Hemato-toxicity	No sex difference	Mjha, Cancer Chemother Phar 1996, 42:380
Capecitabine metabolites	Clearance	Decreased in women	Gieschke, J Pharmacokinet Pharmacodyn 2002, 29:25
Bevacizumab	Clearance	Decreased in women	Liu et al., Cancer Chemother Pharmacol 2008, 62: 779

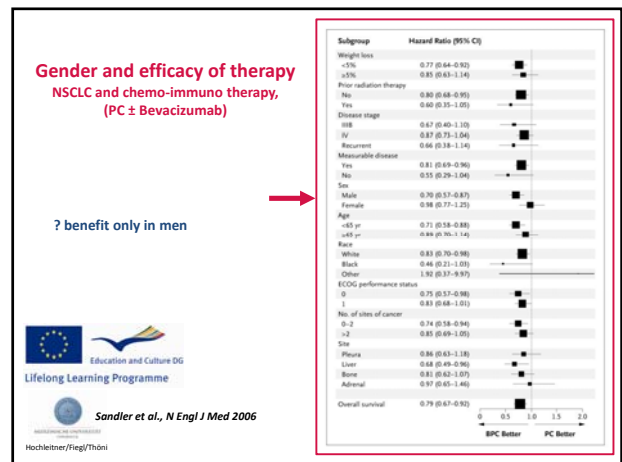


### Biomarkers differentially expressed between males and females with NSCLC

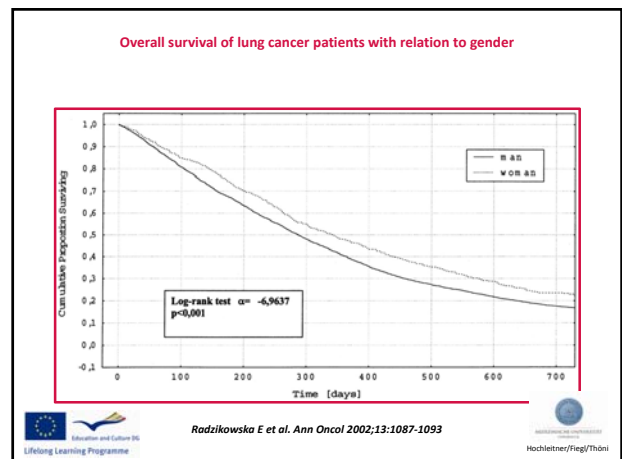
**Table 1. Selection of Biomarkers Differentially Expressed Between Males and Females With NSCLC**

	Lung Cancer in Males	Lung Cancer in Females	Reference
<b>Constitutional genetic differences</b>			
CYP1A1	Lower	Increased expression	19
CYP1B1 null genotype	Less frequent	More frequent	21
CYP1A1 mutation	Less frequent	More frequent	22
CYP1B1 expression	Lower	Higher induce by smoking?	23
Polymorphisms ABCB1	Lower	Higher	29
<b>Molecular markers</b>			
EGFR mutations in codons 12, 13, and 61	Frequent in males with smoking status, predominantly in adenocarcinoma	More common in females with smoking status	40,41
p53 mutations	Less frequent tobacco-related	Tobacco-related p53 mutations more common, higher frequency of non-mutated (G→T)	38,39
EGFR mutations in exons 19 and 21	Less frequent (3-9%)	More frequent (14-23%)	48,49,50
ERCC1	Negative in 52% of males	Negative in 69% of females	66
BRM1	Higher	Lower level	68
BRCA1	Higher	Lower level	71
Bcl-1, Bcl-2, COX-1, Bcl-6, Bcl-11, and Bcl-12	Lower expression	Higher and/or expression	73
VEGFR3	Higher	Lower level	74
Cyclin-B1	Higher	Lower level	75
<b>Transcriptional differences</b>			
HARD10, BPA4T1, SCLY1, BPA4C, GSPY1, GY1	Chromosome Y-linked genes expressed in greater amounts in males	Lower level	97-101
XIST	Very low expression	Gene localized in chromosome X, increased expression in females	95,102,103

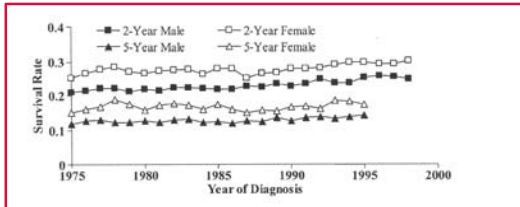
Plancharde et al., Sem Oncol., 36:553 (2009)



### Gender differences in prognosis and cancer treatment outcome



**Gender-specific, relative 2- and 5-year survival rates of patients with lung cancer**



Fu et al., Chest 2005, 127: 768

**Gender differences in basic science**

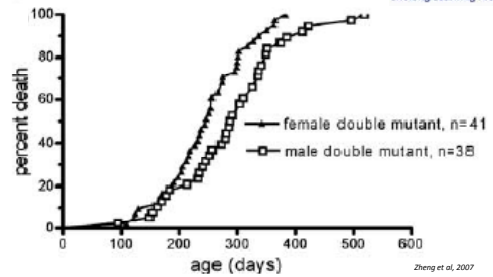
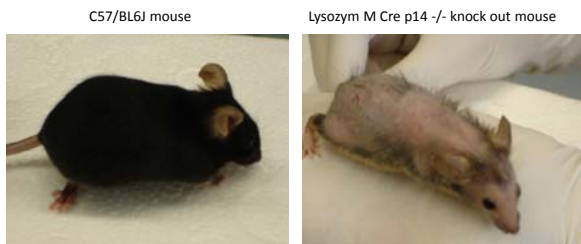


Figure 1: Female mice with adenocarcinoma of the lung die earlier

**Knock out mouse**



© Dr. Nicole Toub, Division of Cell Biology, Biocenter Innsbruck

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Normal mouse = Wild type mouse

Genetic modified mouse  
→ homozygous for the mutation

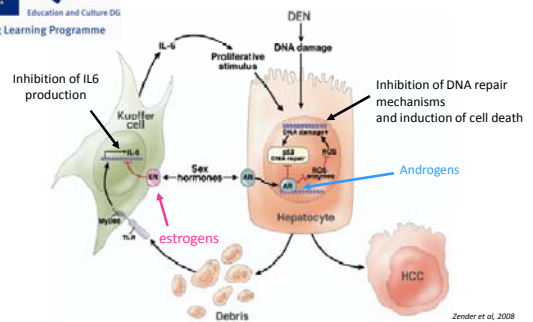


Figure 4: Estrogens protect female mice from liver cancer formation

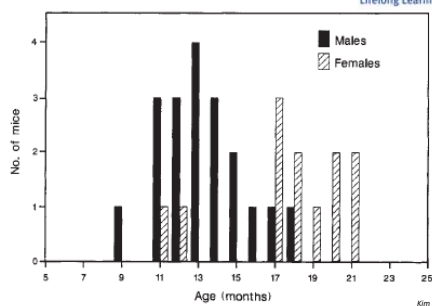


Figure 3: Female mice with hepatic tumors die at later time points



The image is a screenshot of a website page from Charité - Universitätsmedizin Berlin. The page is titled "Institut für Geschlechterforschung in der Medizin" (Institute for Gender Research in Medicine). The header includes the Charité logo and navigation tabs for "INSTITUT", "AKTUELLES", "FORSCHUNG", and "STUDIUM". A sidebar on the left lists various categories: "AKTUELLES", "NEUWACHSEN", "GEMISCHTES", "SYMPOSIUM", "VERANSTÄNDLICHKEITEN", and "STELLANGEBOUDE". The main content area features a red-bordered box with the title "Summer School 2011 on 'Gender Medicine', Eleonora d'Arborea". Below this, the text reads: "Invitation - Summer School on 'Gender Medicine', Eleonora d'Arborea, Sept. 19th - 22nd, 2011 in Sassari, Italy". The text continues: "We cordially invite you, your colleagues, and students to participate in this Summer School on Gender Medicine. We would be greatly pleased to welcome you in Sassari for this important transpirent. The Centre for Biotechnology Development and Biomedical Research at the University of Sassari, Italy is proud to announce the second Summer School on Gender Medicine. This will be organised with all partners of the EUGDM (European curriculum Gender in Medicine) project. These partners include member universities in Berlin, Budapest, Gronoob, Maastricht, Nijmegen and Stockholm. Registration will open on February 1st, 2011 and will close last on June 1st, 2011. For more information please contact us by e-mail to the address: [egdm Summerschool@uni.sassari.it](mailto:egdm Summerschool@uni.sassari.it) or by visiting the EUGDM project website <http://egdm.charite.de/en>. Best Regards, Flavia Franciosi. Veranstalter: European Curriculum in Gender Medicine (EUGDM)". At the bottom of the page, there is a large blue banner that says "DANKE FÜR IHR INTERESSE" (Thank you for your interest), accompanied by the logos of the Charité and the European Union.