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

Univ.-Prof. Dr. Margarethe Hochleitner

Gibt es Geschlechtsunterschiede bei Krebserkrankungen?

Univ.-Prof.in Dr.in Margarethe Hochleitner

Structure

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

GENDER DIFFERENCES IN DER PRÄVENTION

CANCER PREVENTION

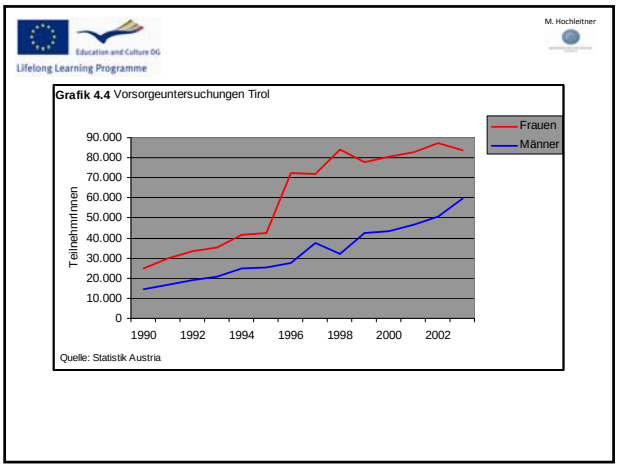
MEDLINE: MAY 3, 2011

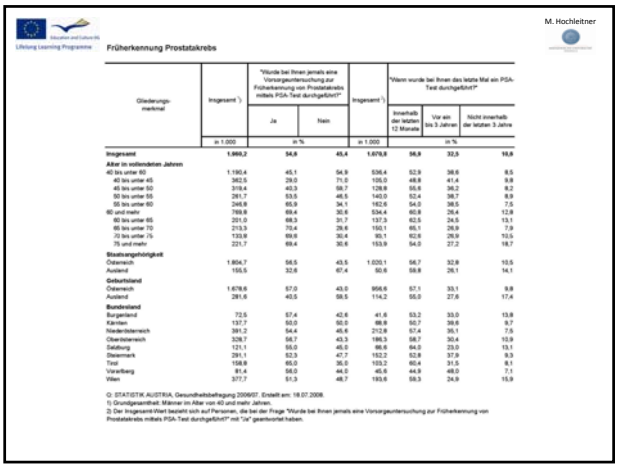
CANCER PREVENTION	84.026
BREAST CANCER PREVENTION	21.351
UTERUS CANCER PREVENTION	9.673
PROSTATE CANCER PREVENTION	7.471
OVARY CANCER PREVENTION	3.681
CANCER AND GENDER MEDICINE	276

Sex + Gender Differences in der Prävention

- Präventionsbedarf? → Frauen/Männer?
- Präventionsempfehlungen → Frauen/Männer?

Bilder: www.clipartconnection.com


Lifelong Learning Programme
M. Hochleitner
Grafik 4.4 Vorsorgeuntersuchungen Tirol
Frauen
Männer
Teilnehmerinnen
90.000
80.000
70.000
60.000
50.000
40.000
30.000
20.000
10.000
0
1990
1992
1994
1996
1998
2000
2002
Quelle: Statistik Austria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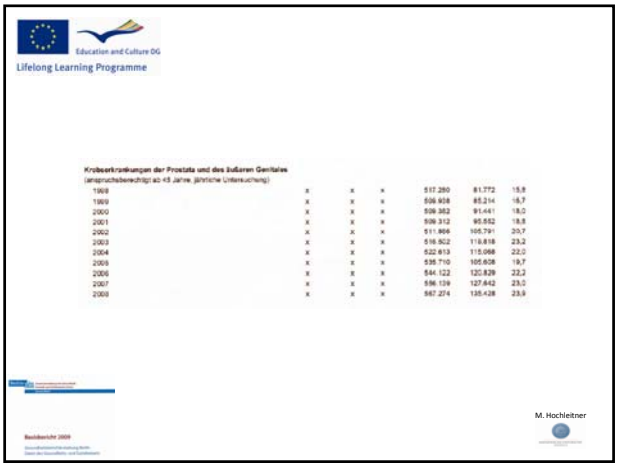
Früherkennung Prostatakrebs


Education and Culture DG
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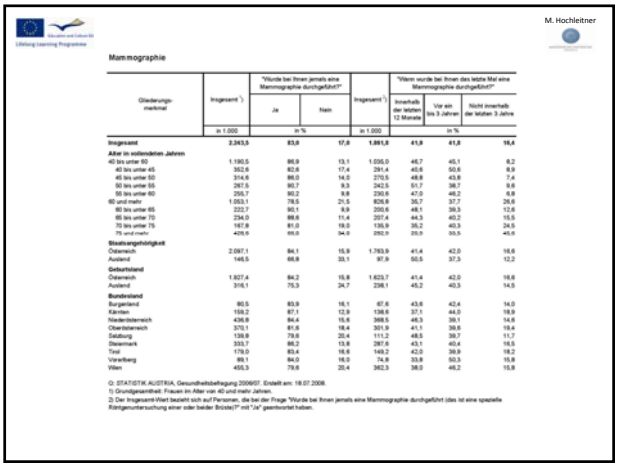
Lifelong Learning Programme
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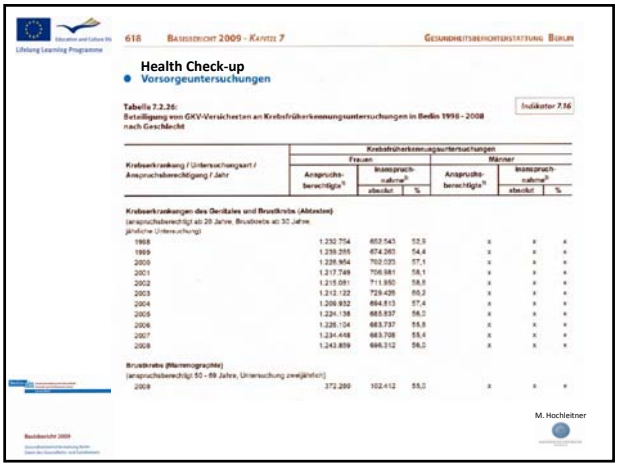
Mammographie


Lifelong Learning Programme
618 Basisbericht 2009 - Kapitel 7
Gesundheitsberichterstattung Berlin
Health Check-up
Vorsorgeuntersuchungen
Indikator 7.16
M. Hochleitner


Hochleitner/Fiegl/Thöni
Education and Culture DG
Lifelong Learning Programme
The best protection
is early detection
Support
Pink
Quick Donation
October
PINKRIBBON
You can find us at
www.pinkribbon.org
Enter>

Awareness

M. Hochleitner

- Herztod ist **männlich besetzt!**

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

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

Gender differences in epidemiology

Hochleitner/Fiegl/Thöni

Causes of Death worldwide

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

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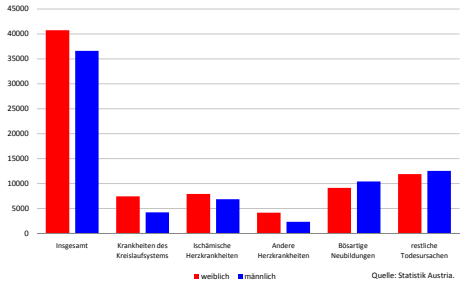
Todesursachen Tirol 2009



Quelle: Statistik Austria.

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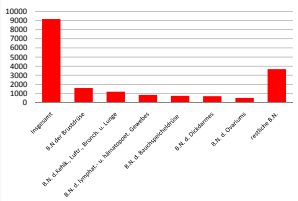
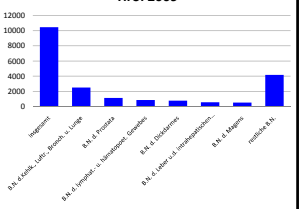
Krebstodesursachen FRAUEN Tirol 2009



Gestorbene weiblich 2009 - Bösartige Neubildungen

Insgesamt	9173
B.N der Brustdrüse	1594
B.N. d.Kehlk., Luftr., Bronch. u. Lunge	1186
B.N. d. lymphat.- u. hämatopoet. Gewebes	930
B.N. d. Bauchspeicheldrüse	721
B.N. d. Dickdarmes	680
B.N. d. Ovariums	489
restliche B.N.	3673

Krebstodesursachen MÄNNER Tirol 2009

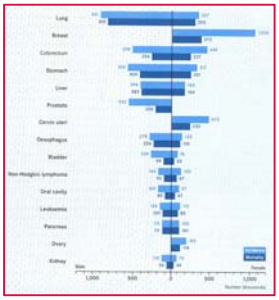


Gestorbene männlich 2009 - Bösartige Neubildungen

Insgesamt	10469
B.N. d.Kehlk., Luftr., Bronch. u. Lunge	2495
B.N. d. Prostata	1125
B.N. d. lymphat.- u. hämatopoet. Gewebes	846
B.N. d. Dickdarmes	771
B.N. d. Leber u.d. intrahepatischen Gallengänge	554
B.N. d. Magens	517
restliche B.N.	4161

Quelle: Statistik Austria, Todesursachenstatistik.

Incidence and mortality of the most common cancers worldwide

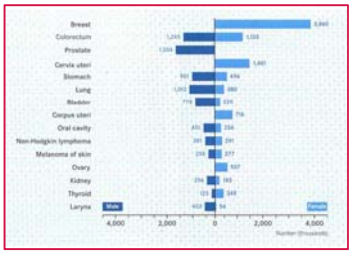


World Cancer Report, WHO, IARC Press, Lyon 2003, p13

Hochleitner/Fiegl/Thöni

Most prevalent cancers worldwide in 2000

expressed as thousands of persons diagnosed with cancer the previous five years

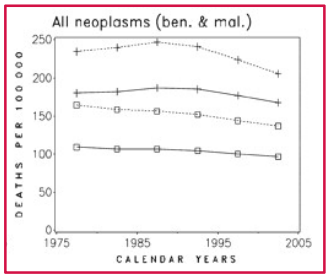


World Cancer Report, WHO, IARC Press, Lyon 2003, p14

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004

Annals of Oncology

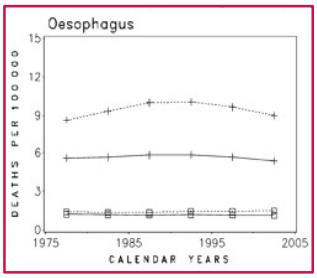


+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004



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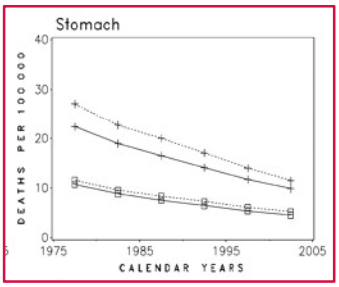
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004

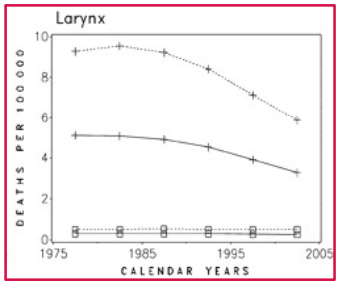


+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004



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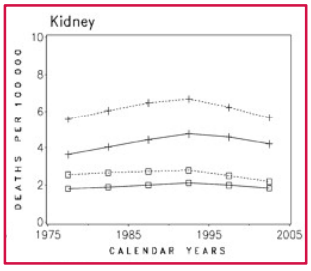
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004

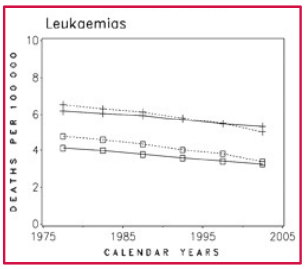


+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004

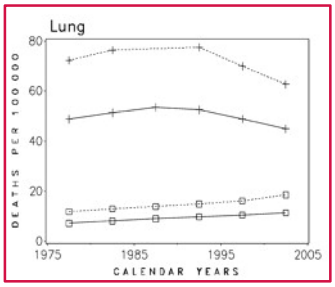


+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004

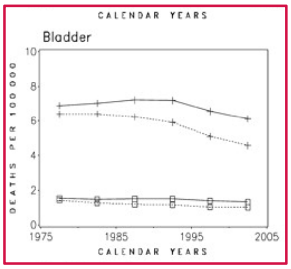


+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Trends in age-standardised death certification rates per 100.000 in the European Union 1975–2004



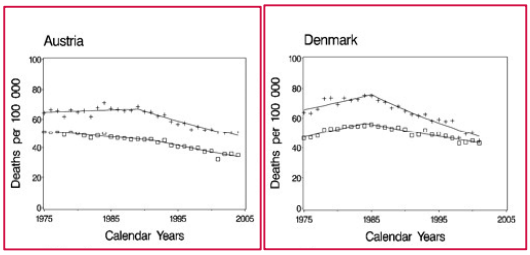
+++, men
□□□, women
——, 35-64 ys old
....., all ages

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Hochleitner/Fiegl/Thöni

Lung cancer mortality in men
Austria and Denmark
1975–2004. , ++++++++all ages; 35–64 years.

Hochleitner/Fiegl/Thöni



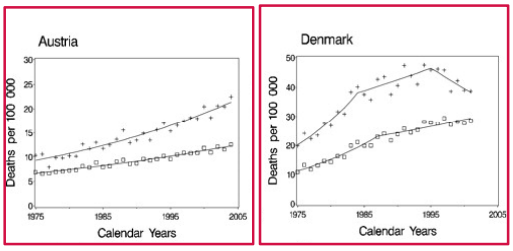
Men

La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Annals of Oncology

Lung cancer mortality in women
Austria and Denmark
1975–2004. , +++++++++all ages; 35–64 years

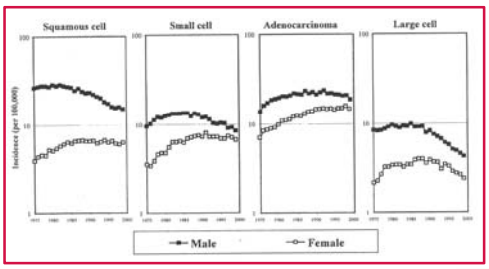
Hochleitner/Fiegl/Thöni



La Vecchia C et al., Ann Oncol 2009; Epub ahead of print

Annals of Oncology

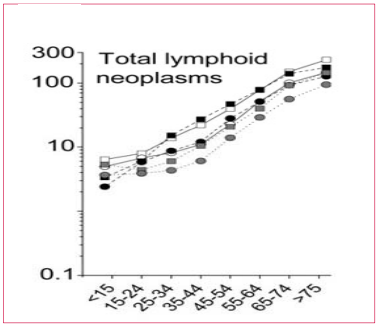
Gender-specific, incidence rates of histologic subtypes of lung cancer



Fu et al., Chest 2005, 127: 768

Hochleitner/Fiegl/Thöni

Incidence of lymphoid neoplasias according to subtype, ethnic background and gender



Hochleitner/Fiegl/Thöni

Morton et al. Blood 2006;107:265.

Gender differences in symptomatology and comorbidities

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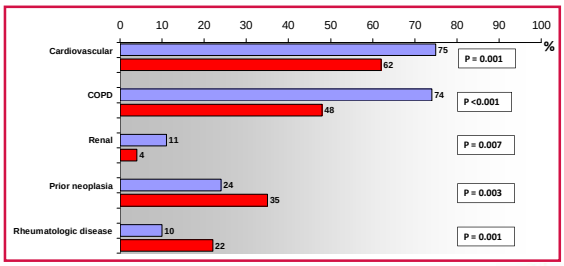
Hochleitner/Fiegl/Thöni

NSCLC: different prevalence of comorbidity in men (blue) and women (red)



TYROL-Studie, Fiegl et al., unpubliziert

Hochleitner/Fiegl/Thöni

Gender difference in pharmakokinetics

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Hochleitner/Fiegl/Thöni

Bild: http://morguefile.com

M. Hochleitner

Medikamente

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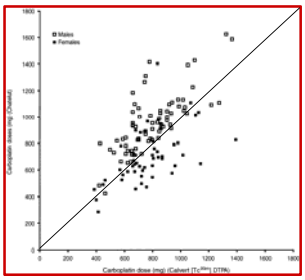
Table 1. Gender differences in pharmacokinetics for cytostatics and novel biologic antitumoral drugs

Substance	Measure	Outcome	Reference
5-FU	5-FU clearance	Lower in women	*Milano et al., JCO 1992; 1171*
5-FU (contin. infusion)	5-FU clearance	No sex difference	*Etienne et al., Eur J Cancer 1998, 34:92*
5-FU	Toxicity	Sex and age predictors	*Stein et al., Cancer 1995, 75:11*
Topotecan	Clearance	Lower in women	*Loos, Antiancer Drugs 11: 673*
Carboplatin	Dosing based on renal function-dependent formula	Women receive lower doses	*Dooley et al., Eur J Cancer 2002, 38:44* **(Slides)**
Paclitaxel	Elimination capacity	Lower in women	*Joerger, Clin Cancer Res 2006, 12:2150* **(Slides)**
Docetaxel, Paclitaxel, Etoposide, Topotecan	Hemato-toxicity: neutropenia	Increased risk in women	*Kloft, Clin Cancer Res 2006, 12:5481*
Sunitinib	Clearance	Decreased in women	*Houk et al., CCR 2009, 2497* **(Slide)**
Erlotinib	Maximum plasma concentration, AUC, terminal elimination half-life	Increased in women	*Frohna, J Clin Pharmakol 2006, 46: 282*
Oxaliplatin	Clearance	Decreased in women	*Bastian, Anticancer Drugs 2003, 14:817*
Cisplatinum	Clearance	No sex difference	*De Jongh, Cancer Chemother Pharmacol 2004, 54:105-112*
Cis/Etoposide	Hemato-toxicity	No sex difference	*Miya, Cancer Chemother Phar 1998, 42:386*
Capecitabine metabolites	Clearance	Decreased in women	*Gieschke, J Pharmacokinet Pharmacodyn 2002, 29:25*
Bevacizumab	Clearance	Decreased in women	*Lu et al., Cancer Chemother Pharmacol 2008, 62: 779*

Hochleitner/Fiegl/Thöni

Carboplatin dosing: gender bias

Inaccurate estimates of GFR



„The doses calculated using the Chatelut formula were significantly higher for males (% diff = 22%) and significantly lower for females (%diff = -6%) when compared with the dose derived from the Calvert formula"

Dooley et al., Eur J Cancer 2002, 38:44

Hochleitner/Fiegl/Thöni

Biomarkers differentially expressed between males and females with NSCLC

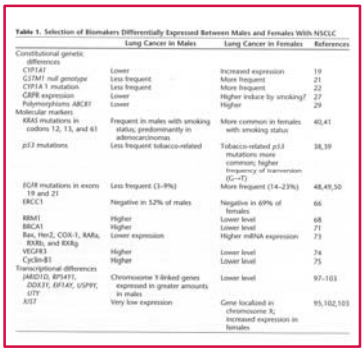


Table 1. Selection of Biomarkers Differentially Expressed Between Males and Females With NSCLC

	Lung Cancer in Males	Lung Cancer in Females	References
Constitutional genetic differences			
CYP1A1	Lower	Increased expression	19
GSTM1 null genotype	Less frequent	More frequent	21
CYP1A 1 mutation	Less frequent	More frequent	22
GRP8 expression	Lower	Higher induce by smoking?	27
Polymorphisms ABCB1	Lower	Higher	29
Molecular markers			
KRAS mutations in codons 12, 13, and 61	Frequent in males with smoking status; predominantly in adenocarcinomas	More common in females with smoking status	40,41
p53 mutations	Less frequent tobacco-related	Tobacco-related p53 mutations more common; higher frequency of transversion (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
RRM1	Higher	Lower level	68
BRCA1	Higher	Lower level	71
Bax, Hre2, COX-1, RARα, RXRb, and RXRg	Lower expression	Higher mRNA expression	73
VEGFR3	Higher	Lower level	74
Cyclin-B1	Higher	Lower level	75
Transcriptional differences (ARID1D, BPY4Y1, DDX3Y, EIF1AY, USPPY, UTY, XIST	Chromosome Y-linked genes expressed in greater amounts in males	Lower level	97–101
	Very low expression	Gene localized in chromosome X; increased expression in females	95,102,103

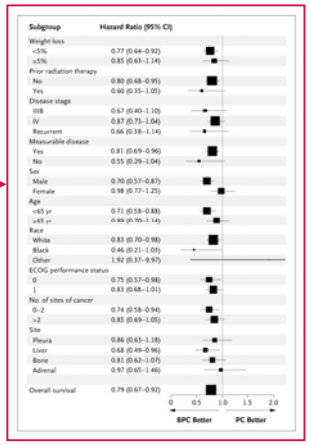
Planchard et al., Sem Oncol., 36:553 (2009)

Hochleitner/Fiegl/Thöni

Gender and efficacy of therapy

NSCLC and chemo-immuno therapy, (PC ± Bevacizumab)

? benefit only in men



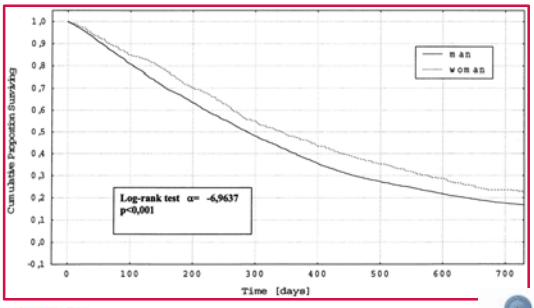
Sandler et al., N Engl J Med 2006

Hochleitner/Fiegl/Thöni

Gender differences in prognosis and cancer treatment outcome

Hochleitner/Fiegl/Thöni

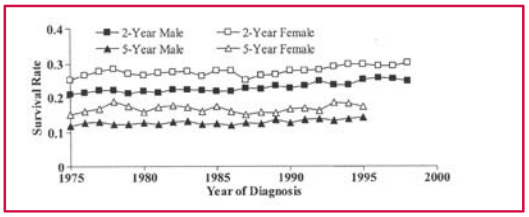
Overall survival of lung cancer patients with relation to gender



Radzikowska E et al. Ann Oncol 2002;13:1087-1093

Hochleitner/Fiegl/Thöni

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



Fu et al., Chest 2005, 127: 768

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Hochleitner/Fiegl/Thöni

Gender differences in basic science

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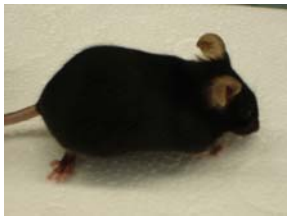
Knock out mouse

M. Hochleitner

C57/BL6J mouse



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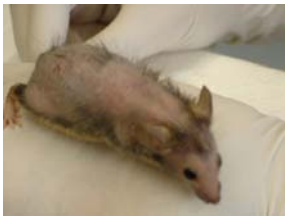
Normal mouse = Wild type mouse

Lysozym M Cre p14 -/- knock out mouse



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Genetic modified mouse
→ homozygous for the mutation

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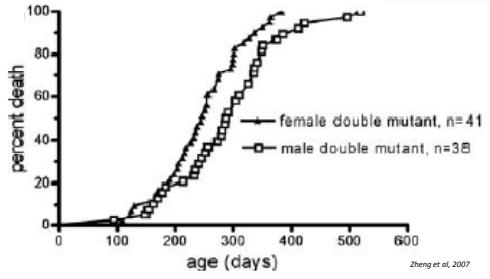
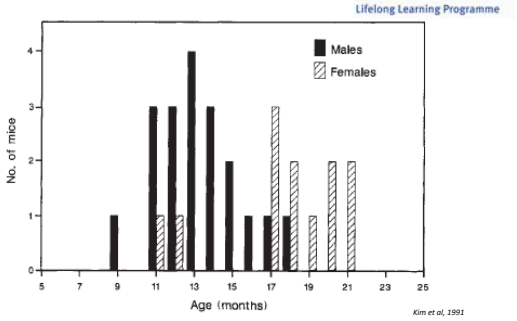


Zheng et al, 2007

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

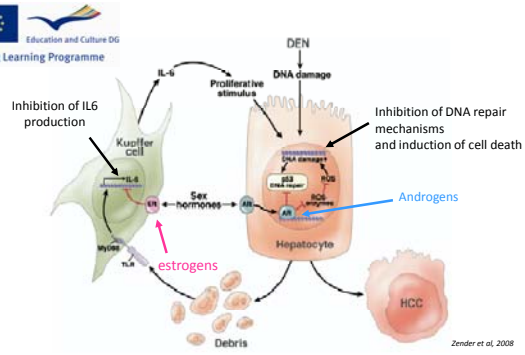
Hochleitner/Fiegl/Thöni



Kim et al, 1991

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

Hochleitner/Fiegl/Thöni



Zender et al, 2008

Figure 4: Estrogens protect female mice from liver cancer formation

Hochleitner/Fiegl/Thöni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