Für Mensch & Umwelt

Umwelt Bundesamt

Forum Frauengesundheit

Umwelt und Brustkrebs

Andreas Gies
Abteilung Umwelthygiene

Umweltbundesamt
Abteilung Umwelthygiene

Human-Biomonitoring und Toxikologie
Innenraumluft Qualität
Umweltmedizin
Umweltgerechtigkeit
Mikrobiologie und Schimmel
Krankheitslasten

70 Beschäftigte
40 Wissenschaftlerinnen und Wissenschaftler
3 Labore: Umweltmedizin
Mikrobiologie
Innenraumluft

Was werden Sie hören?

KREBSERKRANKUNGEN, ANSTIEG? ODER WERDEN WIR NUR ÄLTER UND KRÄNKER?

CHEMIKALIEN UND KREBS

SPÄTE LEHREN AUS FRÜHEN WARNUNGEN: ASBEST UND ANDERE FASERN

HORMONELL ABHÄNGIGE KREBSFORMEN

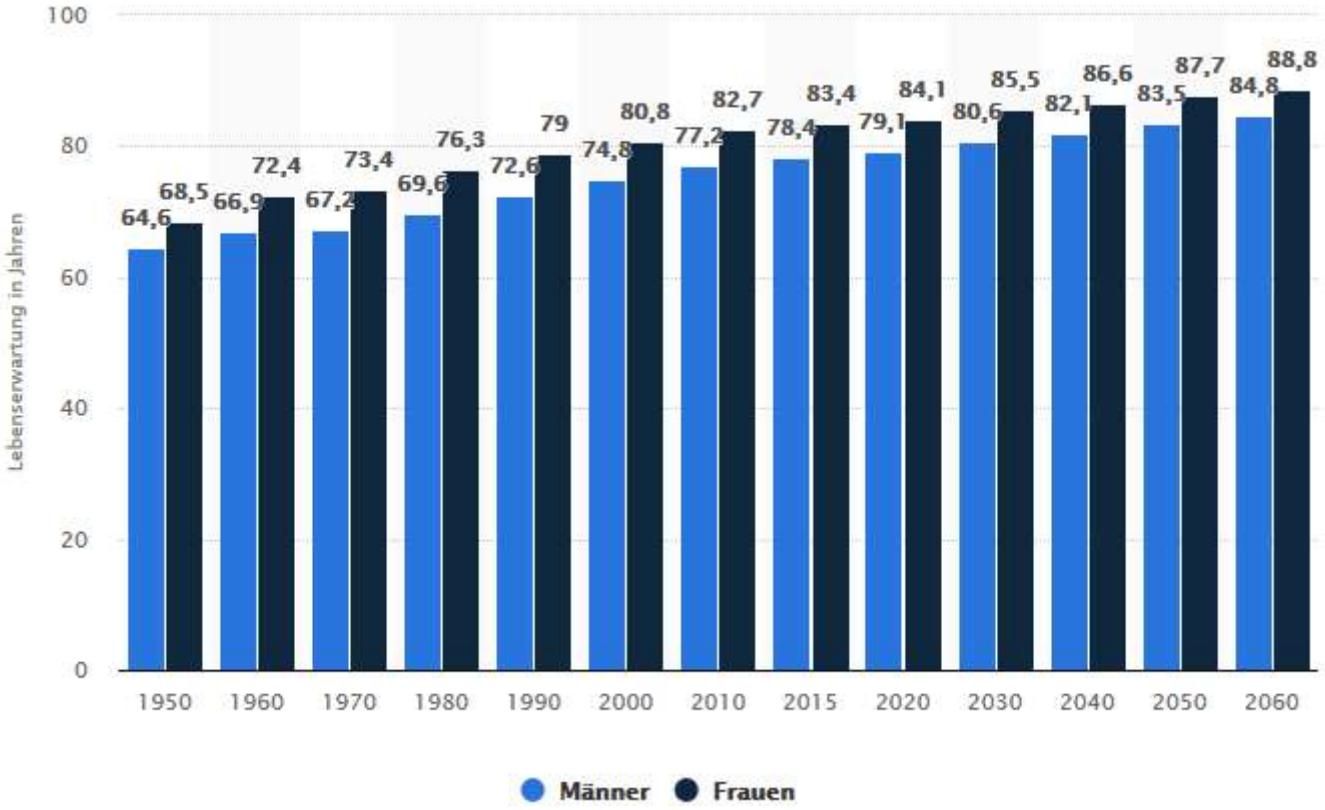
SPÄTE LEHREN AUS FRÜHEN WARNUNGEN II: BISPHENOL A

KRANKHEITSLASTEN

ÜBERRASCHENDES VOM KREBSKATASTER

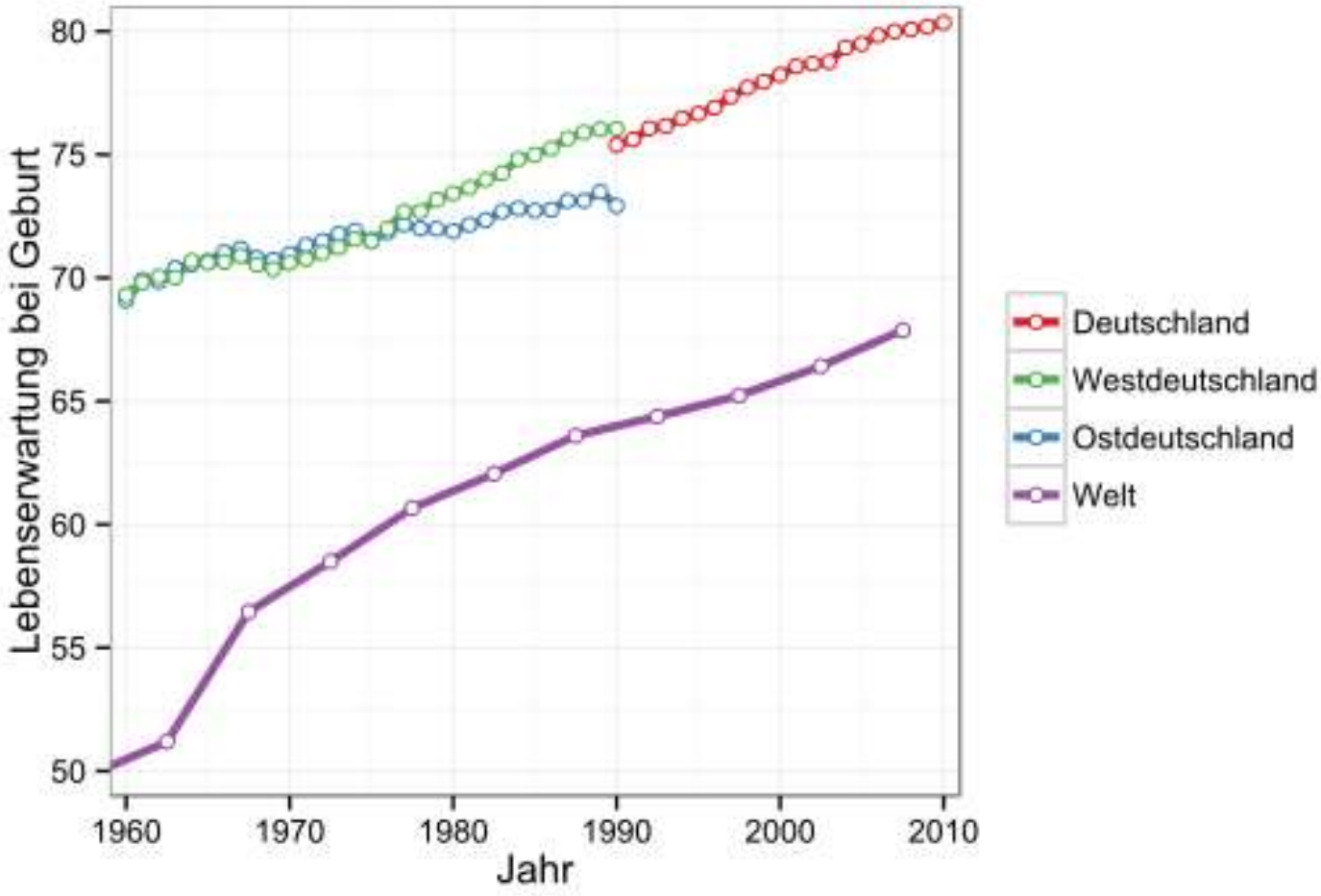
BLICK NACH VORN

Lebenserwartung in Deutschland 1950-2060



wikipedia

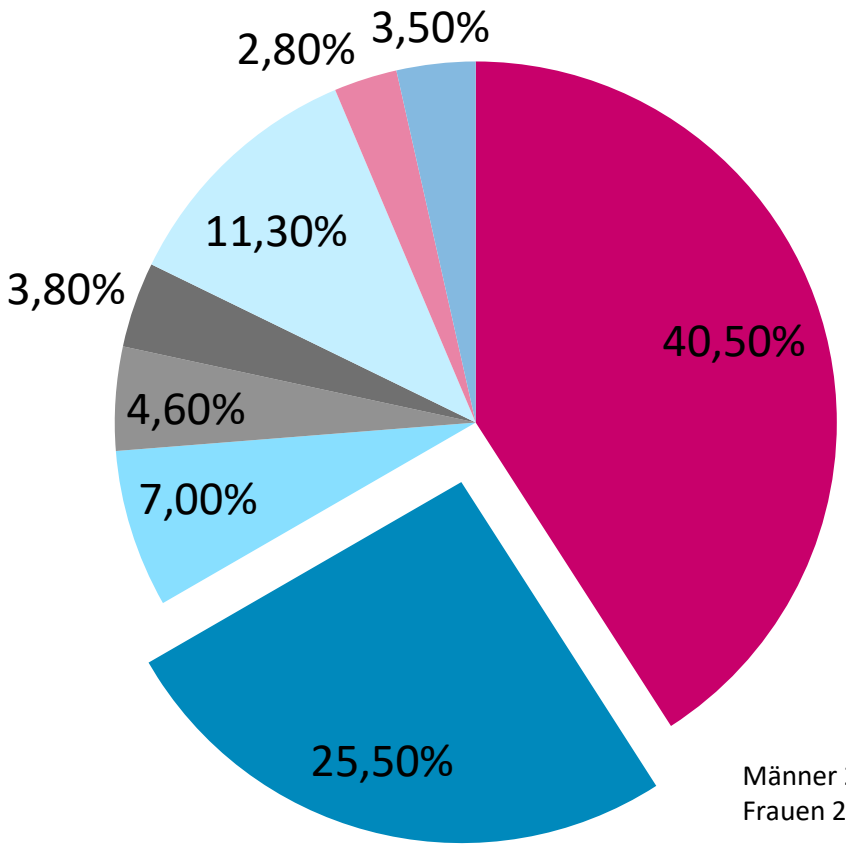
Lebenserwartung in Deutschland und in der Welt 1960-2009



wikipedia

Brustkrebs: Zunahme?

Todesursachen in Deutschland 2012



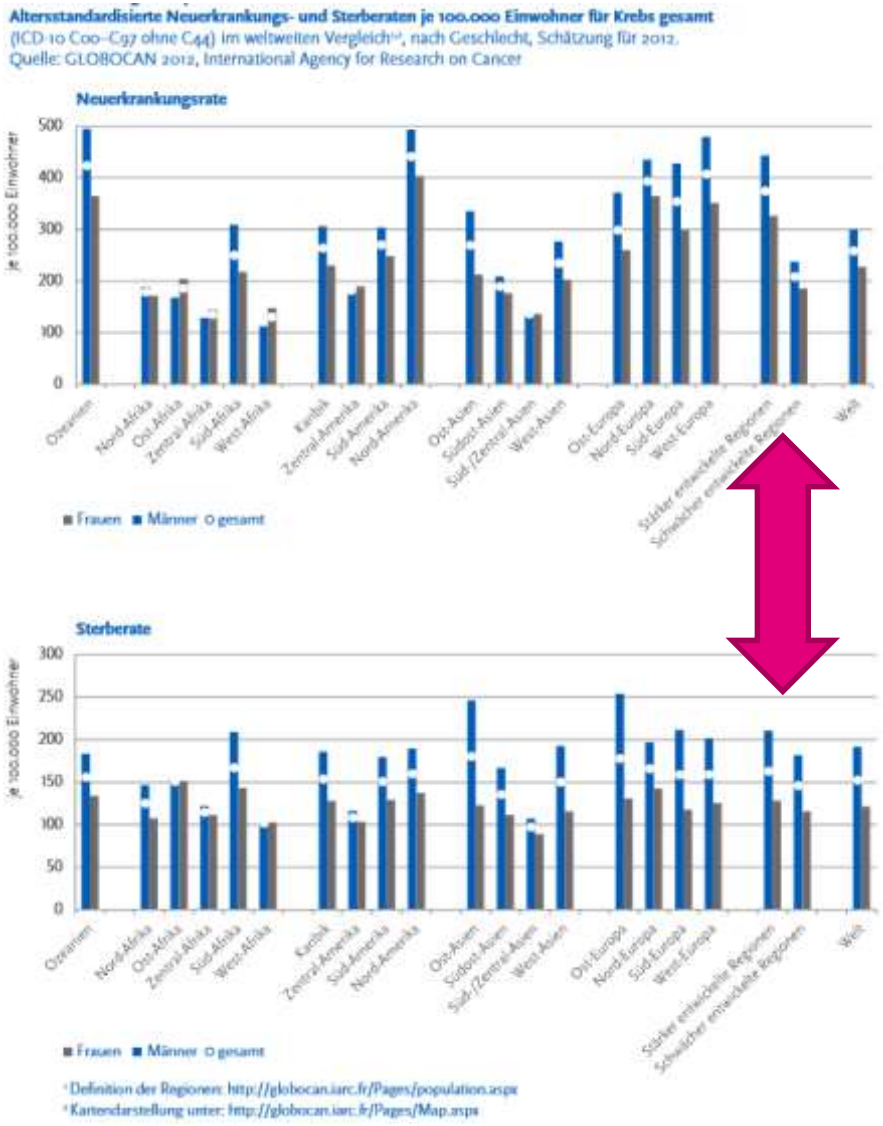
Todesfälle insgesamt 869582

- Kreislaufsystem
- Krebs
- Atmungsorgane
- Verdauungsorgane
- nicht natürlich
- Sonstige
- Nervensystem
- Stoffwechsel, Endokrine

Männer 28,8%
Frauen 22,4%

Quelle: RKI

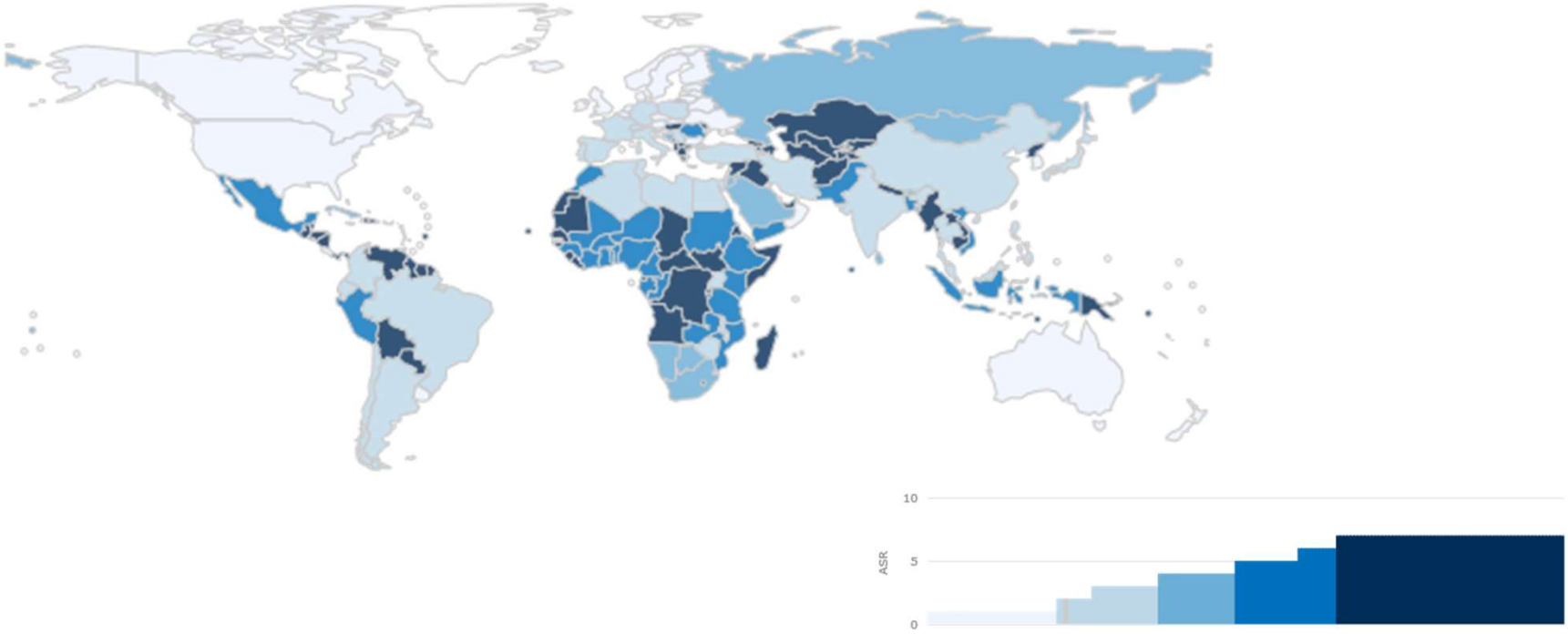
Altersstandardisierte Rate der Krebserkrankungen weltweit



Quelle: RKI

Altersstandardisierte Rate der Krebserkrankungen weltweit

Krebserkrankungen treten in Deutschland im Vergleich mit der Welt und Europa nicht überdurchschnittlich häufig auf



Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F.:GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 30/09/2014.

Krebshäufigkeit in Deutschland

Quelle Krebs in Deutschland RKI 2015

Krebs: Trend in Deutschland

Abbildung 3.14.1b
Absolute Zahl der Neuerkrankungs- und Sterbefälle, nach Geschlecht, ICD-10 C50, Deutschland 1999–2012

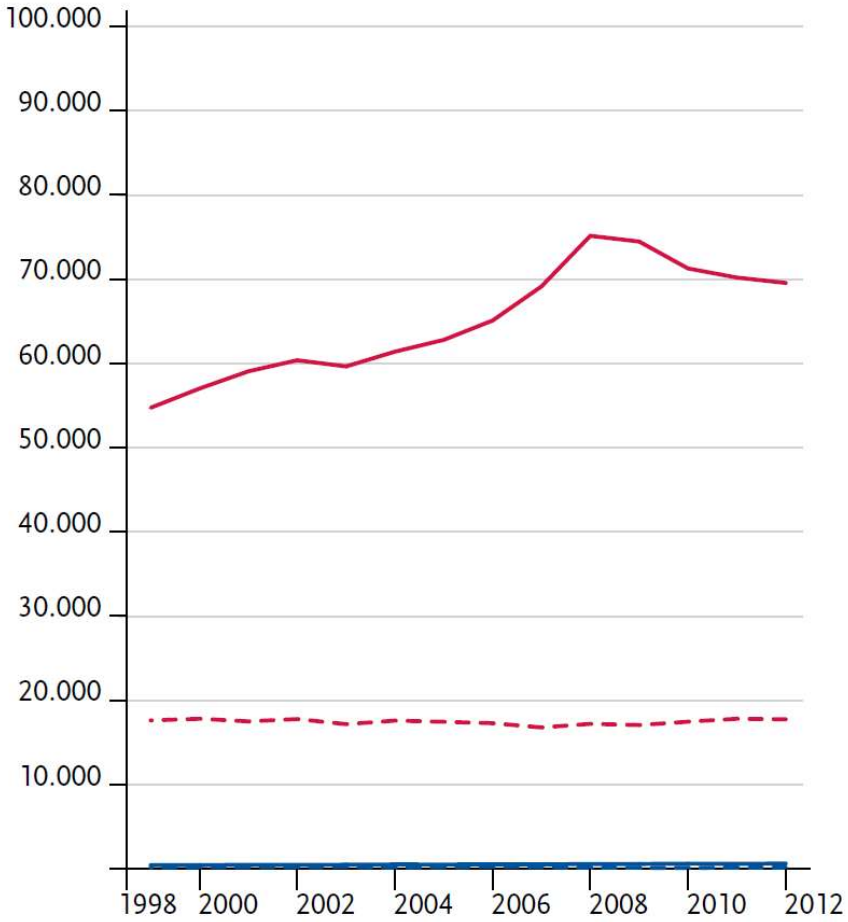


Abbildung 3.14.1a
Altersstandardisierte Erkrankungs- und Sterberaten, nach Geschlecht, ICD-10 C50, Deutschland 1999–2012
je 100.000 (Europastandard)

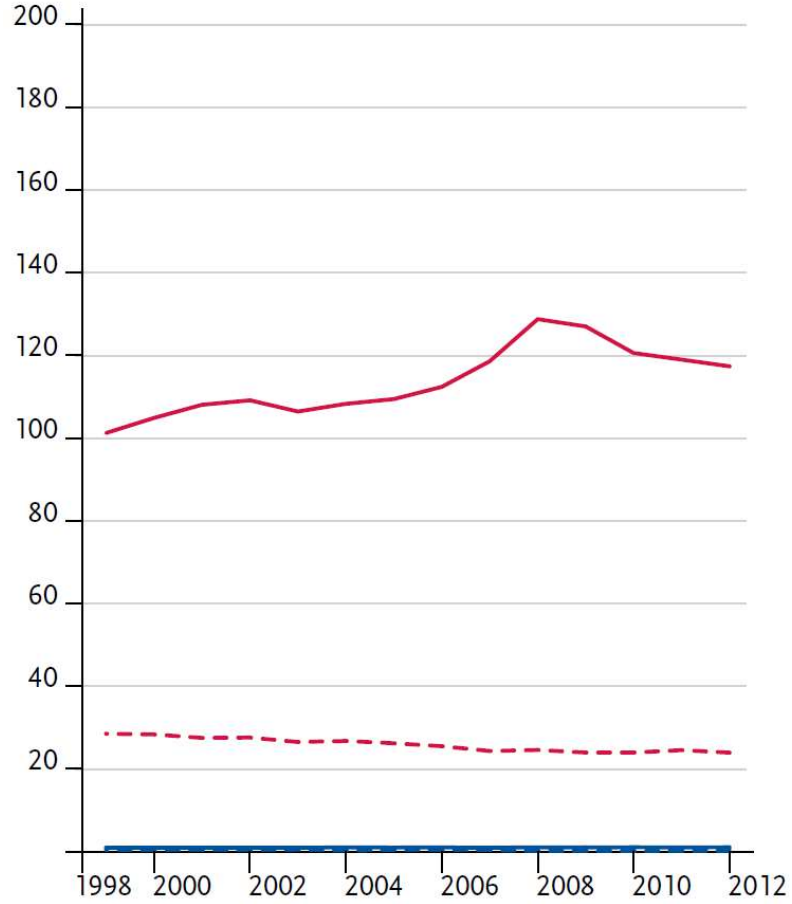
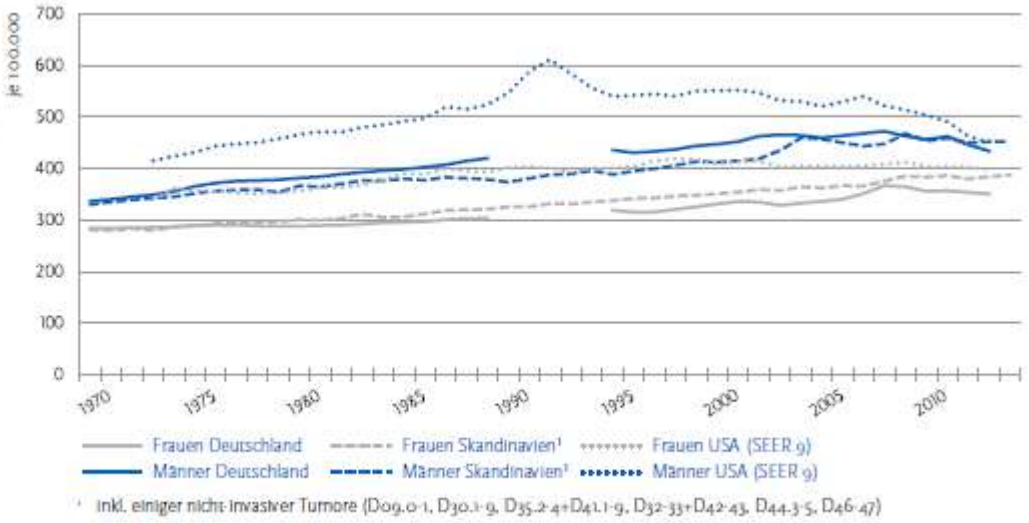
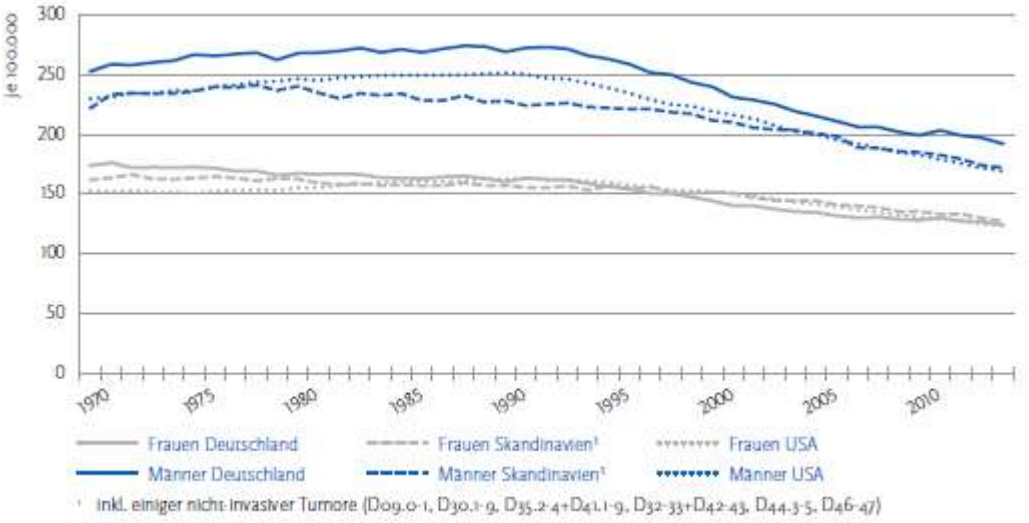


Abbildung 2.2.a2 Altersstandardisierte Neuerkrankungsraten für Krebs gesamt (ICD-10 C00–C97 ohne C44), in Deutschland, Skandinavien und den USA (SEER 9-Register), nach Geschlecht, 1970–2013. Quellen: Zentrum für Krebsregisterdaten, Association of the Nordic Cancer Registries, National Cancer Institute (USA)



¹ inkl. einiger nicht-invasiver Tumore (D09.0-1, D30.1-9, D35.2-4+D41.1-9, D32-33+D42-43, D44.3-5, D46-47)

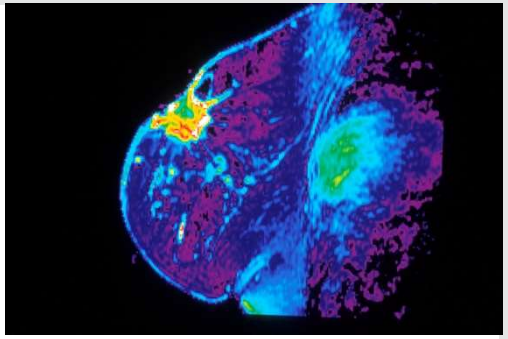
Abbildung 2.2.a3 Altersstandardisierte Sterberaten für Krebs gesamt (ICD-10 C00–C97 ohne C44), in Deutschland, Skandinavien und den USA, nach Geschlecht, 1970–2014. Quellen: Statistisches Bundesamt, Association of the Nordic Cancer Registries, Centers for Disease Control and Prevention (USA)



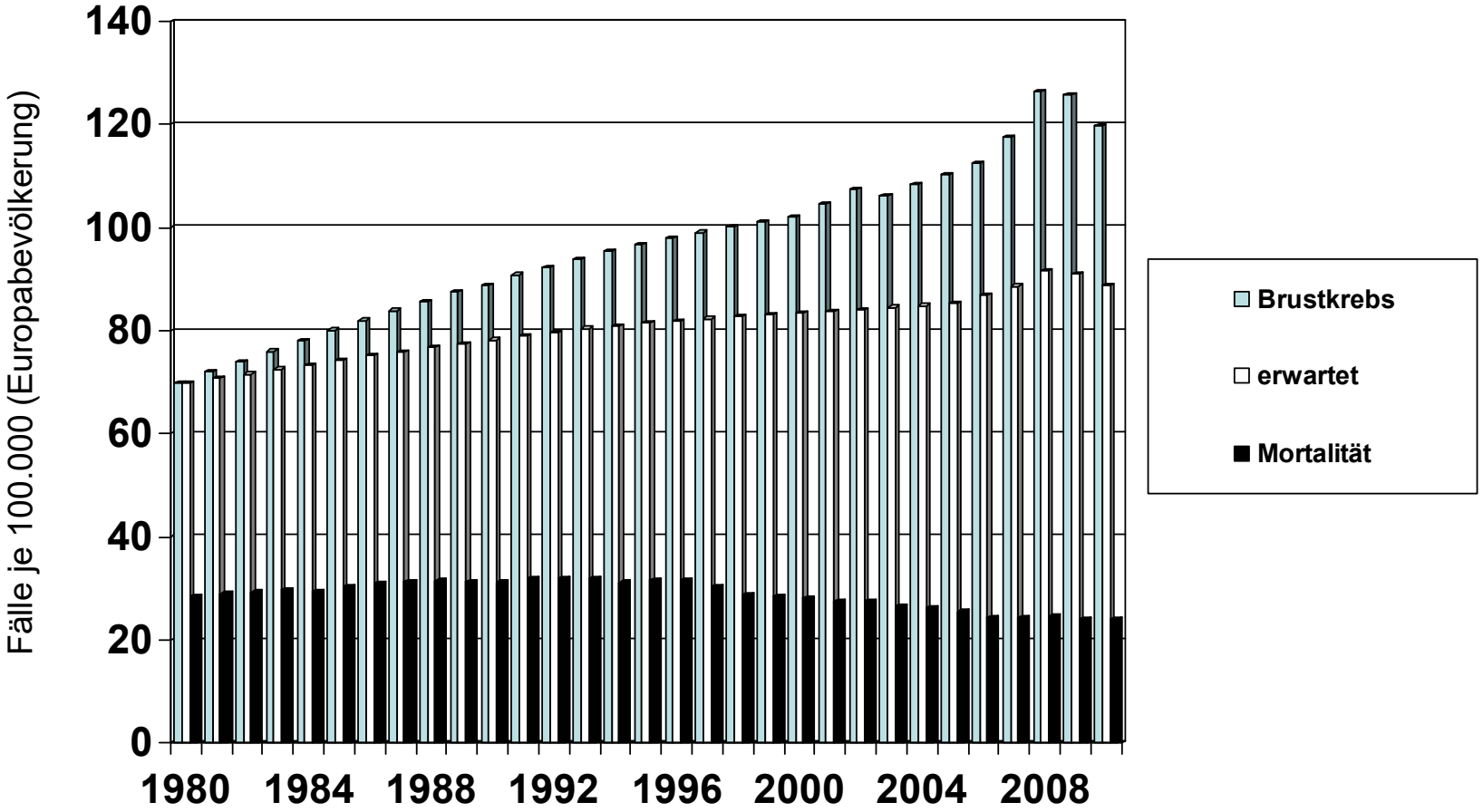
¹ inkl. einiger nicht-invasiver Tumore (D09.0-1, D30.1-9, D35.2-4+D41.1-9, D32-33+D42-43, D44.3-5, D46-47)

Quelle: RKI, Krebs in Deutschland 2016

Trend: Brustkrebs in Deutschland 1980-2010



Quelle: Natl. Cancer Inst., US



Quelle: Dachdokumentation Krebs, RKI 2008, 2014 (recalc)

Hormonanhängige Krebsformen

SCHLUSSFOLGERUNGEN DES WHO / UNEP STATE OF THE SCIENCE REPORT 2012

Eine Rolle von Umwelthormonen bei der Zunahme hormonell abhängiger Krebsformen ist biologisch plausibel

•Die Zunahme der mit Hormonen verbundenen Krebsformen kann nicht durch genetische Faktoren erklärt werden

•Umweltfaktoren einschließlich der Exposition gegenüber Chemikalien spielen eine Rolle, wenige davon konnten jedoch bisher charakterisiert werden

•Für Tumore der Brust, des Endometriums, der Eierstöcke und der Prostata ist die Rolle körpereigener und therapeutischer Hormone gut nachgewiesen. Dies macht es biologisch plausibel, dass Xenoöstrogene auch zum Risiko beitragen

Lebensstil: Risikofaktoren für Brustkrebs

Risikofaktoren für die Entwicklung von Brustkrebs

Risikofaktoren	relatives Risiko
Geschlecht: männlich : weiblich	1:100
Alter: 25 Jahre : 45 Jahre	1 : 20
Körpergewicht: Normalgewicht : Adipositas	1 : 2.5 (+150%)
Menopausealter: 42 Jahre : 52 Jahre	1 : 2.0 (+100%)
Menarchealter: 14 Jahre : 11 Jahre	1 : 1.3 (+30%)
Kinderzahl: mehrere : keine	1 : 1.3 (+30%)
Alter bei erster Geburt: 20 Jahre : 35 Jahre	1 : 1.4 (+40%)
Stillen: Gesamtdauer 5 Jahre : nie	1 : 1.2 (+20%)
Orale Kontrazeptiva: nein : ja	1 : 1.1 (+10%)
Hormonsubstitution: nie : 5-10 Jahre	1 : 1.3 (+30%)
Alkoholkonsum: Abstinenz : ≥ 20 g täglich	1 : 1.3 (+30%)
Antibiotika: nie : insgesamt 50 Tage Einnahme	1 : 1.5 (+45%)

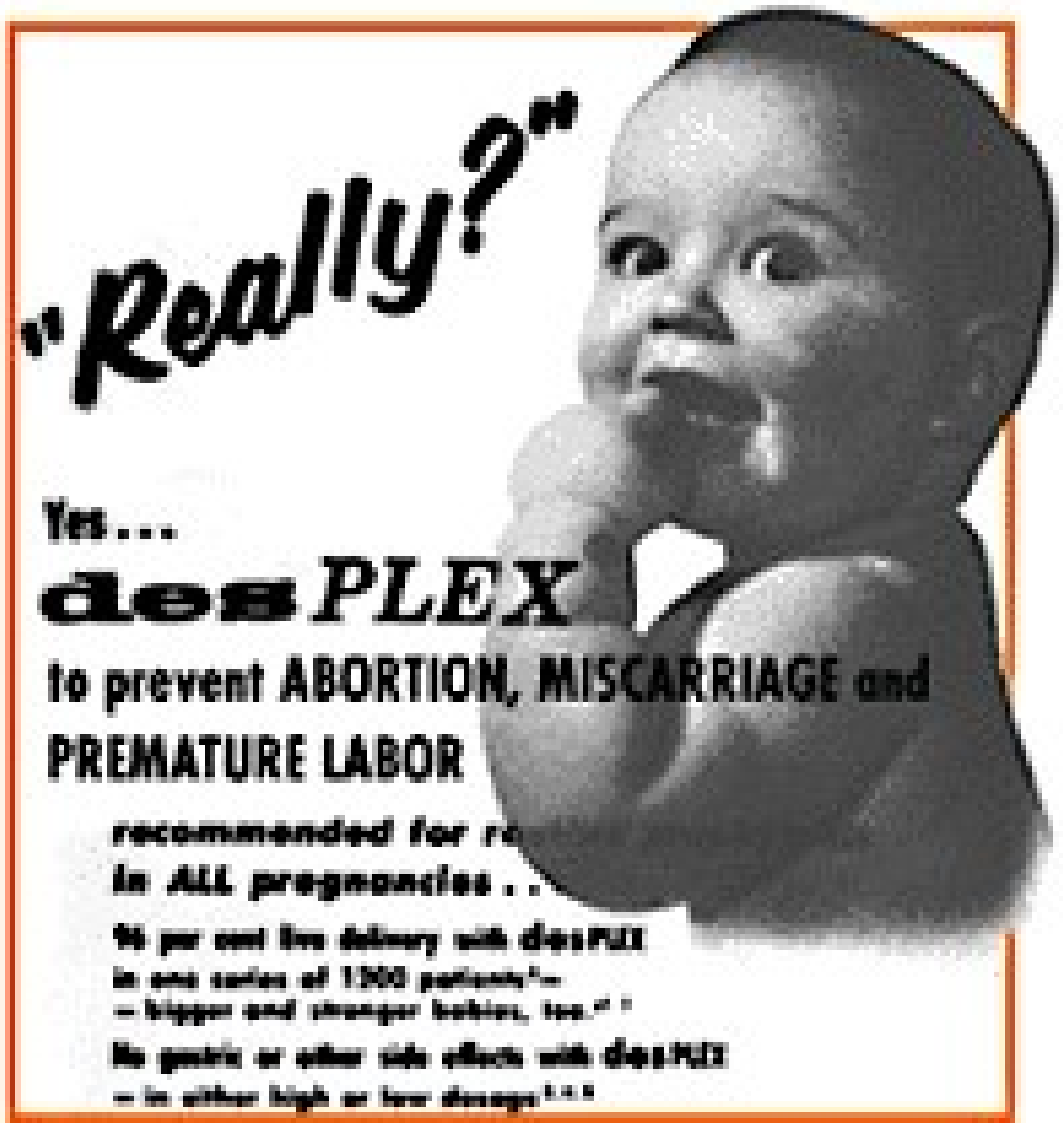
Quelle: Herbert Kuhl Universitäts-Frauenklinik Frankfurt

Berufsgruppen und Krebsrisiko

BERUFE MIT EINEM ERHÖHTEN BRUSTKREBSRISIKO:

- **BERUFE MIT KONTAKT ZU KREBSERREGENDEN UND HORMON-STÖRENDEN SUBSTANZEN**
- **LANDWIRTSCHAFT**
- **BARS UND GLÜCKSSPIELSEKTOR**
- **HERSTELLUNG VON KUNSTSTOFFEN FÜR AUTOS**
- **HERSTELLUNG VON NAHRUNGSMITTELKONSERVEN**
- **METALLVERARBEITUNG**

Quelle: Brophy et al. Environm. Health, 2012, Daten für Kanada


„Really?"
Yes...
desPLEX
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

Brustkrebsentstehung vor der Geburt

Hypothesis: does breast cancer originate in utero?

DIMITRIOS TRICHOPOULOS

Factors that increase the risk of cancer during adult life may also increase the risk of cancer when they act in utero (eg, ionising radiation and diethylstilboestrol in human beings and chemicals in animals). The existing empirical data seem to be compatible with the hypothesis that increased concentrations of oestrogens in pregnancy increase the probability of future occurrence of breast cancer in daughters.

Lancet 1990; **335**: 939–40.

Introduction

Hypothesis

I propose that increased concentrations of oestrogens in pregnancy (possibly with increased concentrations of other hormones in pregnancy) increase the probability of daughters getting breast cancer by creating a "fertile soil" for subsequent cancer initiation. The hypothesis is based on four assumptions: (1) oestrogens are important component factors in breast carcinogenesis;[4] (2) factors which increase the risk of cancer when they act postnatally may also increase the risk of cancer when they act in utero;[22] (3) oestrogen concentrations are at least ten times higher during pregnancy than during other periods of adult life;[31] and (4) in pregnancy, oestrogen concentrations and secretion rates vary widely between individuals,[31] and this variability is partly accounted for by exogenous factors.[7]

Hormonell wirksame Chemikalien

IN SENSIBLEN ZEITFENSTERN, MEIST UM DIE GEBURT / JUVENILENTWICKLUNG

WIRKEN IN GERINGEN KONZENTRATIONEN

ZEITVERZÖGERT

IRREVERSIBEL

IN NIEDRIGEN KONZENTRATIONEN OFT STÄRKER ODER ANDERS ALS IN HOHEN

Luftverschmutzung und Brustkrebs

Ältere Menschen, die dauerhaft einer hohen Feinstaubbelastung ausgesetzt sind, haben einer Studie zufolge ein deutlich erhöhtes Sterberisiko für verschiedene Krebsarten. Foto: Jens Kalaene/Archiv

06. Mai 2016 Süddeutsche Zeitung
Umwelt

Luftverschmutzung erhöht Krebsrisiko erheblich
Ältere Menschen, die dauerhaft einer hohen Feinstaubbelastung ausgesetzt sind, sterben einer Studie zufolge deutlich wahrscheinlicher an Krebs. Das erhöhte Risiko gelte für eine ganze Reihe von Tumorarten, wie ein Team aus Hongkong und Großbritannien im Journal "Cancer Epidemiology, Biomarkers and Prevention" berichtet. Als Basis ihrer Langzeituntersuchung dienten die Daten von 66 280 Menschen ab 65 Jahren in Hongkong.
Als Feinstaub gelten winzige Partikel bis zu einer Größe von 10 Mikrometern. Ursprung der Schadstoff-Teilchen können etwa Dieselruß, Reifenabrieb oder Abgase von Industrie-, Kraftwerks- oder Heizungsanlagen sein.
Im Fokus der aktuellen Studie standen Teilchen mit weniger als 2,5 Mikrometern Durchmesser (PM2,5), die sich tief in den Bronchien und Lungenbläschen festsetzen oder sogar ins Blut übergehen können.
Die Forscher erhoben die Feinstaubwerte an den Wohnorten der Menschen.
Ergebnis: Je 10 Mikrogramm erhöhter Konzentration von Feinstaub pro Kubikmeter Luft stieg demnach das Risiko, an Krebs zu sterben, um insgesamt 22 Prozent.
Bei Frauen stieg das Risiko, an Brustkrebs zu sterben, sogar um 80 Prozent, wie die Forscher erläutern.

Einflüsse auf die Entstehung von Brustkrebs

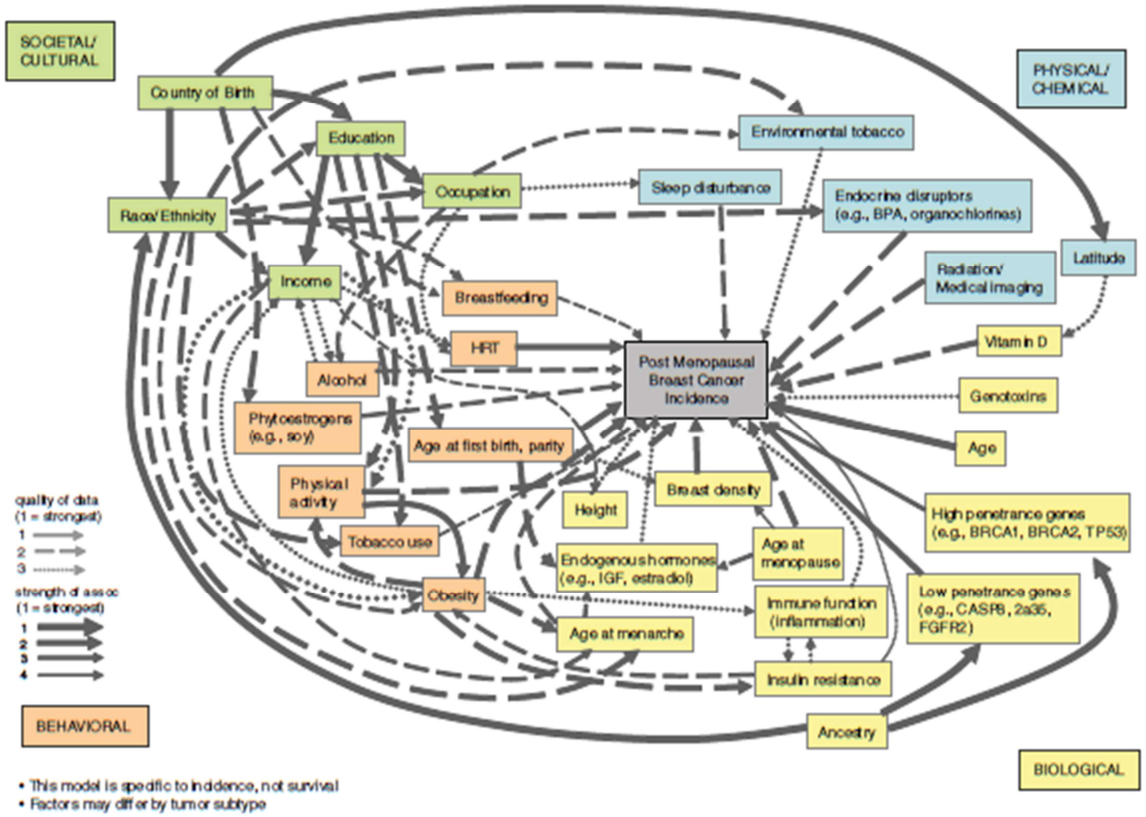


FIGURE 4-2 Illustration of an evidence-based complex-systems model of postmenopausal breast cancer causation. This model displays multiple factors associated with postmenopausal breast cancer causation in four broad domains and shows their interconnections across levels (genes to society) by arrows that indicate variations in the strength of the associations and the quality of the data. SOURCE: Personal communication, R. A. Hiatt, University of California, San Francisco, May 21, 2011. Developed with support from the California Breast Cancer Research Program.

Brustkrebs : Handlungsoptionen

Individuell:

Bewegung
Rauchen
Alkohol
Übergewicht
Vermeidung von Chemikalien: Ernährung, Innenraum

Kommunal:

Eindämmung des motor. Verkehrs, insb. In Wohngebieten
Grünversorgung, Walkability…
Beteiligung Betroffener

Politisch:

Maßnahmen gegen krebserregende und hormonell wirksame Chemikalien
Luftreinhaltung , insbesondere in den Städten
Landwirtschaftswende
Verkehrswende

Leitlinien Umweltvorsorge der Bundesregierung 1986

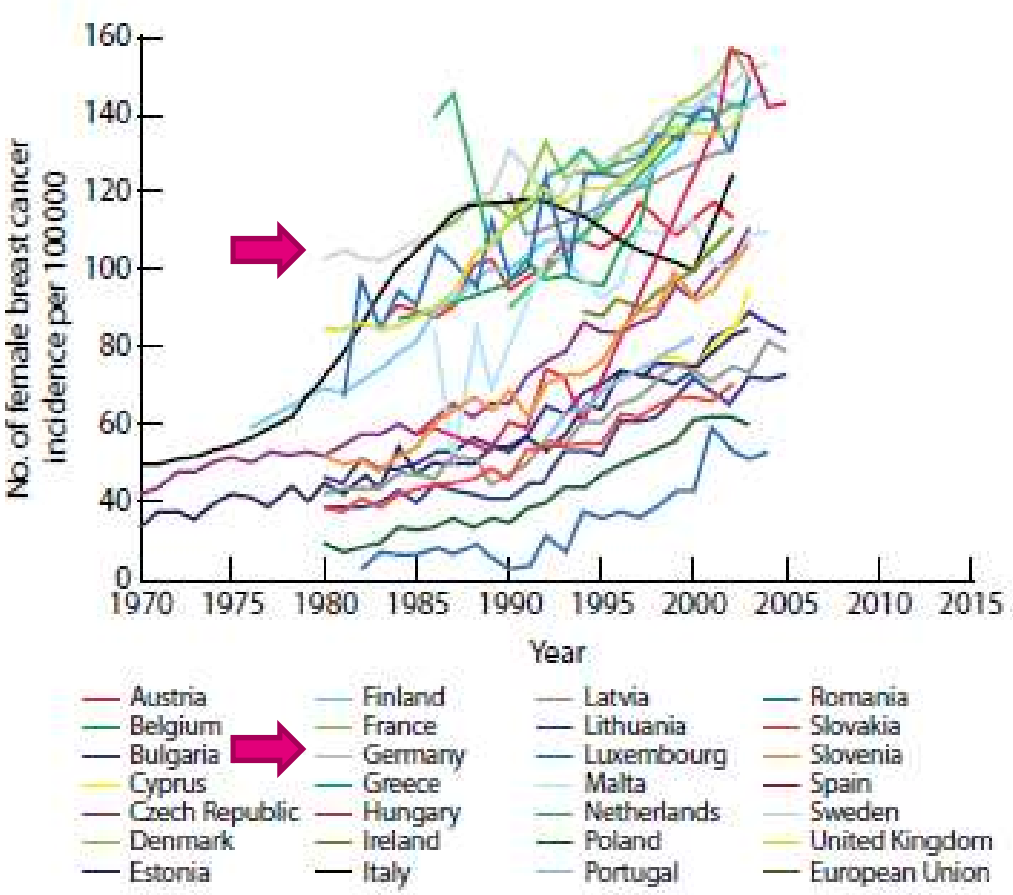
Verantwortliche Umweltpolitik beschränkt sich jedoch nicht auf die Abwehr von Gefahren für Mensch und Umwelt, sondern handelt vorsorgend bereits im Vorfeld der Gefahrenabwehr. Risikovorsorge ist auf die Verminderung oder Vermeidung von Risiken für die Umwelt gerichtet, die nach Art und Umfang etwaiger Schäden sowie nach der Wahrscheinlichkeit ihres Eintritts noch keine Gefahr begründen oder gegenwärtig nicht genau abschätzbar sind. Die Bundesregierung geht dabei mit dem Bundesverwaltungsgericht davon aus, daß „auch solche Schadensmöglichkeiten in Betracht gezogen werden (müssen), die sich nur deshalb nicht ausschließen lassen, weil nach dem derzeitigen Wissensstand bestimmte Ursachenzusammenhänge weder bejaht noch verneint werden können und daher insoweit noch keine Gefahr, sondern nur ein Gefahrenverdacht oder ein „Besorgnispotential" besteht" (BVerwG, Urteil vom 19. Dezember 1985, — 7 C 65.82 —; vgl. insb. Leitsatz 4 zur „Gefahrenunabhängigen Risikovorsorge").

Deutscher Bundestag
10. Wahlperiode

Drucksache 10/6028

19. 09. 86

Altersstandardisierte Erkrankungsraten: Brustkrebs, Frauen, je 100.000



Quelle: WHO / UNEP State of the Science of Endocrine Disrupting Chemicals 2012

Krebs: Lokalisation und Häufigkeit 2012

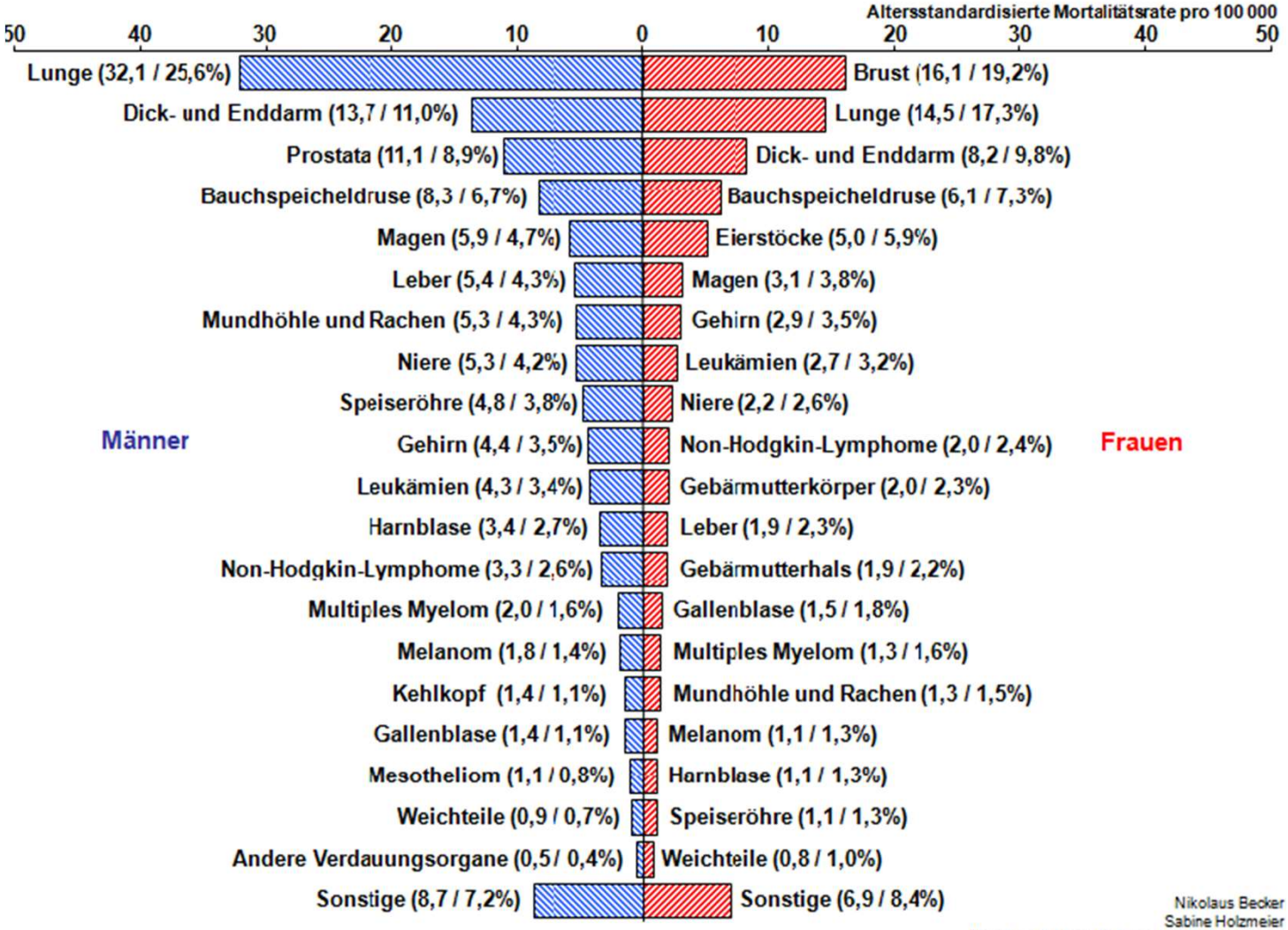
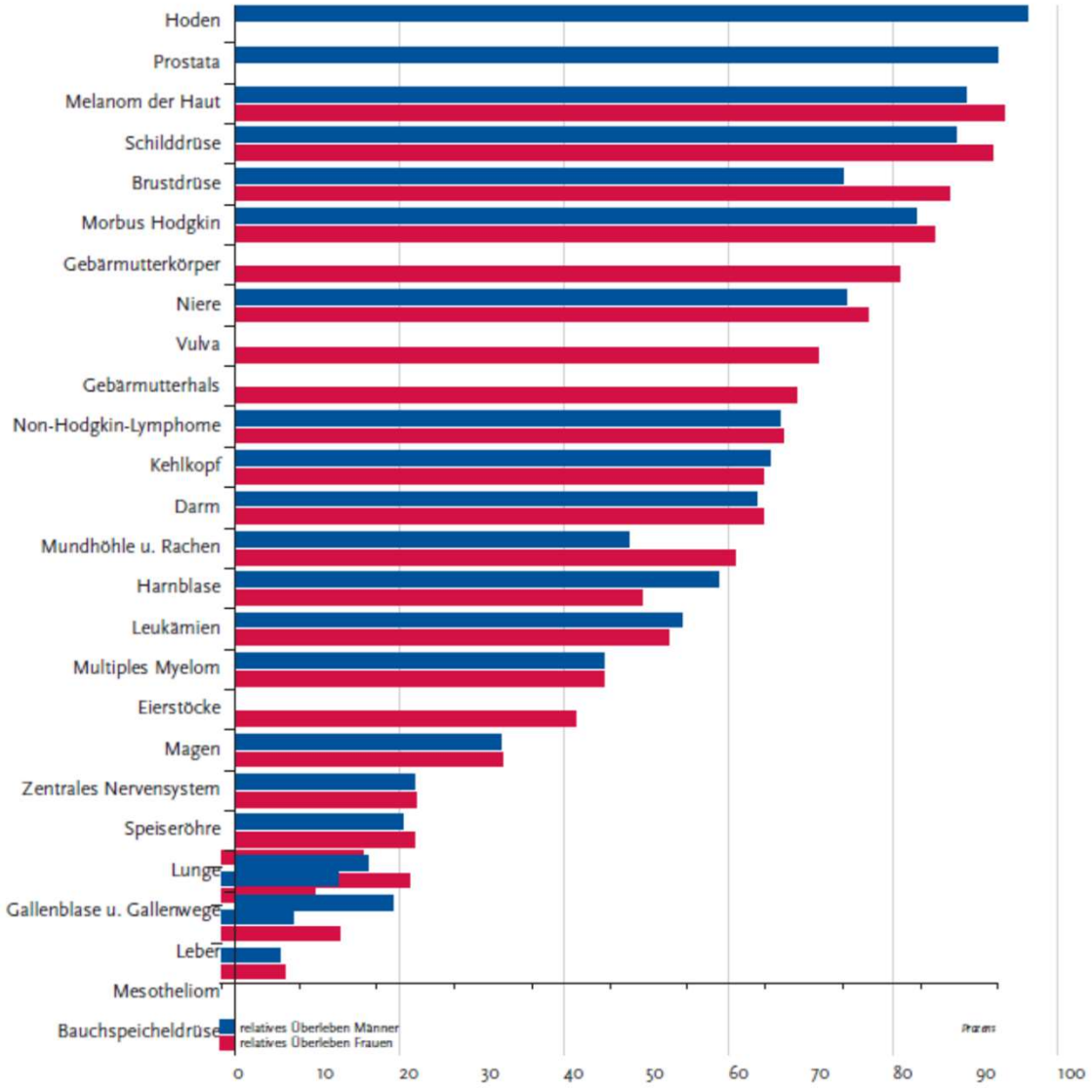


Abbildung 3.1.0
Vergleich der relativen 5-Jahres-Überlebensraten, nach Lokalisation und Geschlecht, Deutschland 2009 - 2010 (Periodenanalyse)



Quelle: RKI

Einflüsse auf die Entstehung von Brustkrebs

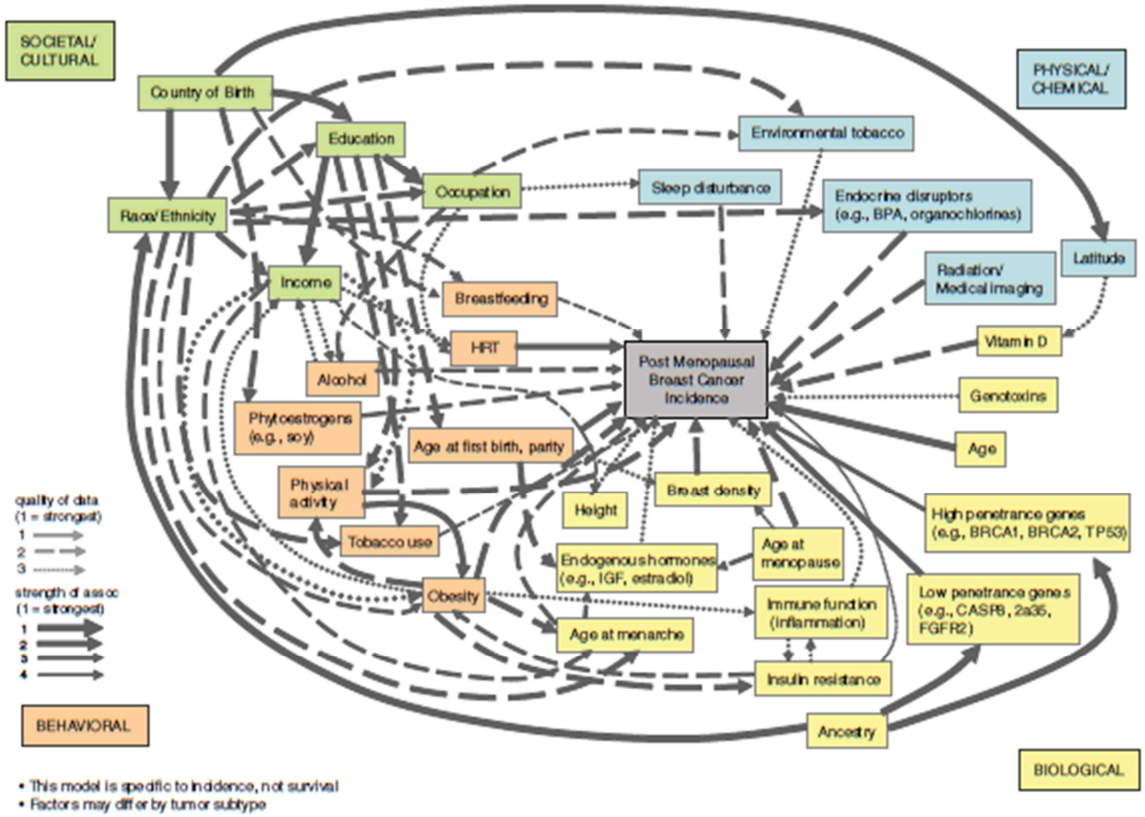


FIGURE 4-2 Illustration of an evidence-based complex-systems model of postmenopausal breast cancer causation. This model displays multiple factors associated with postmenopausal breast cancer causation in four broad domains and shows their interconnections across levels (genes to society) by arrows that indicate variations in the strength of the associations and the quality of the data. SOURCE: Personal communication, R. A. Hiatt, University of California, San Francisco, May 21, 2011. Developed with support from the California Breast Cancer Research Program.

Chemikalien, die Einfluss auf die Brustentwicklung haben

Atrazine A pesticide widely used to control weeds. It is found in food and contaminated drinking water, especially in agricultural areas.

Bisphenol A (BPA) Used to make hard polycarbonate plastic, epoxy resins, and vinyl (PVC). It is found in food can liners, water and baby bottles, and thermal paper for receipts.

Dibutylphthalate Used in consumer products such as paints, modeling clay, and lipstick

Dioxin An industrial byproduct from chlorine bleaching paper pulp and burning PVC and other plastics. People are primarily exposed from food and breast milk.

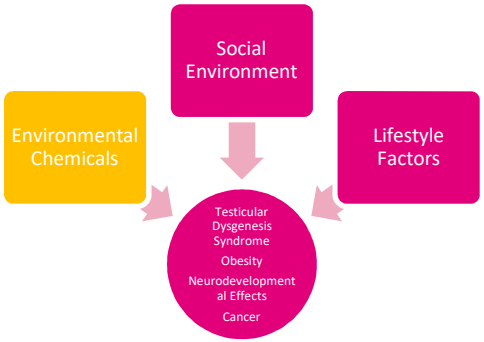
Methoxychlor An organochlorine pesticide that is banned in the U.S. It is commonly found in house dust in older homes.

Nonylphenol A plasticizer (plastic softener) and breakdown product of alkylphenol ethoxylate surfactants used in some laundry and other detergents.

Polybrominated diphenyl ethers (PBDEs) Flame retardants used in furniture, electronics and other products. They have been phased out in the U.S., but are abundant in house dust.

Perfluorooctanoic acid (PFOA) Used in non-stick, stain-resistant, and grease-resistant coatings on cookware, clothing, carpets, furniture, food papers and other products.

Was nehmen Sie nach Hause?



Krebstherapie wird immer erfolgreicher

Krebsprävention hat weithin versagt

Umweltchemikalien spielen bei der Zunahme der Krebserkrankungen offensichtlich eine Rolle

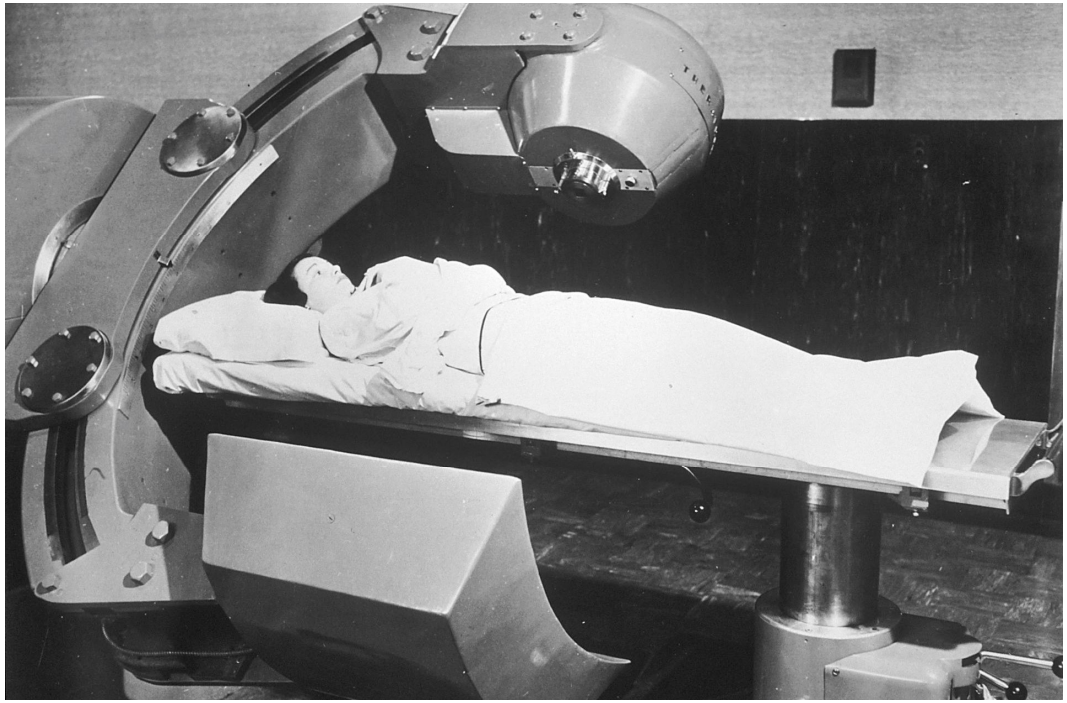
Anteil der Umweltchemikalien zu quantifizieren ist Schwierig, Beteiligung wird aber wohl unterschätzt

Hormonell abhängige Krebsformen steigen stark: Rolle der Umwelthormone

Frühes Erkennen ist möglich und notwendig

Krebs: Rasante Zunahme?

- **ES GIBT JÄHRLICH MEHR KREBSFÄLLE IN DEUTSCHLAND**
- **DIE KREBSKRANKEN MENSCHEN ÜBERLEBEN DIE KRANKHEIT LÄNGER**
- **WIR „ERLEBEN“ DADURCH MEHR KREBS IN UNSERER UMWELT**
- **SEIT 1980 HAT DIE ALTERSSTANDARDISIERTE KREBSRATE UM CA. 50 % ZUGENOMMEN**
- **SEIT CA. 2000 STEIGEN NUR NOCH DIE KREBSERKRANKUNGSRATEN BEI FRAUEN**
- **RAUCHEN ÜBERLAGERT FAST ALLE ANDEREN URSACHEN VON KREBSERKRANKUNGEN**



Quelle: Natl. Cancer Institute

Prozesse und Gemische in der IARC - Klassifizierung

International Agency for Research on Cancer

World Health Organization

- ALUMINIUMPRODUKTION
- VERKOKUNG
- TEERHERSTELLUNG
- RAUCHEN
- GUMMIPRODUKTION
- ISOPROPYLALKOHOLPRODUKTION
- TISCHLEREI / SCHREINEREI
- TEXTILPRODUKTION
- KOKSPRODUKTION
- DIESELABGASE
- INNENRAUM: KOHLEVERBRENNUNG
- EISENGUSS
- ANSTREICHEN
- DRUCKEREIARBEIT
- GLASPRODUKTION
- PRODUKTION VON KOHLEELEKTRODEN
- SCHWEISSEN

International Agency for Research on Cancer

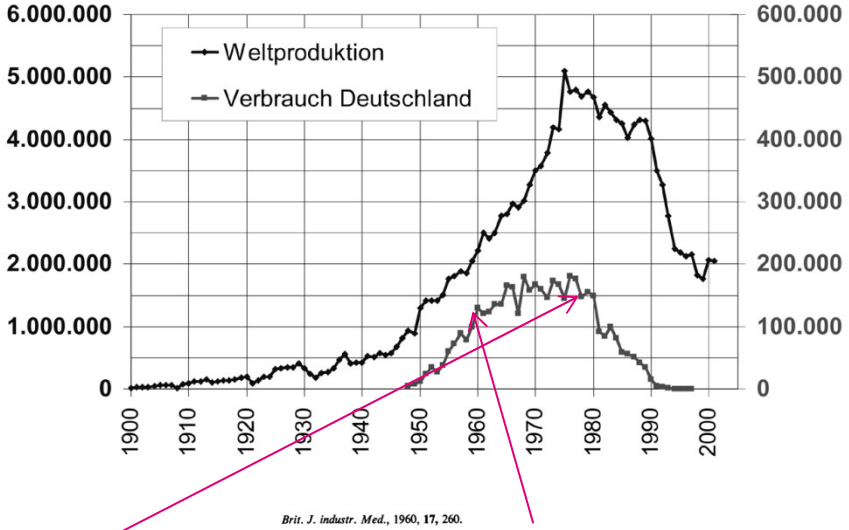
World Health Organization

Substanzen IARC Klassifizierung 2B

- **TITANDIOXID**
- **TOLUOLDIISOCYANATE**
- **TRICHLORESSIGSÄURE**
- **TOXAPHEN**
- **TETRACHLORETHAN**
- **STYROL**
- **VINYLACETAT**
- **KALIUMBROMAT**
- **NITROBENZOL**
- **NITROMETHAN**
- **METHYLQUECKSILBER**
- **HEXACHLORCYCLOHEXAN**
- **1,2-DIOXAN DINITROTOLUOL**
- **ETHYLBENZOL**
- **FURAN**
- **DICHLORESSIGSÄURE**
- **DICHLORVOS**
- **DICHLORETHAN**
- **DEHP**
- **KOHLENSTOFFTERACHLORID**
- **CHLOROFORM**
- **CHLORDECONE (KEPONE)**
- **DDT**
- **BUTYLHYDROXYANISOL (BHA)**
- **BENZOFURAN**
- **ACETALDEHYD**

Späte Lehren aus frühen Warnungen: Asbest und andere Fasern

Asbest: Frühe Warnungen



Brit. J. industr. Med., 1960, **17**, 260.

DIFFUSE PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE IN THE NORTH WESTERN CAPE PROVINCE

BY

J. C. WAGNER, C. A. SLEGGS, and PAUL MARCHAND

From the Pathology Division, Pneumoconiosis Research Unit of the Council for Scientific and Industrial Research, Johannesburg, West End Hospital, Kimberley, and the Department of Thoracic Surgery, University of the Witwatersrand and Johannesburg General Hospital

(RECEIVED FOR PUBLICATION APRIL 24, 1960)

Primary malignant tumours of the pleura are uncommon. Thirty-three cases (22 males, 11 females, ages 31 to 68) of diffuse pleural mesothelioma are described; all but one have a probable exposure to crocidolite asbestos (Cape blue). In a majority this exposure was in the Asbestos Hills which lie to the west of Kimberley in the north west of Cape Province. The tumour is rarely seen elsewhere in South Africa.

Mesothelioma of the pleura is regarded as an uncommon tumour. In the last four years we have seen 33 histologically proven cases; 28 of these had some association with the Cape asbestos field and four cases had been exposed to asbestos in industry.

The tumour is rarely encountered elsewhere in South Africa. During the past five years, with the exception of the present series, no neoplasm of this nature has been diagnosed amongst 10,000 lungs examined at the Pneumoconiosis Bureau in Johannesburg, or in the Pathology Department of the South African Institute for Medical Research. Higginson and Oettle (1957) did not observe a single case in their survey of malignant tumours occurring in the Bantu and Cape Coloured population of Johannesburg and the North Eastern Transvaal.

Our first necropsy specimen of pleural mesothelioma with asbestosis was examined at the Pneumoconiosis Research Unit in February, 1956 (Case 1). During the early months of that year, one of us (C.A.S.) in the Northern Cape, treated six patients with gross pleural thickening. Pleural biopsies from two of them showed the features of mesothelioma. In the ensuing two years, eight further cases were found from this region and five from elsewhere in the Union. During this period C.A.S. had become perturbed at the number of these unusual tumours occurring amongst his patients, and stimulated an investigation. At this stage there were two reasons to suggest that asbestos might be implicated. First, asbestos was found in the lungs of the first case (Case 1), and secondly, 10 of the cases came from a hospital to which suspected cases of tuberculosis were referred from a large asbestos mining area. This hypothesis could not be supported at once from the original histories obtained from the patients, for they included housewives, domestic servants, cattle herders, farmers, a water bailiff, an insurance agent, and an accountant, none of whom were working on the asbestos mines at the time. We therefore undertook a detailed investigation of their past occupation and place of residence, and the association with asbestos exposure was discovered. The cases are summarized in Table 3. Previous biopsy specimens were re-examined, and new cases diagnosed, including asbestos miners. In only one case do the relatives deny that the patient either visited the asbestos mines or was exposed to asbestos.

This is a preliminary publication and the problem is being intensively investigated.

The Asbestos Area of the North-West Cape

According to Hall (1930) asbestos was discovered by Lichenstein near Prieska during his travels between 1803 and 1806. Since then it has been established that the asbestos deposits extend from 20 miles south of Prieska, northwards through the western part of the magisterial district of Hay, to the eastern portion of the magisterial district of Postmasburg and finally, to the western area of the

Umwelt und Krebs

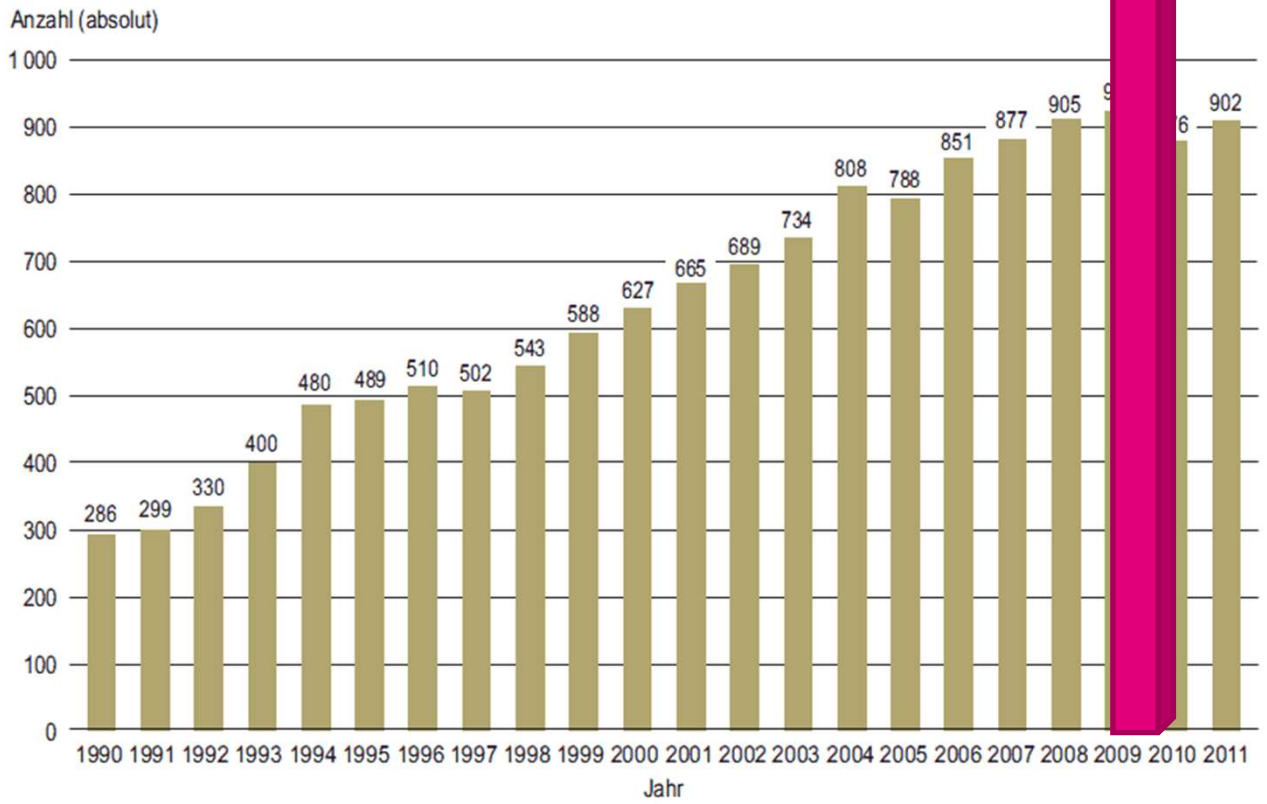
Pleuralmesotheliome

TABELLE 1

Inzidenzen und Häufigkeitsgipfel (Peak) der Mesotheliomerkrankungen weltweit

Land	Inzidenz bei Peak (Erkrankungen pro 1 Million)	Peak (Jahr/Zeitraum)	Erwartete Todesfälle (im Jahr des Maximums)	Studie
Australien	40	2010	1 000	Leigh 2002 (e8)
Großbritannien	38	2016	2 040	Tan 2010 (e9)
Deutschland	20	2015–2020	1 600	Pesch 2010 (e10) Peto 1999 (e11)
Frankreich	20	2020–2040	1 300	Banaei 2000 (e12)
USA	15	2010	2 800	Larson 2007 (e13)
Japan	15	2025–2033	1 200	Azuma 2009 (e14)
Spanien	11	2016	520	Pitarque 2008 (e15)
Niederlande	10	2028	900	Segura 2003 (e16)

GRAFIK

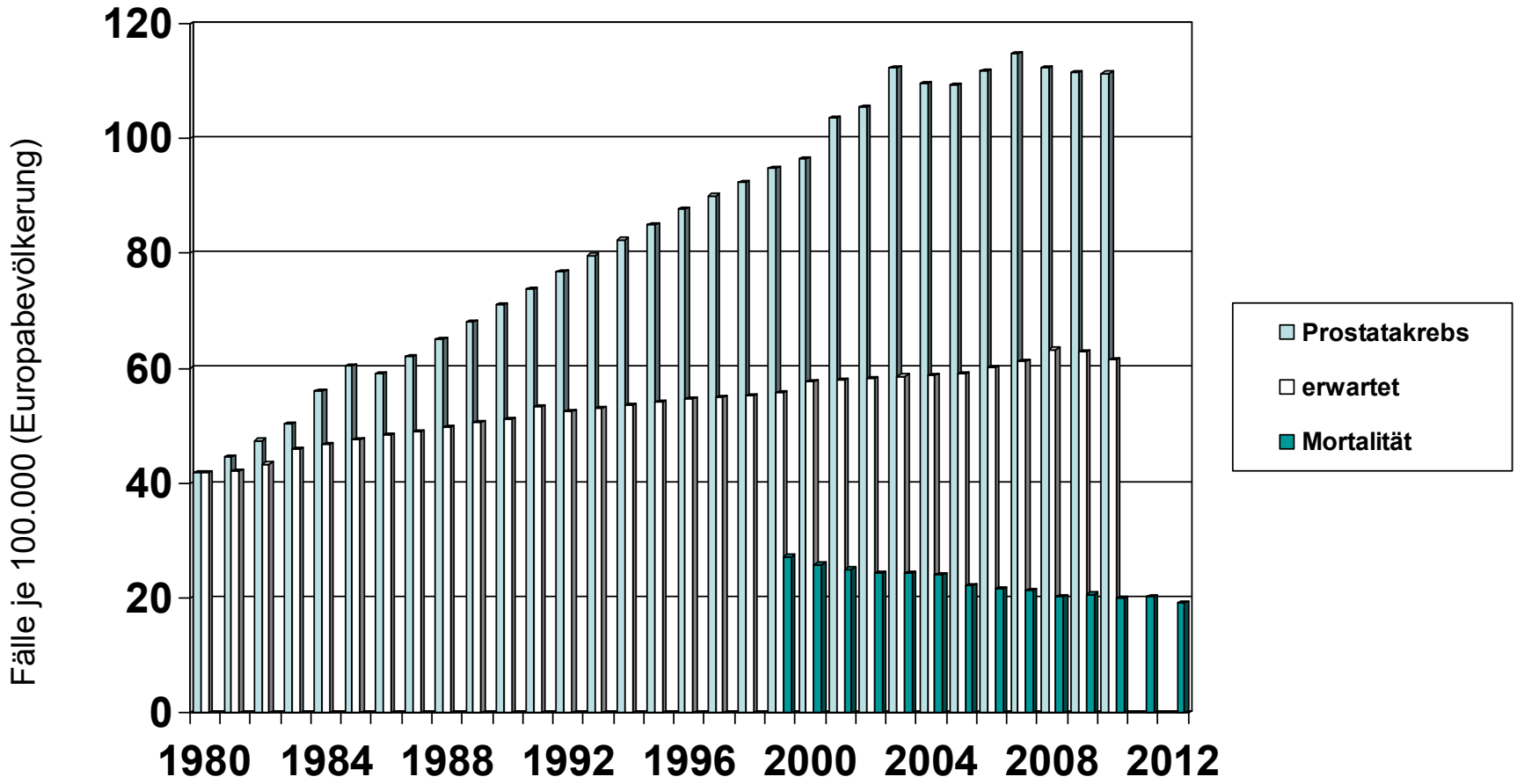


Neu als Berufskrankheit nach Nr. 4105 der Berufskrankheitenverordnung (BKV) anerkannte Mesotheliome in Deutschland.
Quelle: Deutsche Gesetzliche Unfallversicherung (DGUV)

2009: Neuerkrankungen 1590

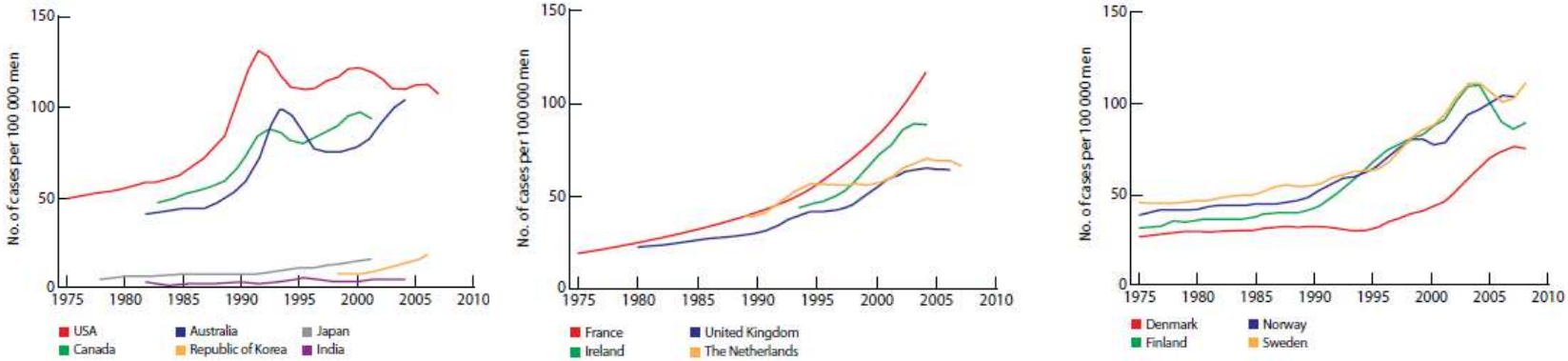
Hormonell abhängige Krebsformen

Trend: Prostatakrebs in Deutschland 1980-2010



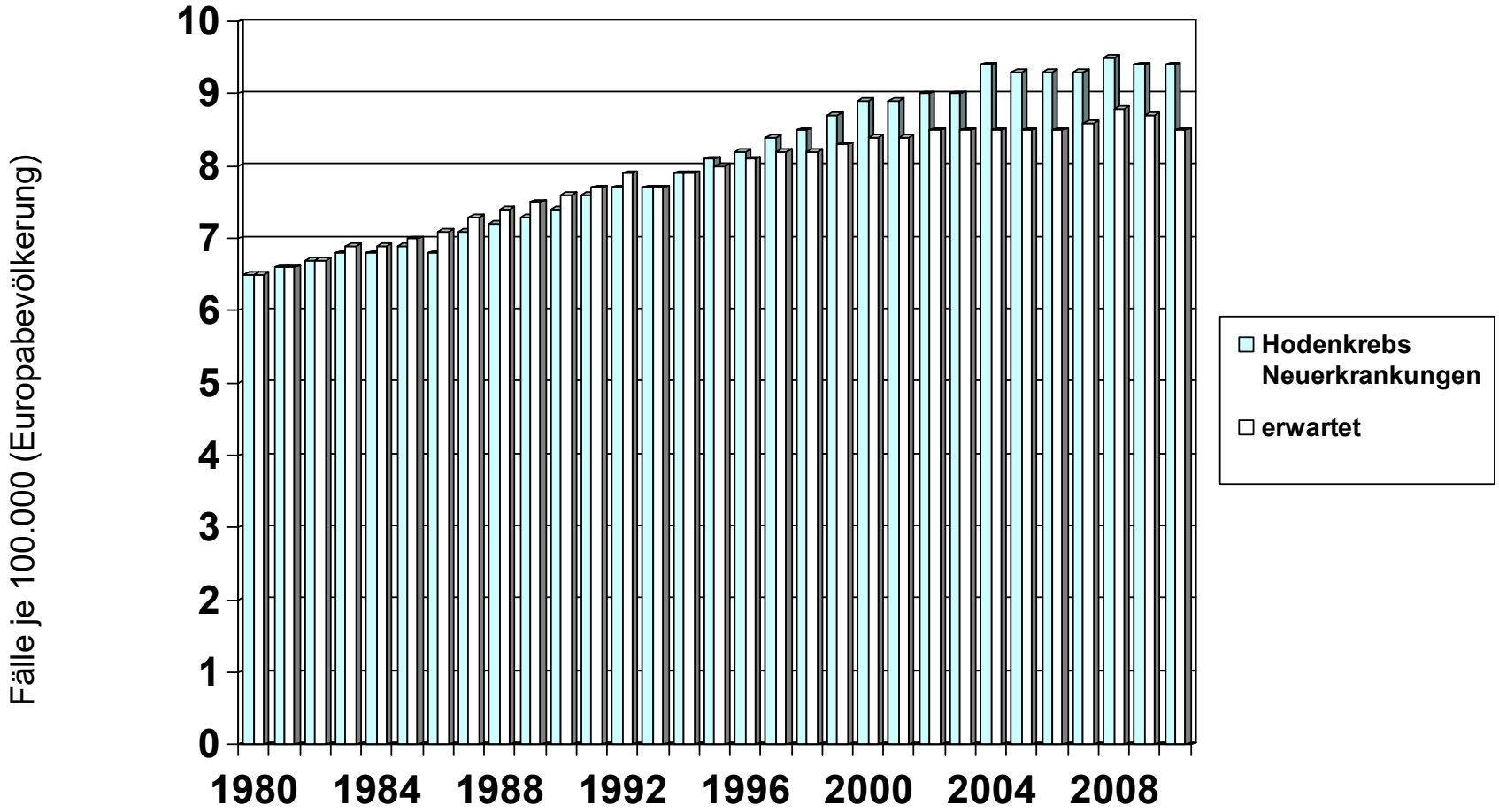
Quelle: Dachdokumentation Krebs, RKI 2008, 2014, recalc.

Altersstandardisierte Erkrankungsraten: Prostatakrebs in verschiedenen Ländern, je 100.000 Männer, altersstandardisiert



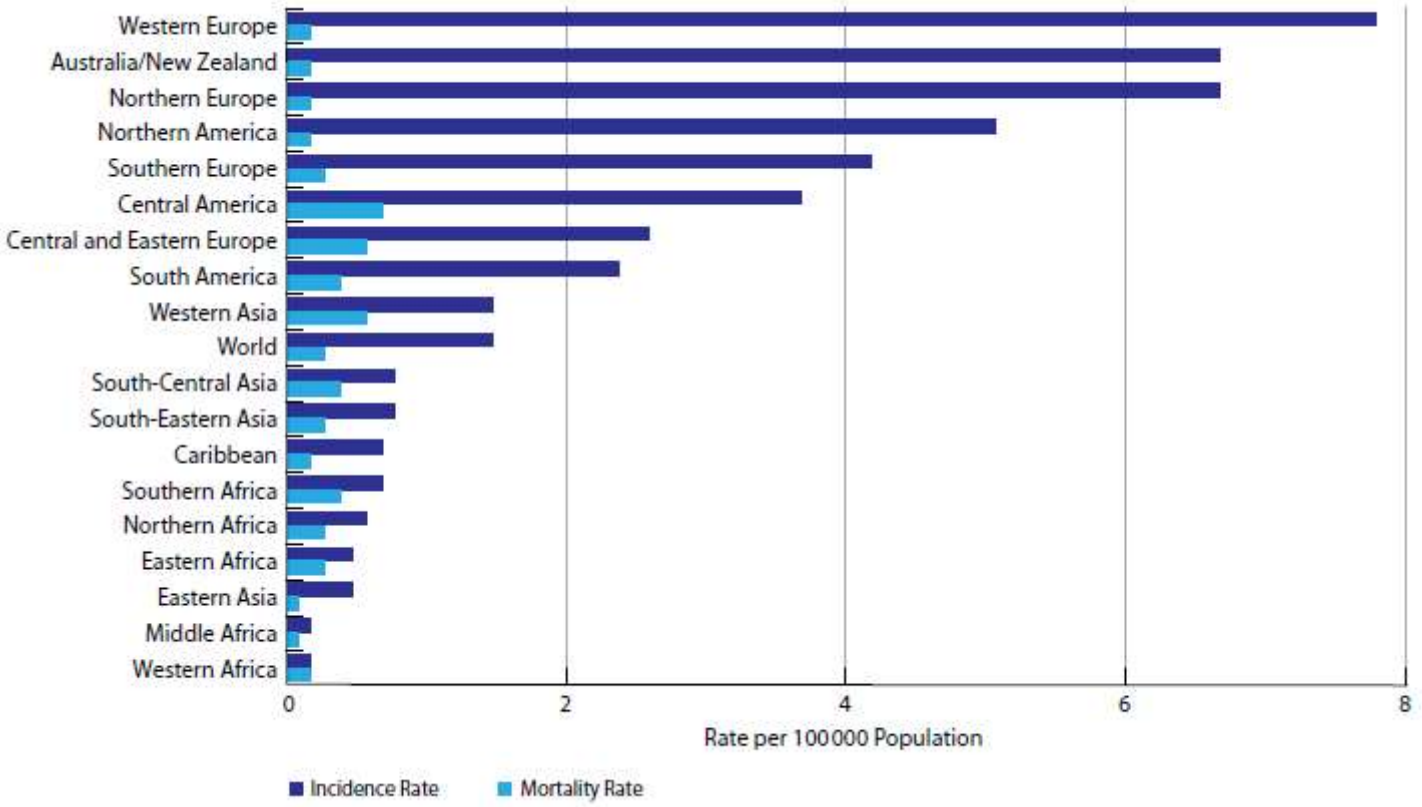
Quelle: WHO / UNEP State of the Science of Endocrine Disrupting Chemicals 2012

Trend: Hodenkrebs in Deutschland 1980-2010

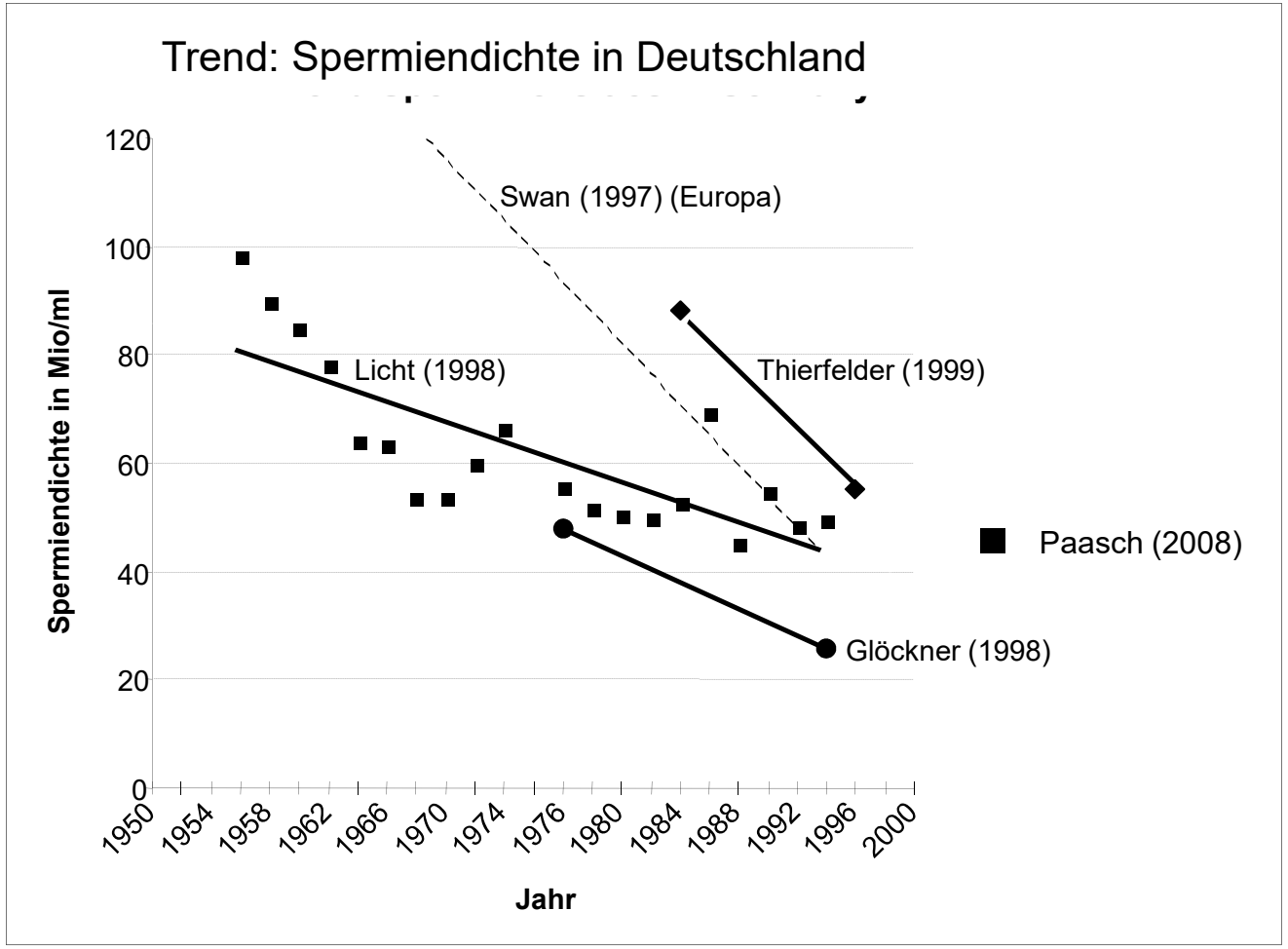


Quelle: Dachdokumentation Krebs, RKI 2008, 2014, recalc.

Altersstandardisierte Erkrankungs- und Sterberaten: Hodenkrebs in verschiedenen Ländern, Männer, je 100.000

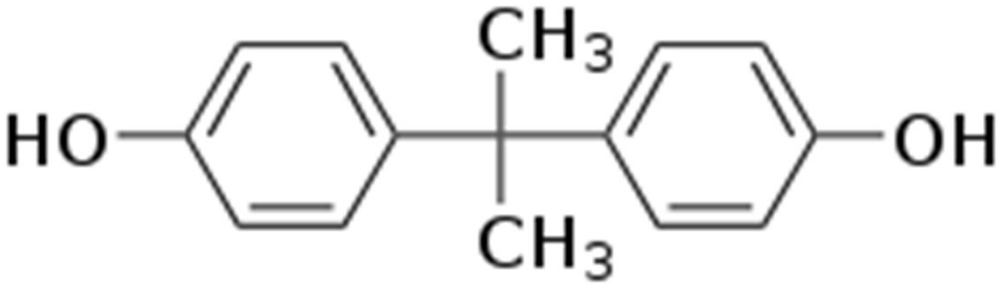


Quelle: WHO / UNEP State of the Science of Endocrine Disrupting Chemicals 2012


Trend: Spermiendichte in Deutschland
Spermiendichte in Mio/ml
120
100
80
60
40
20
0
1950
1954
1958
1962
1966
1970
1974
1976
1980
1984
1988
1992
1996
2000
Jahr
Swan (1997) (Europa)
Licht (1998)
Thierfelder (1999)
Glöckner (1998)
Paasch (2008)

Späte Lehren aus frühen Warnungen II: Bisphenol A

Bisphenol A



- 1.400.000 t werden jährlich in der EU produziert, 3,8 Mio t weltweit
- 5-10% Zuwachs pro Jahr
- Polycarbonate und Epoxidharze
- GE, Bayer und Dow Hauptproduzenten

1938: Erste Hinweise auf die Toxizität von Bisphenol A

612.621.5:547.6

Molecular structure in relation to oestrogenic activity. Compounds without a phenanthrene nucleus

By E. C. Dodds and W. Lawson

From the Courtauld Institute of Biochemistry

(*Communicated by Sir Henry Dale, F.R.S.—Received* 11 *December* 1937)

In earlier publications the oestrogenic activity of a number of synthetic substances has been discussed. The first compounds to be tested contained the phenanthrene ring system, and it was shown (Cook, Dodds and Hewett 1933; Cook and Dodds 1933; Cook, Dodds, Hewett and Lawson 1934; Cook, Dodds and Greenwood 1934) that a high degree of activity is possessed by 9 : 10-dihydroxy-9 : 10-di-*n*-propyl-9 : 10-dihydro-1 : 2 : 5 : 6-dibenzanthracene. Potency was also observed in the highly unsaturated aliphatic acid, clupanodonic acid, whilst a feeble but definite oestrogenic action was found to be possessed by calciferol. Since neither of these compounds contains the phenanthrene ring system, it was considered that this was not essential for oestrogenic properties. A further interesting observation was made in the partial activity of 1-keto-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene. This substance produced an advanced pro-oestrus, but full cornification could not be produced no matter how much of the material was administered.

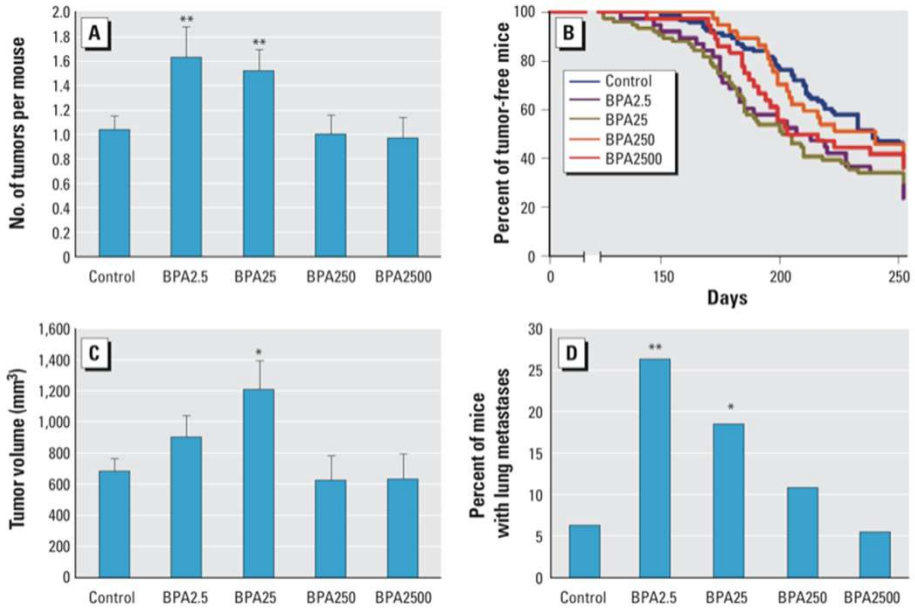
A series of derivatives of acenaphthene was studied because these compounds contain a three-ring system arranged in a manner different from that in phenanthrene. These were tested on ovariectomized rats in the manner described in the above-mentioned publications. Table I shows the

Table I

Derivatives of acenaphthene	Method of preparation	Dose in mg.	% positive
1 : 2-Dihydroxy-1 : 2-di-*n*-propyl acenaphthene	Maxim (1929)	100	Nil
1 : 2-Dihydroxy-1 : 2-diphenyl acenaphthene	Beschke (1909)	100	Nil
1 : 2-Dihydroxy-1 : 2-dibenzyl acenaphthene	Maxim (1929)	100	Nil
1 : 2-Dihydroxy-1 : 2-di-α-naphthyl acenaphthene	—	100	100
		10	100
		1	20
1 : 1-Diphenyl acenaphthenone	Beschke (1909)	100	Nil
1 : 1-Di-α-naphthyl acenaphthenone	—	100	100

Molecular Structure in Relation to Oestrogenic Activity. Compounds without a Phenanthrene Nucleus. E. C. Dodds and W. Lawson *Proceedings of the Royal Society of London. Series B, Biological Sciences* Vol. 125, No. 839 (Apr. 27, 1938), pp. 222-232

Brustkrebs und Umwelthormone: Bisphenol A



Research

Chronic Oral Exposure to Bisphenol A Results in a Nonmonotonic Dose Response in Mammary Carcinogenesis and Metastasis in MMTV-erbB2 Mice

Sarah Jenkins,[1] Jun Wang,[1] Isam Eltoum,[2,3] Renee Desmond,[3,4] and Coral A. Lamartiniere[1,3]

[1]Department of Pharmacology and Toxicology, [2]Department of Anatomic Pathology, [3]Comprehensive Cancer Center, and [4]Department of Medicine, Biostatistics Unit, Division of Preventative Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Background: Bisphenol A (BPA) is a synthetic compound used to produce plastics and epoxy resins. BPA can leach from these products in appreciable amounts, resulting in nearly ubiquitous daily exposure to humans. Whether BPA is harmful to humans, especially when administered orally in concentrations relevant to humans, is a topic of debate.

Objectives: In this study, we investigated the role of chronic oral exposure to BPA during adulthood on mammary carcinogenesis by using a transgenic mouse model that spontaneously develops tumors through overexpression of wild-type erbB2 [mouse mammary tumor virus (MMTV)-erbB2].

Methods: MMTV-erbB2 mice were exposed to 0, 2.5, 25, 250, or 2,500 μg BPA/L drinking water from 56 until 112 days of age (for mechanism of action) or 252 days of age (for tumorigenesis). Cellular and molecular mechanisms of BPA action in the mammary gland were investigated via immunohistochemistry and immunoblotting.

Results: Only low doses of BPA significantly decreased tumor latency and increased tumor multiplicity, tumor burden, and the incidence of metastasis. All BPA doses significantly increased the cell proliferation index, but only the higher doses also increased the apoptotic index in the mammary gland. At the molecular level, 25 μg BPA/L, but not 2,500 μg BPA/L, increased phosphorylation of erbB2, erbB3, insulin-like growth factor 1 receptor, and Akt in the mammary gland.

Discussion: Low, but not high, BPA doses significantly accelerated mammary tumorigenesis and metastasis in MMTV-erbB2 mice. The combined ratio of cell proliferation and apoptosis indices and alterations in protein expression best predicted the ability of each dose of BPA to alter tumorigenesis in this model.

Key words: apoptosis, bisphenol A, BPA, mammary gland, MMTV-erbB2 mice, oral exposure, tumorigenesis. *Environ Health Perspect* 119:1604–1609 (2011). http://dx.doi.org/10.1289/ehp.1103850 [Online 12 October 2011]

The environmental contaminant bisphenol A (BPA) is used in the production of polycarbonate plastics and epoxy resins. These products are used in many common consumer goods, such as food and drink containers, the lacquer lining of canned foods and drinks, infant formula bottles, office water coolers, sales receipts, and some dental sealants. Several recent studies (Brede et al. 2003; Howdeshell et al. 2003; Joskow et al. 2006; Kang et al. 2003) have found that BPA can leach from these products during normal use. Recent reports show that ≥ 90% of the populations studied had detectable concentrations of BPA metabolites in the urine (Calafat et al. 2005, 2008; Wolff et al. 2007). These studies have reported mean values of total urinary BPA to be 1–3 μg BPA/L urine, with values ranging from below the level of detection to > 100 μg BPA/L urine. Estimates of daily BPA intake based on models of BPA pharmacokinetics or exposure sources suggest that the mean adult is exposed to 0.4–1.4 μg BPA/kg body weight (BW), and the 95th percentile of exposure does not exceed 1.5–4.2 μg BPA/kg BW per day [Food and Agricultural Organization/World Health Organization (FAO/WHO) 2010; Lakind and Naiman 2008]. However, estimations of daily human exposure to BPA is a controversial subject that has recently been disputed (Taylor et al. 2011; Vandenberg et al. 2007, 2010).

One concern over BPA stems from its classification as a xenoestrogen. BPA is reported to bind to the estrogen receptors (ER), albeit with an affinity several orders of magnitude less than estradiol, and induce downstream transcriptional activity (Kim et al. 2001; Krishnan et al. 1993; Kuiper et al. 1998). However, alternate targets of BPA action have recently been identified (Bouskine et al. 2009; Takayanagi et al. 2006; Takeshita et al. 2001), and the exact mechanism by which BPA functions is currently unknown. Most of the literature has focused on the effects of short-term BPA exposure, administered during specific windows of early-life development, and the resultant later-life consequences. These studies have shown early-life exposure to BPA in female rodents alters the onset of puberty, disrupts estrous cyclicity and normal mammary gland development, and increases the development of preneoplastic lesions in the mammary gland, cell proliferation, and the incidence of mammary gland hyperplasia in transgenic mice lacking BRCA1 (Durando et al. 2007; Howdeshell et al. 1999; Jones et al. 2010; Markey et al. 2001, 2003; Munoz-de-Toro et al. 2005; Murray et al. 2007; Vandenberg et al. 2008; Wadia et al. 2007).

We have shown recently that oral BPA exposure during the prenatal period or prepubertal period accelerates carcinogenesis in a model of chemically induced mammary cancer (Betancourt et al. 2010; Jenkins et al. 2009). Alterations to cell proliferation and apoptosis in the mammary gland were accompanied by molecular changes, including increased expression and/or activation of the erbB family of receptor tyrosine kinases. These findings led us to hypothesize that a subpopulation of adults exist, namely women with HER2/erbB2-positive breast cancer, that could be negatively affected by chronic BPA exposure during adulthood. Women with breast cancer that overexpresses HER2/erbB2 account for 15–30% of all diagnosed pathology subtypes and are usually associated with an unfavorable clinical outcome (reviewed by Barros et al. 2010).

Materials and Methods

Chemicals and antibodies. BPA was purchased from Sigma Chemical Company (St. Louis, MO). Antibodies to epidermal growth factor receptor (EGFR), erbB2, phosphorylatederbB3, phosphorylatederbB3, insulin-like growth factor 1 receptor (IGF-1R), phosphorylated-IGF-1R, phosphorylated-Bad, PI3K, PTEN, Akt 1, Akt 3, phosphorylatedAkt, glycogen synthase kinase-3-beta (GSK-3β), and phosphorylatedGSK-3β were purchased from Cell Signaling Technologies (Danvers, MA). Antibodies to erbB3 and IGF-1 were purchased from Santa Cruz Biotechnology (Santa Cruz, CA).

Animal care and use. Animal care and use were conducted according to established

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The authors declare they have no actual or potential competing financial interests.

Received 22 April 2011; accepted 29 July 2011.

Prostatakrebs und Umwelthormone: Bisphenol A

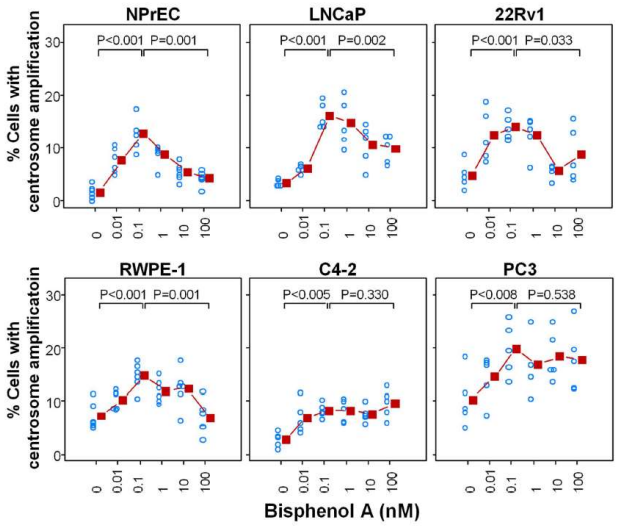

Figure 2. Low doses of BPA have an adverse effect on centrosome numbers in prostate cancer cells. The cell lines NPrEC, RWPE1, LNCaP, C4-2, 22Rv1, and PC3 were treated with medium containing 10% CSS plus 0, 0.01 nM, 0.1 nM, 1 nM, 10 nM and 100 nM BPA for 72 h. Cells were fixed with 100% cold methanol and immunostained for centrosomes and nuclei. The number of centrosomes per cell was scored by fluorescence microscopy. The results are shown as an average determined from five separate experiments. The scatter plot was generated of the percentage of cells with an abnormal number of centrosomes in response to BPA. Analyses was performed using a fixed effect model for each cell line. *Post hoc* comparisons of means were adjusted using Bonferroni's tests. The fold change is the percentage of cells with abnormal centrosomes at 0.1 nM BPA/ the percentage of cells with abnormal centrosomes at 0 nM BPA.
doi:10.1371/journal.pone.0090332.g002

OPEN ACCESS Freely available online

PLOS ONE

Exposure to Bisphenol A Correlates with Early-Onset Prostate Cancer and Promotes Centrosome Amplification and Anchorage-Independent Growth *In Vitro*

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Abstract

Human exposure to bisphenol A (BPA) is ubiquitous. Animal studies found that BPA contributes to development of prostate cancer, but human data are scarce. Our study examined the association between urinary BPA levels and Prostate cancer and assessed the effects of BPA on induction of centrosome abnormalities as an underlying mechanism promoting prostate carcinogenesis. The study, involving 60 urology patients, found higher levels of urinary BPA (creatinine-adjusted) in Prostate cancer patients (5.74 μg/g [95% CI; 2.63, 12.51]) than in non-Prostate cancer patients (1.43 μg/g [95% CI; 0.70, 2.88]) ($p = 0.012$). The difference was even more significant in patients <65 years old. A trend toward a negative association between urinary BPA and serum PSA was observed in Prostate cancer patients but not in non-Prostate cancer patients. *In vitro* studies examined centrosomal abnormalities, microtubule nucleation, and anchorage-independent growth in four Prostate cancer cell lines (LNCaP, C4-2, 22Rv1, PC-3) and two immortalized normal prostate epithelial cell lines (NPrEC and RWPE-1). Exposure to low doses (0.01–100 nM) of BPA increased the percentage of cells with centrosome amplification two- to eight-fold. Dose responses either peaked or reached the plateaus with 0.1 nM BPA exposure. This low dose also promoted microtubule nucleation and regrowth at centrosomes in RWPE-1 and enhanced anchorage-independent growth in C4-2. These findings suggest that urinary BPA level is an independent prognostic marker in Prostate cancer and that BPA exposure may lower serum PSA levels in Prostate cancer patients. Moreover, disruption of the centrosome duplication cycle by low-dose BPA may contribute to neoplastic transformation of the prostate.

Citation: Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, et al. (2014) Exposure to Bisphenol A Correlates with Early-Onset Prostate Cancer and Promotes Centrosome Amplification and Anchorage-Independent Growth *In Vitro*. PLoS ONE 9(3): e90332. doi:10.1371/journal.pone.0090332

Hormonanhängige Krebsformen

SCHLUSSFOLGERUNGEN DES WHO / UNEP STATE OF THE SCIENCE REPORT 2012

Eine Rolle von Umwelthormonen bei der Zunahme hormonell abhängiger Krebsformen ist biologisch plausibel

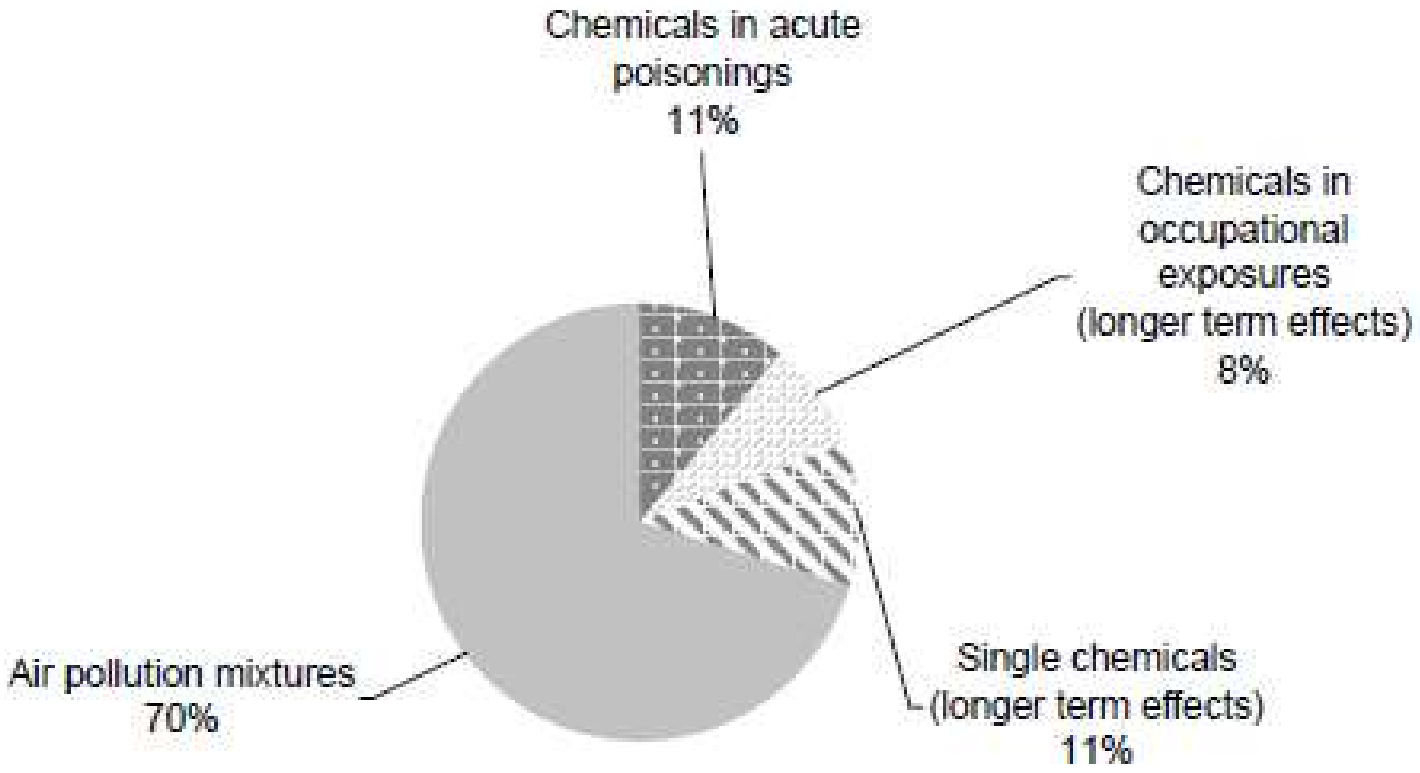
•Die Zunahme der mit Hormonen verbundenen Krebsformen kann nicht durch genetische Faktoren erklärt werden

•Umweltfaktoren einschließlich der Exposition gegenüber Chemikalien spielen eine Rolle, wenige davon konnten jedoch bisher charakterisiert werden

•Für Tumore der Brust, des Endometriums, der Eierstöcke und der Prostata ist die Rolle körpereigener und therapeutischer Hormone gut nachgewiesen. Dies macht es biologisch plausibel, dass Xenoöstrogene auch zum Risiko beitragen

Krankheitslasten

Verteilung bekannter Krankheitslasten durch Chemikalien



Prüss-Ustün *et al. Environmental Health* 2011, **10**:9

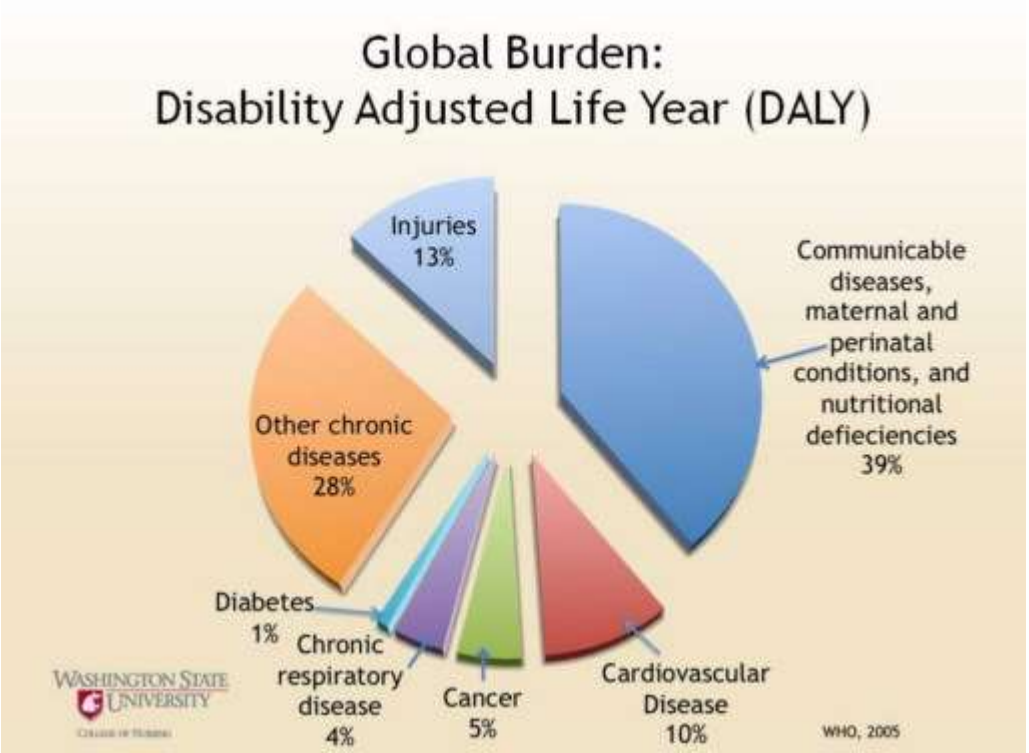
Wie viele gesunde Lebensjahre gehen in Deutschland verloren?

BERECHNUNGEN DER UNIVERSITÄT HELSINKI (EUROPEAN PERSPECTIVES ON ENVIRONMENTAL BURDEN OF DISEASE) 2011

VERLUST VON GESUNDEN LEBENSJAHREN DURCH KREBSERKRANKUNGEN

DISABILITY ADJUSTED LIFE YEARS

DALYS

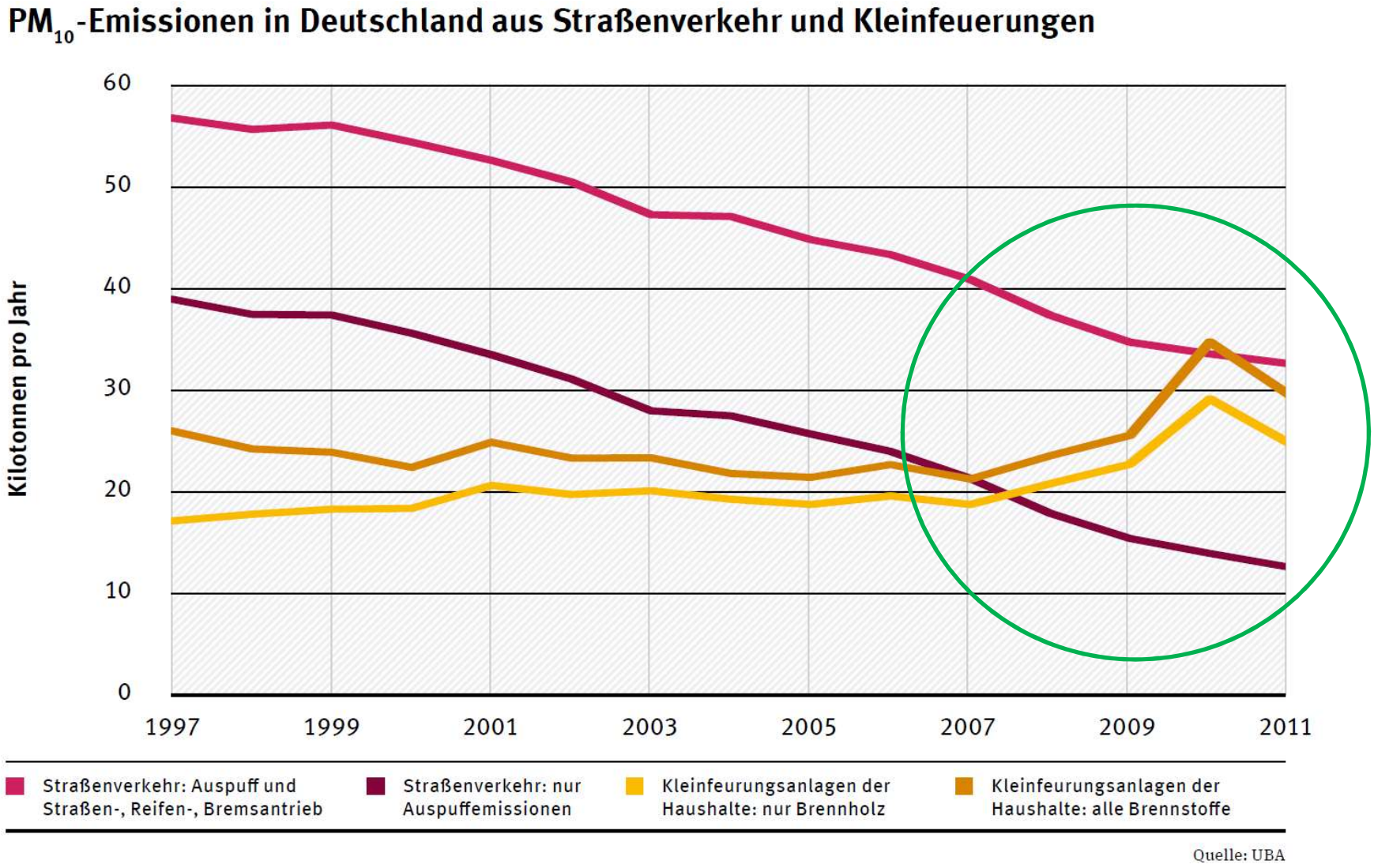


Quelle: Quellenangabe XY und noch mehr Quellen

Krankheitslasten durch Krebserkrankungen durch Chemikalien In Deutschland

SUBSTANZ	ERKRANKUNG	DALY
Benzol	Leukämie	240
Dioxin	Alle Krebsarten	38.800
Passivrauch	Lungenkrebs, Nichtraucher	6.700
PM 2,5	Lungenkrebs	120.600
Radon	Lungenkrebs	67.200

… und Aktualisierungsbedarf



Überraschendes vom Krebskataster

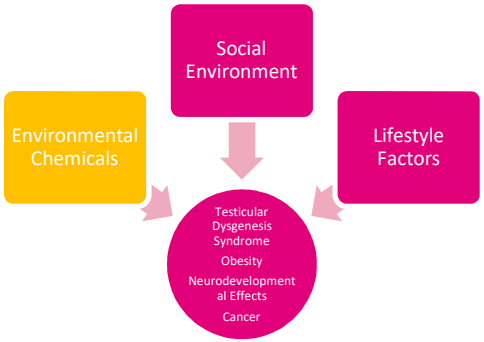
Krebsregister als Warnsystem: Gasbohrungen in Bothel / Rotenburg an der Wümme

Krebslokalisation bzw. -diagnose	Geschlecht	Beobachtete Neuer-krankungen	Erwartete Neuer-krankungen	p-Wert	Signifikanz für diese Untersuchung
Mund + Rachen	m + w	6	12,1	0,9813	n.s.
Verdauungsorgane außer Leber	m	66	61,0	0,2783	n.s.
	w	52	49,7	0,3916	n.s.
Leber	m + w	2	5,2	0,9667	n.s.
Kehlkopf, Lunge	m	43	39,3	0,2957	n.s.
	w	10	16,0	0,9561	n.s.
Knochen, Haut, Weichteilgewebe u.ä.	m + w	32	27,5	0,2183	n.s.
Brustdrüse	w	85	75,2	0,1411	n.s.
Weibliche Genitalorgane	w	28	28,8	0,5863	n.s.
Prostata, Hoden	m	95	82,9	0,1036	n.s.
Niere, Harnorgane	m + w	29	31,5	0,6948	n.s.
Hirntumoren	m + w	7	6,9	0,5345	n.s.
Endokrine Drüsen	m + w	9	4,5	0,0385	n.s.
Leukämien + Lymphome	**m**	**41**	**21,3**	**0,0001**	**signifikant**
	w	15	16,8	0,7010	n.s.

n.s. = nicht signifikant

Quelle: Niedersächsisches Krebsregister

Was nehmen Sie nach Hause?



Krebstherapie wird immer erfolgreicher

Krebsprävention hat weithin versagt

Umweltchemikalien spielen bei der Zunahme der Krebserkrankungen offensichtlich eine Rolle

Anteil der Umweltchemikalien zu quantifizieren ist schwierig, Beteiligung wird aber wohl unterschätzt

Hormonell abhängige Krebsformen steigen stark: Rolle der Umwelthormone

Frühes Erkennen ist möglich und notwendig

Blick nach vorn:

Vorsorgende Umweltpolitik: Reach

Kriterien für Umwelthormone

Mischung von Stoffen

Besser beobachten: HBM, Krebsregister
Integriert betrachten: Chemikalien, Ernährung, Lifestyle

und…

Vielen Dank für Ihre Aufmerksamkeit

Andreas Gies
andreas.gies@uba.de
Twitter: @giesandreas

www.umweltbundesamt.de/themen/gesundheit