Genetica ed epigenetica del cancro: dalla teoria mutazionale stocastica ai nuovi modelli di cancerogenesi

Patrizia Gentilini
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http://www.tumori.net/it3/brochures/documenti/inceneritori/Ambiente_e_Tumori_17_10_11.pdf

La lotta contro il cancro ha combattuto molte battaglie sbagliate,
con le armi sbagliate e sotto i comandanti sbagliati.

Devra Davis

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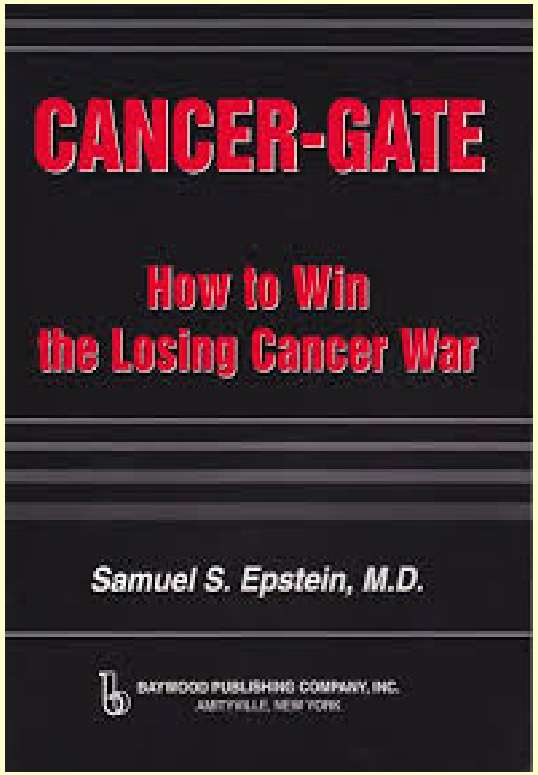
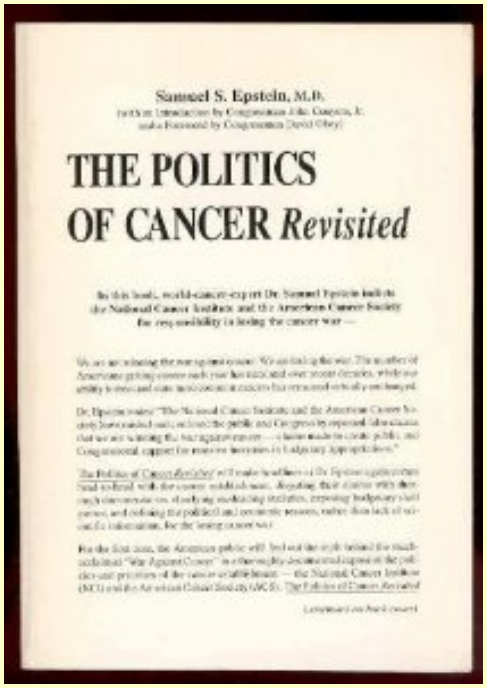
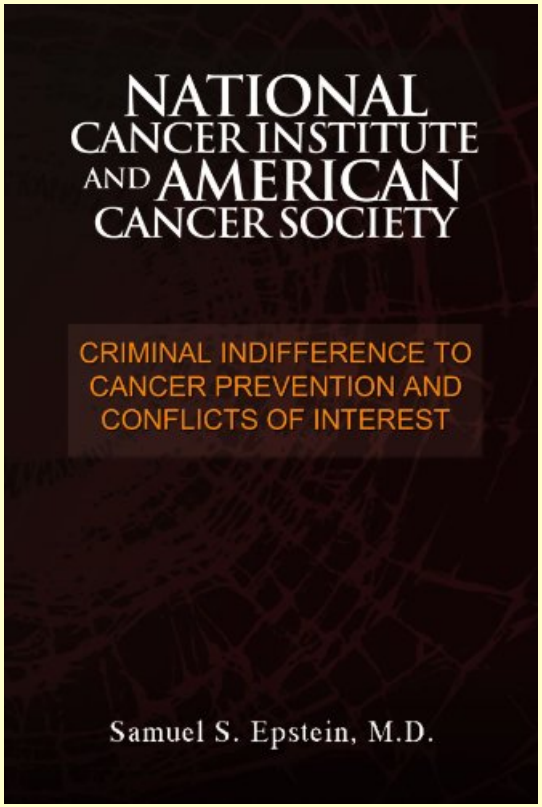
Euro 35,00

La storia segreta della guerra al cancro

edice
EDIZIONI







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http://www.preventcancer.com/

Theories of carcinogenesis: An emerging perspective

C. Sonnenschein, A.M. Soto / Seminars in Cancer Biology 18 (2008) 372–377

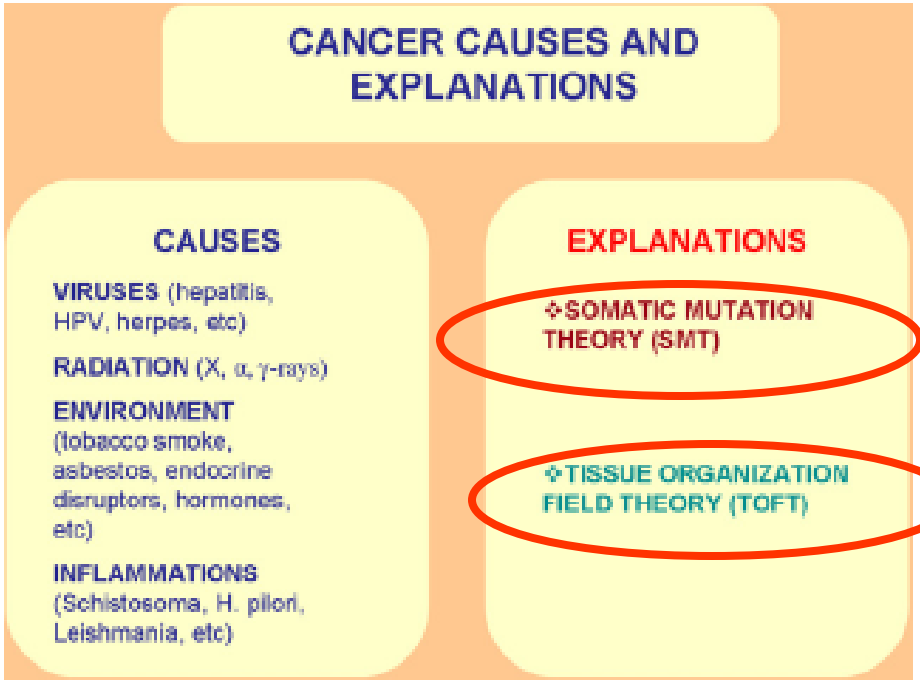


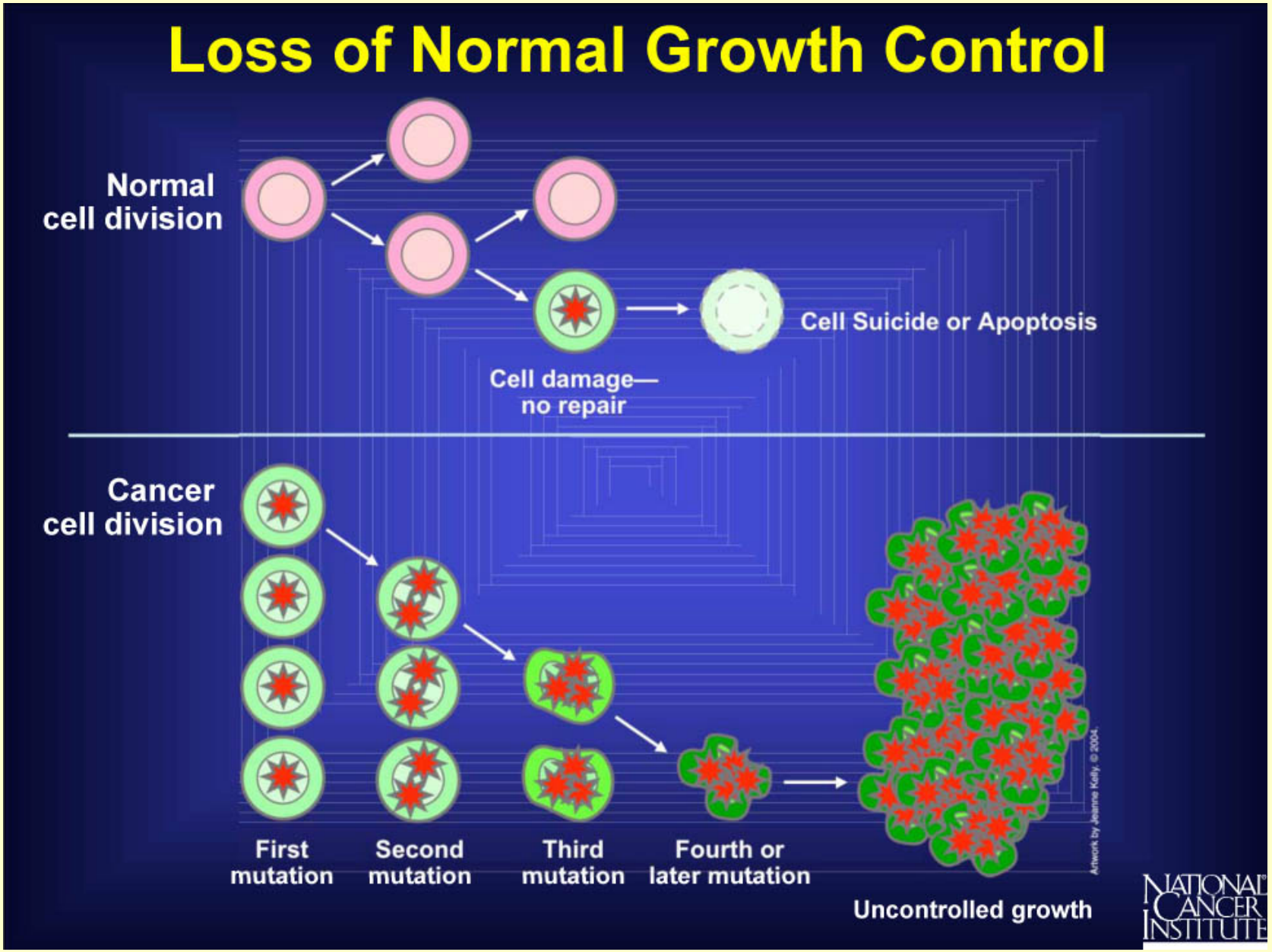
Fig. 1. Differences between the terms "causes" and "explanations" in the context of cancer research.

SEMINARS IN CANCER BIOLOGY 18 (2008) 372-377

SMT
CANCRO = MALATTIA "GENETICA"

"si propone che la maggior parte dei tumori derivi da una singola cellula e che la progressione tumorale sia il risultato di una instabilità genetica acquisita all'interno del clone originale che consente la selezione delle linee cellulari più aggressive"

Nowell 1976


Loss of Normal Growth Control
Normal cell division
Cell Suicide or Apoptosis
Cell damage—no repair
Cancer cell division
First mutation
Second mutation
Third mutation
Fourth or later mutation
Uncontrolled growth
Artwork by Jeanne Kelly, © 2004.
NATIONAL CANCER INSTITUTE

Teoria Mutazionale Somatica (SMT)

"l'insorgenza di mutazioni casuali nei geni che controllano la proliferazione e l'apoptosi sono responsabili del cancro"

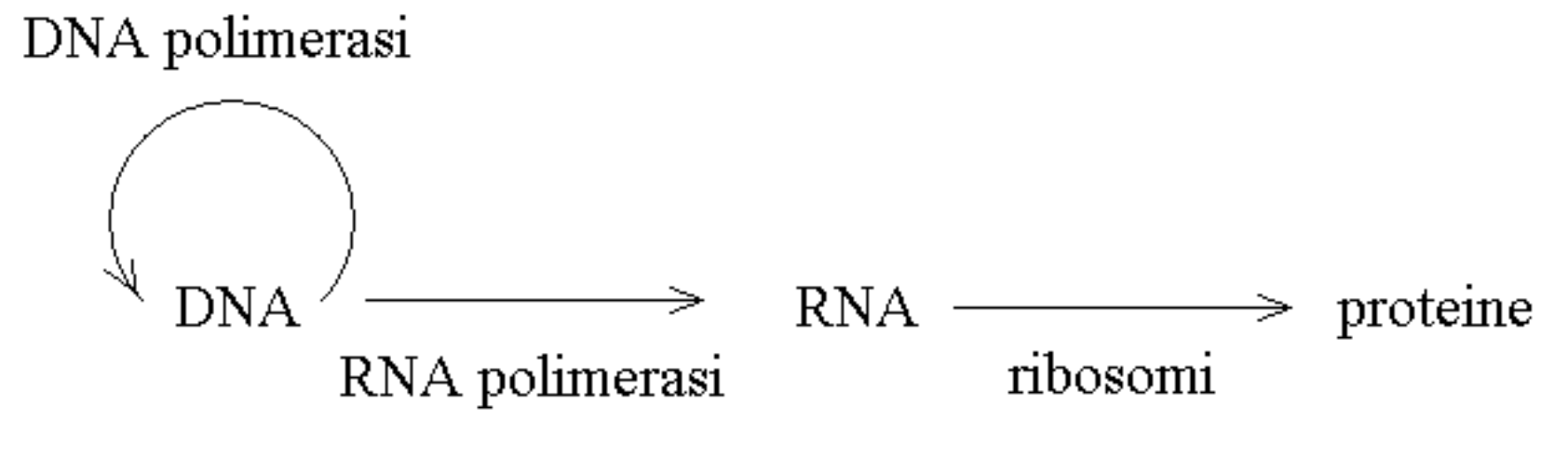
Bertam J.S. 2001

Teoria Mutazionale Somatica (SMT)

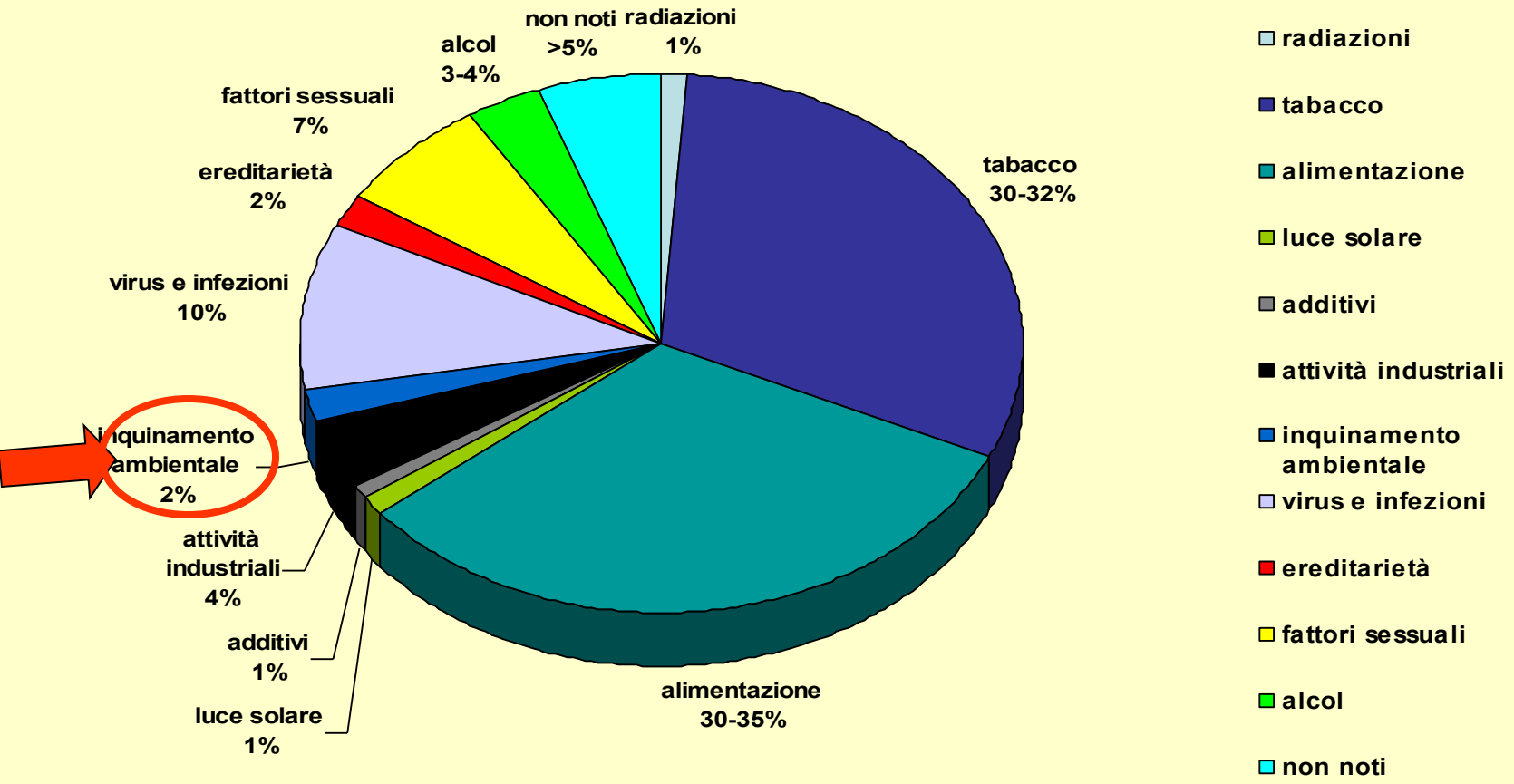
Origine monoclonale della malattia in seguito ad un "incidente genetico", tanto più frequente al crescere dell'età; processo irreversibile con successivo accumulo di mutazioni sequenziali identificabili in:

- Proliferazione svincolata dai normali segnali di crescita
- Insensibilità ai segnali inibitori
- Resistenza alla morte cellulare programmata (apoptosi)
- Riattivazione delle telomerasi (immortalizzazione)
- Attivazione dell'angiogenesi
- Tendenza a metastatizzare
- Instabilità genomica

SMT:
INFORMAZIONE A "SENSO UNICO"



RISCHI ATTRIBUIBILI DI CANCRO
secondo R.Doll e Pito



...

	Quota di tumori attribuibili a vari fattori di rischio	
	USA, 2012*	Regno Unito, 2010**
Fattore di rischio	**%**	**%**
Tabacco	33	19.4
Dieta	5	9.2
Sovrappeso, obesità	20	5,5
Inattività fisica	5	1.0
Abuso di bevande alcoliche	3	4.0
Fattori occupazionali	5	3.7
Infezioni	5	3.1
Radiazioni ionizzanti e esposizione a raggi UV	2	5.3
Inquinamento ambientale	2	–

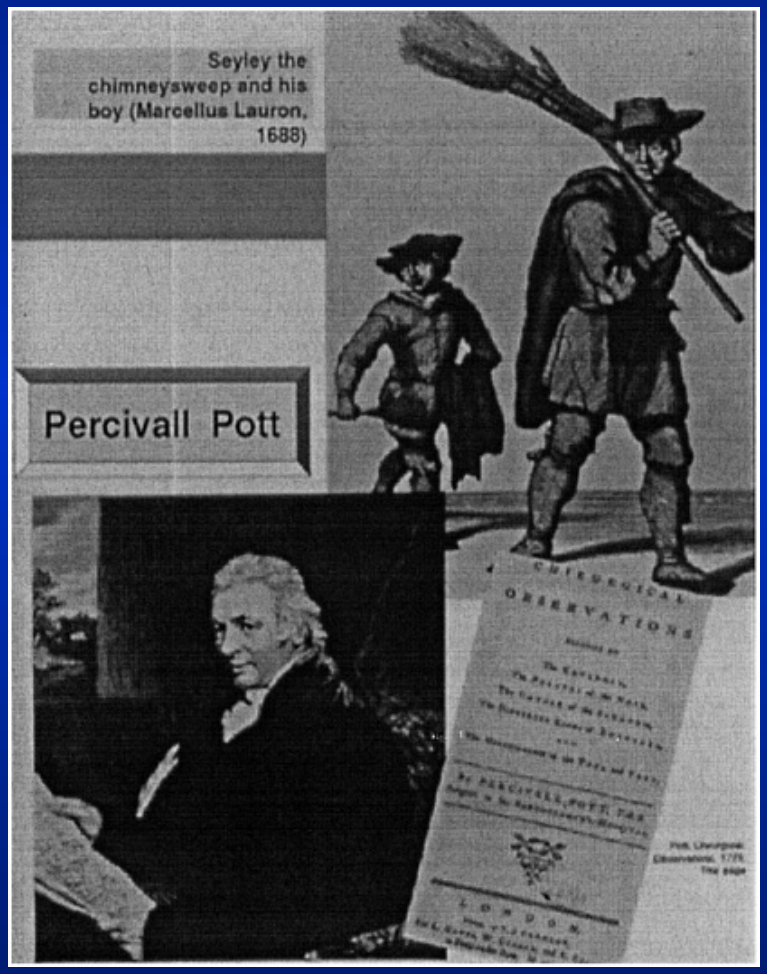
Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors

Lancet 366: 1784-1793, 2003

- analizzata la mortalità per 12 tipi di tumore in 7 aree del mondo
- 9 fattori di rischio indagati: 5 legati allo stile di vita, 2 a virus e 2 a polluzione aerea
- questi 9 fattori insieme, spiegano dal 39% al 41% di tutti i tumori

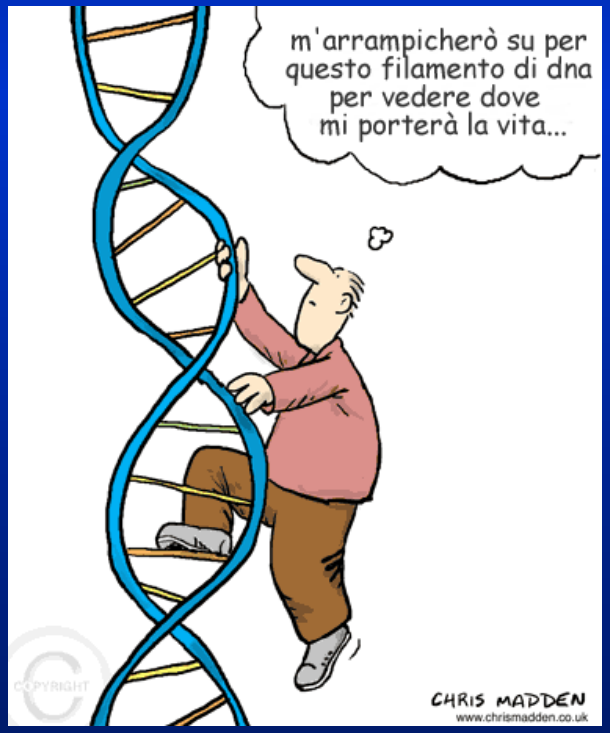
essi non possono pertanto essere assunti come esemplificativi del fenomeno cancro nel suo complesso

…eppure le cause ambientali/occupazionali del cancro erano state studiate da secoli con rigore e lungimiranza!

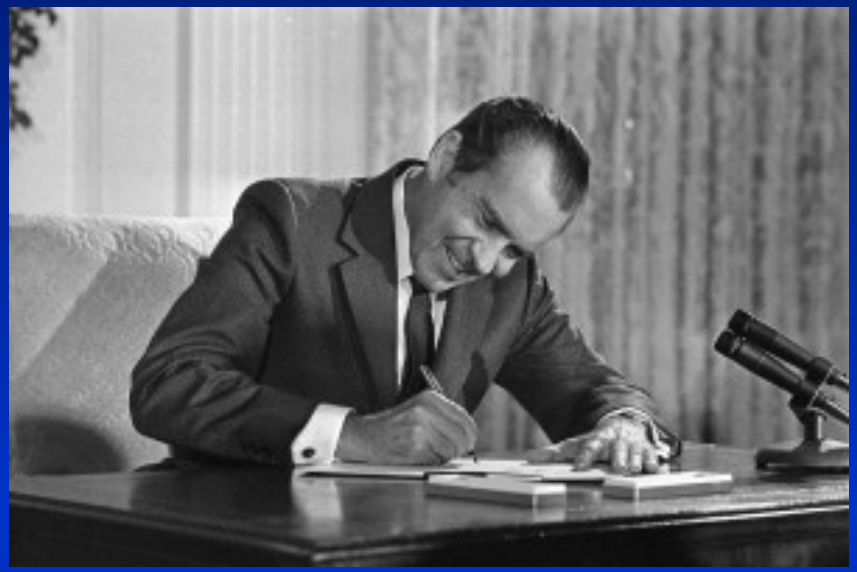


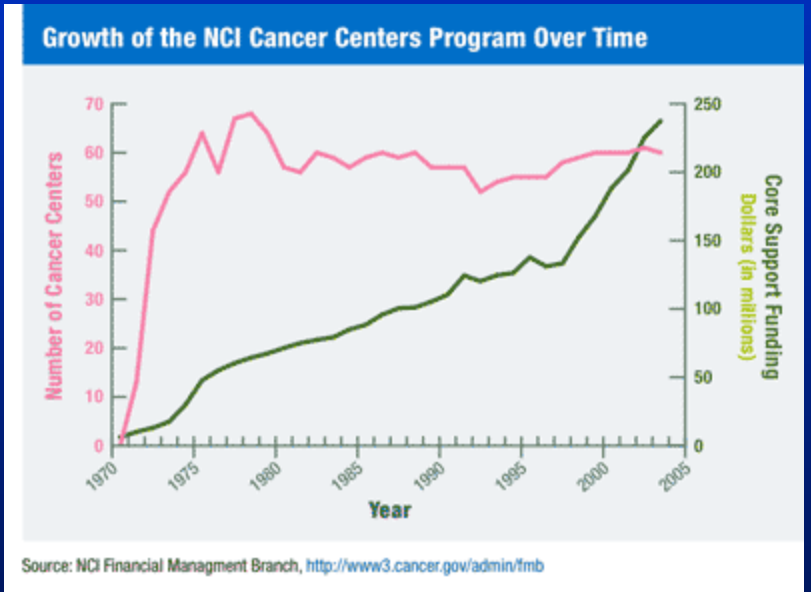
CANCRO = MALATTIA GENETICA

Tutta l'attenzione si sposta dalla ricerca delle cause allo studio delle modalità con cui si compie la trasformazione neoplastica

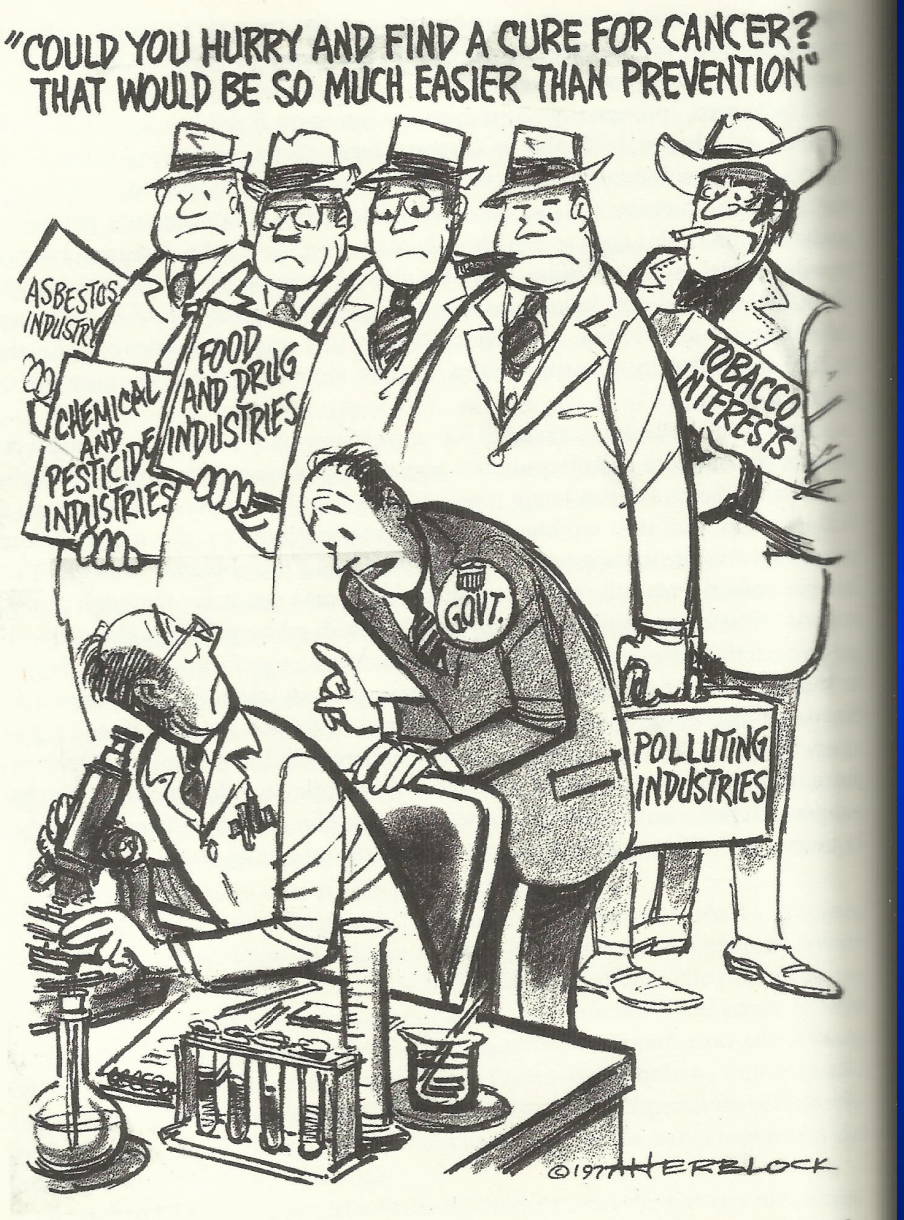


WAR ON CANCER: NATIONAL CANCER ACT 1971





Targeted Therapy: The Hype



Vignetta del 1977 di Herblock. *Could you hurry and find a cure for cancer? That would be so much easier than prevention*, © by The Herb Block Foundation.

GUERRA AL CANCRO: RISULTATI DOPO 30 ANNI

(Dati dell'American Cancer Society 2005)

Table 1.

Relative survival* (%) during three time periods, by cancer site in the USA.†

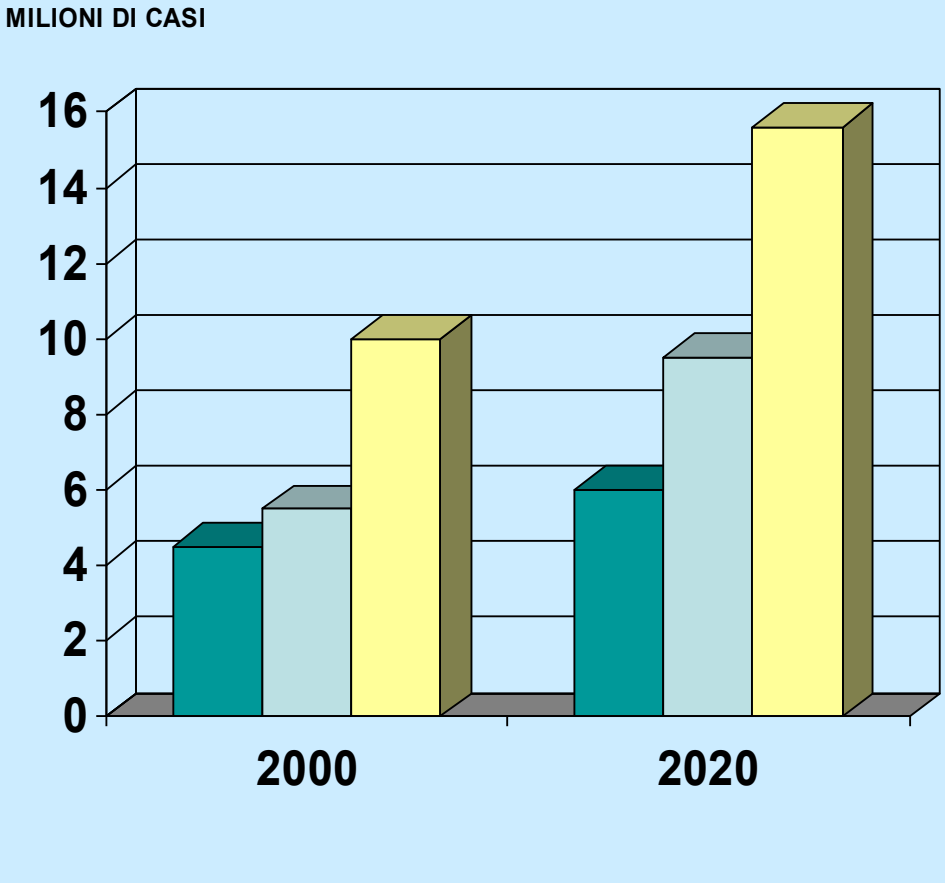
Site	1974–1976	1983–1985	1995–2000
All sites	50	53	64
Breast (female)	75	78	88
Colon	50	58	63
Leukaemia	34	41	46
Lung and bronchus	13	14	15
Melanoma of the skin	80	85	91
Non-Hodgkin lymphoma	47	54	59
Ovary	37	41	44‡
Pancreas	3	3	4
Prostate	67	75	99
Rectum	49	55	64
Urinary bladder	73	78	82

*Five-year relative survival rates based on follow-up of patients through 2001.

†Source: American Cancer Society, 2005 [1].

‡Recent changes in classification of ovarian cancer have affected 1995–2000 survival rates [1].

INCIDENZA DEL CANCRO NEL MONDO: PROIEZIONI FINO AL 2020



(WHO,2006)

INCIDENZA DEL CANCRO

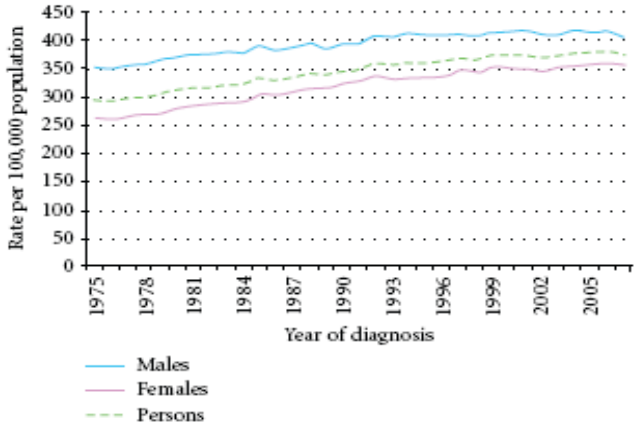


FIGURE 1: Age standardized (European) incidence rates for all cancers excluding nonmelanoma skin cancer, Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer in Research organisation, accessed on 18/2/2011 [10].

INCIDENZA e MORTALITA' CANCRO della MAMMELLA

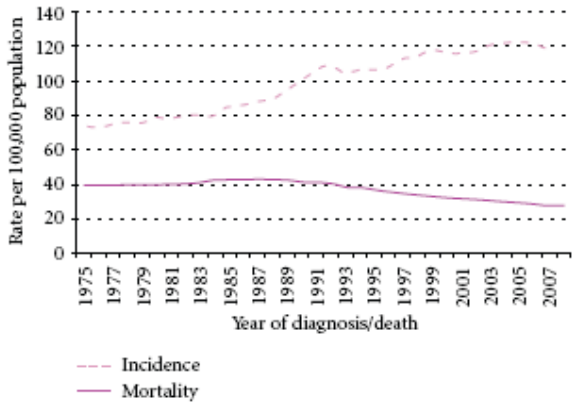


FIGURE 2: Age standardized (European) incidence and mortality rates for breast cancer in females in Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer Research organisation, accessed on 18/2/2011 [10].

INCIDENZA e MORTALITA' CANCRO della PROSTATA

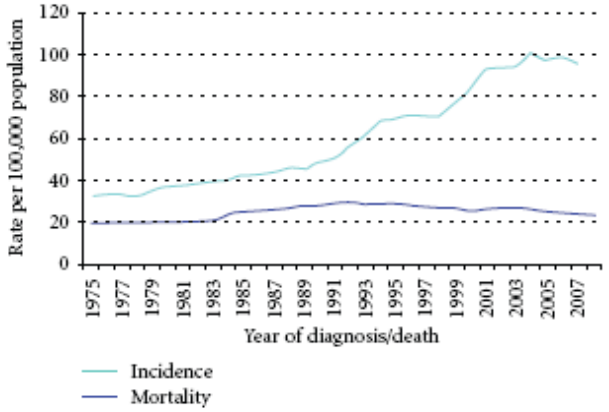


FIGURE 3: Age standardized (European) incidence and mortality rates for prostate cancer in males in Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer Research organisation, accessed on 18/2/2011 [10].

I NUMERI DEL CANCRO IN ITALIA 2013 (AIOM-AIRTUM)

- “Si stima che nel 2013, in Italia, verranno diagnosticati circa 366.000 nuovi casi di tumore maligno (circa 1.000 al giorno), di cui 200.000 negli uomini e circa 166.000 nelle donne”.

- La probabilità di ammalarsi di un qualunque tumore nel corso della vita (0-84 anni) riguarda un uomo ogni 2 ed una donna ogni 3”

Malati e tartassati, i drammi del cancro
AVVENIRE 15 maggio 2012

http://www.avvenire.it/Cronaca/Pagine/malati-e-tartassati.aspx

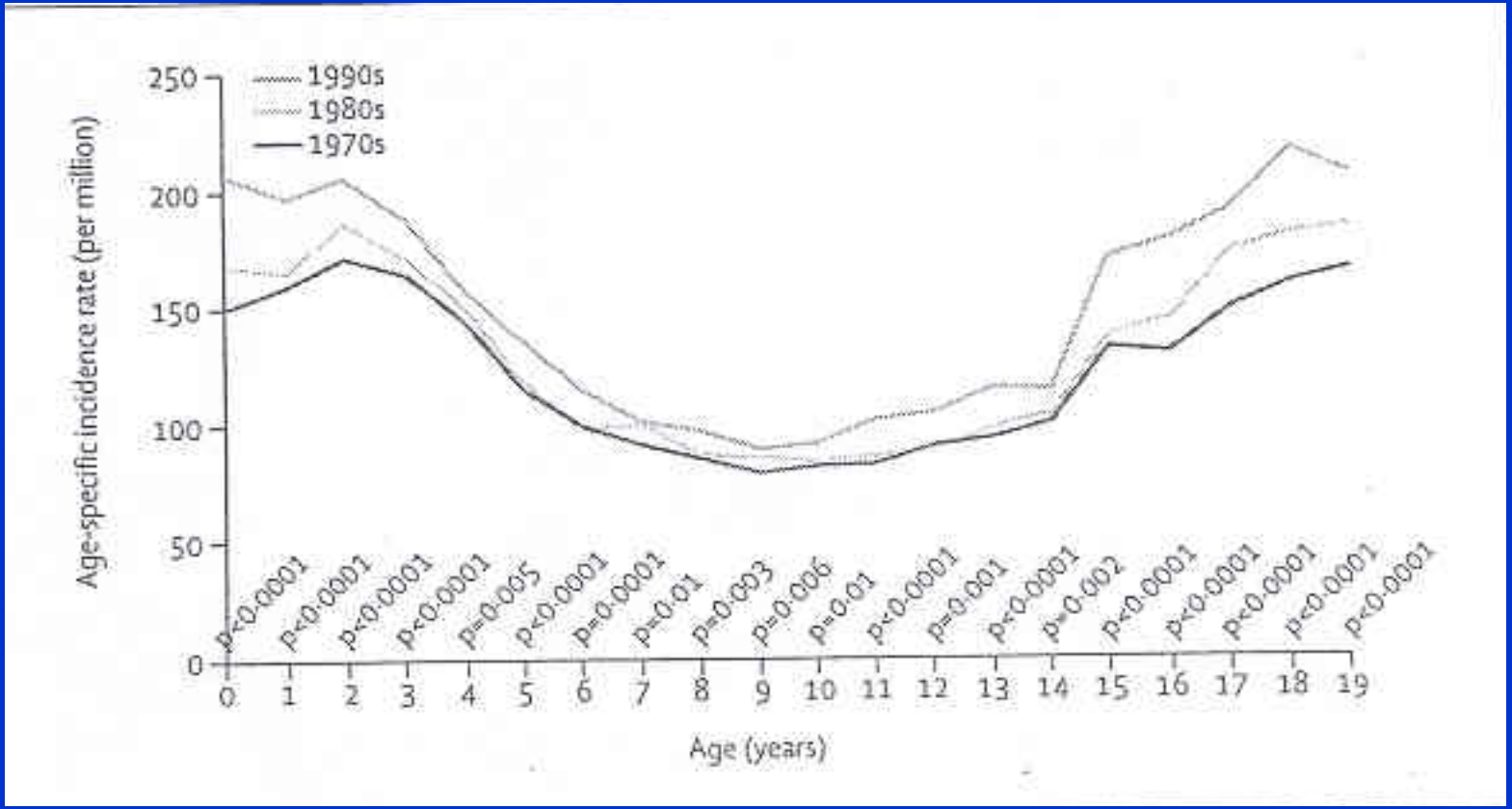
Spesa annuale per le cure oncologiche in Italia:

- 960 mila pazienti con diagnosi di tumore negli ultimi 5 anni
- 776 mila “caregivers” (assistenti: familiari, infermieri, badanti...)
- 36,4 miliardi di euro il costo ogni anno (cure + assistenza)

Principali critiche alla SMT

- Incremento dei tumori nell'infanzia e nell'adolescenza (non solo quindi patologie conseguenti all'allungamento della vita)
- Incremento contestuale di cancro e di patologie endocrino-metaboliche, cronico-degenerative ed immunomediate
- L'incremento dei tumori in aree ad alto tasso di inquinamento ambientale
- La scarsa/nulla considerazione della diffusione ormai ubiquitaria di agenti cancerogeni e tossici (diossine, PCB, pesticidi…) che modulano, in modo non certo casuale, l'espressione genica *("paradosso del progresso")*

INCIDENZA DI NEOPLASIE NELL'INFANZIA E NELL'ADOLESCENZA IN EUROPA (anni 1970-1999)



(Lancet, Dic. 2004)

Tasso di incidenza tumori pediatrici (0-14 anni) / milione bambini

1988-1992	Italia	**146**
1998-2002	Italia	**175.4***
2003-2005	Italia	**168.5**
1990-2000	Europa	140
1987-2004	Germania	141
1990-1999	Francia	138
1995-2004	Svizzera	141
1992-2004	USA	158

***Statisticamente significativo**

Epidemiologia e Prevenzione - Tumori infantili
Rapporto AIRTUM 2008 (Associazione Italiana Registri Tumori)

Incidenza da 0 a 14 anni di: tutti i tumori, linfomi, leucemie, S.N.C. in Paesi Nordici (NORDCAN), U.S.A. (SEER) ed Italia (AIRTUM) 2003-2008

	NORDCAN		SEER		AIRTUM	
	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS
Leukaemia	54.	48.	55.3	46.6	56.1	51.6
Lymphoma, all	19.	11.	19.3	11.3	32.4	17.8
All tumours of the CNS	42.	39.	42.0	39.0	30.6	27.2
Others	54.	52.	62.1	62.2	71.7	66.2
All malignant tumours and non-malignant of the CNS	169.	150.	178.7	159.1	190.8	162.8

Tabella 2. Tassi di incidenza standardizzati per età (per 1.000.000) nel periodo 2003-2008, per tutte le neoplasie e i tre gruppi più frequenti, nel pool AIRTUM, nei Paesi nordici e negli Stati Uniti nei bambini di 0-14 anni d'età.

Table 2. Age-standardized rates (per 1,000,000) in 2003-2008, for all tumour types and the three most frequent types, in the AIRTUM pool, the Nordic Countries, and the USA in children aged 0-14 years.

Fonte: Rapporto AIRTUM 2012 - I tumori dei bambini e degli adolescenti. *Epidemiol Prev* 2013;37(1) Suppl 1:1-296.

I TUMORI IN ITALIA - RAPPORTO 2012

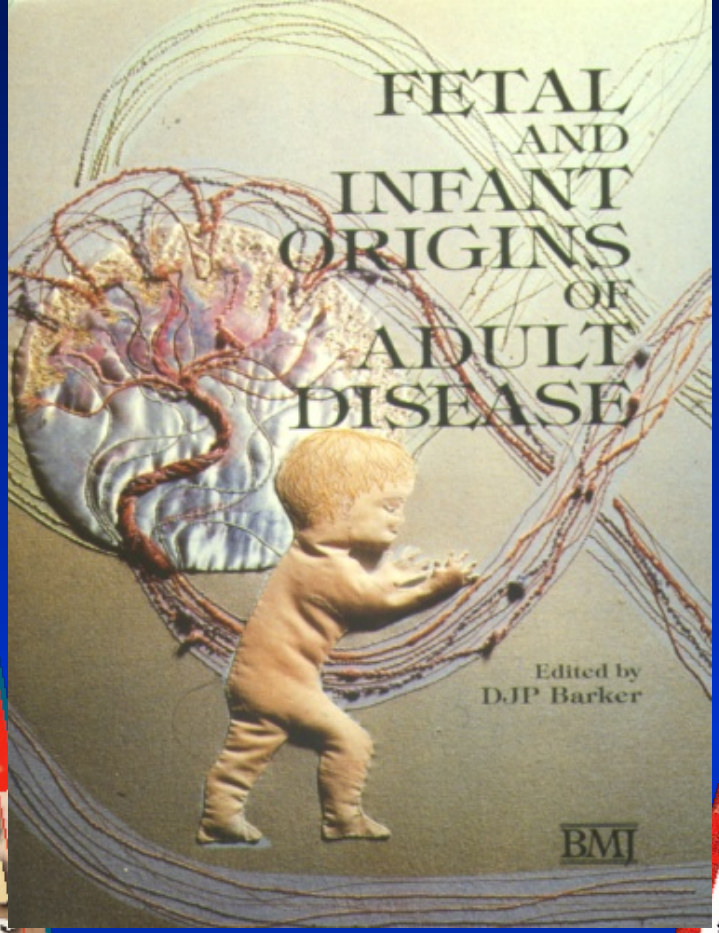
I tumori dei bambini e degli adolescenti

Negli adolescenti (15-19 anni) si osserva un aumento significativo per tutte le neoplasie maligne (APC: +2,0%), il complesso dei linfomi (APC: +2,9%) e il linfoma di Hodgkin in particolare (APC: +3,6%), il carcinoma della tiroide (APC: +6,1%) e il melanoma (APC: +8,1%). La leucemia linfoblastica risulta l'unica neoplasia in significativa diminuzione in questo gruppo d'età sul lungo periodo. Le tendenze recenti (1998-2008) confermano l'aumento dei tumori maligni solo nelle ragazze e l'aumento importante di carcinomi della tiroide (APC: +7,9%) in maschi e femmine. Sempre sul periodo recente si registra una diminuzione di tumori dell'osso nelle ragazze basato su solo 46 casi.

Combating Environmental Causes of Cancer

David C. Christiani, M.D., M.P.H.

During the past three decades, increases in the incidence of some childhood cancers, such as leukemia and brain tumors, may implicate prenatal exposure to environmental carcinogens — and more than 300 industrial chemicals have been detected in umbilical-cord blood.


FETAL
AND
INFANT
ORIGINS
OF
ADULT
DISEASE
Edited by
D.J.P Barker
BMJ

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Newsweek
Where Health Begins
Obesity, Cancer and Heart Attacks: How Your Odds Are Set in the Womb

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The oceans—why 70% of our planet is in danger
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After a flawed election, how the world can help
TIME
How the first nine months shape the rest of your life
The new science of fetal origins
BY ANNIE MURPHY PAUL

TOXICOLOGICAL SCIENCES 78, 248–257 (2004)
DOI: 10.1093/toxsci/kfh062
Advance Access publication January 12, 2004

A Novel Effect of Dioxin: Exposure during Pregnancy Severely Impairs Mammary Gland Differentiation

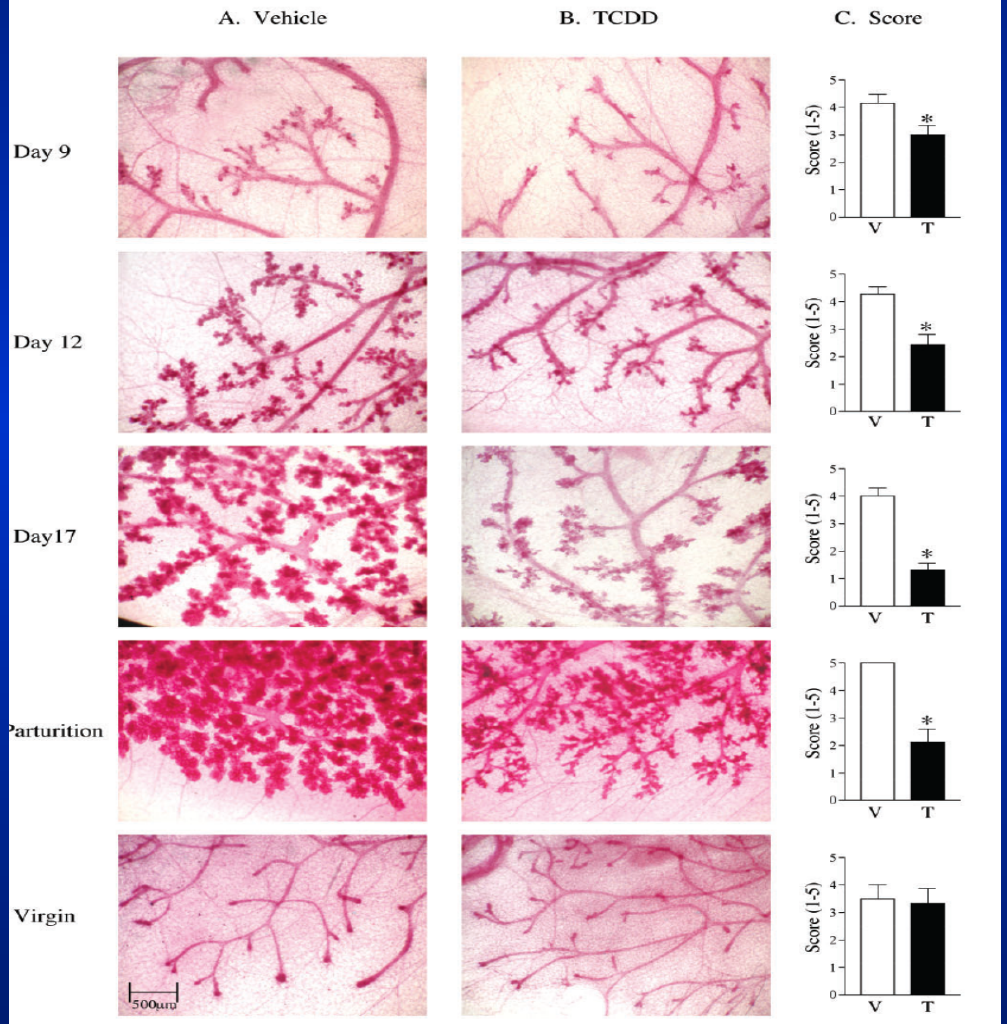


FIGURE 2

© 2008 The Authors
Journal compilation © 2008 Nordic Pharmacological Society. Basic & Clinical Pharmacology & Toxicology, 102, 125–133

Doi: 10.1111/j.1742-7843.2007.00165.x

MiniReview

Does Breast Cancer Start in the Womb?

Ana M. Soto, Laura N. Vandenberg, Maricel V. Maffini and Carlos Sonnenschein

Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA, USA

(Received June 28, 2007; Accepted September 7, 2007)

BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 102(2008) 125-133

Deserto lichenico e mortalità per cancro al polmone

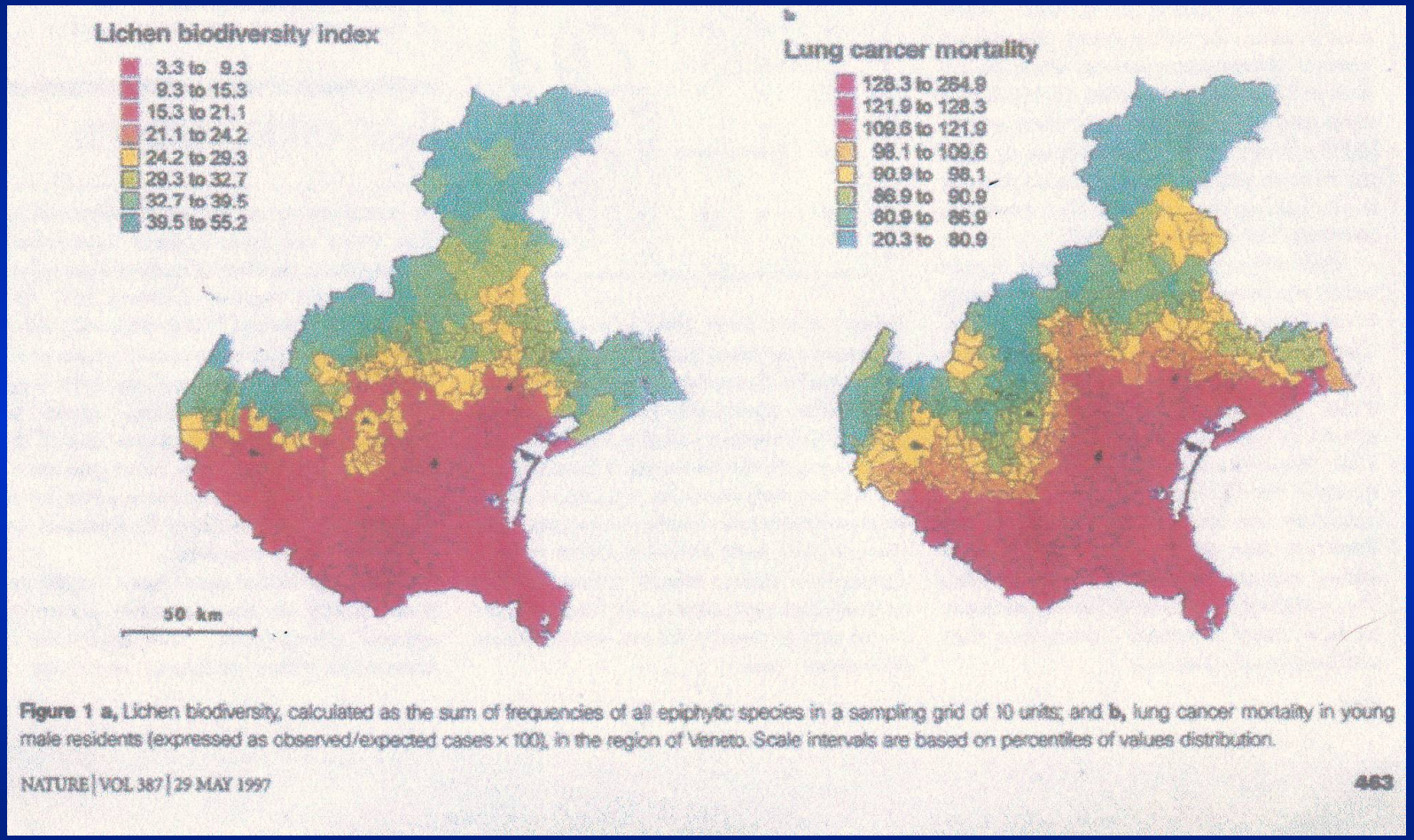


Figure 1 a, Lichen biodiversity, calculated as the sum of frequencies of all epiphytic species in a sampling grid of 10 units; and **b,** lung cancer mortality in young male residents (expressed as observed/expected cases × 100), in the region of Veneto. Scale intervals are based on percentiles of values distribution.

NATURE | VOL 387 | 29 MAY 1997

Cislaghi C. Lichens, air pollution and lung cancer Nature. 1997 May 29;387(6632):463-4

The carcinogenicity of outdoor air pollution

Published Online
October 24, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70487-X

For more on the IARC Monographs see http://monographs.iarc.fr/

Upcoming meetings
June 3–10, 2014, Volume 110: Perfluoro-octanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

Monograph Working Group Members
J Samet (USA)–Chair; P H N Saldiva (Brazil); M Brauer, G Chen, P White (Canada); W Huang (China); L E Knudsen, P Møller, O Raaschou-Nielsen (Denmark); U Heinrich (Germany); K Balakrishnan (unable to attend; India); F Forastiere (Italy); T Yorifuji (Japan); D H Phillips, P Vineis (UK); J Chow, D M. DeMarini (unable to attend), R Henderson, F Laden, D L Morgan (unable to attend), J J Schauer (USA)

Invited Specialists
G Hoek (The Netherlands); A J Cohen, A Russell (USA);

Representatives
E Durand, M Redaelli, for the French Agency for Food, Environmental and Occupational Health and Safety, France; Z Zuber, for the European Commission

Observers
G B Copley, D Morgott, J A Tomenson, for CONCAWE, Belgium; P Crosignani, for the International Society of the Doctors for the Environment (ISDE), Italy; B Fervers, for the Centre Léon Bérard, France; G Guillosou, for Eurelectric, Belgium

IARC/WHO Secretariat
R Baan, L Benbrahim-Tallaa, V Bouvard, A Burton, G Byrnes, R Carel, R Denholm, C Dickens, C Dora, F El Ghissassi,

In October, 2013, 24 experts from 11 countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of outdoor air pollution. This assessment was the last in a series that began with specific combustion products and sources of air pollution and concluded with the complex mixture that contains all of them. The results of this most recent assessment will be published as volume 109 of the IARC Monographs.[1]

Outdoor air pollution is a mixture of multiple pollutants originating from a myriad of natural and anthropogenic sources. Transport, power generation, industrial activity, biomass burning, and domestic heating and cooking are the predominant anthropogenic sources in many locations.[2] The mix of pollutants in outdoor air varies substantially over space and time, showing not only the diversity of sources, but the effect of atmospheric processes, including oxidation and weather. Diverse approaches are used to measure air pollution and some countries have established monitoring networks that typically record levels of regulated pollutants, such as respirable particulate matter (PM_{10}), fine particulate matter ($PM_{2.5}$), NO_2, SO_2, and O_3. $PM_{2.5}$ is increasingly used as an indicator pollutant, with annual average concentrations ranging from less than 10 to more than 100 μg/m³ globally. Pollution levels in western Europe and North America have generally declined since the late 20th century, but they are increasing in some rapidly industrialising countries, notably in Asia. In many areas, WHO and national air quality guidelines for $PM_{2.5}$ and other pollutants are routinely and substantially exceeded.[3] Occupational exposures to outdoor air pollution, although not routinely monitored, are also of concern for certain groups of workers, such as traffic police, drivers, and street vendors.

The IARC Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as carcinogenic to humans (IARC Group 1), based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence.

The findings regarding the carcinogenicity of outdoor air pollution as a mixture, and of particulate matter specifically, are remarkably consistent in epidemiological research, studies of cancer in experimental animals, and a wide range of studies of mechanisms related to cancer. Particularly, an increased risk of lung cancer was consistently observed in cohort and case-control studies including millions of people and many thousands of lung cancer cases from Europe, North America, and Asia. The largest and most informative studies were a pooled analysis of data from ten European countries and a large nationwide cohort study in the USA.[4,5] Many studies estimated quantitative levels of outdoor air pollutants, most often as mass concentration of particulate matter, and adjusted for a wide range of potential confounders including tobacco smoking. Increased risk associated with outdoor air pollution was also seen in studies restricted to never smokers.[6] Positive exposure-response relations were consistently observed in studies that provided such data. Notably, virtually all of the studies were done in areas where annual average levels of $PM_{2.5}$ range from about 10 to 30 μg/m³, which represents approximately the lower third of exposures worldwide. Nevertheless, increased risk of lung cancer was observed even in those areas where $PM_{2.5}$ concentrations are less than the current health-based guidelines.[4]

There was limited epidemiological evidence for bladder cancer associated with various metrics of exposure to outdoor air pollution, including occupational and residential exposure to traffic or traffic emissions, in studies that were adjusted for tobacco smoking. However, most studies assessed exposure only by employment in occupations with potentially high exposure to outdoor air pollution, so the results did not weigh heavily in the evaluation.

The Working Group also reviewed evidence regarding the carcinogenicity of outdoor air pollution in experimental animals. As part of this process, the IARC's earlier evaluations of diesel engine exhaust and of emissions from the combustion of coal and wood were updated and confirmed. All of these agents can be present in outdoor air and were shown previously to cause benign and malignant lung tumours in mice or rats.

Only a few studies have assessed the occurrence of cancer in animals exposed directly to outdoor air pollution by inhalation. Studies of mice exposed to traffic-related outdoor air pollution in São Paulo, Brazil, showed an increase in the incidence of lung adenoma, and an increase in the incidence and tumour multiplicity of urethane-induced adenomas in a dose-dependent manner.[7] Several studies in which mice were injected subcutaneously with organic solvent-extracted material from particles collected from outdoor air pollution, showed increased incidence of injection-site tumours, including fibrosarcomas, and pulmonary adenoma or adenocarcinoma.[8,9]

The findings of carcinogenicity in humans and animals are strongly supported by a large, diverse body of evidence showing genetic and related effects in exposed humans and animals and a wide range of experimental systems. Studies of people exposed occupationally to outdoor air pollution have shown enhanced frequencies, relative to controls, of chromosome aberrations and micronuclei in lymphocytes.[10,11]

S.E.N.T.I.E.R.I - Studio Epidemiologico Nazionale Territori e Insediamenti Esposti a Rischi da Inquinamento (Epidemiol Prev 2011; (5-6) Suppl 4).

- Studio dell'ISS, esaminate le statistiche di mortalità di 44 delle 57 aree da tempo identificati come "siti da bonificare" nel periodo 1995-2002

- 298 Comuni con 5,5 milioni di abitanti

- eccesso di mortalità rispetto alle medie regionali: 10 mila morti in più in otto anni rispetto al numero atteso considerando tutte le cause di morte.

INCIDENZA DI CANCRO IN 23 SIN SERVITI DA UN REGISTRO TUMORI
(dati presentati il 9 maggio 2013 a Siracusa, ISS-AIRTUM)

- Studio condotto su 23 siti Sin serviti da un Registro Tumori

- Popolazione complessiva di circa 2 milioni di persone, anni 1996-2005

- Nell'insieme dei 23 Sin, si è registrato per il cancro rispetto a quanto atteso :
  - + 9% nei maschi
  - +7% in più nelle femmine
  - 700 i casi individuati complessivamente di tumori infantili e adolescenziali.

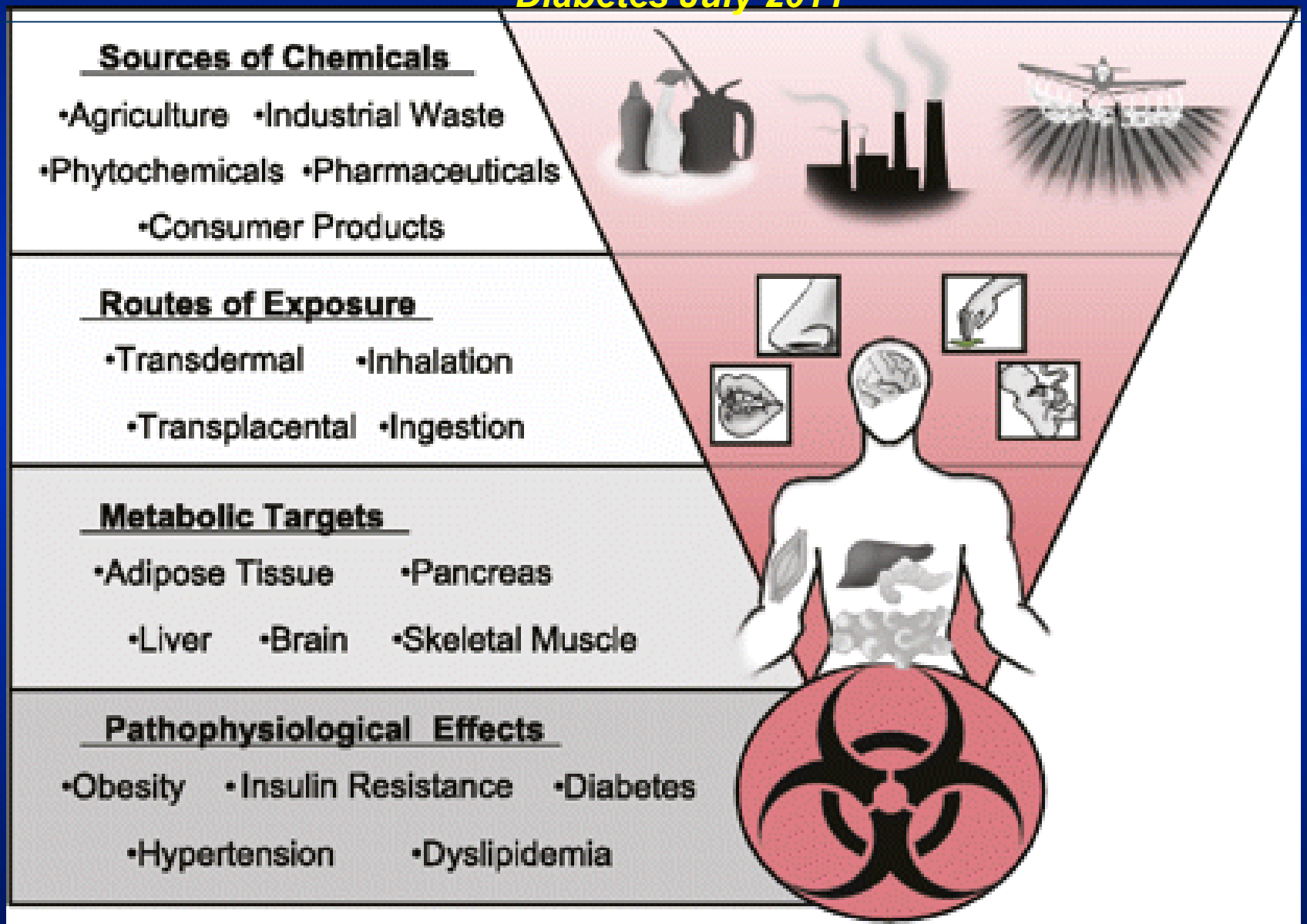
- In entrambi i sessi eccessi di tumori maligni a:
  - esofago, colon-retto, fegato, colecisti e vie biliari, pancreas, laringe, polmone, rene e vie urinarie, vescica, melanoma e linfoma non Hodgkin.

- Nei maschi eccessi di:
  - mesotelioma e tumori maligni di prostata, testicolo ed encefalo;
- Nelle femmine eccessi di:
  - tumori della mammella, del sistema linfoemopoietico, in particolare della leucemia mieloide cronica

The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

Brian A. Neel1 and Robert M. Sargis2⇓

Diabetes July 2011



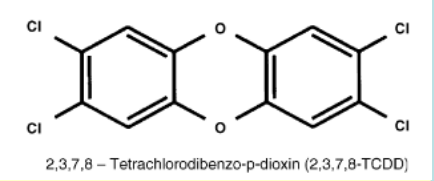
Inquinanti immessi “a norma di legge” dai grandi impianti in Italia

TABELLA 2
ALCUNI DEGLI INQUINANTI IMMESSI IN ARIA ED ACQUA IN ITALIA NEL 2005
(dal registro nazionale INES)

Inquinanti	Effetto cancerogeno secondo IARC	Unità misura	Emissioni in aria	Emissioni in acqua	Emissioni totali
Arsenico (As) e composti	1	kg/a	1981.3	6035.3	8016.6
Cadmio (Cd) e composti	1	kg/a	825.5	2207.5	3033.0
Cromo (Cr) e composti	1	kg/a	11063.5	128963.1	140026.6
Nichel (Ni) e composti	1	kg/a	37247.3	43365.8	80613.1
Benzene, toluene, etilbenzene, xileni (BTEX)	1*	kg/a	540499.6*	175067.8	715567.4
Mercurio (Hg) e composti	2b	kg/a	2821.2	1065.9	3887.1
Piombo (Pb) e composti	2a	kg/a	97063.6	17903.5	114967.1
Diossine (PCDD) + furani (PCDF)	1**	g/a	103.0	-----	103.0

** solo benzene*

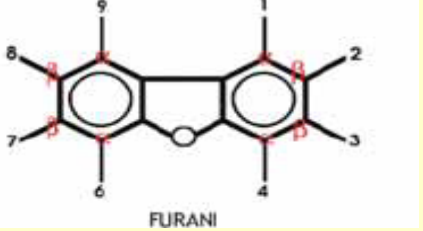
http://www.tumori.net/it3/brochures/documenti/inceneritori/Ambiente_e_Tumori_17_10_11.pdf



2,3,7,8 – Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)

DIOSSINA, DIOSSINE e PCB (policlorobifenili)

A.Schecter Envir. Res.101(2006) 419-428


FURANI

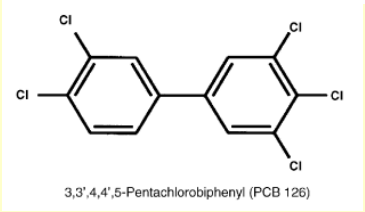
FAMIGLIA di 419 sostanze

CAPOSTIPITE: TCDD o "diossina di Seveso"

DIBENZO-P-DIOSSINE (PCDD): 75 congeneri

DIBENZO-P-FURANI (PCDF): 135 congeneri

PCB: 209 congeneri: 12 d.l. (dioxin like)



3,3',4,4',5-Pentachlorobiphenyl (PCB 126)

CARATTERISTICHE:

DIOSSINE E FURANI: prodotti involontari da sintesi di pesticidi o combustioni, in particolari condizioni (T, cloro, catalizzatori).

PCB : prodotti volontariamente per uso industriale (fluidi per trasformatori, addittivi per vernici, carta, fino agli anni 80'

Molecole estremamente persistenti, termostabili, lipofile

Tempi di dimezzamento: TCDD: uomo 7- 11 anni, sottosuolo fino a 100 anni

ASSUNZIONE

Diossine: per oltre il 95% tramite catena alimentare (latticini, pesce, carni) fenomeni di bioaccumulo e biomagnificazione

PCB : importante anche la via respiratoria e transcutanea

Unità di misura per assunzione nell'uomo: picogrammo (pg) miliardesimo di mg

2001 UE: soglia di assunzione di 2 pg/kg/die

2012: E.P.A. soglia di assunzione di 0,7 pg/kg

TOSSICITA':

Diverso di tossicità dei vari congeneri rispetto alla TCDD (la più tossica in assoluto) (TEQ)

AZIONE ONCOGENA E DI "INTERFERENTI ENDOCRINI"

TAPPE SALIENTI

1997: TCDD : riconosciuta cancerogeno certo per l'uomo IARC 1 ad azione multiorgano

2001: Convenzione di Stoccolma vieta produzione, uso e rilascio di 12 POPs fra cui diossine e PCB

2009: PCB 126 e pentafurano riconosciuti cancerogeni certi al pari della diossina di Seveso

2013: IARC riconosce anche i PCB cancerogeni certi per l'uomo (IARC 1)

Sviluppo di tumori mammari in cavie trattate al 15°giorno dal concepimento con 1µg/Kg TCDD e al 50° giorno dalla nascita con 30 mg/kg di Dimetildibenzoantracene (DMBA) o solo DMBA

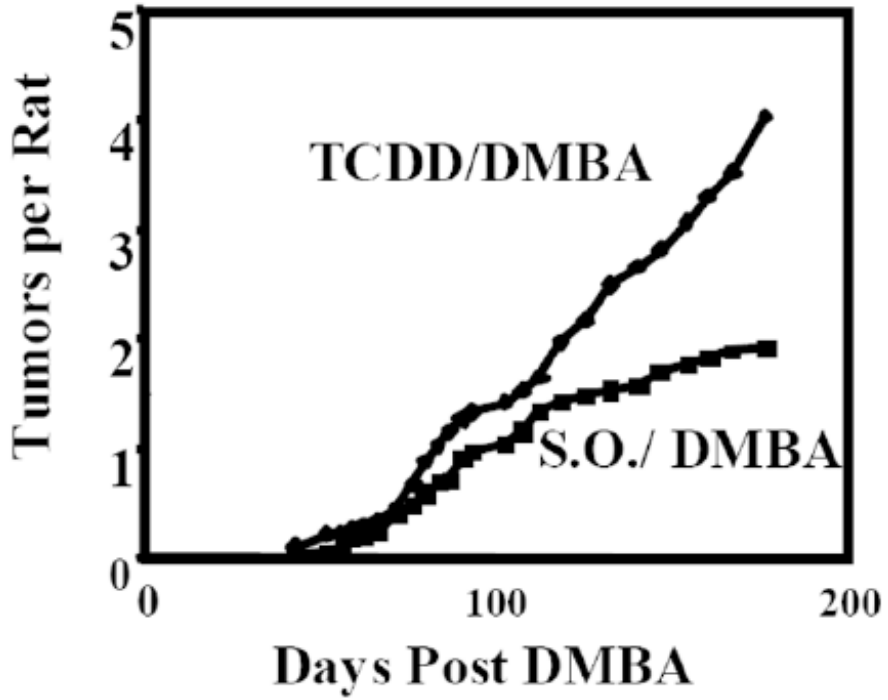


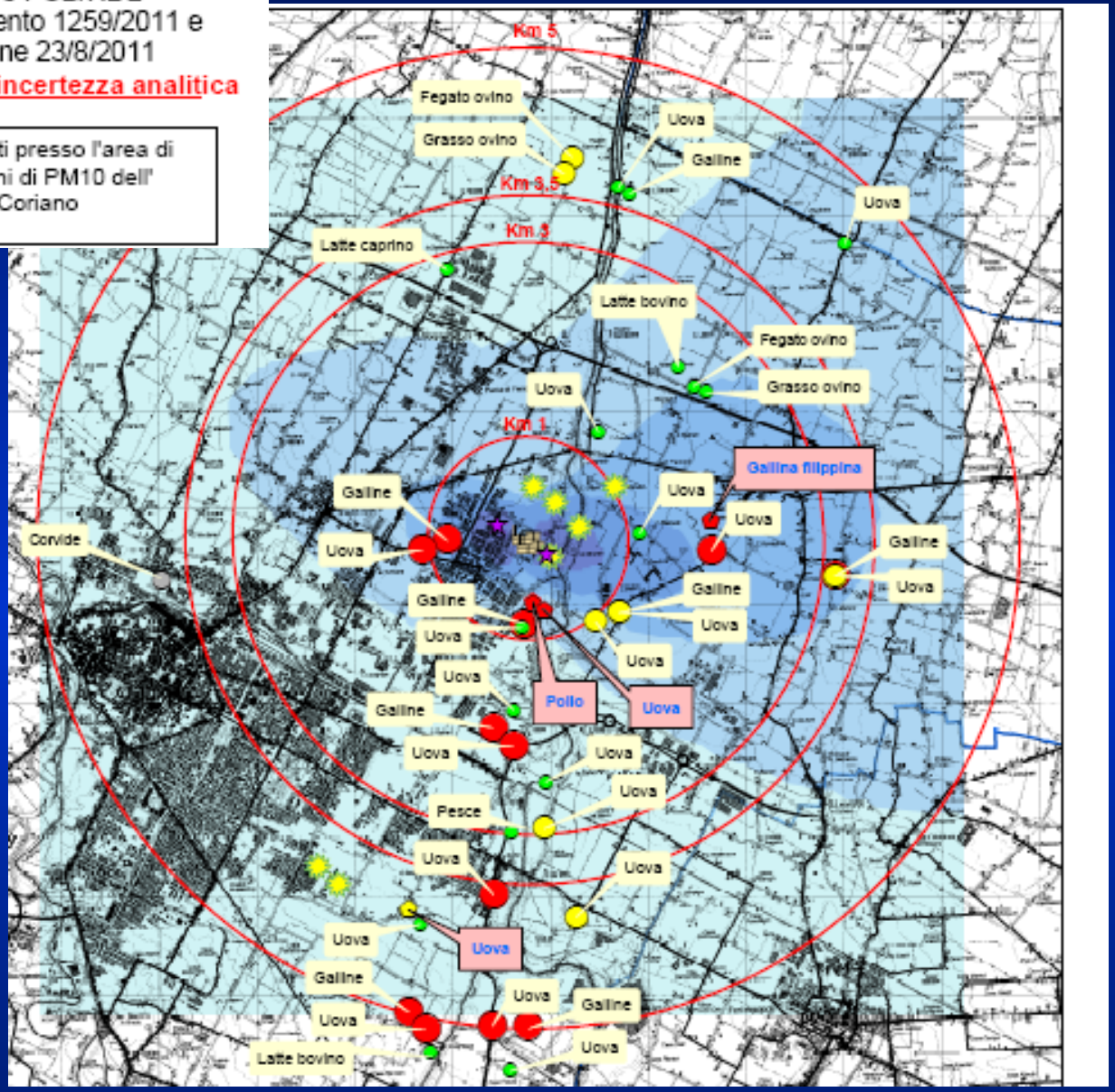
Figure 1.
Ontogeny of palpable mammary tumors in female rats exposed prenatally to TCDD and treated with DMBA on day 50 post-partum. Pregnant female Sprague-Dawley CD rats were treated with 1 µg/kg body weight or an equivalent volume of the solvent (sesame oil) on day 15 post-conception. DMBA was administered by gavage at 30 mg/kg body wt to 50-day-old female offspring. The TCDD/DMBA group and the sesame oil/DMBA group contained 29 and 30 female rats/group, respectively. (Figure from ref. 18.)

Reprod Toxicol. 2007 ; 23(3): 391–396.

Diossine, PCB/DL e PCB/NDL
Conformità al Regolamento 1259/2011 e alla Raccomandazione 23/8/2011

Senza tenere conto dell'incertezza analitica

Campionamenti effettuati presso l'area di ricaduta delle emissioni di PM10 dell' inceneritore di Coriano



Conforme

NON Conforme al Regolamento

NON Conforme alla Raccomandazione

http://www.comune.forli.fc.it/upload/forli/gestionedocumentale/Relazione%20finale%20tavolo_784_27809.pdf

http://www.comune.forli.fc.it/upload/forli/gestionedocumentale/Relazione%20finale%20tavolo_784_27809.pdf

Tabella 12 –Campioni effettuati nel 2011 per il controllo dei PCDD/F e PCB in matrici di origine animale, giudicati in base alle nuove normative 2012 (tenendo conto anche dei 5 campioni ISDE) senza considerare l'incertezza analitica

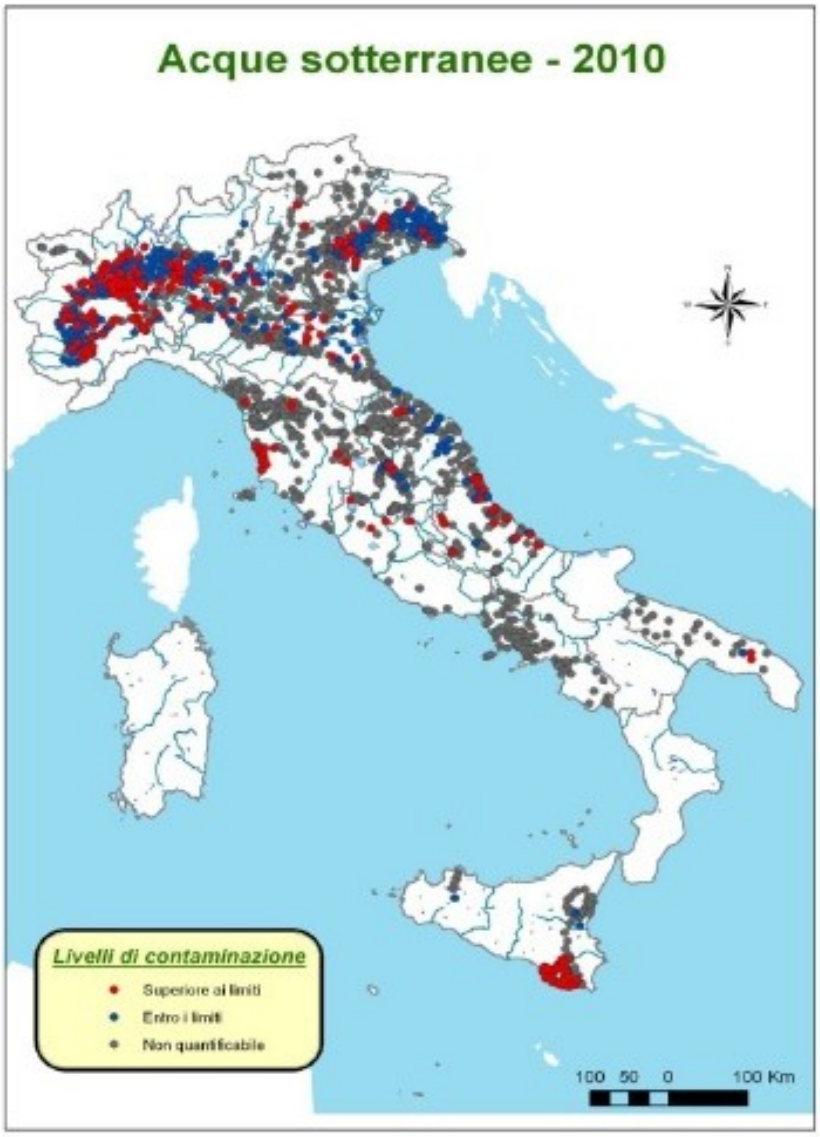
Matrice di origine animale	Numero campioni	N° campioni non conformi al Regolamento (CE) N°1881/2006 modificato dal Regolamento (UE) 1259/2011	N° campioni non conformi alla Raccomandazione Commissione Europea (23/8/2011)	N° campioni conformi
Galline/Pollo	12	8	3	1
Uova	24	7	6	11
Tessuto adiposo ovino	3	0	2	1
Fegato ovino	3	1	n.a.	2
Latte ovino	3	0	0	3
Latte bovino	3	0	1*	2
Latte caprino	2	0	1	1
Pesce	1	0	0	1
Totale matrici animali	51	16	13	22
Vegetali	10	0	10	0
Totale	61	16	22	23

http://www.agricolturaitalianaonline.gov.it/index.php/contenuti/studi_e_ricerche/statistiche/produzione/piu_pesticidi_ma_calano_i_principi_

USO PESTICIDI IN ITALIA (Dati Istat/ISPRA 2010/11)

- Circa 800 i prodotti presenti sul mercato
- distribuiti mediamente sui suoli agricoli ogni anno oltre 150.000 ton
- Quantitativo medio distribuito: 5,64 chilogrammi per ettaro !
- In Italia si distribuisce il 33% della quantità totale di insetticidi utilizzati nell'intero territorio comunitario
- Presenza di pesticidi nelle acque

RAPPORTO ISPRA 2013



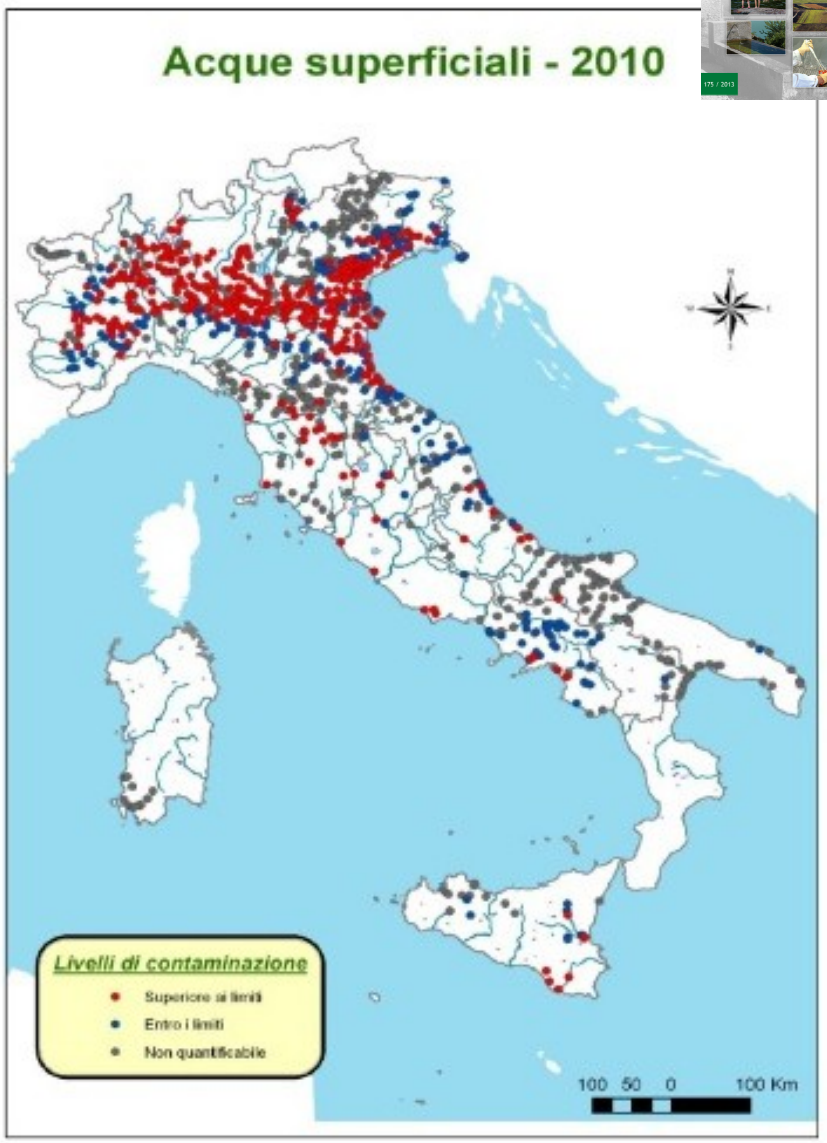


Fig. 6.3 – *Livelli di contaminazione delle acque, anno 2010.*

RAPPORTO NAZIONALE PESTICIDI NELLE ACQUE ITALIANE
rapporto ISPRA ed.2013

Presenza di residui nel : 55,1% delle acque superficiali
28,2% delle acque sotterranee

Rinvenuti 166 tipologie di pesticidi - a fronte dei 118 del 2007-2008

Livelli superiori ai limiti delle acque potabili nel: 34,4% delle acque superficiali
12,3% di quelle sotterranee

Largamente presenti anche sostanze fuori commercio da tempo, come l'atrazina e la simazina.

Presenti fino a 23 sostanze diverse in solo campione: "*a causa dell'assenza di dati sperimentali sugli effetti combinati delle miscele e di adeguate metodologie di valutazione, esiste la possibilità che il rischio derivante dall'esposizione ai pesticidi sia attualmente sottostimato e si impone una particolare cautela anche verso i livelli di contaminazione più bassi*"

Health impact and damage cost assessment of pesticides in Europe (Environ Int. 2012 Nov 15;49:9-17..)

Fantke P, Friedrich R, Jolliet O.

Institute of Energy Economics and the Rational Use of Energy (IER), University of Stuttgart, Hessbruehlstr. 49a, 70565 Stuttgart, Germany. Electronic address: peter@dynamicrop.org

Abstract

- *"…..We quantify health impacts and related damage costs from exposure to 133 pesticides applied in 24 European countries in 2003 adding up to almost 50% of the total pesticide mass applied in that year.*

……..

- *Only 13 substances applied to 3 crop classes (grapes/vines, fruit trees, vegetables) contribute to 90% of the overall health impacts of about 2000 disability-adjusted life years in Europe per year corresponding to annual damage costs of 78 million Euro."*

Toxicol Appl Pharmacol. 2013 Feb 9. pii: S0041-008X(13)00054-9.

Pesticides and human chronic diseases: evidences, mechanisms, and perspectives.

- " There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as:
  - different types of cancers,
  - diabetes,
  - neurodegenerative disorders like Parkinson, Alzheimer, and SLA,
  - birth defects, and reproductive disorders"

- "There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like :
  - respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD),
  - cardiovascular disease such as atherosclerosis and coronary artery disease,
  - chronic nephropathies
  - autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis, chronic fatigue syndrome, and aging. *……"*

Table 1. Pesticides associated with cancer in the AHS cohort.

Cancer type	Pesticide(s)	Chemical family	Categorical exposure cutoff value	RR or OR[a] (95% CI)	*p*-Value for trend	References
All cancers	Diazinon	OP	> 109 LD[b]	1.58 (1.10–2.28)	0.007	Beane Freeman et al. 2005
			Highest IWLD[b]	1.41 (1.03–1.95)	0.033	
	EPTC	Thiocarbamate	> 50 LD[c]	1.28 (1.09–1.50)	< 0.01	van Bemmel et al. 2008
			> 112 IWLD[c]	1.16 (1.01–1.35)	0.02	
Lung	Chlorpyrifos	OP	> 56 LD[b]	2.18 (1.31–3.64)	0.002	Lee et al. 2004a
			> 417 IWLD[b]	1.80 (1.00–3.23)	0.036	
	Diazinon	OP	> 109 LD[b]	3.46 (1.57–7.65)	0.001	Beane Freeman et al. 2005
			Highest IWLD[b]	1.55 (0.65–3.72)	0.22	
	Dicamba	Benzoic acid	> 224 LD[b]	3.10 (1.20–7.70)	0.04	Alavanja et al. 2004
	Dieldrin	OC	> 50 LD[b]	5.30 (1.50–18.6)	0.005	
			> 9 LD[d]	2.80 (1.10–7.20)	0.02	Purdue et al. 2006
	Metolachlor	Chloroacetanilide	Highest IWLD[d]	3.50 (1.60–7.70)	0.002	
			> 457 LD[b]	4.10 (1.60–10.4)	0.015	Alavanja et al. 2004
	Pendimethalin	Dinitroaniline	> 224 LD[b]	3.50 (1.10–10.5)	0.005	
			>116 LD[b]	2.40 (1.10–5.30)	0.29	Hou et al. 2006
			> 539 IWLD[b]	1.10 (0.50–2.60)	0.94	
Pancreas	EPTC	Thiocarbamate	> 118 IWLD[d]	2.50 (1.10–5.40)	0.01	Andreotti et al. 2009
	Pendimethalin	Dinitroaniline	> 117 IWLD[d]	3.00 (1.30–7.20)	0.01	
Colon	Aldicarb	Carbamate	> 56 LD[b]	4.10 (1.30–12.8)	0.001	Lee et al. 2007a
	Dicamba	Benzoic acid	> 116 LD[b]	3.29 (1.40–7.73)	0.02	Samanic et al. 2006
			> 739 IWLD[b]	2.57 (1.28–5.17)	0.002	
	EPTC	Thiocarbamate	> 50 LD[c]	2.09 (1.26–3.47)	< 0.01	van Bemmel et al. 2008
			> 112 IWLD[c]	2.05 (1.34–3.14)	< 0.01	
	Imazethapyr	Imidazolinone	> 311 IWLD (proximal)[b]	2.73 (1.42–5.25)	0.001	Koutros et al. 2009
			> 311 IWLD (distal)[b]	1.21 (0.55–2.68)	0.75	
	Trifluralin	Dinitroaniline	> 224 LD[b]	1.48 (0.78–2.80)	0.12	Kang et al. 2008
			> 1176 IWLD[b]	1.76 (1.05–2.95)	0.036	
Rectum	Chlordane	OC	> 9 LD[d]	2.70 (1.10–6.80)	0.03	Purdue et al. 2006
			Highest IWLD[d]	2.10 (0.90–5.30)	0.04	
	Chlorpyrifos	OP	> 56 LD[b]	3.25 (1.60–6.62)	0.035	Lee et al. 2004a
			> 417 IWLD[b]	3.16 (1.42–7.03)	0.057	
			>109 LD[b]	2.70 (1.20–6.40)	0.008	Lee et al. 2007a
	Pendimethalin	Dinitroaniline	> 116 LD[c]	4.30 (1.50–12.7)	0.007	Hou et al. 2006
			> 539 IWLD[c]	3.60 (1.20–11.3)	0.02	
	Toxaphene	OC	> 56 LD[b]	4.30 (1.20–15.8)	0.123	Lee et al. 2007a
Leukemia	Chlordane/Heptachlor	OC	> 9 LD[d]	2.60 (1.20–6.00)	0.02	Purdue et al. 2006
			Highest IWLD[d]	2.10 (0.80–5.50)	0.10	
	Chlorpyrifos	OP	> 56 LD[b]	2.15 (0.96–4.81)	0.36	Lee et al. 2004a
			> 417 IWLD[b]	3.01 (1.35–6.69)	0.15	
	Diazinon	OP	> 39 LD[c]	3.36 (1.08–10.5)	0.026	Beane Freeman et al. 2005
			Highest IWLD[c]	2.88 (0.92–9.03)	0.053	
	EPTC	Thiocarbamate	> 50 LD[c]	2.36 (1.16–4.84)	0.02	van Bemmel et al. 2008
			> 112 IWLD[c]	1.87 (0.97–3.59)	0.05	
	Fonofos	OP	> 609 IWLD[c]	2.67 (1.06–6.70)	0.04	Mahajan et al. 2006a
All LH	Alachlor	Chloroacetanilide	> 116 LD[c]	2.04 (0.89–4.65)	0.02	Lee et al. 2004b
			> 710 IWLD[c]	2.42 (1.00–5.89)	0.03	
	Chlorpyrifos	OP	> 56 LD[b]	1.43 (0.86–2.36)	0.26	Lee et al. 2004a
			> 417 IWLD[b]	1.99 (1.22–3.26)	0.09	
	Diazinon	OP	> 39 LD[c]	1.84 (0.89–3.82)	0.094	Beane Freeman et al. 2005
			Highest IWLD[c]	2.01 (1.02–3.94)	0.049	
	Permethrin	Pyrethroid	> 50 LD[c]	1.64 (1.07–2.52)	0.35	Rusiecki et al. 2009
			> 220 IWLD[c]	1.31 (0.84–2.04)	0.60	
NHL	Lindane	OC	> 22 LD[d]	2.10 (0.80–5.50)	0.12	Purdue et al. 2006
			Highest IWLD[d]	2.60 (1.10–6.40)	0.04	
Multiple myeloma	Permethrin	Pyrethroid	> 50 LD[c]	5.72 (2.76–11.8)	< 0.01	Rusiecki et al. 2009
			> 220 IWLD[c]	5.01 (2.41–10.4)	< 0.01	
Bladder	Imazethapyr	Imidazolinone	> 311 IWLD[b]	2.37 (1.20–4.68)	0.01	Koutros et al. 2009
Prostate	Fonofos	OP	> 56 LD[c]	1.77 (1.03–3.05)	0.02	Mahajan et al. 2006a (for applicators
			> 315 IWLD[c]	1.83 (1.12–3.00)	0.01	with a family history of prostate cancer)
	Methylbromide	Halogenated alkane	Highest IWLD[e]	3.47 (1.37–8.76)	0.004	Alavanja et al. 2003
Brain	Chlorpyrifos	OP	> 56 LD[b]	2.58 (0.73–9.17)	0.076	Lee et al. 2004a
			> 417 IWLD[b]	4.03 (1.18–13.8)	0.036	
Melanoma	Carbaryl	Carbamate	> 175 LD[b]	4.11 (1.33–12.7)	0.07	Mahajan et al. 2007
			Highest intensity score[b]	1.54 (0.61–3.86)	0.92	

S. Weichenthal et al. A review of pesticide exposure and cancer incidence in the agricultural health study cohort Environm Health Perspect. 2010 vol 118 1117- 1125

Agricultural pesticide exposure and the molecular connection to lymphomagenesis

The Journal of Experimental Medicine, Vol. 206, No. 7, 1473-1483 2009

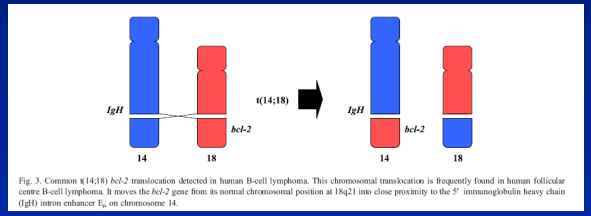


Fig. 3. Common t(14;18) *bcl-2* translocation detected in human B-cell lymphoma. This chromosomal translocation is frequently found in human follicular centre B-cell lymphoma. It moves the *bcl-2* gene from its normal chromosomal position at 18q21 into close proximity to the 5′ immunoglobulin heavy chain (IgH) intron enhancer E_μ on chromosome 14.

- in un gruppo di agricoltori esposti a pesticidi in Francia e seguito per 9 anni si è dimostrato una drammatica espansione di cloni di linfociti con la traslocazione 14;18, primo passaggio per la successiva evoluzione linfomatosa.

- Questo studio è di fondamentale importanza perché per la prima volta viene fatta luce sui meccanismi molecolari che mettono in relazione l'esposizione ai pesticidi con le malattie del sangue

- Identica alterazione si è registrato nella popolazione più esposta al'incidente di Seveso e che ha presentato un incremento di linfomi, mielomi e leucemie

Legame fra Pesticidi & Diossine!

Carcinogenesis vol.27 no.10 pp.2001–2007, 2006
doi:10.1093/carcin/bgl011
Advance Access publication March 16, 2006

t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Table III. Prevalence and frequency of t(14;18) translocations by plasma TCDD levels, zone of residence and diagnosis of chloracne

	t(14;18)-positive subjects		t(14;18) frequency[a]	
	%	(Positive/total)	Mean	(95% CI)
Plasma TCDD				
<10 p.p.t.	34.7	(25/72)	4.2[b]	(2.9–6.2)
10.0–475.0 p.p.t.	34.7	(25/72)	9.9[b]	(6.8–14.5)
Zone of residence at the time of the accident				
Reference	42.4	(14/33)	4.3[c]	(2.3–8.0)
R	26.9	(7/26)	4.9[c]	(2.2–10.7)
B	29.4	(10/34)	7.2[c]	(3.8–13.6)
A	37.3	(19/51)	9.3[c]	(5.8–14.8)
Chloracne after the accident				
No	35.2	(32/91)	6.2	(3.7–10.6)
Yes	34.0	(18/53)	6.7	(4.7–9.6)

CARCINOGENESIS (2006) vol 27 no 10 pp 2001-2007

ANALISI DELLA MORTALITA PER TUMORI DEL SANGUE A SEVESO A 25 ANNI DALL' INCIDENTE

TABLE 5. Results of Poisson regression analyses of mortality in the Seveso, Italy, area, 1976–2001, for selected causes of death: number of deaths, rate ratios, and 95% confidence intervals for the polluted zones (A, B, and R) compared with the reference zone*,†

Cause of death (ICD-9‡ code)	Zone A			Zone B			Zone R		
	No.	RR‡	95% CI‡	No.	RR	95% CI	No.	RR	95% CI
Lymphatic and hematopoietic tissue (200–208)	6	2.23	1.00, 4.97	28	1.59	1.09, 2.33	124	0.99	0.82, 1.20
Hodgkin's disease (201)	0	0		3	2.15	0.67, 6.86	9	0.94	0.46, 1.89
Non-Hodgkin's lymphoma (200, 202)	3	3.35	1.07, 10.46	7	1.23	0.58, 2.60	40	0.99	0.71, 1.38
Multiple myeloma (203)	2	4.34	1.07, 17.52	5	1.68	0.69, 4.10	24	1.10	0.71, 1.69
Leukemia (204–208)	1	0.89	0.12, 6.31	13	1.73	1.00, 3.02	51	0.96	0.72, 1.29
Lymphatic leukemia (204)	0	0		3	1.30	0.41, 4.10	23	1.41	0.90, 2.21
Myeloid leukemia (205)	1	2.12	0.30, 15.17	6	1.97	0.87, 4.46	16	0.74	0.44, 1.24
Leukemia, unspecified (208)	0	0		4	2.38	0.87, 6.52	10	0.84	0.43, 1.62

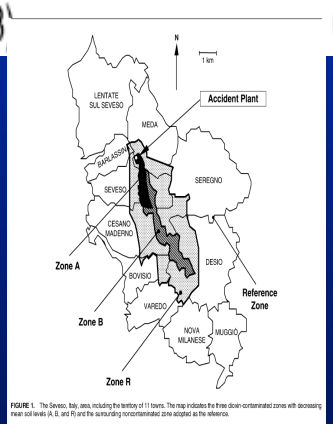
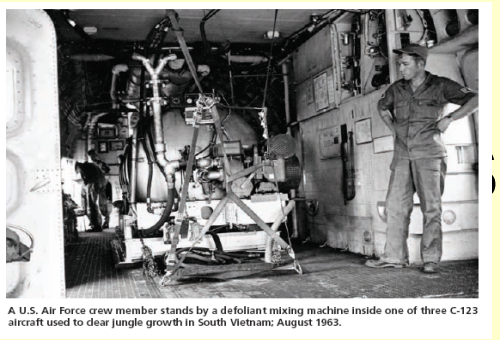


FIGURE 1. The Seveso, Italy, area, including the territory of 11 towns. The map indicates the three dioxin-contaminated zones with decreasing mean soil levels (A, B, and R) and the surrounding noncontaminated zone adopted as the reference.

Am J Epidemiol 2008;167:847–858

DIOSSINE , PESTICIDI….E TRISTI RICORDI:

DALL'AGENTE "ORANGE" ….A SEVESO!



A U.S. Air Force crew member stands by a defoliant mixing machine inside one of three C-123 aircraft used to clear jungle growth in South Vietnam; August 1963.

SEVESO: TRICLOROFENOLO

(+ diossine)

2,4 D + 2,4,5 T

"**agente orange**"

mix vietato!!!

Ancora in commercio come diserbanti e auxina

Variazioni dell'espressione genica in relazione alle diverse tipologie di inquinamento ambientale

Environ Health Pers. Vol 116 num 11 2008 :1519-1525

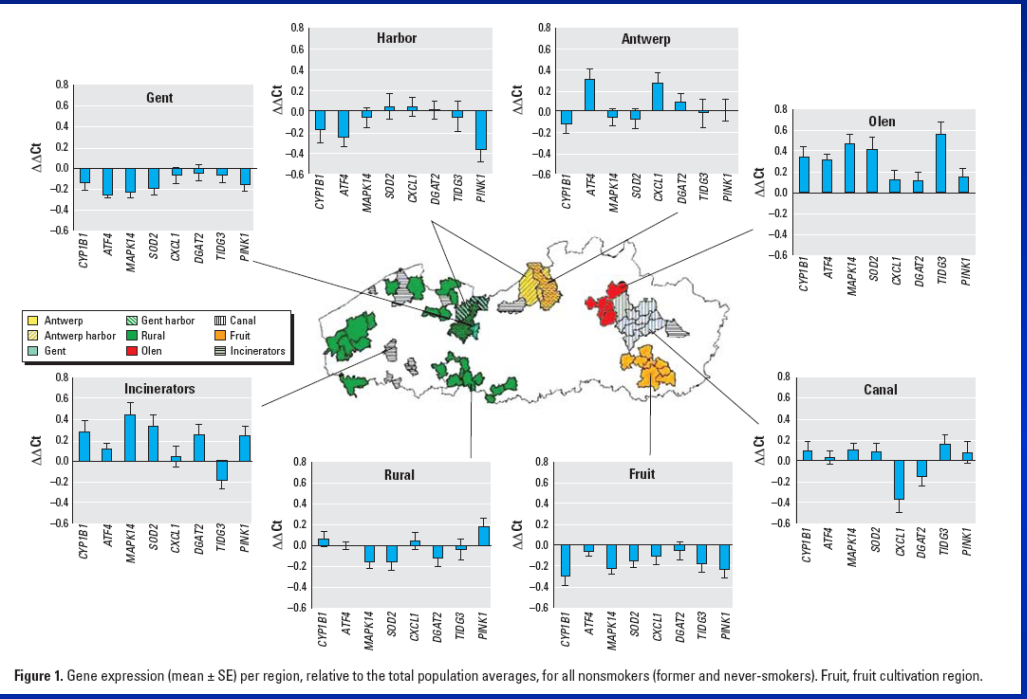


Figure 1. Gene expression (mean ± SE) per region, relative to the total population averages, for all nonsmokers (former and never-smokers). Fruit, fruit cultivation region.

- Studio su 398 individui sani residenti da almeno 5 anni in 8 distretti delle Fiandre a diversa pressione ambientale
- Insediamenti industriali di vario tipo: chimico, metallurgico, raffinerie di petrolio inceneritori ed agricoltura intensiva
- Indagati i livelli ematici ed urinari di Cea e PSA, metalli pesanti, diossine, PCB, IPA etc.
- Su leucociti periferici indagata l'espressione di geni che regolano attività metaboliche, risposta immunitaria, proliferazione e differenziazione.
- Lo studio ha dimostrato che esistono molteplici e significative correlazioni fra espressione genica ed inquinanti ambientali

Tissue Organization Field Theory (TOFT)
NUOVO PARADIGMA: EPIGENETICA

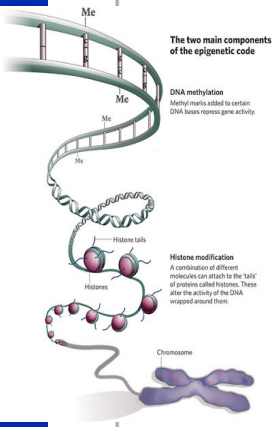
Review

Cell PRESS

Epigenetic transgenerational actions of environmental factors in disease etiology

Michael K. Skinner, Mohan Manikkam and Carlos Guerrero-Bosagna

Review



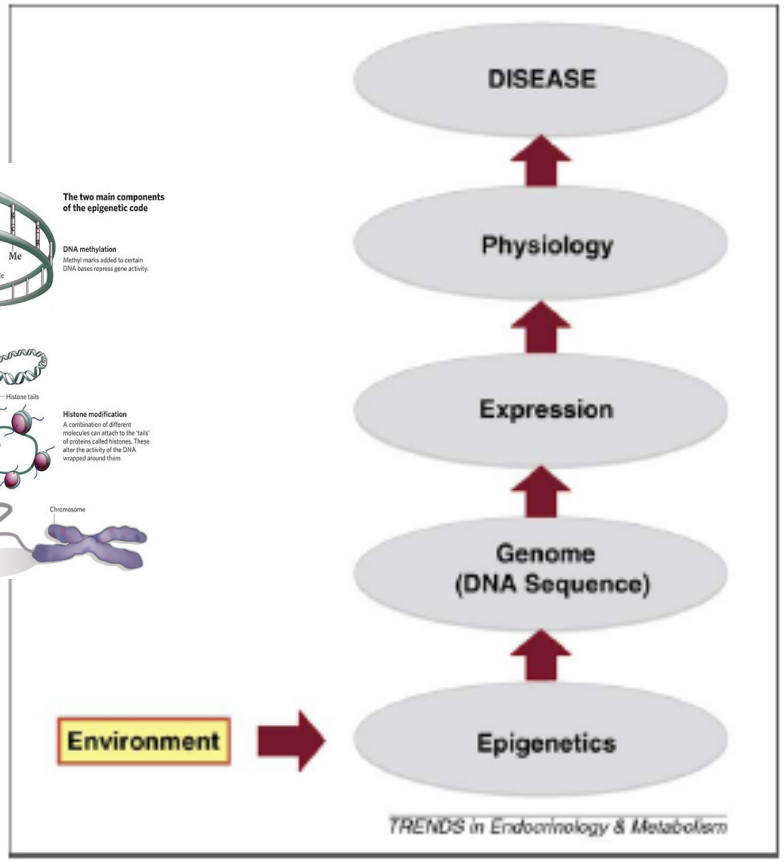


Figure 1. Proposed etiology of how the environment effects disease. The cascade of molecular and physiological processes following an environmental exposure to promote disease is shown.

http://www.nature.com/news/2006/060508/images/441143a-i2.0.jpg

- L'**Ambiente** agisce più direttamente sull'**epigenoma** (ipo/ipermetilazione, assetto cromatinico-*hystone code*, RNA minori..) e attraverso questo sul **genoma**

- Possiamo anche dire che **l'evoluzione del fenotipo individuale anche patologico (!)** è determinato dall'**epigenoma** più che dal **genoma**

- **In questo senso non è azzardato considerare che la quasi totalità delle malattie è ascrivibile all'ambiente**

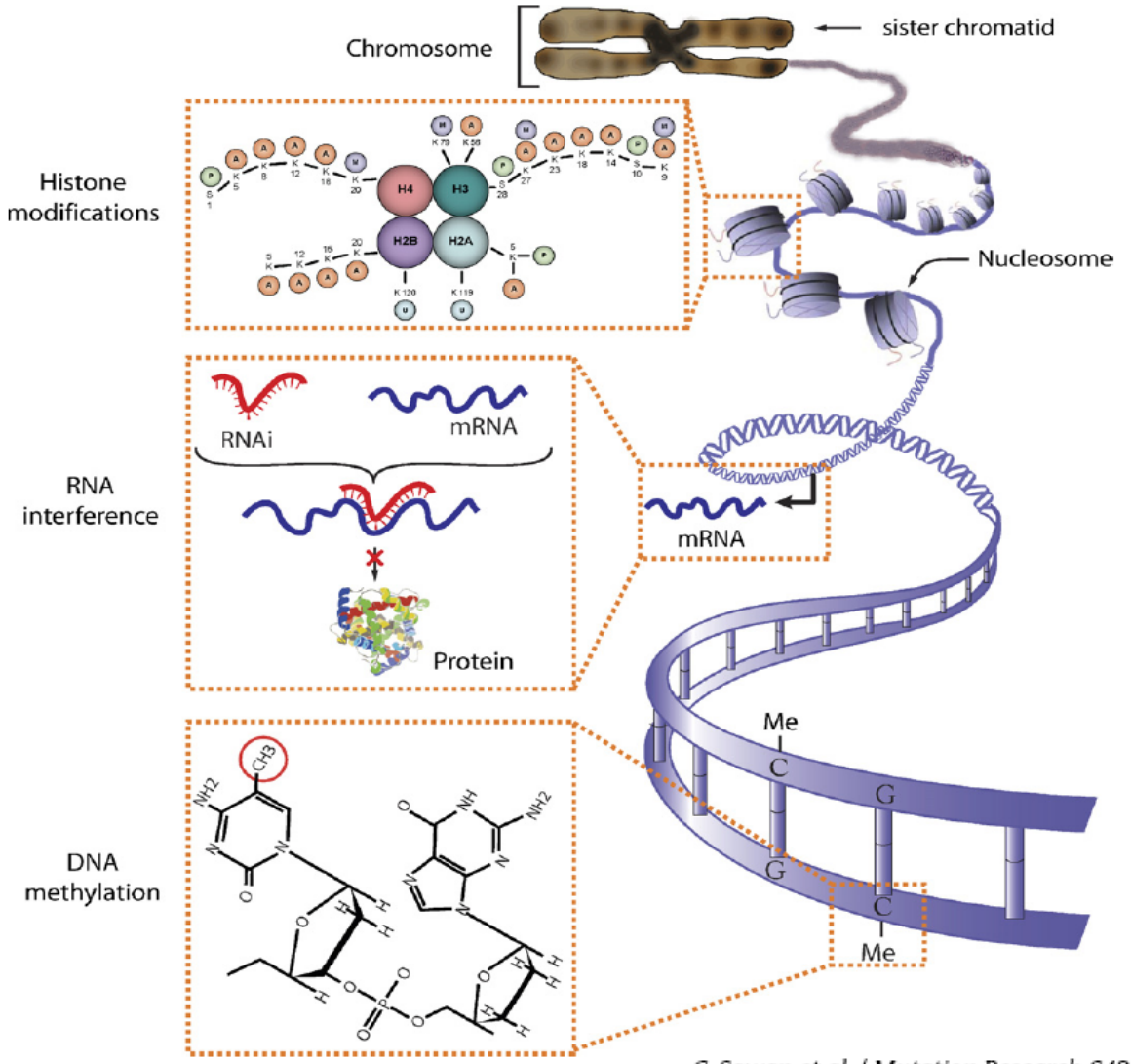
Brena RM, Costello JF. ***Genome-epigenome interactions in cancer***. *Hum Mol Genet*. 2007 Apr 15;16(R1):R96-R105.

Mini review

Epigenetic drivers and genetic passengers on the road to cancer

Carla Sawan, Thomas Vaissière, Rabih Murr, Zdenko Herceg*

International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, Rhone-Alpes, 69008 Lyon, France



C. Sawan et al. / Mutation Research 642 (2008) 1–13

Fig. 1. Different types of epigenetic information. DNA methylation, histone modifications, and RI regulation. DNA methylation is a covalent modification of the cytosine (C) that is located 5′ to a guanine (G) in a CpG dinucleotide. Histone (chromatin) modifications refer to covalent post-translational modifications of N-terminal tails of four core histones (H3, H4, H2A, and H2B). The most recent mechanism of epigenetic inheritance involves RNAs, which either in the form microRNA or Xist can alter gene expression states in a heritable manner.

"It is now generally accepted that human cancer cells harbor global epigenetic abnormalities and that epigenetic alterations may be the key to tumor initiation and development"

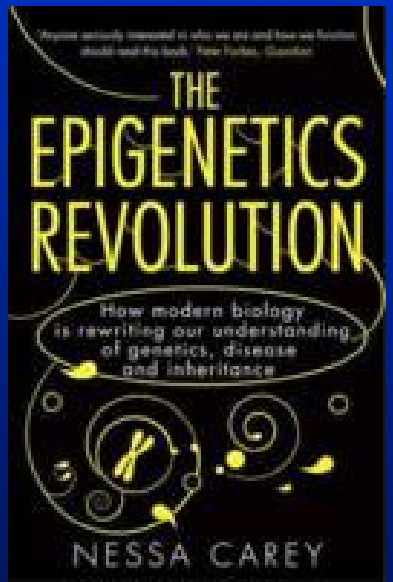
Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis 2010;31:27–36;

TISSUE ORGANISATION FIELD THEORY (TOFT)

- La carcinogenesi è un problema di alterata organizzazione tissutale che può insorgere già nel momento della programmazione fetale
- I cancerogeni distruggono la normale architettura tissutale alterando la comunicazione fra cellula e cellula e compromettendo di conseguenza l'integrità del genoma
- le mutazioni genetiche sono l'effetto e non la causa della malattia
- Il cancro non è quindi un evento casuale ma la conseguenza di modificazione epigenetiche indotte dall'ambiente
- L'esposizione dei gameti e il periodo della vita intrauterina sono cruciali per la programmazione fetale
- Il processo può essere reversibile

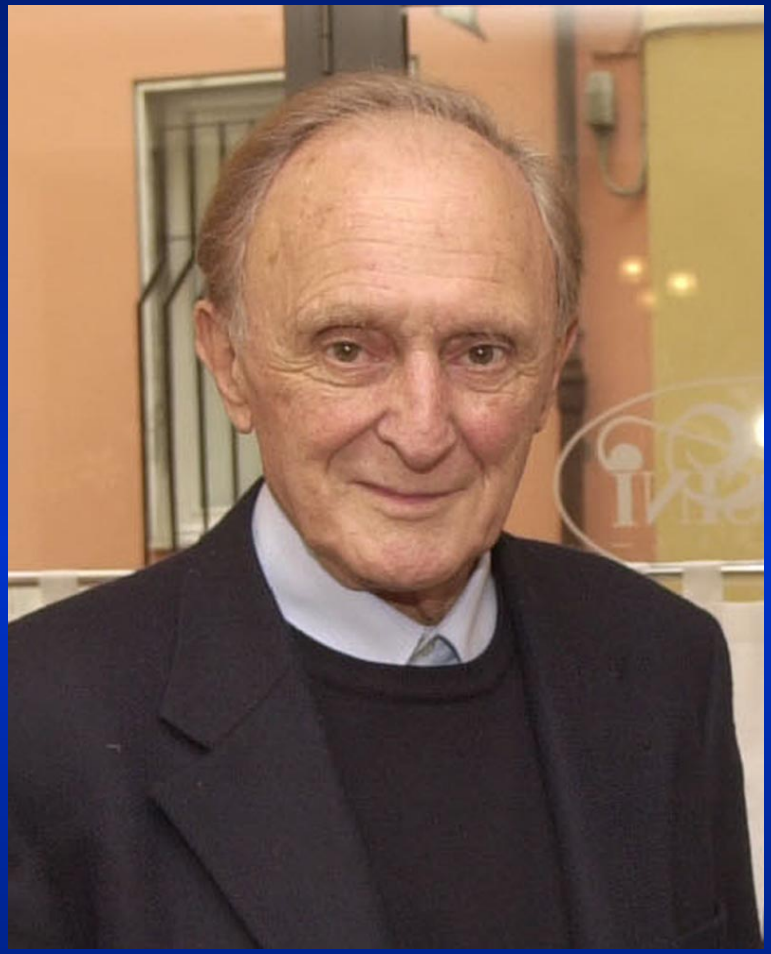
Cosa cambia con il nuovo paradigma dell'epigenetica??

L'AMBIENTE ACQUISTA UN RUOLO ASSOLUTAMENTE CENTRALE E PRIORITARIO NELLA GENESI DEL NOSTRO FENOTIPO E DELLE NOSTRE MALATTIE



…..la dimostrazione è con politiche di Prevenzione Primaria si contrasta efficacemente anche il cancro!

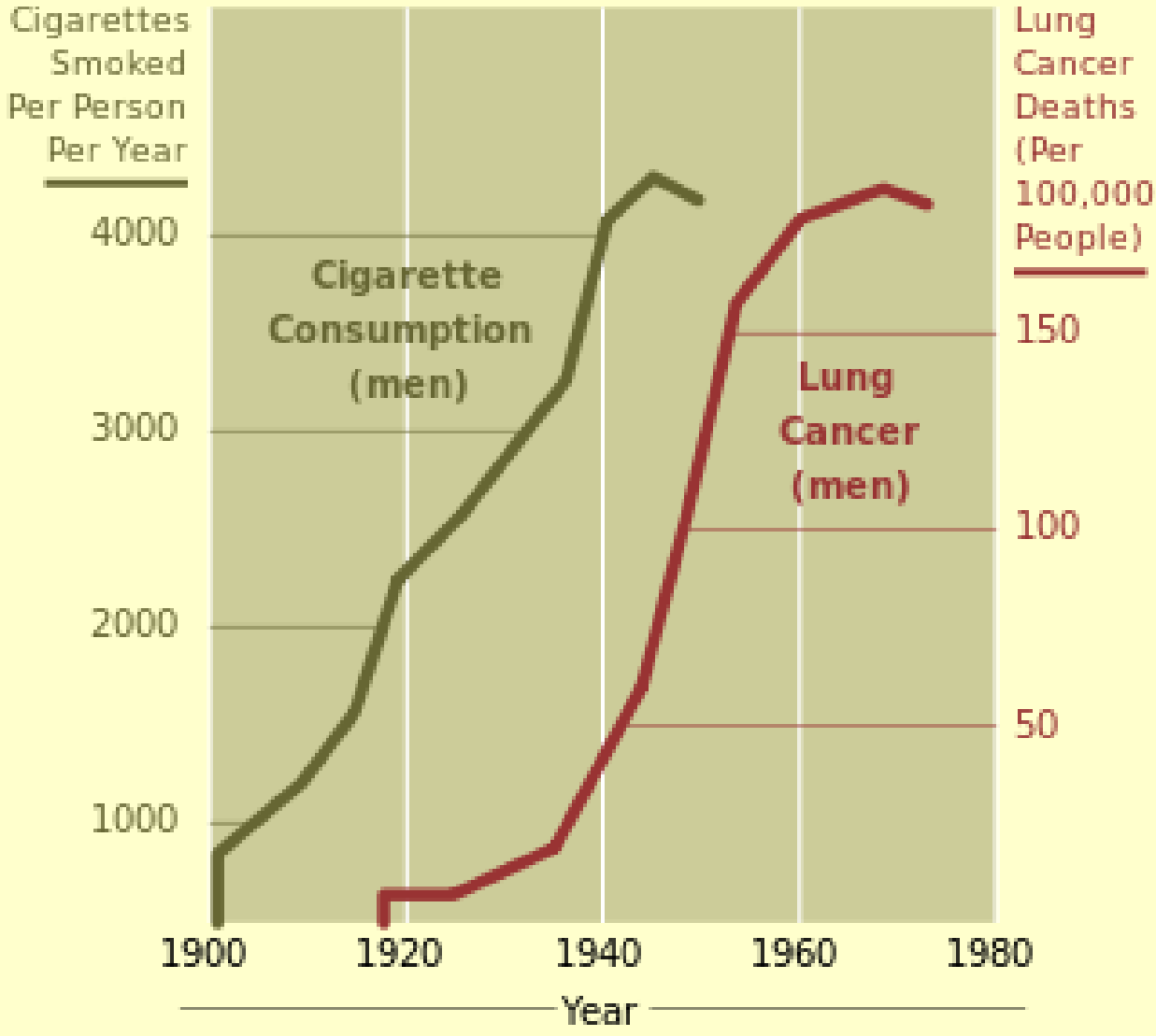
“PREVENZIONE PRIMARIA”



“Agire sulle cause delle malattie, prima che queste si manifestino, riducendo l’esposizione delle popolazioni agli agenti tossici e cancerogeni…la Prevenzione Primaria tutela la salute e protegge il ricco come il povero, ma non porta onori, fama o denari ed è purtroppo negletta ai governi ed alle istituzioni”….

Lorenzo Tomatis

20-Year Lag Time Between Smoking and Lung Cancer



In Svezia, dove dal 1970 sono stati messi al bando diversi pesticidi, i linfomi sono in diminuzione

Acta Oncologica, 2008; 47: 347–354

informa
healthcare

INVITED ARTICLE

Pesticides, soft-tissue sarcoma and non-Hodgkin lymphoma – historical aspects on the precautionary principle in cancer prevention

LENNART HARDELL

Department of Oncology, University Hospital, SE-701 85 Örebro and Department of Natural Sciences, Örebro University, SE-701 82 Örebro, Sweden

Abstract

Background. After the 2nd World War a long range of chemical agents have been introduced on the market, both in Sweden and most other countries. From the 1950's several pesticides gained increasing use in agriculture and forestry. In the 1970's public concern increased in Sweden especially regarding use of phenoxy herbicides to combat deciduous wood, although statements from different authorities were reassuring of the safety. *Materials and methods.* At the end of the 1970's the author and his colleagues published the first scientific evidence of an association between exposure to phenoxyacetic acids, chlorophenols and certain malignant tumours, i.e., soft-tissue sarcoma and malignant lymphoma. The study subjects were also exposed to contaminating dioxins such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Later studies showed also an association between certain persistent organic pollutants such as polychlorinated biphenyls and non-Hodgkin lymphoma (NHL) with an interaction with titers of antibodies to Epstein-Barr virus early antigen. These results have been corroborated in other studies. *Discussion.* Over the years industry and its allied experts have attacked our studies, but in 1997 IARC classified TCDD as a human carcinogen, Group I. The increasing incidence of NHL in Sweden levelled off about 1990. The author postulated that the regulation or ban of the use of chlorophenols, certain phenoxy herbicides and some persistent organic pollutants in Sweden back in the 1970s has contributed to the now decreasing incidence of NHL. Unfounded criticism from industry experts may prohibit the precautionary principle and early warnings of cancer risk can be ignored. Cancer risks by certain chlorinated phenols may serve as a model of how the precautionary principle should be used by taking early warnings seriously.

MIGLIORANDO LA QUALITA' DELL'ARIA RIDUZIONE DOPO SOLO 3 ANNI ANCHE DEI DECESSI PER CANCRO AL POLMONE!

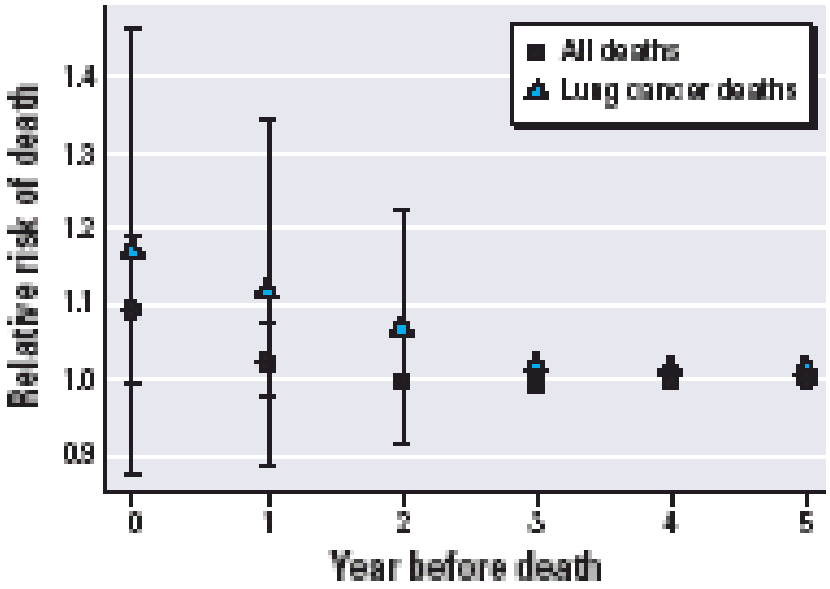
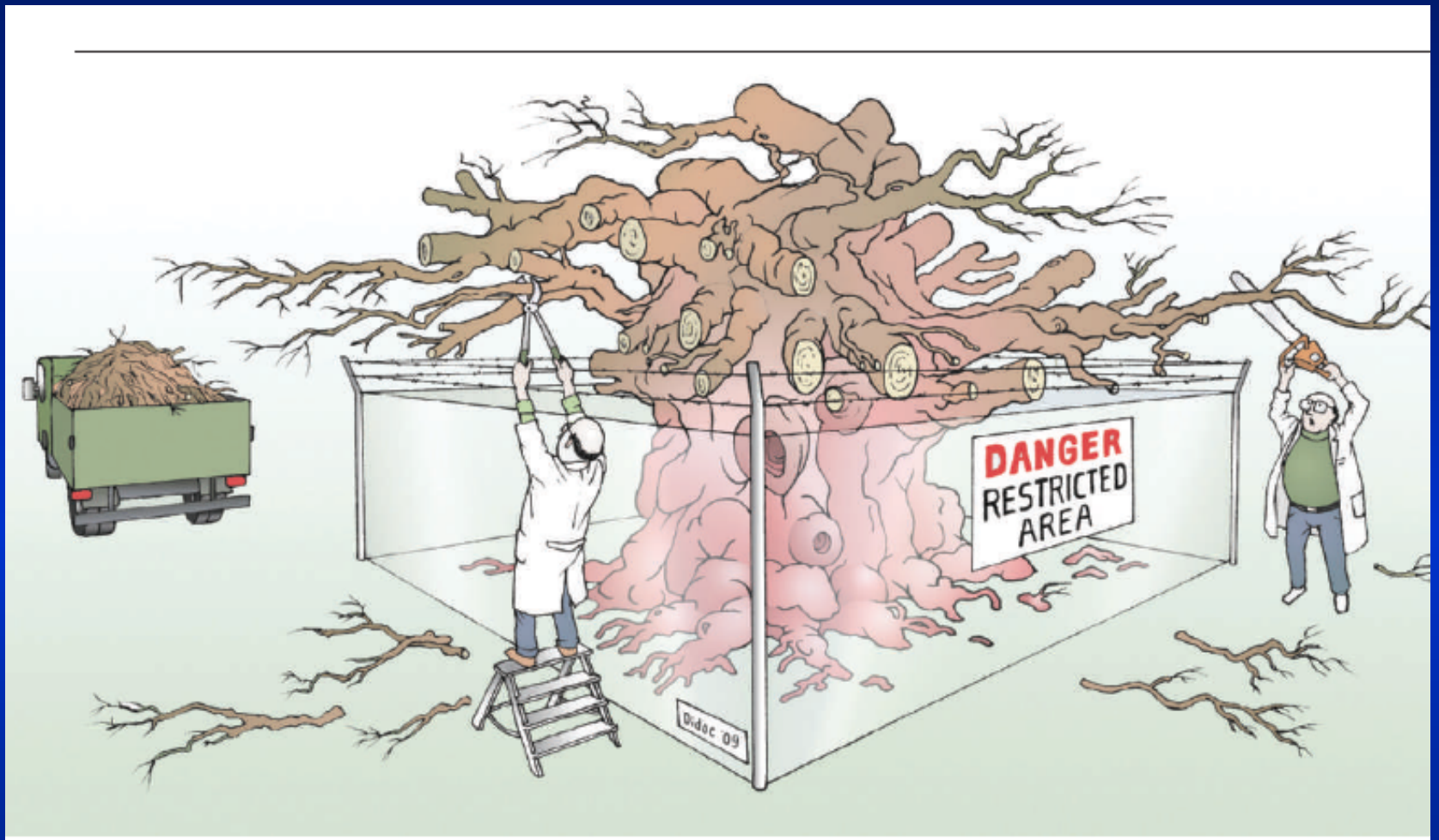


Figure 5. The model-averaged estimated effect of a 10-μg/m^3 increase in $PM_{2.5}$ on all-cause mortality and on lung cancer mortality. The estimated effect for lung cancer remains elevated up to 3 years preceding the death. Also shown are the pointwise 95% CIs for each lag, based on jacknife estimates.

Schwartz J. et al. (Environmental Health Perspectives, 2008 – vol. 116, n. 1)



A change of strategy in the war on cancer

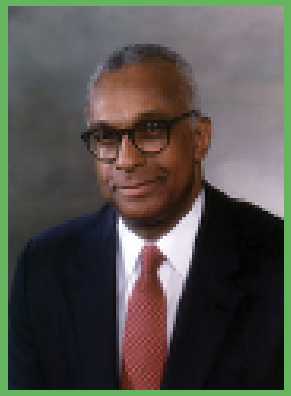
Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

NATURE|Vol 459|28 May 2009

The President
The White House
Washington, DC 20500

Dear Mr. President:

Though overall cancer incidence and mortality have continued to decline in recent years, the disease continues to devastate the lives of far too many Americans. In 2009 alone, approximately 1.5 million American men, women, and children were diagnosed with cancer, and 562,000 died from the disease. With the growing body of evidence linking environmental exposures to cancer, the public is becoming increasingly aware of the unacceptable burden of cancer resulting from environmental and occupational exposures that could have been prevented through appropriate national action. The Administration's commitment to the cancer community and recent focus not been addressed adequately by the National Cancer Program. The American people—even before they are born—are bombarded continually with myriad combinations of these dangerous exposures. The Panel urges you most strongly to use the power of your office to remove the carcinogens and other toxins from our food, water, and air that needlessly increase health care costs, cripple our Nation's productivity, and devastate American lives.



The President's Cancer Panel

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair
Charles R. Drew Professor of Surgery
Howard University College of Medicine
Washington, DC 20059

Margaret L. Kripke, Ph.D.
Vivian L. Smith Chair and Professor Emerita
The University of Texas
M.D. Anderson Cancer Center
Houston, TX 77030

10 April 2010

Informazione e Rischi Ambientali

"il modo con cui si confezionano le conoscenze sui rischi ambientali ha poco a che fare con i casi della scienza. Ogniqualvolta si solleva una questione di salute pubblica che ha ripercussioni per miliardi di dollari sulla vendita di un determinato tipo di beni

l' onere della prova imposto a chi esamina i rischi può diventare tanto elevato da risultare insostenibile"

Devra Davis in:

La Storia segreta della guerra al cancro

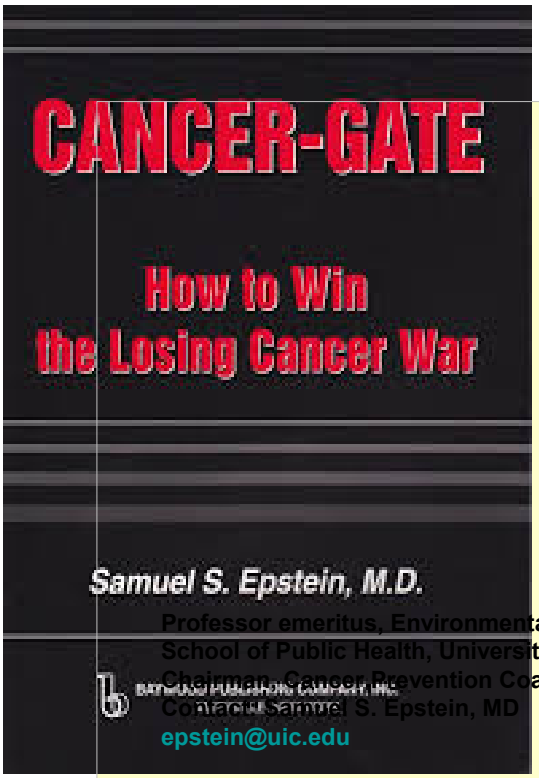
Genetica ed epigenetica del cancro: dalla teoria mutazionale stocastica ai nuovi modelli di cancerogenesi

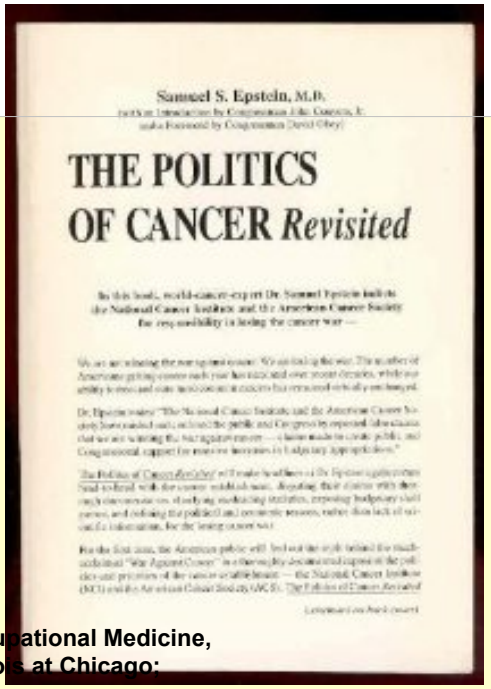
Patrizia Gentilini
patrizia.gentilini@villapacinotti.it

http://www.tumori.net/it3/brochures/documenti/inceneritori/Ambiente_e_Tumori_17_10_11.pdf

con le armi sbagliate e sotto i comai

Devra Davis





Professor emeritus, Environmental & Occupational Medicine,
School of Public Health, University of Illinois at Chicago;
Chairman, Cancer Prevention Coalition;
Contact: Samuel S. Epstein, MD 312-996-2297 312-996-2297
epstein@uic.edu

http://www.preventcancer.com/

Theories of carcinogenesis: An emerging perspective

C. Sonnenschein, A.M. Soto / Seminars in Cancer Biology 18 (2008) 372–377

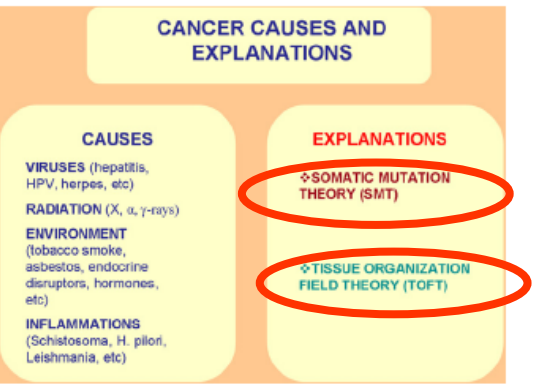


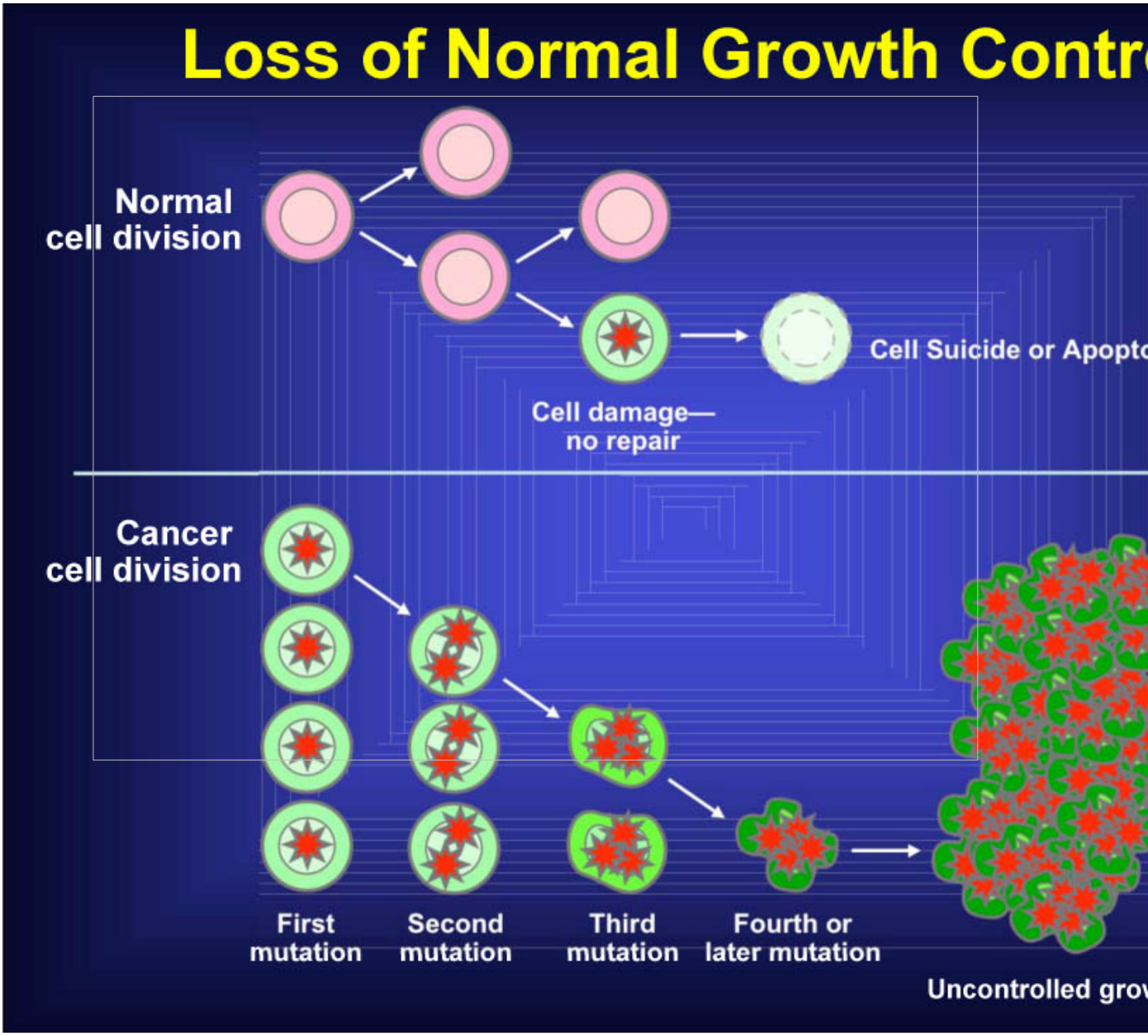
Fig. 1. Differences between the terms "causes" and "explanations" in the context of cancer research.

SEMINARS IN CANCER BIOLOGY 18 (2008) 372-377

SMT
CANCRO = MALATTIA “GENETICA”

“si propone che la maggior parte dei tumori derivi da una singola cellula e che la progressione tumorale sia il risultato di una instabilità genetica acquisita all’interno del clone originale che consente la selezione delle linee cellulari più aggressive”

Nowell 1976


Loss of Normal Growth Contr
Normal cell division
Cell Suicide or Apopto
Cell damage— no repair
Cancer cell division
First mutation
Second mutation
Third mutation
Fourth or later mutation
Uncontrolled grov

Teoria Mutazionale Somatica (SMT)

"l'insorgenza di mutazioni casuali nei geni che controllano la proliferazione e l'apoptosi sono responsabili del cancro"

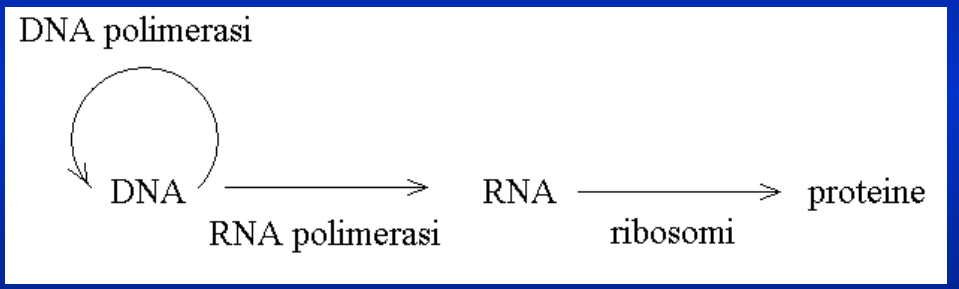
Bertam J.S. 2001

Teoria Mutazionale Somatica (SMT)

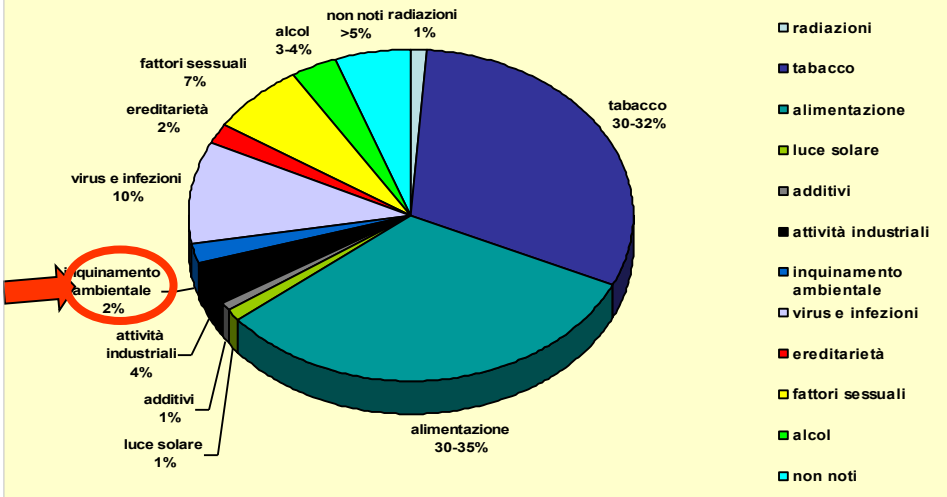
Origine monoclonale della malattia in seguito ad un "incidente genetico", tanto più frequente al crescere dell'età; processo irreversibile con successivo accumulo di mutazioni sequenziali identificabili in:

- Proliferazione svincolata dai normali segnali di crescita
- Insensibilità ai segnali inibitori
- Resistenza alla morte cellulare programmata (apoptosi)
- Riattivazione delle telomerasi (immortalizzazione)
- Attivazione dell'angiogenesi
- Tendenza a metastatizzare
- Instabilità genomica

SMT:
INFORMAZIONE A "SENSO UNICO"



RISCHI ATTRIBUIBILI DI CANCRO
secondo R.Doll e Pito



...

	Quota di tumori attribuibili a vari fattori di rischio	
	USA, 2012*	Regno Unito, 2010**
Fattore di rischio	**%**	**%**
Tabacco	33	19.4
Dieta	5	9.2
Sovrappeso, obesità	20	5,5
Inattività fisica	5	1.0
Abuso di bevande alcoliche	3	4.0
Fattori occupazionali	5	3.7
Infezioni	5	3.1
Radiazioni ionizzanti e esposizione a raggi UV	2	5.3
Inquinamento ambientale	2	–

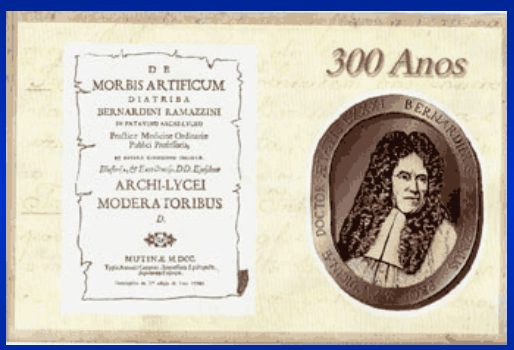
Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors

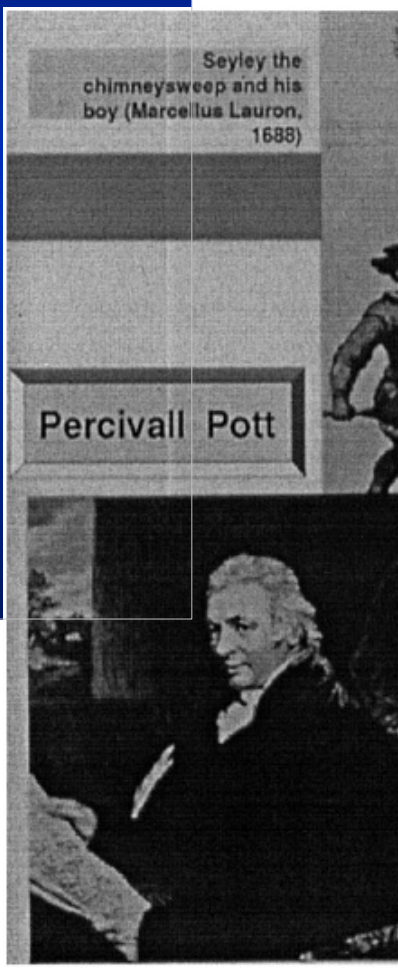
Lancet 366: 1784-1793, 2003

- analizzata la mortalità per 12 tipi di tumore in 7 aree del mondo
- 9 fattori di rischio indagati: 5 legati allo stile di vita, 2 a virus e 2 a polluzione aerea
- questi 9 fattori insieme, spiegano dal 39% al 41% di tutti i tumori

essi non possono pertanto essere assunti come esemplificativi del fenomeno cancro nel suo complesso

…eppure le cause ambientali/occupazionali del cancro erano state studiate da secoli con rigore e lungimiranza!

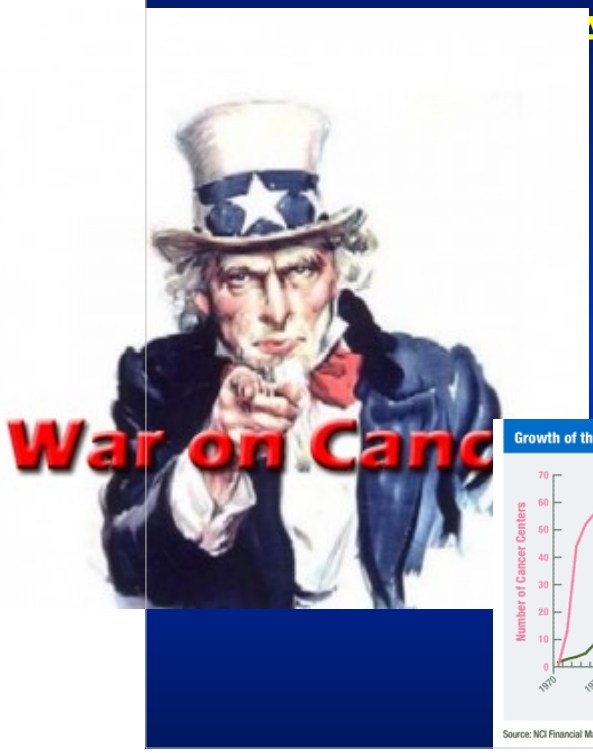


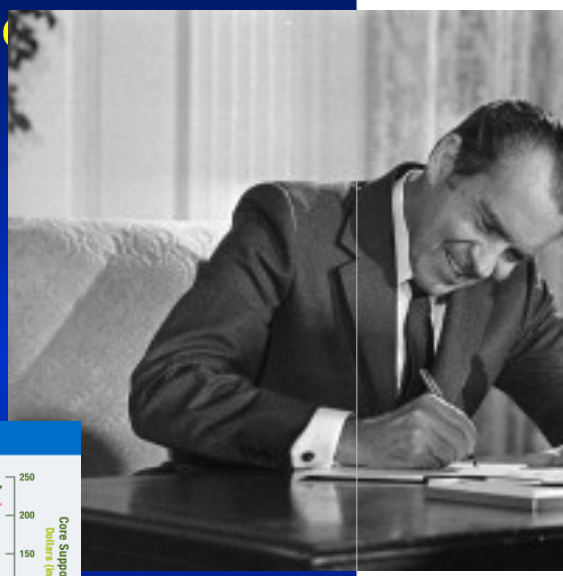


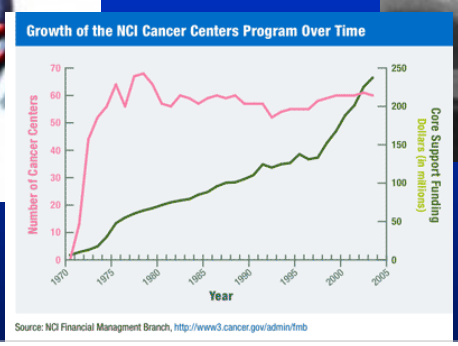
CANCRO = MALATTIA GENETICA

Tutta l'attenzione si sposta dalla ricerca delle cause allo studio delle modalità con cui si compie la trasformazione neoplastica

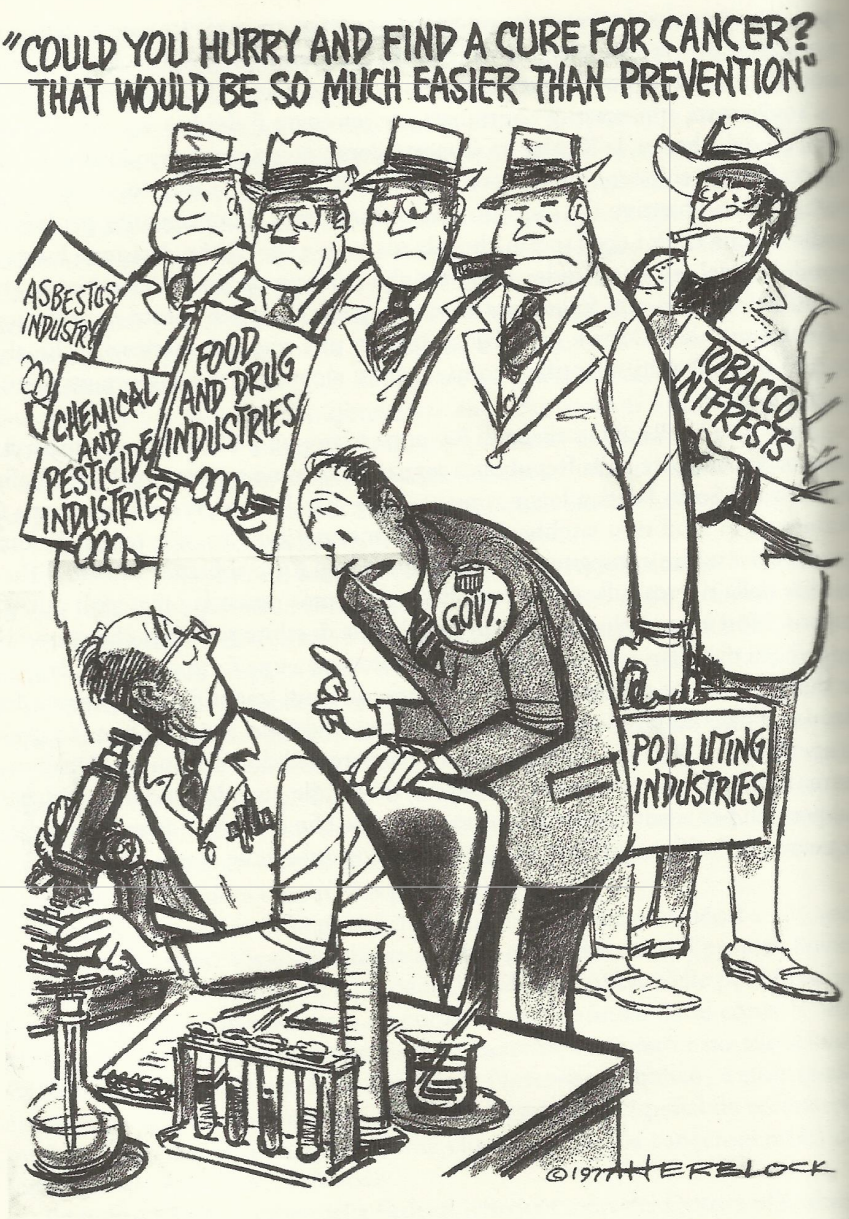
ATIONAL CANC







Targeted Therapy: The Hype



Vignetta del 1977 di Herblock. *Could you hurry and find a cure for cancer? That would be so much easier than prevention*, © by The Herb Block Foundation.

GUERRA AL CANCRO: RISULTATI DOPO 30 ANNI

(Dati dell'American Cancer Society 2005)

Table 1.

Relative survival* (%) during three time periods, by cancer site in the USA.†

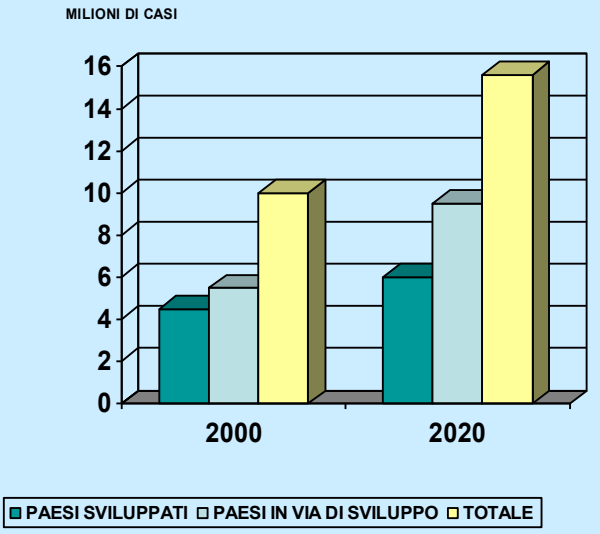
Site	1974–1976	1983–1985	1995–2000
All sites	50	53	64
Breast (female)	75	78	88
Colon	50	58	63
Leukaemia	34	41	46
Lung and bronchus	13	14	15
Melanoma of the skin	80	85	91
Non-Hodgkin lymphoma	47	54	59
Ovary	37	41	44‡
Pancreas	3	3	4
Prostate	67	75	99
Rectum	49	55	64
Urinary bladder	73	78	82

*Five-year relative survival rates based on follow-up of patients through 2001.

†Source: American Cancer Society, 2005 [1].

‡Recent changes in classification of ovarian cancer have affected 1995–2000 survival rates [1].

INCIDENZA DEL CANCRO NEL MONDO: PROIEZIONI FINO AL 2020



(WHO,2006)

INCIDENZA DEL CANCRO

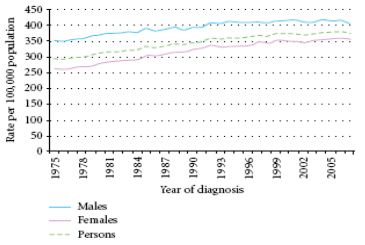


FIGURE 1: Age standardized (European) incidence rates for all cancers excluding nonmelanoma skin cancer, Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer in Research organisation, accessed on 18/2/2011 [10].

INCIDENZA e MORTALITA' CANCRO della MAMMELLA

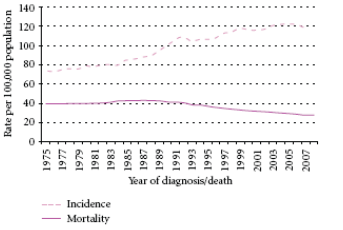


FIGURE 2: Age standardized (European) incidence and mortality rates for breast cancer in females in Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer Research organisation, accessed on 18/2/2011 [10].

INCIDENZA e MORTALITA' CANCRO della PROSTATA

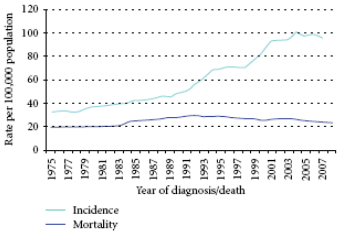


FIGURE 3: Age standardized (European) incidence and mortality rates for prostate cancer in males in Great Britain 1975–2008. Figure taken from the web-site of the UK Cancer Research organisation, accessed on 18/2/2011 [10].

I NUMERI DEL CANCRO IN ITALIA 2013 (AIOM-AIRTUM)

- “Si stima che nel 2013, in Italia, verranno diagnosticati circa 366.000 nuovi casi di tumore maligno (circa 1.000 al giorno), di cui 200.000 negli uomini e circa 166.000 nelle donne”.

- La probabilità di ammalarsi di un qualunque tumore nel corso della vita (0-84 anni) riguarda un uomo ogni 2 ed una donna ogni 3”

Malati e tartassati, i drammi del cancro
AVVENIRE 15 maggio 2012
http://www.avvenire.it/Cronaca/Pagine/malati-e-tartassati.aspx

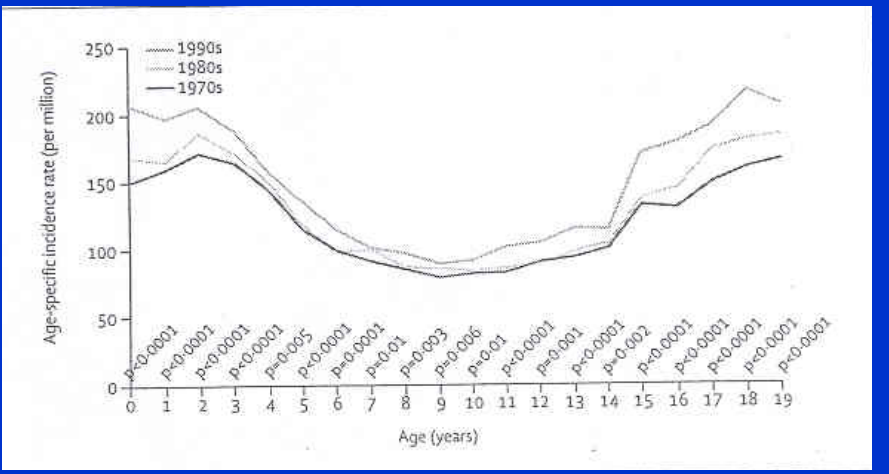
Spesa annuale per le cure oncologiche in Italia:

- 960 mila pazienti con diagnosi di tumore negli ultimi 5 anni
- 776 mila “caregivers” (assistenti: familiari, infermieri, badanti...)
- 36,4 miliardi di euro il costo ogni anno (cure + assistenza)

Principali critiche alla SMT

- Incremento dei tumori nell'infanzia e nell'adolescenza (non solo quindi patologie conseguenti all'allungamento della vita)
- Incremento contestuale di cancro e di patologie endocrino-metaboliche, cronico-degenerative ed immunomediate
- L'incremento dei tumori in aree ad alto tasso di inquinamento ambientale
- La scarsa/nulla considerazione della diffusione ormai ubiquitaria di agenti cancerogeni e tossici (diossine, PCB, pesticidi…) che modulano, in modo non certo casuale, l'espressione genica *("paradosso del progresso")*

INCIDENZA DI NEOPLASIE NELL'INFANZIA E NELL'ADOLESCENZA IN EUROPA (anni 1970-1999)



(Lancet, Dic. 2004)

Tasso di incidenza tumori pediatrici (0-14 anni) / milione bambini

1988-1992	Italia	**146**
1998-2002	Italia	**175.4***
2003-2005	Italia	**168.5**
1990-2000	Europa	140
1987-2004	Germania	141
1990-1999	Francia	138
1995-2004	Svizzera	141
1992-2004	USA	158

***Statisticamente significativo**

Epidemiologia e Prevenzione - Tumori infantili
Rapporto AIRTUM 2008 (Associazione Italiana Registri Tumori)

Incidenza da 0 a 14 anni di: tutti i tumori, linfomi, leucemie, S.N.C. in Paesi Nordici (NORDCAN), U.S.A. (SEER) ed Italia (AIRTUM) 2003-2008

	NORDCAN		SEER		AIRTUM	
	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS
Leukaemia	54.	48.	55.3	46.6	56.1	51.6
Lymphoma, all	19.	11.	19.3	11.3	32.4	17.8
All tumours of the CNS	42.	39.	42.0	39.0	30.6	27.2
Others	54.	52.	62.1	62.2	71.7	66.2
All malignant tumours and non-malignant of the CNS	169.	150.	178.7	159.1	190.8	162.8

Tabella 2. Tassi di incidenza standardizzati per età (per 1.000.000) nel periodo 2003-2008, per tutte le neoplasie e i tre gruppi più frequenti, nel pool AIRTUM, nei Paesi nordici e negli Stati Uniti nei bambini di 0-14 anni d'età.
Table 2. Age-standardized rates (per 1,000,000) in 2003-2008, for all tumour types and the three most frequent types, in the AIRTUM pool, the Nordic Countries, and the USA in children aged 0-14 years.

Fonte: Rapporto AIRTUM 2012 - I tumori dei bambini e degli adolescenti. *Epidemiol Prev* 2013;37(1) Suppl 1:1-296.

I TUMORI IN ITALIA - RAPPORTO 2012

I tumori dei bambini e degli adolescenti

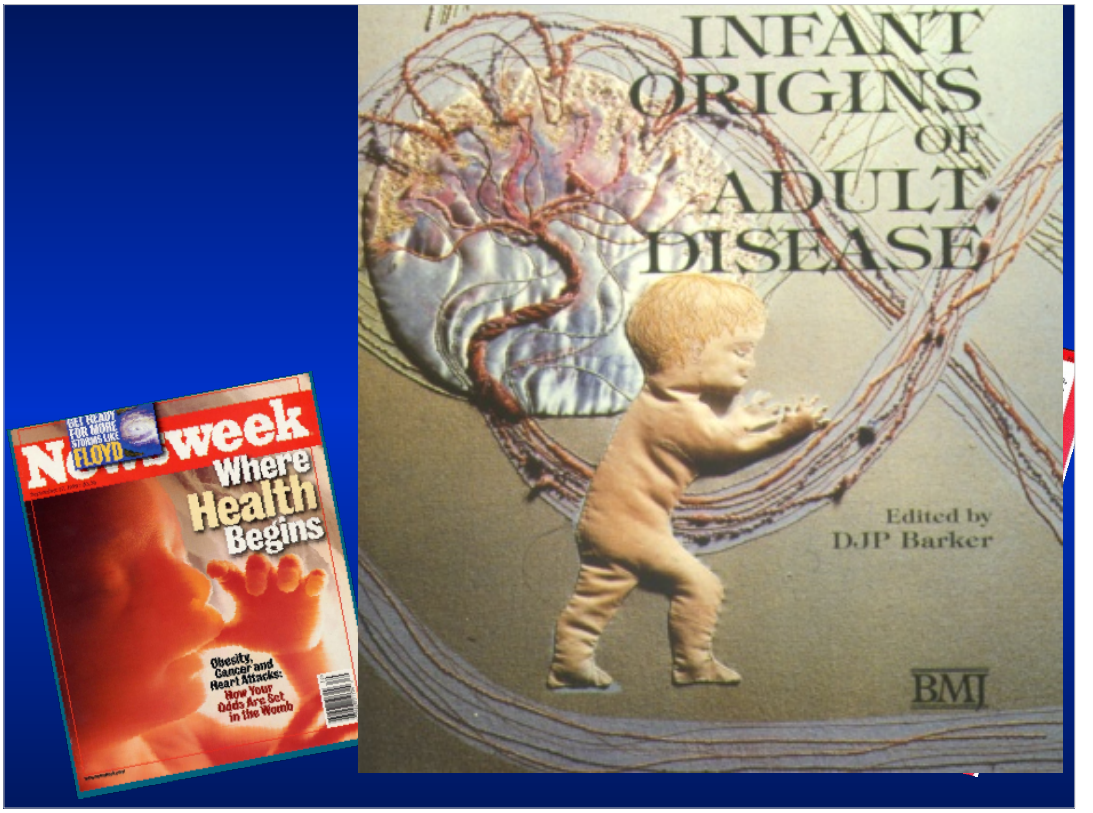
Negli adolescenti (15-19 anni) si osserva un aumento significativo per tutte le neoplasie maligne (APC: +2,0%), il complesso dei linfomi (APC: +2,9%) e il linfoma di Hodgkin in particolare (APC: +3,6%), il carcinoma della tiroide (APC: +6,1%) e il melanoma (APC: +8,1%). La leucemia linfoblastica risulta l'unica neoplasia in significativa diminuzione in questo gruppo d'età sul lungo periodo. Le tendenze recenti (1998-2008) confermano l'aumento dei tumori maligni solo nelle ragazze e l'aumento importante di carcinomi della tiroide (APC: +7,9%) in maschi e femmine. Sempre sul periodo recente si registra una diminuzione di tumori dell'osso nelle ragazze basato su solo 46 casi.

Combating Environmental Causes of Cancer

David C. Christiani, M.D., M.P.H.

During the past three decades, increases in the incidence of some childhood cancers, such as leukemia and brain tumors, may implicate prenatal exposure to environmental carcinogens — and more than 300 industrial chemicals have been detected in umbilical-cord blood.

N ENGL J MED 364;9 NEJM.ORG MARCH 3, 2011


GET READY FOR MORE STORMS LIKE FLOYD
Where Health Begins
Obesity, Cancer and Heart Attacks: How Your Odds Are Set in the Womb
INFANT ORIGINS OF ADULT DISEASE
Edited by D.J.P. Barker
BMJ

TOXICOLOGICAL SCIENCES 78, 248–257 (2004)
DOI: 10.1093/toxsci/kfh062
Advance Access publication January 12, 2004

A Novel Effect of Dioxin: Exposure during Pregnancy Severely Impairs Mammary Gland Differentiation

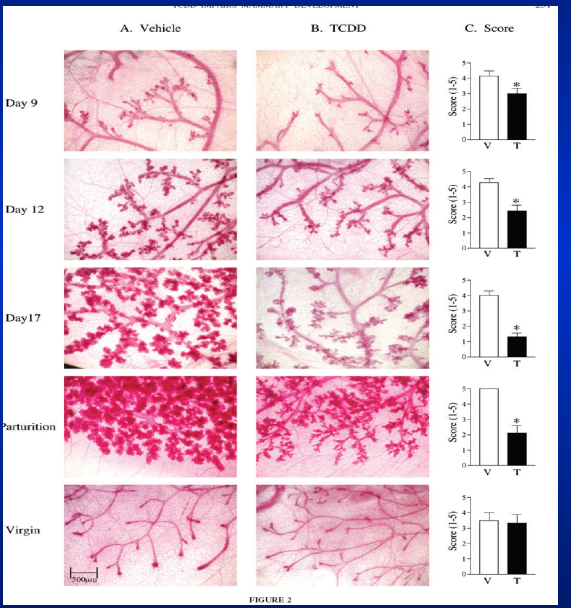


FIGURE 2

© 2008 The Authors
Journal compilation © 2008 Nordic Pharmacological Society. Basic & Clinical Pharmacology & Toxicology, 102, 125–133
Doi: 10.1111/j.1742-7843.2007.00165.x

MiniReview

Does Breast Cancer Start in the Womb?

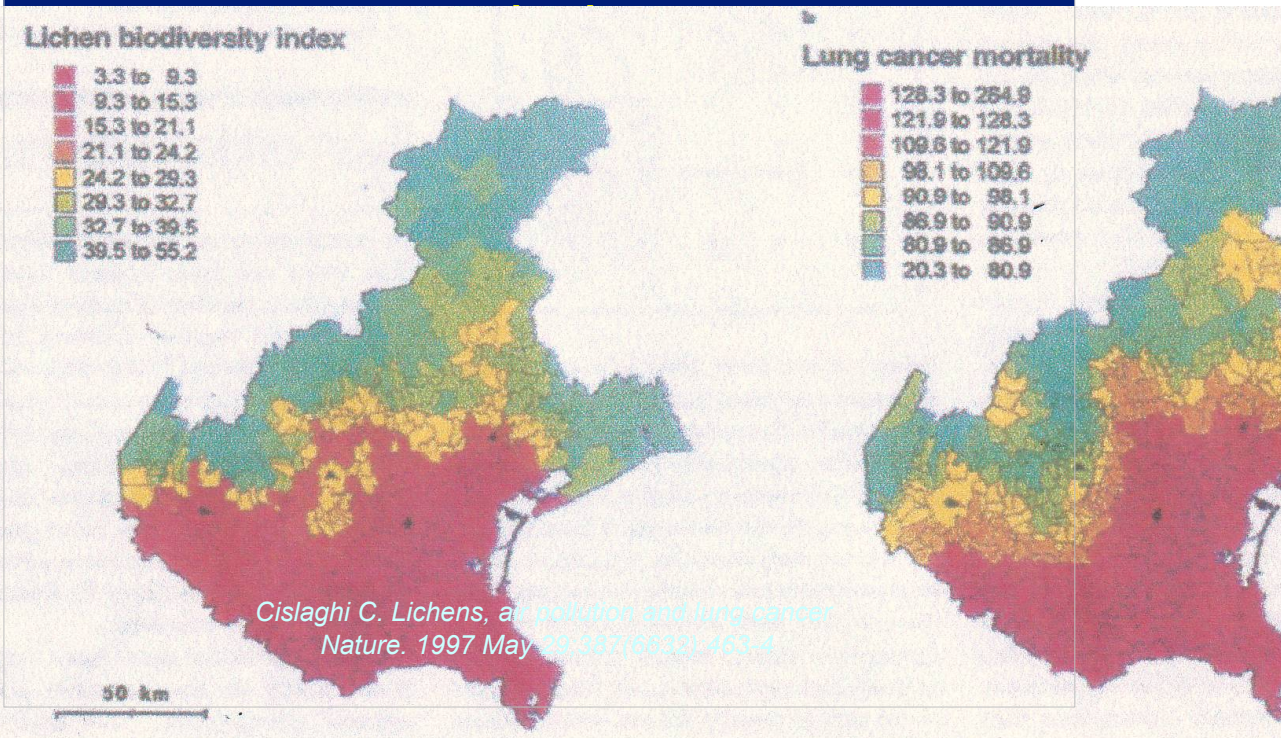
Ana M. Soto, Laura N. Vandenberg, Maricel V. Maffini and Carlos Sonnenschein

Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA, USA

(Received June 28, 2007; Accepted September 7, 2007)

BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 102(2008) 125-133

Deserto lichenico e mortalità per



Cislaghi C. Lichens, air pollution and lung cancer. Nature. 1997 May 29;387(6632):463-4.

Figure 1 a, Lichen biodiversity, calculated as the sum of frequencies of all epiphytic species in a sampling grid of 10 units; and **b,** lung can male residents (expressed as observed/expected cases × 100), in the region of Veneto. Scale intervals are based on percentiles of values dist

The carcinogenicity of outdoor air pollution

Published Online
October 24, 2013
http://dx.doi.org/10.1016/
S1470-2045(13)70487-X

For more on the IARC Monographs see http://monographs.iarc.fr/

Upcoming meetings
June 3–10, 2014, Volume 110: Perfluoro-octanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

Monograph Working Group Members
J Samet (USA)—Chair; P H N Saldiva (Brazil); M Straif; G Chen; P White (Canada); W Huang (China); L E Knudsen, P Møller, O Raaschou-Nielsen (Denmark); U Heinrich (Germany); K Balakrishnan (unable to attend; India); F Forastiere (Italy); T Yorifuji (Japan); D M Phillips, P Vineis (UK); J Chow, D M DeMarini (unable to attend), R Henderson, F Laden, D L Morgan (unable to attend), J J Schauer (USA)

Invited Specialists
G Hoek (The Netherlands); A J Cohen, A Russell (USA);

Representatives
E Durand, M. Radadi, for the French Agency for Food, Environmental and Occupational Health and Safety, France; Z Zubec, for the European Commission

Observers
G B Copley, D Morgott, J A Tumenson, for CONCAWE, Belgium; P Crosignani, for the International Society of the Doctors for the Environment (ISDE), Italy; B Fervers, for the Centre Léon Bérard, France; G Guillosou, for Eurelectric, Belgium

IARC/WHO Secretariat
R Baan, L Benbrahim-Tallaa, V Bouvard, A Borton, G Byrnes, R Carel, R Denkinho, C Dickens, C Dora, F El Ghissassi, K Straif, Y Grosse, B Lauby-Secretan, N Ndiaye, H Ohgaki, N Sahmoud, L Stewart, V Tan, J Wilbourn

In October, 2013, 24 experts from 11 countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of outdoor air pollution. This assessment was the last in a series that began with specific combustion products and sources of air pollution and concluded with the complex mixture that contains all of them. The results of this most recent assessment will be published as volume 109 of the IARC Monographs.[1]

Outdoor air pollution is a mixture of multiple pollutants originating from a myriad of natural and anthropogenic sources. Transport, power generation, industrial activity, biomass burning, and domestic heating and cooking are the predominant anthropogenic sources in many locations.[2] The mix of pollutants in outdoor air varies substantially over space and time, showing not only the diversity of sources, but the effect of atmospheric processes, including oxidation and weather. Diverse approaches are used to measure air pollution and some countries have established monitoring networks that typically record levels of regulated pollutants, such as respirable particulate matter (PM_{10}), fine particulate matter ($PM_{2.5}$), NO_2, SO_2, and O_3. $PM_{2.5}$ is increasingly used as an indicator pollutant, with annual average concentrations ranging from less than 10 to more than 100 μg/m³ globally. Pollution levels in western Europe and North America have generally declined since the late 20th century, but they are increasing in some rapidly industrialising countries, notably in Asia. In many areas, WHO and national air quality guidelines for $PM_{2.5}$ and other pollutants are routinely and substantially exceeded.[3] Occupational exposures to outdoor air pollution, although not routinely monitored, are also of concern for certain groups of workers, such as traffic police, drivers, and street vendors.

The IARC Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as carcinogenic to humans (IARC Group 1), based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence.

The findings regarding the carcinogenicity of outdoor air pollution as a mixture, and of particulate matter specifically, are remarkably consistent in epidemiological research, studies of cancer in experimental animals, and a wide range of studies of mechanisms related to cancer. Particularly, an increased risk of lung cancer was consistently observed in cohort and case-control studies including millions of people and many thousands of lung cancer cases from Europe, North America, and Asia. The largest and most informative studies were a pooled analysis of data from ten European countries and a large nationwide cohort study in the USA.[4,5] Many studies estimated quantitative levels of outdoor air pollutants, most often as mass concentration of particulate matter, and adjusted for a wide range of potential confounders including tobacco smoking. Increased risk associated with outdoor air pollution was also seen in studies restricted to never smokers.[6] Positive exposure-response relations were consistently observed in studies that provided such data. Notably, virtually all of the studies were done in areas where annual average levels of $PM_{2.5}$ range from about 10 to 30 μg/m³, which represents approximately the lower third of exposures worldwide. Nevertheless, increased risk of lung cancer was observed even in those areas where $PM_{2.5}$ concentrations are less than the current health-based guidelines.[4]

There was limited epidemiological evidence for bladder cancer associated with various metrics of exposure to outdoor air pollution, including occupational and residential exposure to traffic or traffic emissions, in studies that were adjusted for tobacco smoking. However, most studies assessed exposure only by employment in occupations with potentially high exposure to outdoor air pollution, so the results did not weigh heavily in the evaluation.

The Working Group also reviewed evidence regarding the carcinogenicity of outdoor air pollution in experimental animals. As part of this process, the IARC's earlier evaluations of diesel engine exhaust and of emissions from the combustion of coal and wood were updated and confirmed. All of these agents can be present in outdoor air and were shown previously to cause benign and malignant lung tumours in mice or rats.

Only a few studies have assessed the occurrence of cancer in animals exposed directly to outdoor air pollution by inhalation. Studies of mice exposed to traffic-related outdoor air pollution in São Paulo, Brazil, showed an increase in the incidence of lung adenoma, and an increase in the incidence and tumour multiplicity of urethane-induced adenomas in a dose-dependent manner.[7] Several studies in which mice were injected subcutaneously with organic solvent-extracted material from particles collected from outdoor air pollution, showed increased incidence of injection-site tumours, including fibrosarcomas, and pulmonary adenoma or adenocarcinoma.[8,9]

The findings of carcinogenicity in humans and animals are strongly supported by a large, diverse body of evidence showing genetic and related effects in exposed humans and animals and a wide range of experimental systems. Studies of people exposed occupationally to outdoor air pollution have shown enhanced frequencies, relative to controls, of chromosome aberrations and micronuclei in lymphocytes.[10,11]

S.E.N.T.I.E.R.I - Studio Epidemiologico Nazionale Territori e Insediamenti
[illegible] iol Prev 2011; (5-6) Suppl 4).

nale per le bonifiche (SIN) nel Progetto SENTIERI

l'ISS, esaminate le statistiche
di 44 delle 57 aree da tempo
come "siti da bonificare" nel
95-2002

ni con 5,5 milioni di abitanti

i mortalità rispetto alle medie
0 mila morti in più in otto anni
numero atteso considerando
se di morte.

INCIDENZA DI CANCRO IN 23 SIN SERVITI DA UN REGISTRO TUMORI

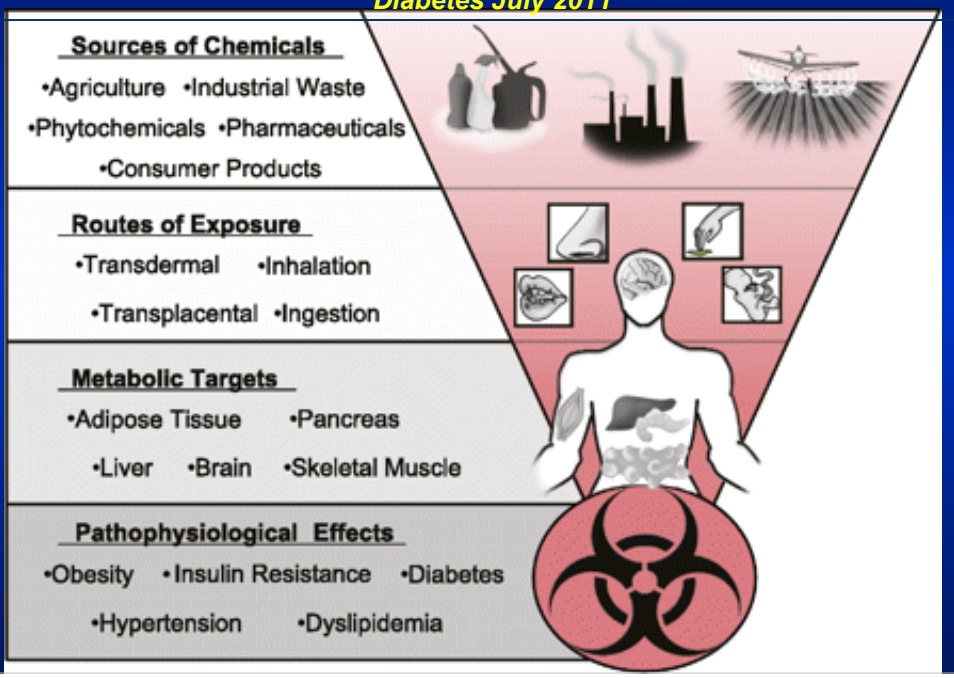
(dati presentati il 9 maggio 2013 a Siracusa, ISS-AIRTUM)

- Studio condotto su 23 siti Sin serviti da un Registro Tumori
- Popolazione complessiva di circa 2 milioni di persone, anni 1996-2005
- Nell'insieme dei 23 Sin, si è registrato per il cancro rispetto a quanto atteso :
  - + 9% nei maschi
  - +7% in più nelle femmine
  - 700 i casi individuati complessivamente di tumori infantili e adolescenziali.
- In entrambi i sessi eccessi di tumori maligni a:
  - esofago, colon-retto, fegato, colecisti e vie biliari, pancreas, laringe, polmone, rene e vie urinarie, vescica, melanoma e linfoma non Hodgkin.
- Nei maschi eccessi di:
  - mesotelioma e tumori maligni di prostata, testicolo ed encefalo;
- Nelle femmine eccessi di:
  - tumori della mammella, del sistema linfoemopoietico, in particolare della leucemia mieloide cronica

The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

Brian A. Neel1 and Robert M. Sargis2⇓

Diabetes July 2011



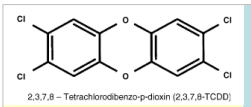
Inquinanti immessi “a norma di legge” dai grandi impianti in Italia

TABELLA 2
ALCUNI DEGLI INQUINANTI IMMESSI IN ARIA ED ACQUA IN ITALIA NEL 2005
(dal registro nazionale INES)

Inquinanti	Effetto cancerogeno secondo IARC	Unità misura	Emissioni in aria	Emissioni in acqua	Emissioni totali
Arsenico (As) e composti	1	kg/a	1981.3	6035.3	8016.6
Cadmio (Cd) e composti	1	kg/a	825.5	2207.5	3033.0
Cromo (Cr) e composti	1	kg/a	11063.5	128963.1	140026.6
Nichel (Ni) e composti	1	kg/a	37247.3	43365.8	80613.1
Benzene, toluene, etilbenzene, xileni (BTEX)	1*	kg/a	540499.6*	175067.8	715567.4
Mercurio (Hg) e composti	2b	kg/a	2821.2	1065.9	3887.1
Piombo (Pb) e composti	2a	kg/a	97063.6	17903.5	114967.1
Diossine (PCDD) + furani (PCDF)	1**	g/a	103.0	-----	103.0

** solo benzene*

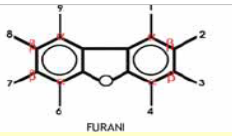
http://www.tumori.net/it3/brochures/documenti/inceneritori/Ambiente_e_Tumori_17_10_11.pdf



2,3,7,8 – Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)

DIOSSINA, DIOSSINE e PCB (policlorobifenili)

A.Schecter Envir. Res.101(2006) 419-428



FURANI

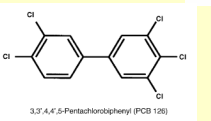
FAMIGLIA di 419 sostanze

CAPOSTIPITE: TCDD o "diossina di Seveso"

DIBENZO-P-DIOSSINE (PCDD): 75 congeneri

DIBENZO-P-FURANI (PCDF): 135 congeneri

PCB: 209 congeneri: 12 d.l. (dioxin like)



3,3',4,4',5-Pentachlorobiphenyl (PCB 126)

CARATTERISTICHE:

DIOSSINE E FURANI: prodotti involontari da sintesi di pesticidi o combustioni, in particolari condizioni (T, cloro, catalizzatori).

PCB : prodotti volontariamente per uso industriale (fluidi per trasformatori, addittivi per vernici, carta, fino agli anni 80'

Molecole estremamente persistenti, termostabili, lipofile

Tempi di dimezzamento: TCDD: uomo 7- 11 anni, sottosuolo fino a 100 anni

ASSUNZIONE

Diossine: per oltre il 95% tramite catena alimentare (latticini, pesce, carni) fenomeni di bioaccumulo e biomagnificazione

PCB : importante anche la via respiratoria e transcutanea

Unità di misura per assunzione nell'uomo: picogrammo (pg) miliardesimo di mg

2001 UE: soglia di assunzione di 2 pg/kg/die

2012: E.P.A. soglia di assunzione di 0,7 pg/kg

TOSSICITA':

Diverso di tossicità dei vari congeneri rispetto alla TCDD (la più tossica in assoluto) (TEQ)

AZIONE ONCOGENA E DI "INTERFERENTI ENDOCRINI"

TAPPE SALIENTI

1997: TCDD : riconosciuta cancerogeno certo per l'uomo IARC 1 ad azione multiorgano

2001: Convenzione di Stoccolma vieta produzione, uso e rilascio di 12 POPs fra cui diossine e PCB

2009: PCB 126 e pentafurano riconosciuti cancerogeni certi al pari della diossina di Seveso

2013: IARC riconosce anche i PCB cancerogeni certi per l'uomo (IARC 1)

Sviluppo di tumori mammari in cavie trattate al 15°giorno dal concepimento con 1µg/Kg TCDD e al 50° giorno dalla nascita con 30 mg/kg di Dimetildibenzoantracene (DMBA) o solo DMBA

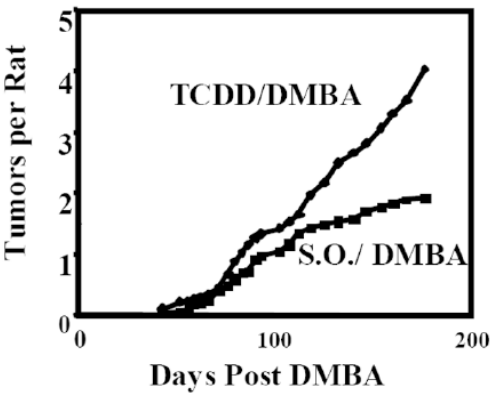
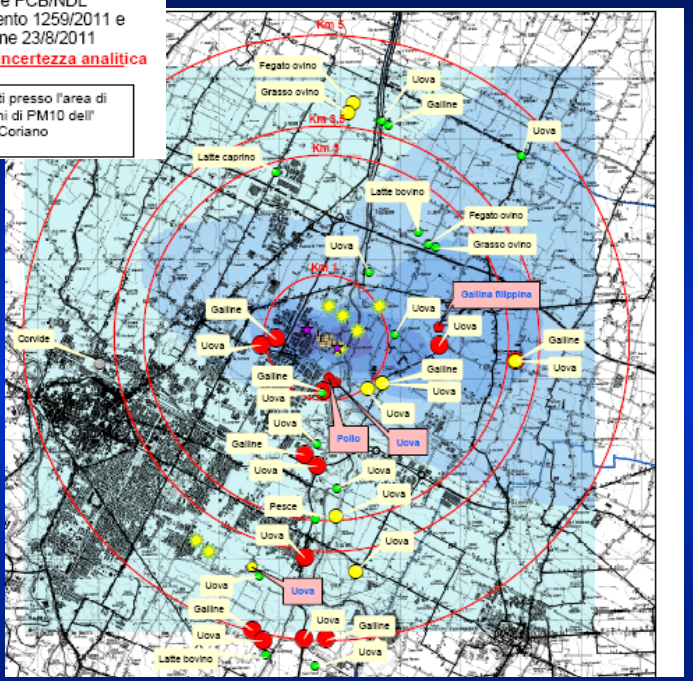


Figure 1.
Ontogeny of palpable mammary tumors in female rats exposed prenatally to TCDD and treated with DMBA on day 50 post-partum. Pregnant female Sprague-Dawley CD rats were treated with 1 µg/kg body weight or an equivalent volume of the solvent (sesame oil) on day 15 post-conception. DMBA was administered by gavage at 30 mg/kg body wt to 50-day-old female offspring. The TCDD/DMBA group and the sesame oil/DMBA group contained 29 and 30 female rats/group, respectively. (Figure from ref. 18.)

Reprod Toxicol. 2007 ; 23(3): 391–396.

Diossine, PCB/DL e PCB/NDL
Conformità al Regolamento 1259/2011 e alla Raccomandazione 23/8/2011
Senza tenere conto dell'incertezza analitica

Campionamenti effettuati presso l'area di ricaduta delle emissioni di PM10 dell' inceneritore di Coriano



Conforme

NON Conforme al Regolamento

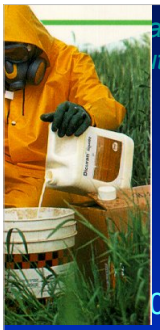
NON Conforme alla Raccomandazione

http://www.comune.forli.fc.it/upload/forli/gestionedocumentale/Relazione%20finale%20tavolo_784_27809.pdf

http://www.comune.forli.fc.it/upload/forli/gestionedocumentale/Relazione%20finale%20tavolo_784_27809.pdf

Tabella 12 –Campioni effettuati nel 2011 per il controllo dei PCDD/F e PCB in matrici di origine animale, giudicati in base alle nuove normative 2012 (tenendo conto anche dei 5 campioni ISDE) senza considerare l'incertezza analitica

Matrice di origine animale	Numero campioni	N° campioni non conformi al Regolamento (CE) N°1881/2006 modificato dal Regolamento (UE) 1259/2011	N° campioni non conformi alla Raccomandazione Commissione Europea (23/8/2011)	N° campioni conformi
Galline/Pollo	12	8	3	1
Uova	24	7	6	11
Tessuto adiposo ovino	3	0	2	1
Fegato ovino	3	1	n.a.	2
Latte ovino	3	0	0	3
Latte bovino	3	0	1*	2
Latte caprino	2	0	1	1
Pesce	1	0	0	1
Totale matrici animali	51	16	13	22
Vegetali	10	0	10	0
Totale	61	16	22	23

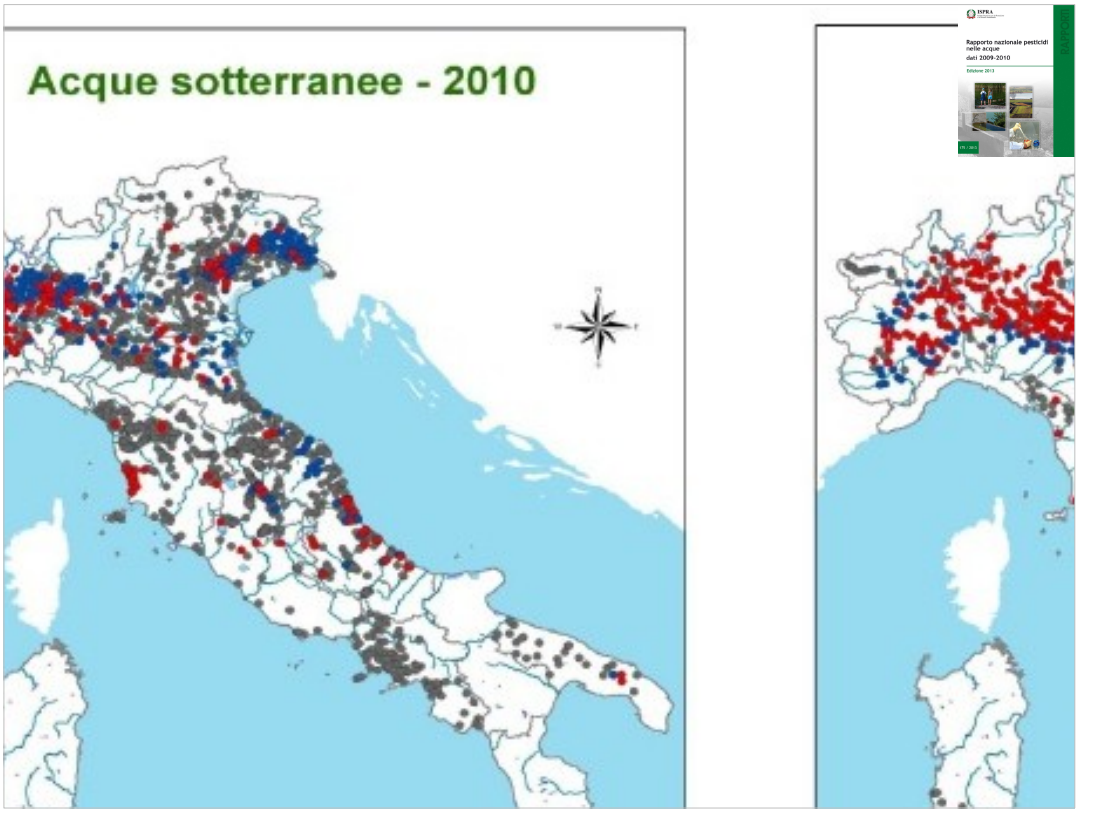


agricolturaitalianaonline.gov.it/index.php
ti/studi_e_ricerche/statistiche/produzione/piu_pesticidi_ma_calano_i_principi_

USO PESTICIDI IN ITALIA
(Dati Istat/ISPRA 2010/11)

00 i prodotti presenti sul mercato

- distribuiti mediamente sui suoli agricoli ogni anno oltre 150.000 ton
- Quantitativo medio distribuito: 5,64 chilogrammi per ettaro !
- In Italia si distribuisce il 33% della quantità totale di insetticidi utilizzati nell'intero territorio comunitario
- Presenza di pesticidi nelle acque


Acque sotterranee - 2010
ISPRA
Rapporto nazionale pesticidi nelle acque
dati 2009-2010
Edizione 2013

RAPPORTO NAZIONALE PESTICIDI NELLE ACQUE ITALIANE
rapporto ISPRA ed.2013

Presenza di residui nel : 55,1% delle acque superficiali
28,2% delle acque sotterranee

Rinvenuti 166 tipologie di pesticidi - a fronte dei 118 del 2007-2008

Livelli superiori ai limiti delle acque potabili nel: 34,4% delle acque superficiali
12,3% di quelle sotterranee

Largamente presenti anche sostanze fuori commercio da tempo, come l'atrazina e la simazina.

Presenti fino a 23 sostanze diverse in solo campione: "*a causa dell'assenza di dati sperimentali sugli effetti combinati delle miscele e di adeguate metodologie di valutazione, esiste la possibilità che il rischio derivante dall'esposizione ai pesticidi sia attualmente sottostimato e si impone una particolare cautela anche verso i livelli di contaminazione più bassi*"

Health impact and damage cost assessment of pesticides in Europe (Environ Int. 2012 Nov 15;49:9-17..)

Fantke P, Friedrich R, Jolliet O.
Institute of Energy Economics and the Rational Use of Energy (IER), University of Stuttgart, Hessbruehlstr. 49a, 70565 Stuttgart, Germany. Electronic address: peter@dynamicrop.org

Abstract

- *"…..We quantify health impacts and related damage costs from exposure to 133 pesticides applied in 24 European countries in 2003 adding up to almost 50% of the total pesticide mass applied in that year.*

……..

- *Only 13 substances applied to 3 crop classes (grapes/vines, fruit trees, vegetables) contribute to 90% of the overall health impacts of about 2000 disability-adjusted life years in Europe per year corresponding to annual damage costs of 78 million Euro."*

Toxicol Appl Pharmacol. 2013 Feb 9. pii: S0041-008X(13)00054-9.

Pesticides and human chronic diseases: evidences, mechanisms, and perspectives.

" There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as:

- different types of cancers,
- diabetes,
- neurodegenerative disorders like Parkinson, Alzheimer, and SLA,
- birth defects, and reproductive disorders"

"There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like :

- respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD),
- cardiovascular disease such as atherosclerosis and coronary artery disease,
- chronic nephropathies
- autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis, chronic fatigue syndrome, and aging. ……"

Table 1. Pesticides associated with cancer in the AHS cohort.

Cancer type	Pesticide(s)	Chemical family	Categorical exposure cutoff value	RR or OR[a] (95% CI)	*p*-Value for trend	References
All cancers	Diazinon	OP	> 109 LD[b]	1.58 (1.10–2.28)	0.007	Beane Freeman et al. 2005
			Highest IWLD[b]	1.41 (1.03–1.95)	0.033	
	EPTC	Thiocarbamate	> 50 LD[c]	1.28 (1.09–1.50)	< 0.01	van Bemmel et al. 2008
			> 112 IWLD[c]	1.16 (1.01–1.35)	0.02	
Lung	Chlorpyrifos	OP	> 56 LD[b]	2.18 (1.31–3.64)	0.002	Lee et al. 2004a
			> 417 IWLD[b]	1.80 (1.00–3.23)	0.036	
	Diazinon	OP	> 109 LD[b]	3.46 (1.57–7.65)	0.001	Beane Freeman et al. 2005
			Highest IWLD[b]	1.55 (0.65–3.72)	0.22	
	Dicamba	Benzoic acid	> 224 LD[b]	3.10 (1.20–7.70)	0.04	Alavanja et al. 2004
	Dieldrin	OC	> 50 LD[b]	5.30 (1.50–18.6)	0.005	
			> 9 LD[d]	2.80 (1.10–7.20)	0.02	Purdue et al. 2006
	Metolachlor	Chloroacetanilide	Highest IWLD[d]	3.50 (1.60–7.70)	0.002	
			> 457 LD[b]	4.10 (1.60–10.4)	0.015	Alavanja et al. 2004
	Pendimethalin	Dinitroaniline	> 224 LD[b]	3.50 (1.10–10.5)	0.005	
			>116 LD[b]	2.40 (1.10–5.30)	0.29	Hou et al. 2006
			> 539 IWLD[b]	1.10 (0.50–2.60)	0.94	
Pancreas	EPTC	Thiocarbamate	> 118 IWLD[d]	2.50 (1.10–5.40)	0.01	Andreotti et al. 2009
	Pendimethalin	Dinitroaniline	> 117 IWLD[d]	3.00 (1.30–7.20)	0.01	
Colon	Aldicarb	Carbamate	> 56 LD[b]	4.10 (1.30–12.8)	0.001	Lee et al. 2007a
	Dicamba	Benzoic acid	> 116 LD[b]	3.29 (1.40–7.73)	0.02	Samanic et al. 2006
			> 739 IWLD[b]	2.57 (1.28–5.17)	0.002	
	EPTC	Thiocarbamate	> 50 LD[c]	2.09 (1.26–3.47)	< 0.01	van Bemmel et al. 2008
			> 112 IWLD[c]	2.05 (1.34–3.14)	< 0.01	
	Imazethapyr	Imidazolinone	> 311 IWLD (proximal)[b]	2.73 (1.42–5.25)	0.001	Koutros et al. 2009
			> 311 IWLD (distal)[b]	1.21 (0.55–2.68)	0.75	
	Trifluralin	Dinitroaniline	> 224 LD[b]	1.48 (0.78–2.80)	0.12	Kang et al. 2008
			> 1176 IWLD[b]	1.76 (1.05–2.95)	0.036	
Rectum	Chlordane	OC	> 9 LD[d]	2.70 (1.10–6.80)	0.03	Purdue et al. 2006
			Highest IWLD[d]	2.10 (0.90–5.30)	0.04	
	Chlorpyrifos	OP	> 56 LD[b]	3.25 (1.60–6.62)	0.035	Lee et al. 2004a
			> 417 IWLD[b]	3.16 (1.42–7.03)	0.057	
			>109 LD[b]	2.70 (1.20–6.40)	0.008	Lee et al. 2007a
	Pendimethalin	Dinitroaniline	> 116 LD[c]	4.30 (1.50–12.7)	0.007	Hou et al. 2006
			> 539 IWLD[c]	3.60 (1.20–11.3)	0.02	
	Toxaphene	OC	> 56 LD[b]	4.30 (1.20–15.9)	0.123	Lee et al. 2007a
Leukemia	Chlordane/Heptachlor	OC	> 9 LD[d]	2.60 (1.20–6.00)	0.02	Purdue et al. 2006
			Highest IWLD[d]	2.10 (0.80–5.50)	0.10	
	Chlorpyrifos	OP	> 56 LD[b]	2.15 (0.96–4.81)	0.36	Lee et al. 2004a
			> 417 IWLD[b]	3.01 (1.35–6.69)	0.15	
	Diazinon	OP	> 39 LD[c]	3.36 (1.08–10.5)	0.026	Beane Freeman et al. 2005
			Highest IWLD[c]	2.88 (0.92–9.03)	0.053	
	EPTC	Thiocarbamate	> 50 LD[c]	2.36 (1.16–4.84)	0.02	van Bemmel et al. 2008
			> 112 IWLD[c]	1.87 (0.97–3.59)	0.05	
	Fonofos	OP	> 609 IWLD[c]	2.67 (1.06–6.70)	0.04	Mahajan et al. 2006a
All LH	Alachlor	Chloroacetanilide	> 116 LD[c]	2.04 (0.89–4.65)	0.02	Lee et al. 2004b
			> 710 IWLD[c]	2.42 (1.00–5.89)	0.03	
	Chlorpyrifos	OP	> 56 LD[b]	1.43 (0.98–2.36)	0.26	Lee et al. 2004a
			> 417 IWLD[b]	1.99 (1.22–3.26)	0.09	
	Diazinon	OP	> 39 LD[c]	1.84 (0.89–3.82)	0.094	Beane Freeman et al. 2005
			Highest IWLD[c]	2.01 (1.02–3.94)	0.049	
	Permethrin	Pyrethroid	> 50 LD[c]	1.64 (1.07–2.52)	0.35	Rusiecki et al. 2009
			> 220 IWLD[c]	1.31 (0.84–2.04)	0.60	
NHL	Lindane	OC	> 22 LD[d]	2.10 (0.90–5.50)	0.12	Purdue et al. 2006
			Highest IWLD[d]	2.60 (1.10–6.40)	0.04	
Multiple myeloma	Permethrin	Pyrethroid	> 50 LD[c]	5.72 (2.76–11.8)	< 0.01	Rusiecki et al. 2009
			> 220 IWLD[c]	5.01 (2.41–10.4)	< 0.01	
Bladder	Imazethapyr	Imidazolinone	> 311 IWLD[b]	2.37 (1.20–4.68)	0.01	Koutros et al. 2009
Prostate	Fonofos	OP	> 56 LD[c]	1.77 (1.03–3.05)	0.02	Mahajan et al. 2006a (for applicators
			> 315 IWLD[c]	1.83 (1.12–3.00)	0.01	with a family history of prostate cancer)
	Methylbromide	Halogenated alkane	Highest IWLD[e]	3.47 (1.37–8.76)	0.004	Alavanja et al. 2003
Brain	Chlorpyrifos	OP	> 56 LD[b]	2.58 (0.73–9.17)	0.076	Lee et al. 2004a
			> 417 IWLD[b]	4.03 (1.18–13.9)	0.036	
Melanoma	Carbaryl	Carbamate	> 175 LD[b]	4.11 (1.33–12.7)	0.07	Mahajan et al. 2007
			Highest intensity score[b]	1.54 (0.61–3.86)	0.92	
	Terrazole	OC	254 LD[d]	2.90 (1.10–8.10)	0.03	Purdue et al. 2006

S. Weichenthal et al. A review of pesticide exposure and cancer incidence in the agricultural health study cohort Environm Health Perspect. 2010 vol 118 1117- 1125

Agricultural pesticide exposure and the molecular connection to lymphomagenesis

The Journal of Experimental Medicine, Vol. 206, No. 7, 1473-1483 2009

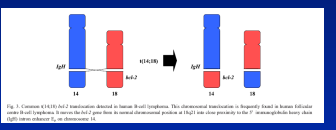


Fig. 1. Common t(14;18) bcl-2 translocation detected in human B cell lymphoma. This chromosomal translocation is frequently found in human follicular center B cell lymphoma. It moves the bcl-2 gene from its normal chromosomal position at 18q21 into close proximity to the 3′ immunoglobulin heavy chain (IgH) intron enhancer E_μ on chromosome 14.

- <u>in un gruppo di agricoltori esposti a pesticidi</u> in Francia e seguito per 9 anni si è dimostrato una <u>drammatica espansione di cloni di linfociti con la traslocazione 14;18</u>, primo passaggio per la successiva evoluzione linfomatosa.

- Questo studio è di fondamentale importanza perché <u>per la prima volta viene fatta luce sui meccanismi molecolari che</u> mettono in relazione l'esposizione ai pesticidi con le malattie del sangue

- Identica alterazione si è registrato nella popolazione più esposta all'incidente di Seveso e che ha presentato un incremento di linfomi, mielomi e leucemie

Legame fra Pesticidi & Diossine!

Carcinogenesis vol.27 no.10 pp.2001–2007, 2006
doi:10.1093/carcin/bgl011
Advance Access publication March 16, 2006

t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Table III. Prevalence and frequency of t(14;18) translocations by plasma TCDD levels, zone of residence and diagnosis of chloracne

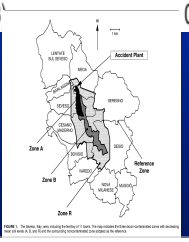
	t(14;18)-positive subjects		t(14;18) frequency[a]	
	%	(Positive/total)	Mean	(95% CI)
Plasma TCDD				
<10 p.p.t.	34.7	(25/72)	4.2[b]	(2.9–6.2)
10.0–475.0 p.p.t.	34.7	(25/72)	9.9[b]	(6.8–14.5)
Zone of residence at the time of the accident				
Reference	42.4	(14/33)	4.3[c]	(2.3–8.0)
R	26.9	(7/26)	4.9[c]	(2.2–10.7)
B	29.4	(10/34)	7.2[c]	(3.8–13.6)
A	37.3	(19/51)	9.3[c]	(5.8–14.8)
Chloracne after the accident				
No	35.2	(32/91)	6.2	(3.7–10.6)
Yes	34.0	(18/53)	6.7	(4.7–9.6)

CARCINOGENESIS (2006) vol 27 no 10 pp 2001-2007

ANALISI DELLA MORTALITA PER TUMORI DEL SANGUE A SEVESO A 25 ANNI DALL' INCIDENTE

TABLE 5. Results of Poisson regression analyses of mortality in the Seveso, Italy, area, 1976–2001, for selected causes of death: number of deaths, rate ratios, and 95% confidence intervals for the polluted zones (A, B, and R) compared with the reference zone*,†

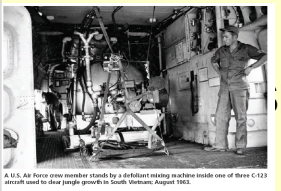
Cause of death (ICD-9‡ code)	Zone A			Zone B			Zone R		
	No.	RR‡	95% CI‡	No.	RR	95% CI	No.	RR	95% CI
Lymphatic and hematopoietic tissue (200–208)	6	2.23	1.00, 4.97	28	1.59	1.09, 2.33	124	0.99	0.82, 1.20
Hodgkin's disease (201)	0	0		3	2.15	0.67, 6.86	9	0.94	0.46, 1.89
Non-Hodgkin's lymphoma (200, 202)	3	3.35	1.07, 10.46	7	1.23	0.58, 2.60	40	0.99	0.71, 1.38
Multiple myeloma (203)	2	4.34	1.07, 17.52	5	1.68	0.69, 4.10	24	1.10	0.71, 1.69
Leukemia (204–208)	1	0.89	0.12, 6.31	13	1.73	1.00, 3.02	51	0.96	0.72, 1.29
Lymphatic leukemia (204)	0	0		3	1.30	0.41, 4.10	23	1.41	0.90, 2.21
Myeloid leukemia (205)	1	2.12	0.30, 15.17	6	1.97	0.87, 4.46	16	0.74	0.44, 1.24
Leukemia, unspecified (208	0	0		4	2.38	0.87, 6.52	10	0.84	0.43, 1.62



Am J Epidemiol 2008;167:847–858

DIOSSINE , PESTICIDI….E TRISTI RICORDI:

DALL'AGENTE "ORANGE" ….A SEVESO!



A U.S. Air Force crew member stands by a defoliant mixing machine inside one of three C-123 aircraft used to clear jungle growth in South Vietnam; August 1963.

SEVESO: TRICLOROFENOLO

(+ diossine)

2,4 D + 2,4,5 T

"**agente orange**"

mix vietato!!!

Ancora in commercio come diserbanti e auxina

Variazioni dell'espressione genica in relazione alle diverse tipologie di inquinamento ambientale

Environ Health Pers. Vol 116 num 11 2008 :1519-1525

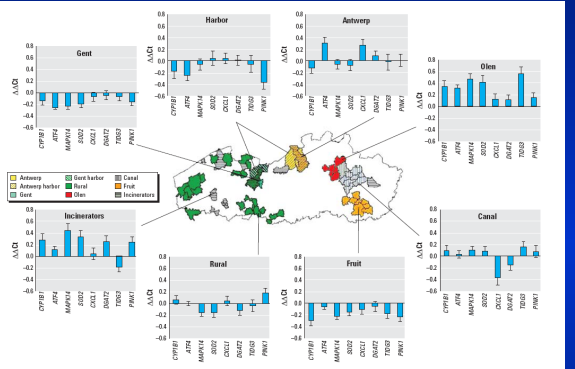


Figure 1. Gene expression (mean ± SE) per region, relative to the total population averages, for all nonsmokers (former and never-smokers). Fruit, fruit cultivation region.

- Studio su 398 individui sani residenti da almeno 5 anni in 8 distretti delle Fiandre a diversa pressione ambientale

- Insediamenti industriali di vario tipo: chimico, metallurgico, raffinerie di petrolio inceneritori ed agricoltura intensiva

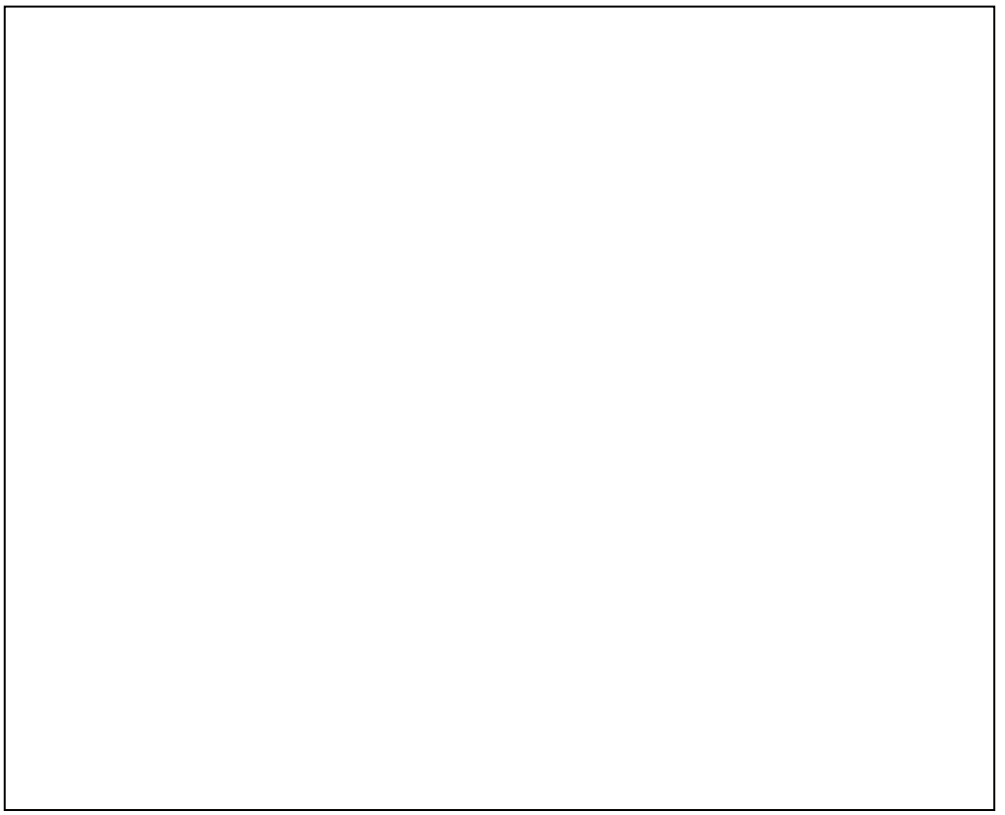
- Indagati i livelli ematici ed urinari di Cea e PSA, metalli pesanti, diossine, PCB, IPA etc.

- Su leucociti periferici indagata l'espressione di geni che regolano attività metaboliche, risposta immunitaria, proliferazione e differenziazione.

- Lo studio ha dimostrato che esistono molteplici e significative correlazioni fra espressione genica ed inquinanti ambientali

Tissue Organization Field Theory (TOFT)

NUOVO PARADIGMA: EPIGENETICA



Mini review

Epigenetic drivers and genetic passengers on the road to cancer

Carla Sawan, Thomas Vaissière, Rabih Murr, Zdenko Herceg *

International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, Rhone-Alpes, 69008 Lyon, France

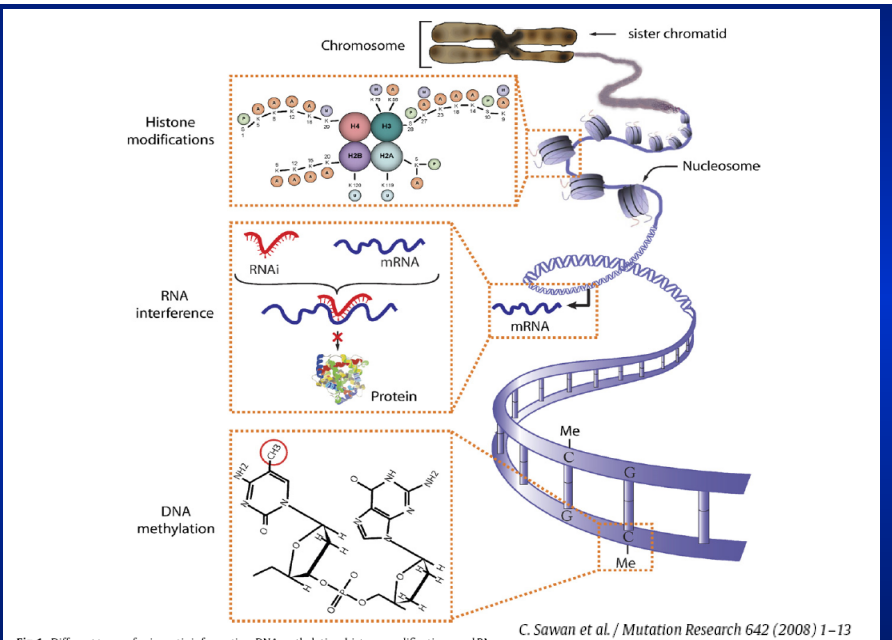


Fig. 1. Different types of epigenetic information. DNA methylation, histone modifications, and RI regulation. DNA methylation is a covalent modification of the cytosine (C) that is located 5′ to a guanine (G) in a CpG dinucleotide. Histone (chromatin) modifications refer to covalent post-translational modifications of N-terminal tails of four core histones (H3, H4, H2A, and H2B). The most recent mechanism of epigenetic inheritance involves RNAs, which either in the form microRNA or Xist can alter gene expression states in a heritable manner.

"It is now generally accepted that human cancer cells harbor global epigenetic abnormalities and that epigenetic alterations may be the key to tumor initiation and development"

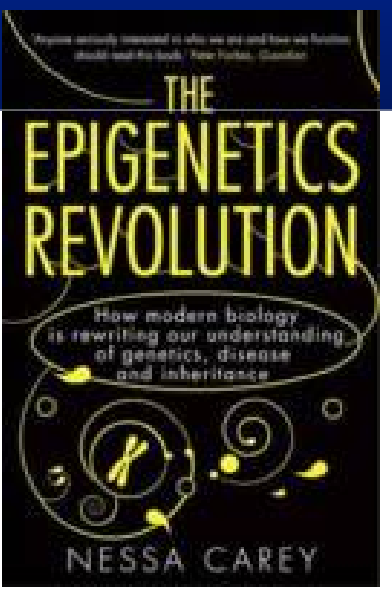
Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis 2010;31:27–36;

TISSUE ORGANISATION FIELD THEORY (TOFT)

- La carcinogenesi è un problema di alterata organizzazione tissutale che può insorgere già nel momento della programmazione fetale
- I cancerogeni distruggono la normale architettura tissutale alterando la comunicazione fra cellula e cellula e compromettendo di conseguenza l'integrità del genoma
- le mutazioni genetiche sono l'effetto e non la causa della malattia
- Il cancro non è quindi un evento casuale ma la conseguenza di modificazione epigenetiche indotte dall'ambiente
- L'esposizione dei gameti e il periodo della vita intrauterina sono cruciali per la programmazione fetale
- Il processo può essere reversibile

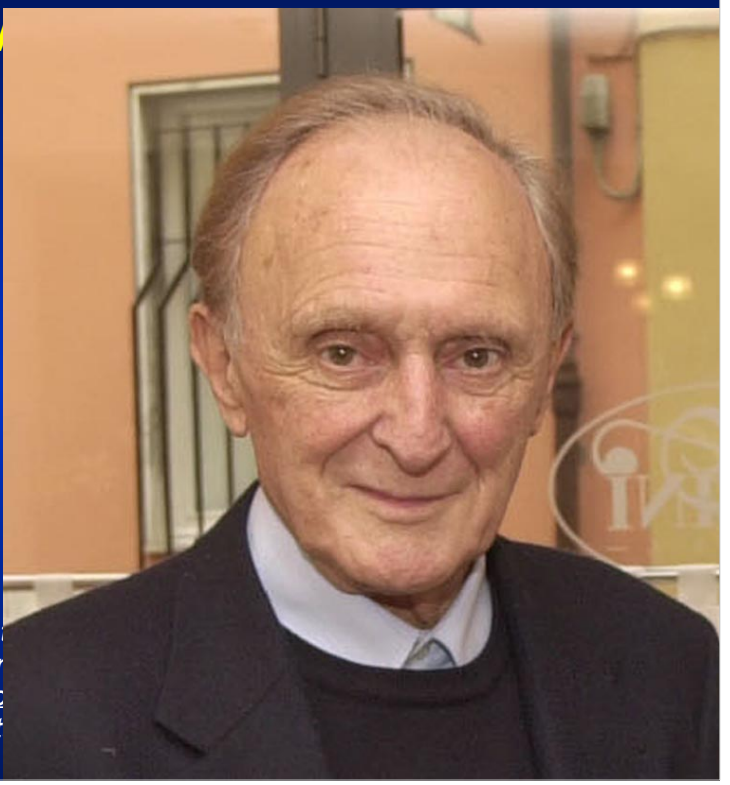
Cosa cambia con il nuovo paradigma dell'epigenetica??

L'AMBIENTE ACQUISTA UN RUOLO ASSOLUTAMENTE CENTRALE E PRIORITARIO NELLA GENESI DEL NOSTRO FENOTIPO E DELLE NOSTRE MALATTIE



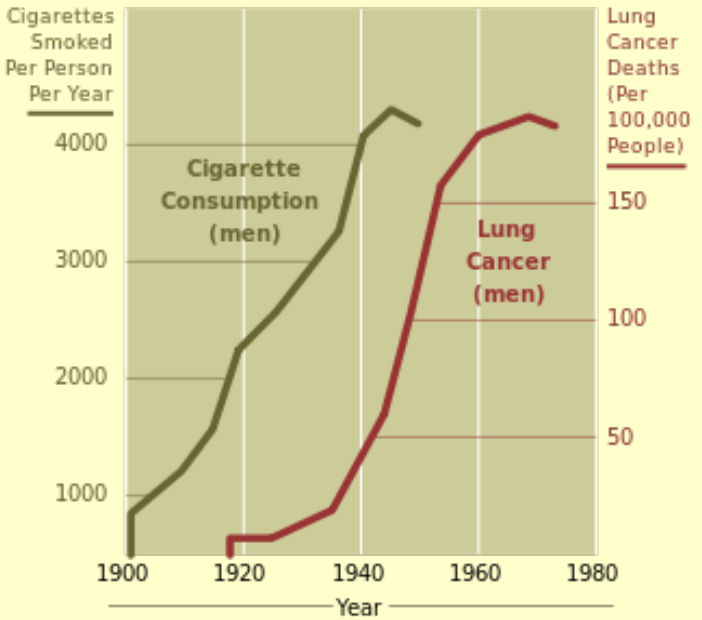
…..la dimostrazione è con politiche di Prevenzione Primaria si contrasta efficacemente anche il cancro!

“PREV



“Agire sulle cause delle mala
l’esposizione delle popolazio
Primaria tutela la salute e pro
denari ed è purtroppo neglet

20-Year Lag Time Between Smoking and Lung Cancer



In Svezia, dove dal 1970 sono stati messi al bando diversi pesticidi, i linfomi sono in diminuzione

Acta Oncologica, 2008; 47: 347–354

informa
healthcare

INVITED ARTICLE

Pesticides, soft-tissue sarcoma and non-Hodgkin lymphoma – historical aspects on the precautionary principle in cancer prevention

LENNART HARDELL

Department of Oncology, University Hospital, SE-701 85 Örebro and Department of Natural Sciences, Örebro University, SE-701 82 Örebro, Sweden

Abstract

Background. After the 2nd World War a long range of chemical agents have been introduced on the market, both in Sweden and most other countries. From the 1950's several pesticides gained increasing use in agriculture and forestry. In the 1970's public concern increased in Sweden especially regarding use of phenoxy herbicides to combat deciduous wood, although statements from different authorities were reassuring of the safety. *Materials and methods.* At the end of the 1970's the author and his colleagues published the first scientific evidence of an association between exposure to phenoxyacetic acids, chlorophenols and certain malignant tumours, i.e., soft-tissue sarcoma and malignant lymphoma. The study subjects were also exposed to contaminating dioxins such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Later studies showed also an association between certain persistent organic pollutants such as polychlorinated biphenyls and non-Hodgkin lymphoma (NHL) with an interaction with titers of antibodies to Epstein-Barr virus early antigen. These results have been corroborated in other studies. *Discussion.* Over the years industry and its allied experts have attacked our studies, but in 1997 IARC classified TCDD as a human carcinogen, Group I. The increasing incidence of NHL in Sweden levelled off about 1990. The author postulated that the regulation or ban of the use of chlorophenols, certain phenoxy herbicides and some persistent organic pollutants in Sweden back in the 1970s has contributed to the now decreasing incidence of NHL. Unfounded criticism from industry experts may prohibit the precautionary principle and early warnings of cancer risk can be ignored. Cancer risks by certain chlorinated phenols may serve as a model of how the precautionary principle should be used by taking early warnings seriously.

MIGLIORANDO LA QUALITA' DELL'ARIA RIDUZIONE DOPO SOLO 3 ANNI ANCHE DEI DECESSI PER CANCRO AL POLMONE!

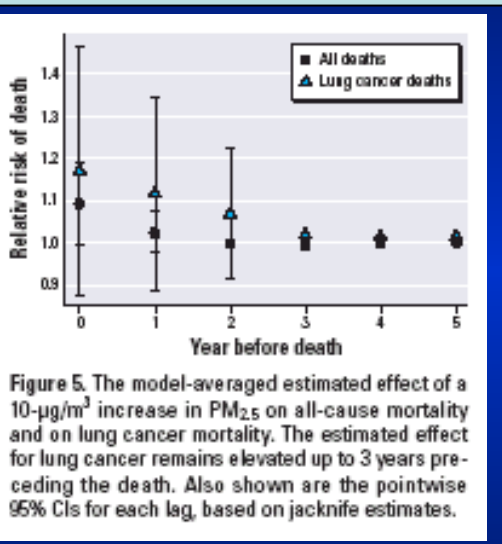
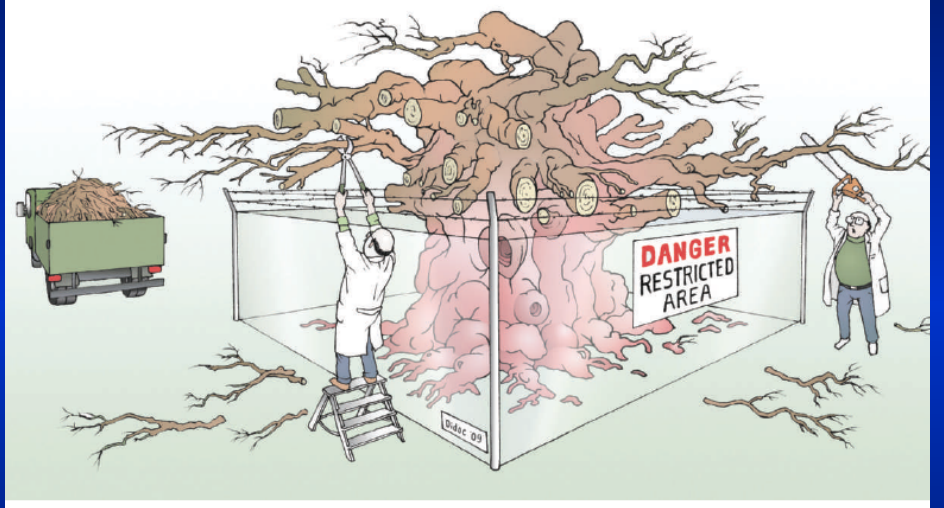


Figure 5. The model-averaged estimated effect of a 10-μg/m^3 increase in $PM_{2.5}$ on all-cause mortality and on lung cancer mortality. The estimated effect for lung cancer remains elevated up to 3 years preceding the death. Also shown are the pointwise 95% CIs for each lag, based on jacknife estimates.

Schwartz J. et al. (Environmental Health Perspectives, 2008 – vol. 116, n. 1)



A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

NATURE|Vol 459|28 May 2009

The President
The White House
Washington, DC 20500

Dear Mr. President:

Though overall cancer incidence and mortality have continued to decline in recent years, the disease continues to devastate the lives of far too many Americans. In 2009 alone, approximately 1.5 million American men, women, and children were diagnosed with cancer, and 562,000 died from the disease. With the growing body of evidence linking environmental exposures to cancer, the public is becoming increasingly aware of the unacceptable burden of cancer resulting from environmental and occupational exposures that could have been prevented through appropriate national action. The Administration's commitment to the cancer community and recent focus not been addressed adequately by the National Cancer Program. The American people—even before they are born—are bombarded continually with myriad combinations of these dangerous exposures. The Panel urges you most strongly to use the power of your office to remove the carcinogens and other toxins from our food, water, and air that needlessly increase health care costs, cripple our Nation's productivity, and devastate American lives.

10 April 2010

Informazione e Rischi Ambientali

"il modo con cui si confezionano le conoscenze sui rischi ambientali ha poco a che fare con i casi della scienza. Ogniqualvolta si solleva una questione di salute pubblica che ha ripercussioni per miliardi di dollari sulla vendita di un determinato tipo di beni

l' onere della prova imposto a chi esamina i rischi può diventare tanto elevato da risultare insostenibile"

Devra Davis in:

La Storia segreta della guerra al cancro