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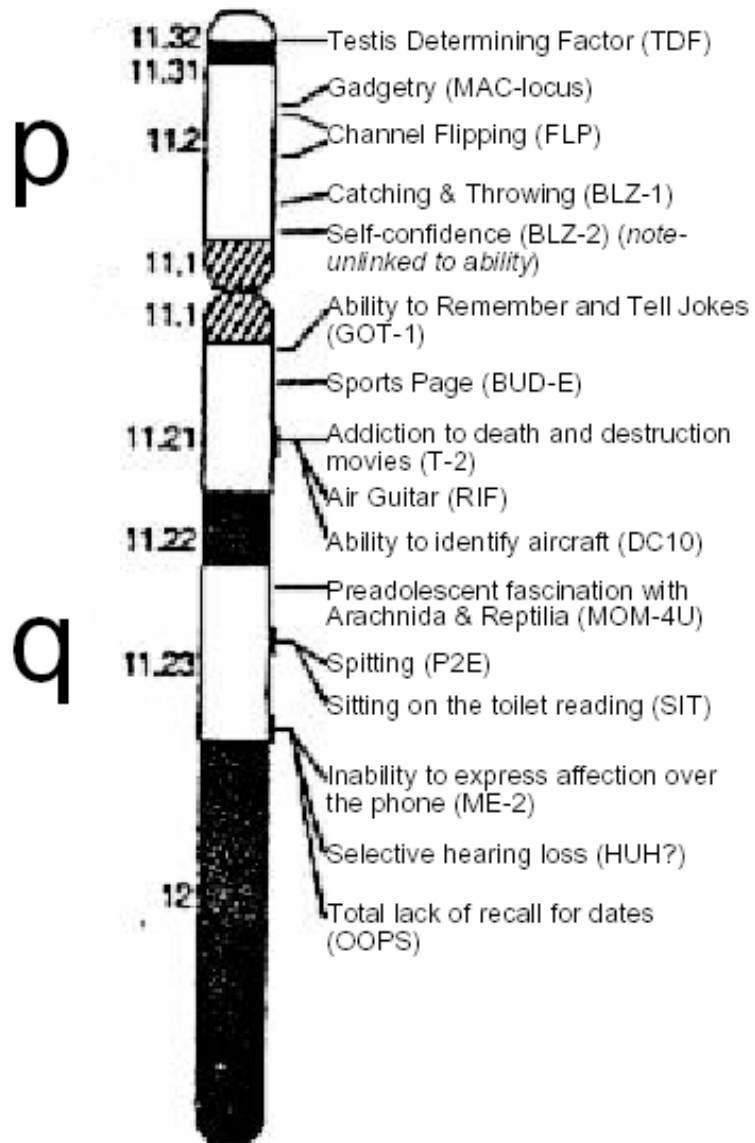
Ma la causa sta nei geni ... ?

How many disease are due to
“inheritance”, or to “genes”?

Long-lasting debate: “nature” vs “nurture”, i.e. how many diseases (and physiological traits) are attributable to genes and how many to the environment

e.g.

- 1. “The Bell Curve” by Herrnstein and Murray (1994) claimed that afro-americans have lower IQs for genetic reasons**
- 2. Is homosexuality a genetic “disease”?**
- 3. Is depression genetically-based?**
- 4. What about schizophrenia?**
- 5. ...and cancer?**
- 6. ... and how many cases of baldness or myopia are attributable to genes?**



“The Y Chromosome”

**In fact many objections were already raised in a seminal paper by
Richard Lewontin (1972), against the “environment” vs.
“heritability” dilemma**

The basic confusion is between heritability and genetic determination.

**Heritability has to do with DIFFERENCES: ratio of variation
inherited by parents to total variation**

**A characteristic is “genetically determined” if it is coded in and
caused by DNA in a normal environment**

The two very often do not overlap, e.g.:

*** humans have 5 fingers, and this is totally genetically determined; however, heritability of 6 or 4 fingers is almost zero (changes in numbers of fingers are caused by defects of development, eg thalidomide, not by heredity)**

*** wearing earrings in 1950 had a very strong heritability (it occurred only in women, today also in men): it was related to having XX vs XY; however, it was not genetically determined (same for skirts)**

Therefore, when researchers say that IQ has 60% heritability, academic performance 50% and occupational status 40%, this does not mean that such characteristics are inherited THROUGH GENES (DNA), i.e. that there is genetic determination, but only that there is strong association between the characteristic in the index subject and the same characteristic in the parents:

ENVIRONMENTAL CHARACTERISTICS THEMSELVES ARE HERITABLE

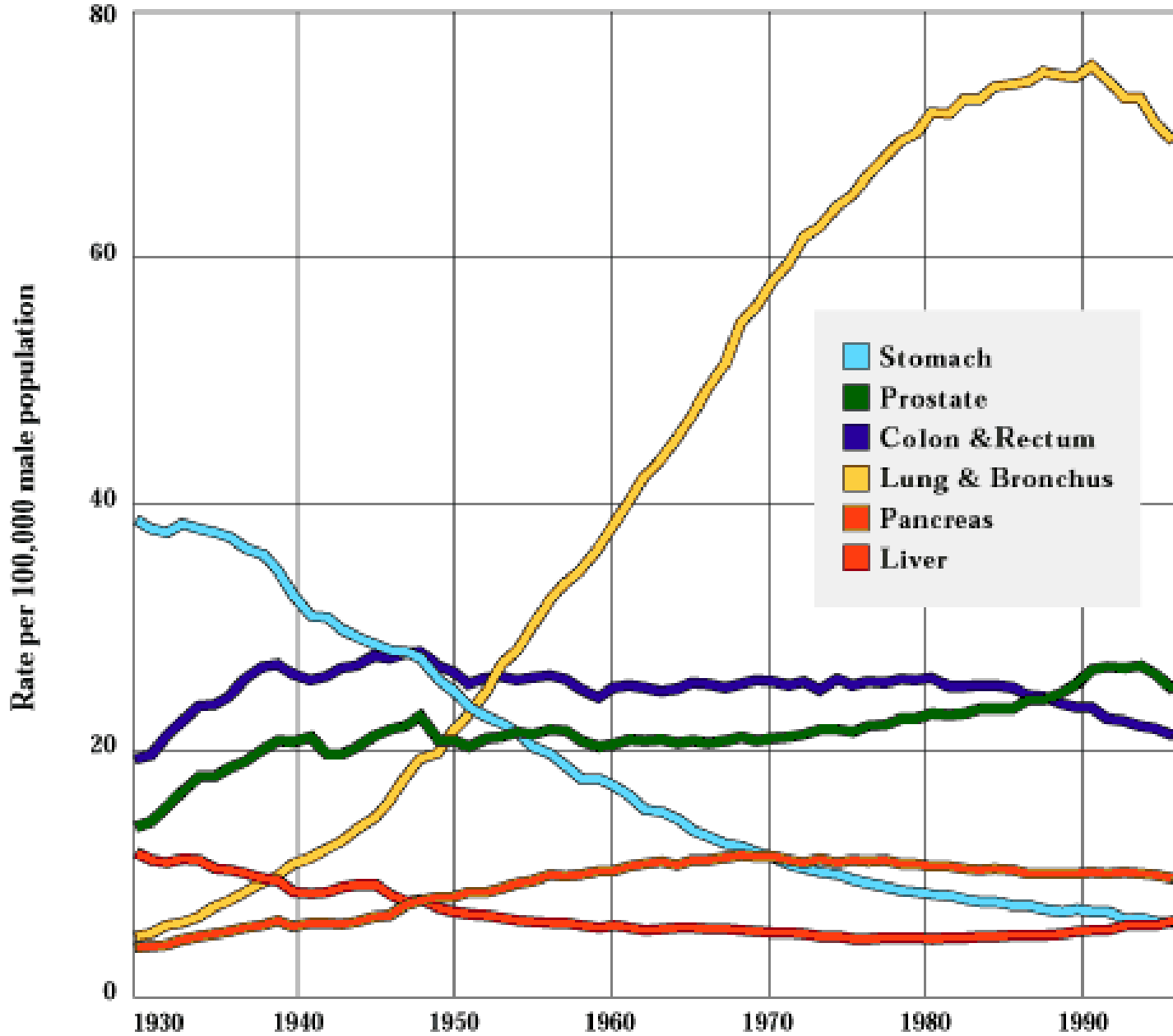
Evidence that cancer is not
mainly due to heredity

1. migrants
2. time trends
3. early epidemiological studies
4. twins

Annual incidence of cancer (per million) in migrants from Japan to Hawaii, in the Japanese and in Hawaiian Caucasians

	Migrants	Japanese	Hawaii Caucasians
Colon 371	78	368	
Stomach	397	1,331	217

US cancer incidence, males



MUELLER (University of Koln, 1939)

	Lung cancer	Other diseases
Non-smokers	3	14
Light smokers	27	41
Heavy smokers	56	31
Total	86	86

Observations in twins show that when only one smokes his/her risk of lung cancer is >20 times higher than in the non-smoker twin. I.e. what counts is exposure, not the genetic make-up

Evidence of carcinogenicity

Definition of Sufficient

The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence

P Vineis (1), M Alavanja (2), P Buffler (3), E Fontham (4), S Franceschi (5), YT Gao (6), PC Gupta (7), A Hackshaw (8), E Matos (9), J Samet (10), F Sitas (11), J Smith (3), L Stayner (5), K Straif (5), MJ Thun (12), HE Wichmann (13), AH Wu (14), D Zaridze (15), R Peto (16), R Doll (16)

*Tobacco and cancer: recent epidemiological
evidence*

(JNCI, january 2004)

Cancer sites for which there is “sufficient” evidence of carcinogenicity of tobacco smoking according to the IARC Working Group: number of studies on which the evaluation was based and average relative risk. CC=case-control

Cancer site	Number of studies		RR
	CC	Cohort	
Lung	>100	37	15-30
Urinary tract	50	24	3
Upper aero-digestive tract:			
Oral cavity,			
Oro-and hypopharynx	28	6 (a)	4-5 (b)
Oesophagus	45	19 (c)	1.5-5
Larynx	25	5	10 (b)
Pancreas	38	27	2-4

(Vineis et al, JNCI 2004 Jan 21;96(2):99-106)

Nasal cavity, paranasal sinuses	9	1	1.5-2.5	
Nasopharynx		19	2	1.5-2.5
Stomach		44	27	1.5-2
Liver		29	29	1.5-2.5
Kidney		13	8	1.5-2.0
Uterine cervix		49	14 (d)	1.5-2.5
Myeloid leukemia (e)	not	12	1.5-2	
		reviewed		

Plus SUFFICIENT EVIDENCE FOR ETS

- (a) also considers studies on pharynx unspecified
- (b) wide range of RR, after adjustment for alcohol
- (c) oesophagus in general, irrespective of histologic type
- (d) includes studies on CIS, CIN
- (e) all leukemias

(Vineis et al, JNCI 2004 Jan 21;96(2):99-106)

“...tobacco is a potent multisite carcinogen with a worldwide impact, causing cancers of the lung, upper aero-digestive tract (oral cavity, nasal cavity, nasal sinuses, pharynx, larynx, esophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney, uterine cervix and myeloid leukemia”

“The mechanistic evidence concerning the measurement of metabolites of tobacco compounds, the formation of DNA or protein adducts, and the spectrum of gene mutations substantiates and elucidates the genetic and molecular changes induced by exposure to tobacco smoke, thus addressing earlier criticisms pertaining to the limited understanding of the mechanisms of tobacco carcinogenicity”

ETS: meta-analysis for the IARC
Monograph

“Of the (about 35) studies, four have an Odds Ratio or relative risk lower than 1.0, 19 have an Odds Ratio between 1.1 and 2.0, and 10 greater than two (suggesting a doubling of the risk or more). This unbalanced distribution cannot be attributed to chance. Both case-control and cohort studies report positive findings. Publication bias, that is a more frequent publication of positive findings than of negative findings, has been ruled out in the meta-analysis”

“300 unpublished studies would be needed to explain the overall Odds Ratio that has been found, a clearly implausible assumption. Besides, a meta-analysis that takes into account several different sources of bias (particularly misclassification of exposure), by the same author, finds that the results are stable and cannot be explained by bias”

Evidence from molecular epidemiology strongly supports the judgment that Environmental Tobacco Smoke is carcinogenic to humans

- metabolites of the tobacco-specific carcinogenic nitrosamine NNK (NNAL) have been found in the urine of never smokers exposed to ETS

- the amount of NNK metabolites in the urine of ETS-exposed never smokers is approximately 1-5% of the amount in smokers, a value proportional to the risk of lung cancer

NB: epidemiological evidence is sufficient on its own

What about mechanisms?

Example of bladder cancer:

- Black tobacco is 2.5 times more carcinogenic to the human bladder than blond tobacco
- Black tobacco contains 2.5 more arylamines (e.g. 4-aminobiphenyl) than blond tobacco
- Arylamines are well-known industrial bladder carcinogens
 - Arylamines are metabolized by N-acetyltransferase (a polymorphic enzyme)

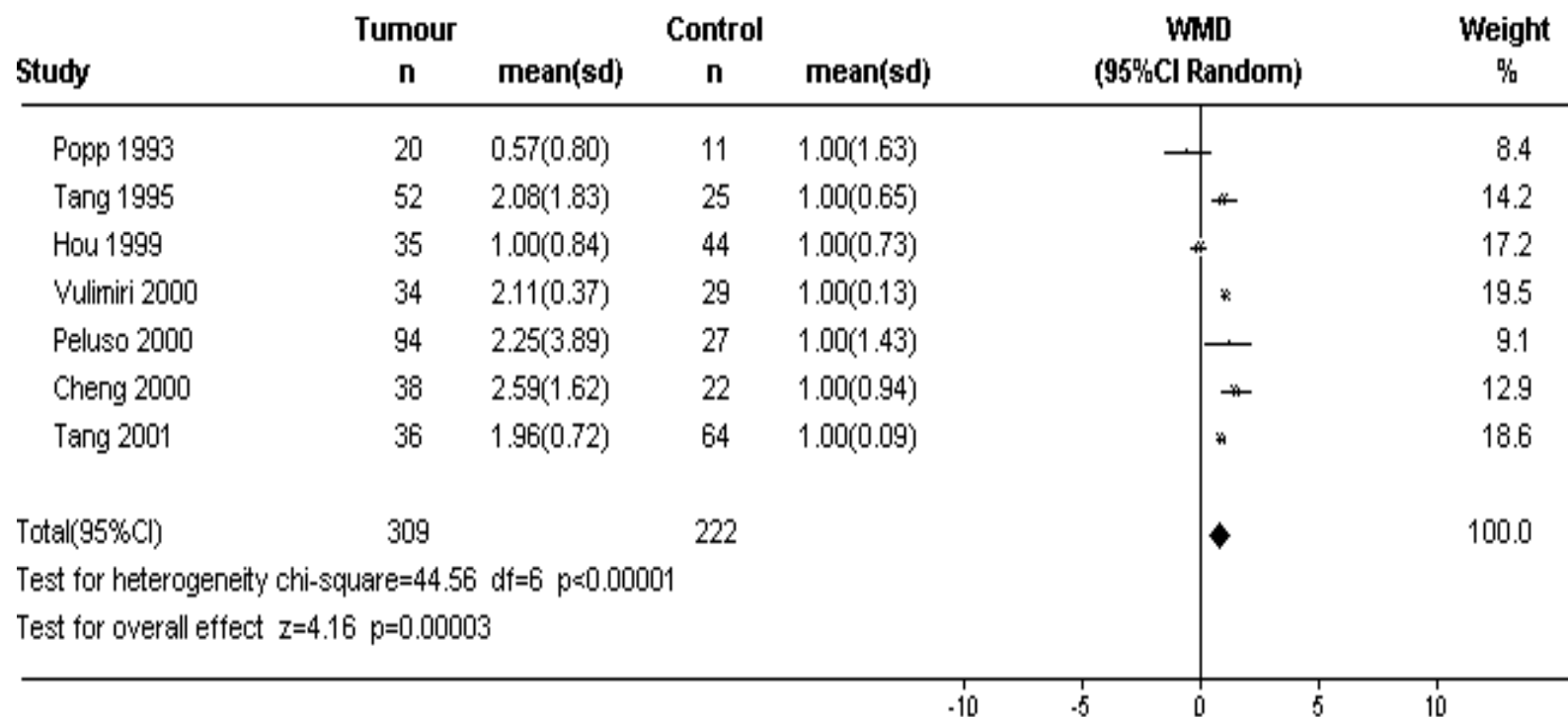
Means and Ses of 4-aminobiphenyl hemoglobin adducts in black and blond tobacco smokers

	Acetylation phenotype	
	slow	fast
non-smokers	31.7 (3.8)	19.4 (4.9)
blond tobacco	118 (13)	86.4 (14.5)
black tobacco	175 (11)	117.5 (13.7)

(Bartsch, Vineis et al, JNCI 82: 1826, 1990)

“Bulky” DNA adducts in WBC and cancer: a
meta-analysis
of 6 case-control studies and one cohort study
on cancer (Veglia et al, CEBP, Vol.12,
February 2003)

Meta-analysis of studies on bulky DNA adducts and cancer. Random effect model. Current smokers only.



**Do DNA repair polymorphisms modulate the level
of bulky DNA adducts ?**

An analysis among EPIC healthy subjects

Phenotype-genotype relationships within the EPIC prospective investigation

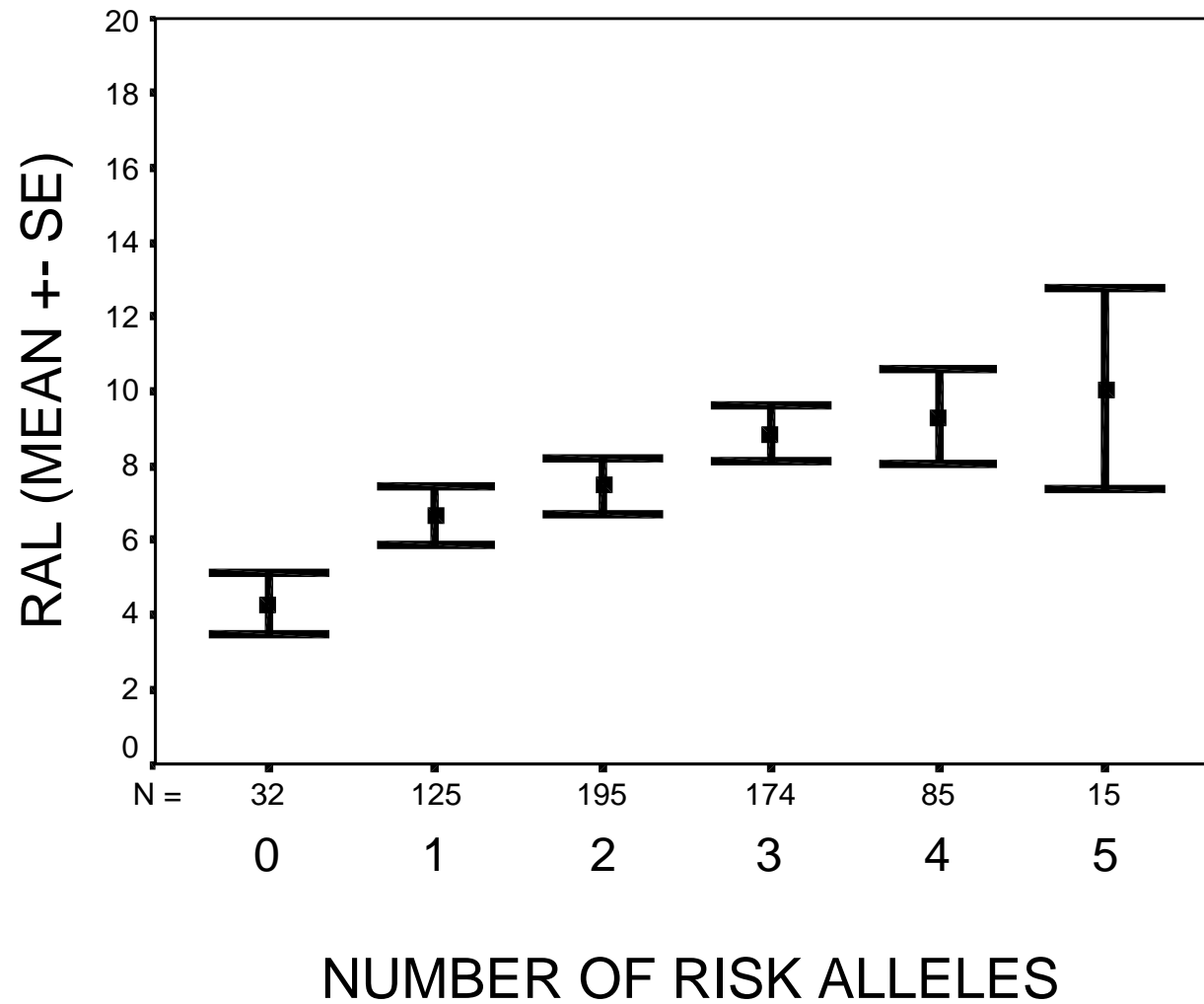
EPIC is a prospective study on diet and cancer in more than 500,000 volunteers recruited in 10 European countries, with blood stored in liquid nitrogen for 450,000

DNA adducts used as intermediate marker in sub-samples

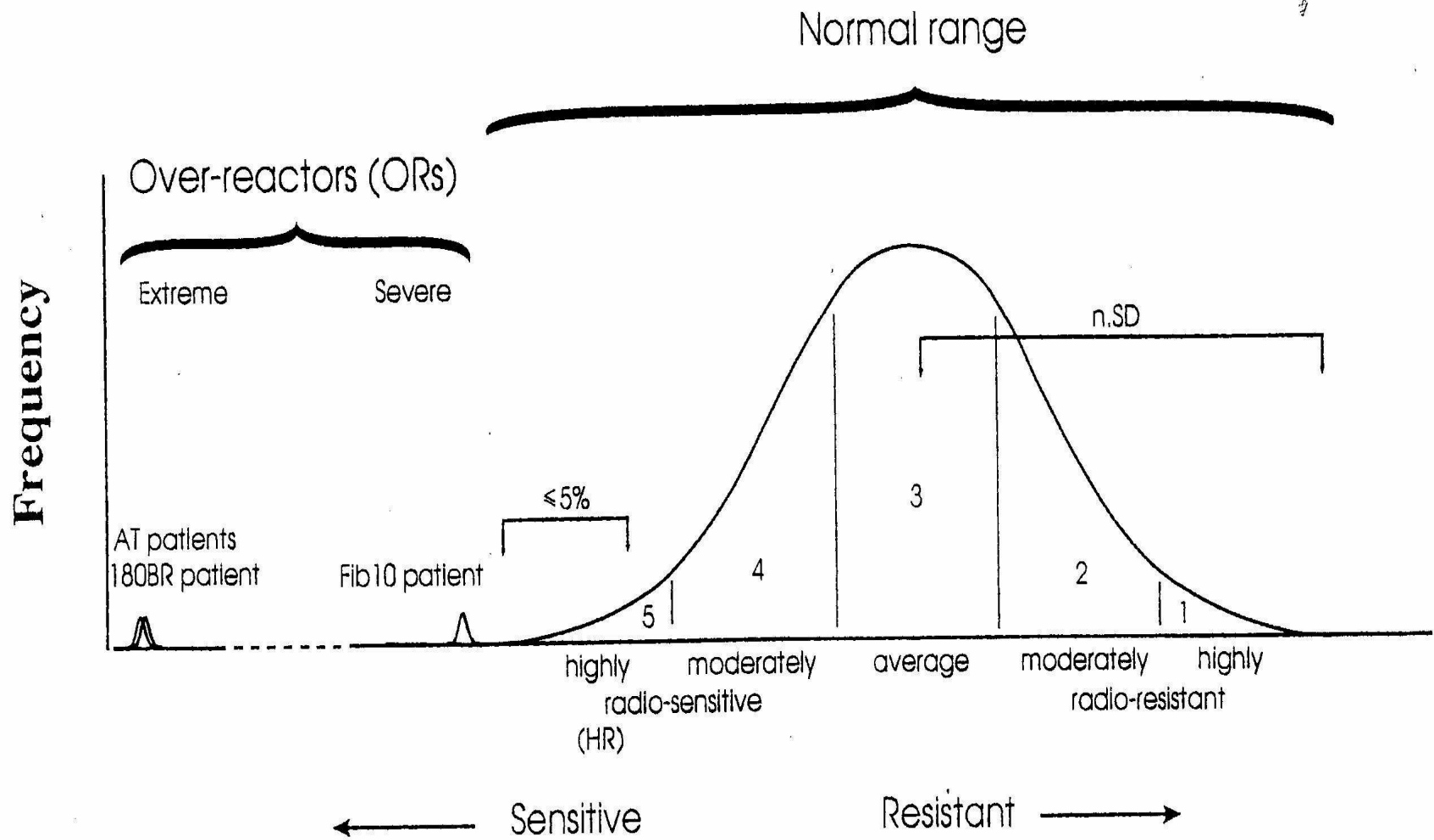
**Mean levels of DNA adducts (^{32}P -postlabelling
RAL $\times 10^9$) by number of variant alleles, after
adjustment (least-square method) for age, gender,
center, year of recruitment, and smoking
habits (N=628)(Matullo et al, submitted)**

**XRCC1 28152G/A Arg399Gln, BER, chr. 19q13.2
XPD 35931A/C Lys751Gln, NER, chr. 19q13.2-13.3
XRCC3 18067C/T Thr241Met, DSB/ICL, chr. 14q32.3**

Number of variant alleles	Mean adducts (Std Error)
0	4.9 (1.7)
1	6.0 (0.9)
2	7.9 (0.8)
3	9.1 (0.8)
4	9.7 (1.1)
5	10.6 (2.6)
p for trend	0.01
(no subjects with 6 alleles)	



**Distribution of susceptibility in the
population: the radiation model**



What causes lung cancer?

- **Benzopyrene?**
- **Cigarettes?**
- **Weak willpower?**
- **Advertising / marketing?**
- **War? General John J Pershing says “you ask me what we need to win this war. I answer tobacco as much as bullets” (1918)**
- **Bonsack machine?**
- **Profit motive / competition / surplus value?**
- **Turkish artillerymen? 1853: During the Crimean War British soldiers learn how cheap and convenient the cigarettes used by their Turkish allies are**

(courtesy of G Davey Smith)

Per concludere:

- la grande maggioranza dei tumori sono dovuti all'ambiente o a particolari comportamenti, non ai geni**
- il fumo è una causa di almeno 12 tipi diversi di tumori**
- eliminando il fumo elimineremmo il 90% dei tumori polmonari e il 30% delle morti precoci**
- l'enfasi sulla genetica è comprensibile dal punto di vista scientifico ma non ha fondamento per la prevenzione delle malattie più comuni**