Testimony to the IOM Committee on the Environmental Causes of Breast Cancer

Focus on active and passive tobacco smoking

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Evidence of Biological Plausibility

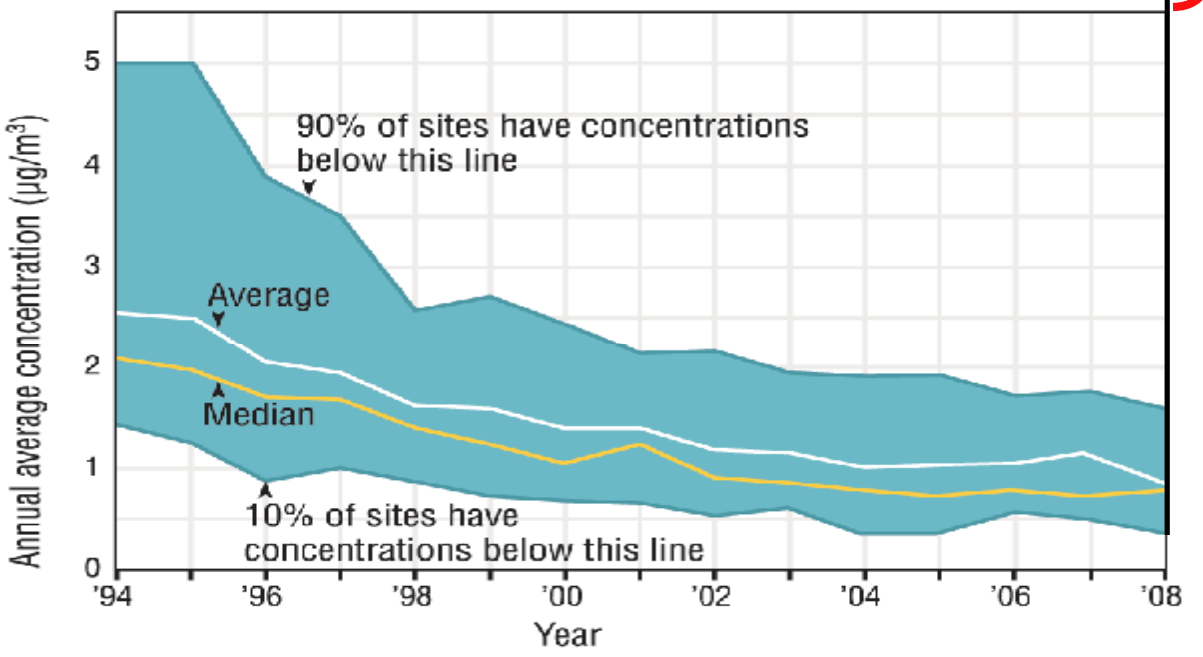
Tobacco smoke contains at least 20 chemicals known to induce mammary tumors in rodents

Benzene
Benzo[a]pyrene
Dibenz[a,h]anthracene
Dibenzo[a,e]pyrene
Dibenzo[a,h]pyrene
Dibenzo[a,i]pyrene
Dibenzo[a,l]pyrene
Dibenzo[a,l]pyrene

Acrylamide
Acrylonitrile
1,3-butadiene
Isoprene
Nitromethane
N-Nitrosodiethylamine
N-Nitrosodi-n-butylamine

Propylene oxide
Urethane
Vinyl chloride
4-Aminobiphenyl
Nitrobenzene
Ortho-toluidine

Exposure to benzene in ETS-polluted environments greatly exceeds ambient exposure from other sources



[a] **Coverage:** 21 monitoring sites nationwide (out of a total of 348 sites measuring benzene in 2008) that have sufficient data to assess benzene trends since 1994.

Data source: *U.S. EPA, 2009*

5-22 ug/m³ In cigarette smoke-polluted environments

Chemicals from tobacco smoke reach breast tissue of active smokers

- Nicotine and cotinine can be found in breast milk
- Evidence that DNA adducts or p53 mutations accumulate in breast tissue
  - benzo[a]pyrene
  - 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)

However,

The epidemiological evidence remains controversial.

Consensus Group Conclusions regarding ***active*** smoking and breast cancer.

IARC 2004: "Evidence suggesting lack of carcinogenicity"

Surgeon General, 2004: "Evidence suggestive of no causal relationship"

CalEPA 2005: "Data provide support for a causal association"

Canadian Panel 2009: "Consistent with causality"

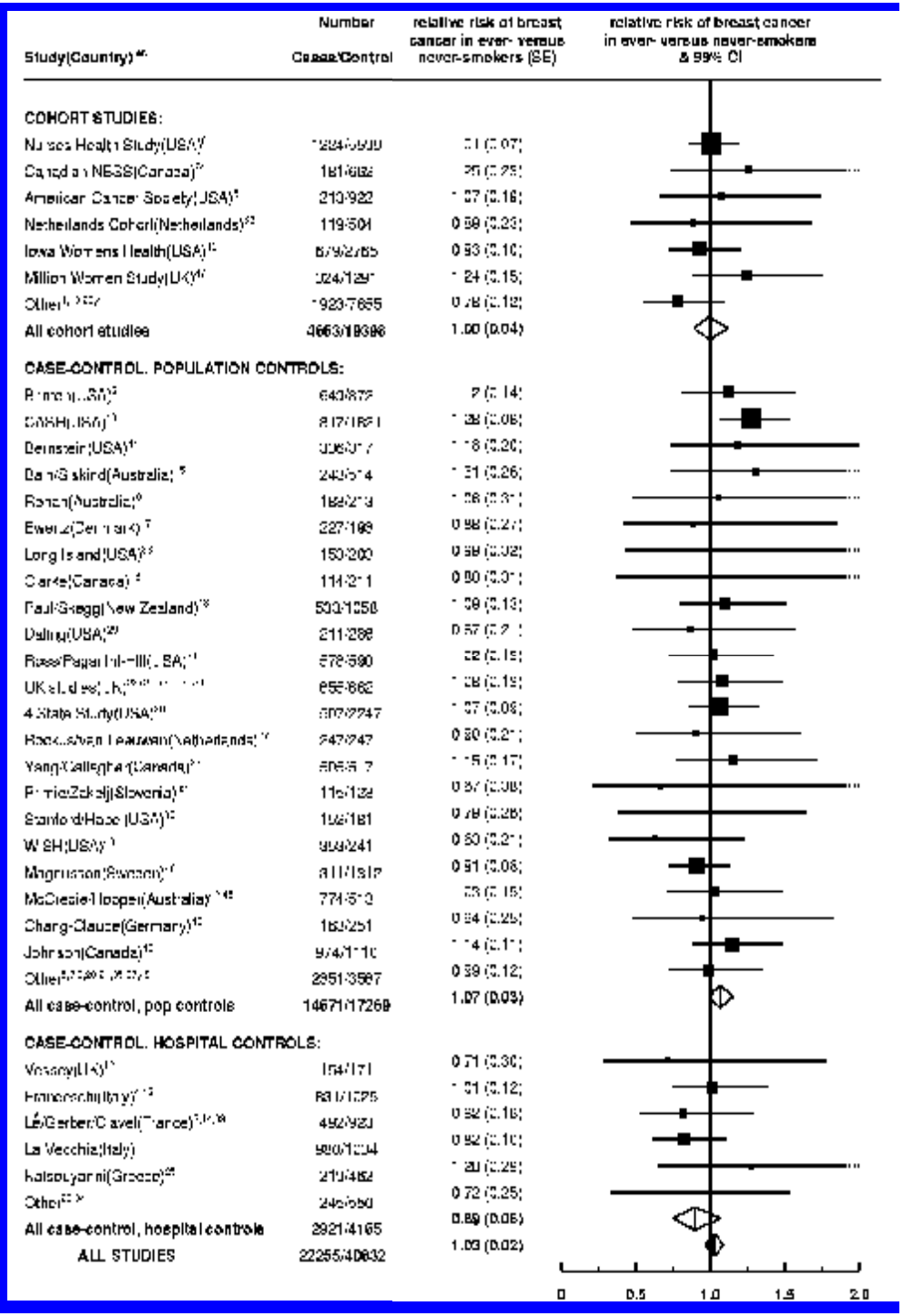
IARC 2009: "Limited evidence"

Strongest evidence against an association

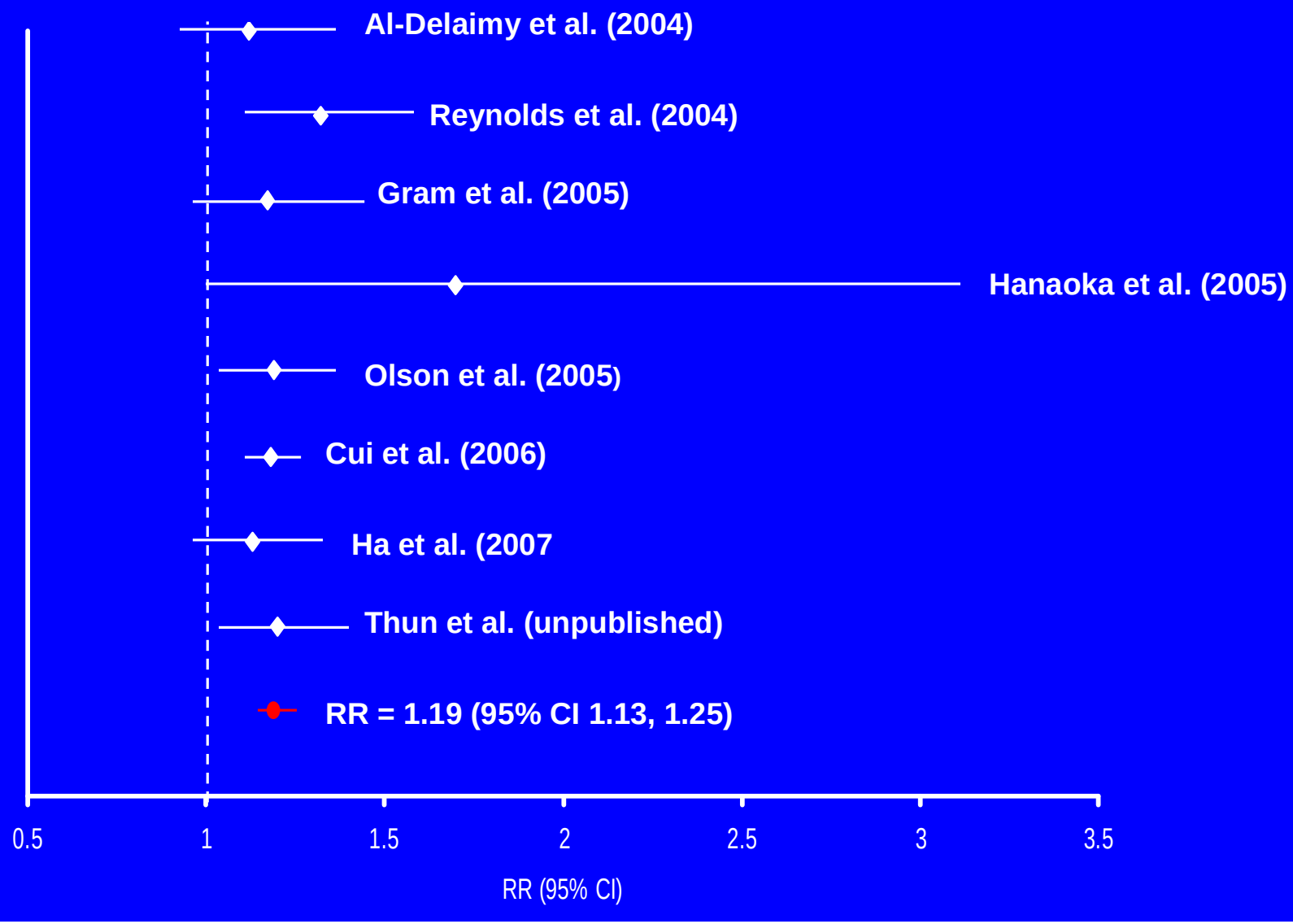
Collaborative Group on Hormonal Factors in Breast Cancer 2002: Results on tobacco consumption & breast cancer in women who reported drinking no alcohol.

No material difference between ever and never smokers

- RR 1.03 (95%CI 0.98-1.07, NS)



IARC Monograph 100E, 2009: Recent cohort studies of active smoking and breast cancer incidence for *current vs. never*



Consensus group conclusions regarding ***passive*** smoking and breast cancer.

IARC 2004: Collective evidence is "inconsistent"

CalEPA 2005: "Consistent with causal association in younger, primarily premenopausal women"

Surgeon General's Report, 2006: "Suggestive but not sufficient to infer a causal relationship"

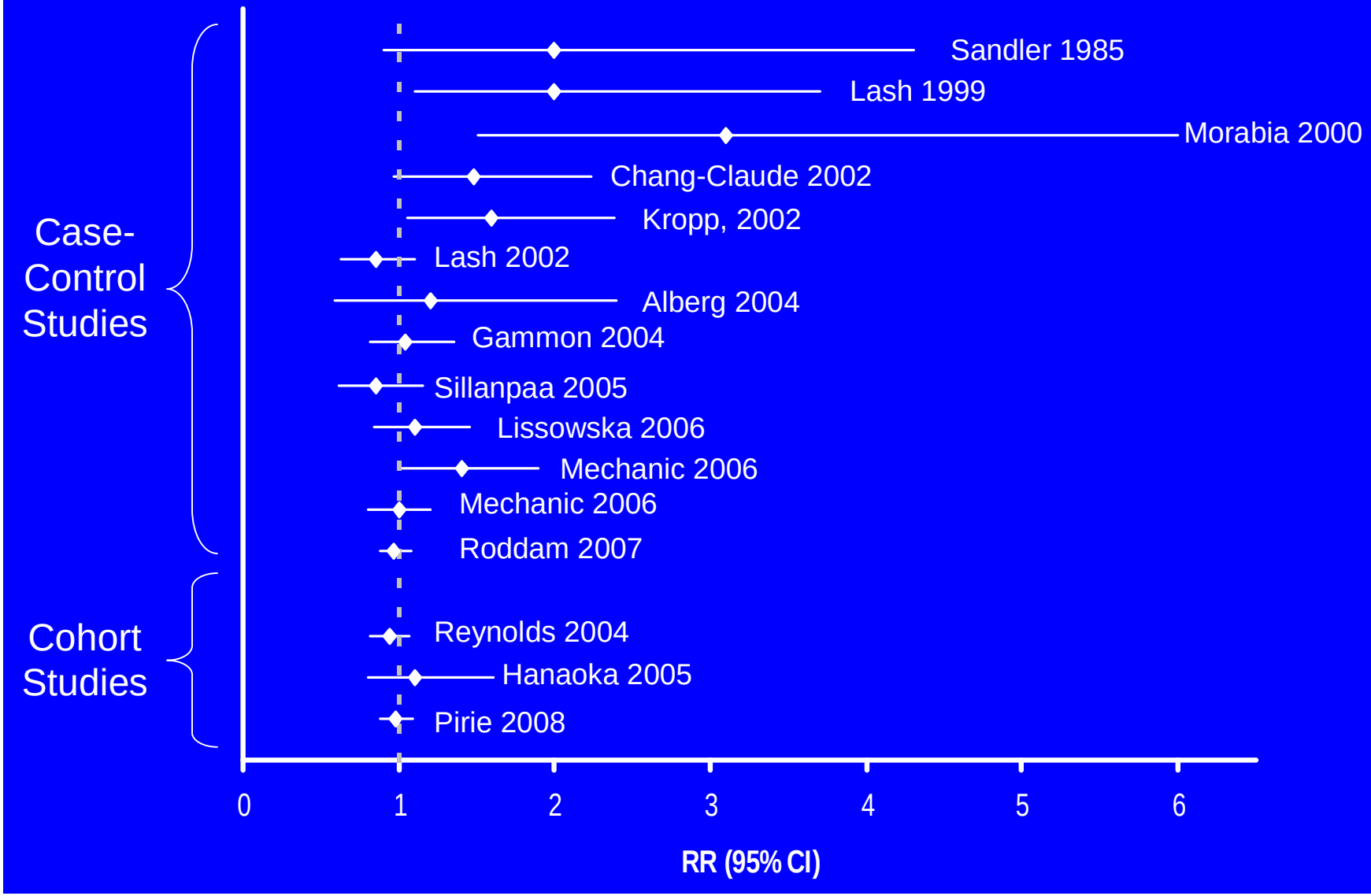
Canadian Panel 2009: "Consistent with causality" for premenopausal cancer

IARC 2009: Not classified

For passive smoking

Interpretation of the evidence depends heavily on which studies are given considered most informative.

IARC Monograph 100E, 2009: Case-control and cohort of active smoking and breast cancer incidence for ever vs. never exposed to *passive* smoke.

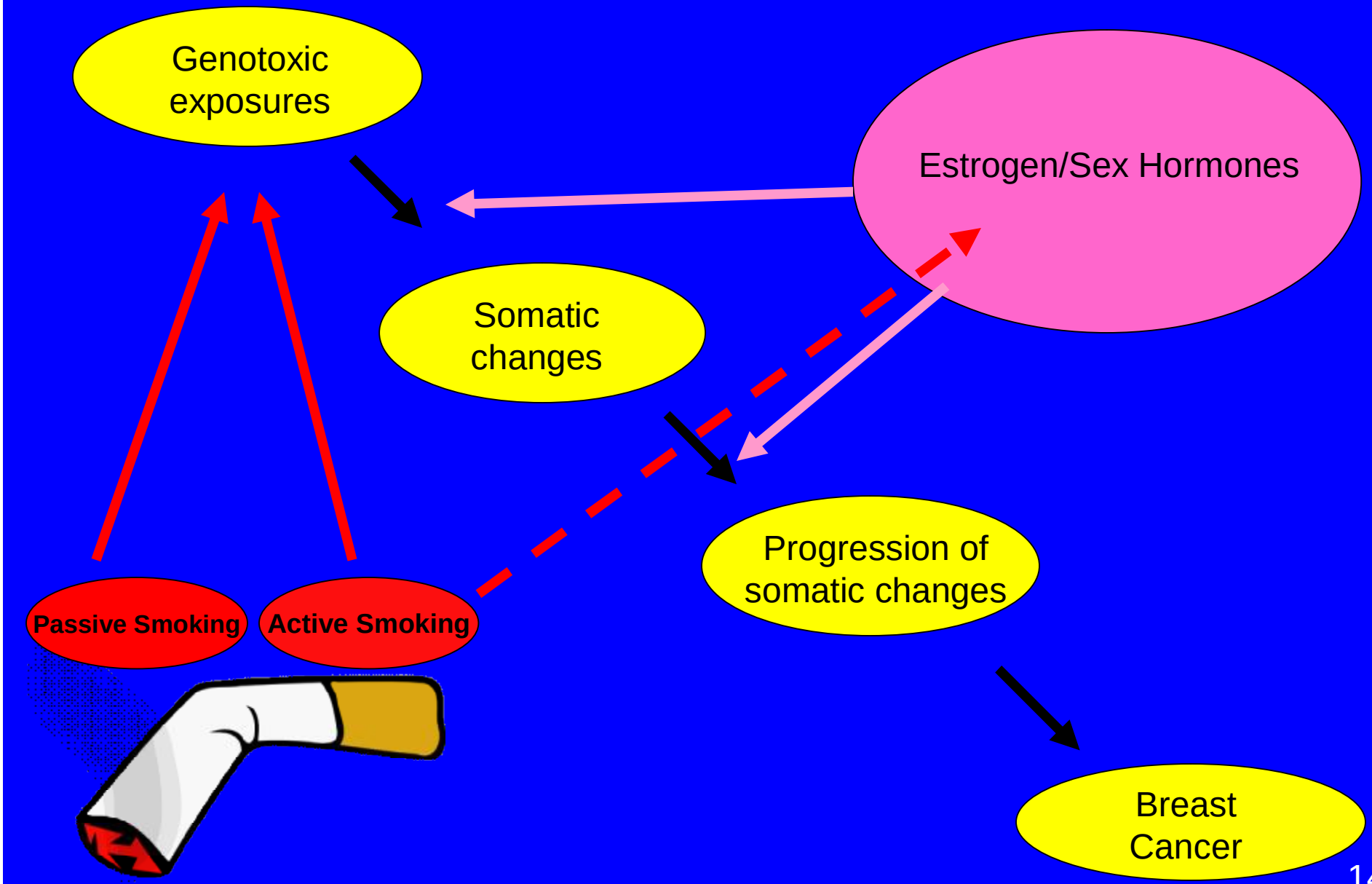


Uncertainty about how to reconcile:

- Why the association with breast cancer is as strong or stronger for passive than for active smoking in some case-control studies?
- Why the association is stronger in case-control than in cohort studies?
- Appropriateness of emphasis on

  a posteriori rather than *a priori* hypotheses

Hypothetical model of how tobacco smoke affects breast carcinogenesis



Indirect evidence for anti-estrogenic effects of active smoking

Smokers have:

- Lower risk of endometrial cancer
- Higher risk of osteoporosis
- Earlier age at natural menopause
- Attenuated effect of HRT on lipid profiles and serum estrone

If this model is correct, then:

- One would expect stronger association for passive than active smoking
- The most informative studies would be those with the most detailed information on ETS exposure.

However

- There is currently no direct evidence that this model is correct

- It is difficult to rule out the alternative explanation that detailed self-reported information on ETS exposure in early life may be biased in case-control studies.

Conclusions

Efforts to define the relationship between tobacco smoke (active & passive) and breast cancer present both challenges & opportunities.

Challenges include:

- The difficulty of measuring ETS exposure reliably during specific time periods in early life

- The lack of (and need for) established biomarkers of how tobacco smoke affects the metabolism of estrogen & other sex hormones

- The lack of (and need for) biomarkers of breast cancer promotion to use in population studies.

The opportunities include:

- Research that differentiates the complementary processes of initiation and promotion may provide a clearer understanding of the potentially complex relationship between environmental carcinogens and human breast cancer.

Recommendations for future research

1. Clarify the effect(s) of tobacco smoke on estrogen/sex hormones
2. Determine whether these hormonal changes occur with active but not passive smoking
3. Examine whether any hormonal biomarkers related to tobacco smoke are also related to breast cancer.
4. Examine the joint effect of biomarkers of initiation & biomarkers of promotion on breast cancer risk.

Thank you

Extra slides

Established risk factors for breast cancer

Factors that Increase Risk

- Earlier age at menarche
- Later age at menopause
- Later age at first birth
- Fewer births
- Exogenous hormone use *
- Weight gain and obesity *
- Alcohol consumption *
- Ionizing radiation *
- Exposure to chemical carcinogens *

Factors that Decrease Risk

- Breast Feeding *
- Physical Activity *

*** Modifiable Risk Factors**

Surgeon General's Report

CalEPA

12 Studies in Common

Hirayama 1984
Sandler 1985a
Smith 1994
Morabia 1996
Millikin 1998
Jee 1999
Delfino 2000
Johnson 2000
Wartenberg 2000
Nishino 2001
Egan 2002
Kropp 2002

SGR

Gammon 2004
Reynolds 2004
Shrubsole 2004
Hanaoka 2005
Liu 2000
Bonner 2005

CalEPA

Gammon 2004
Reynolds 2004
Shrubsole 2004
Hanaoka 2004
Lash 1999
Zhao 1999
Lash 2002

IARC

IARC

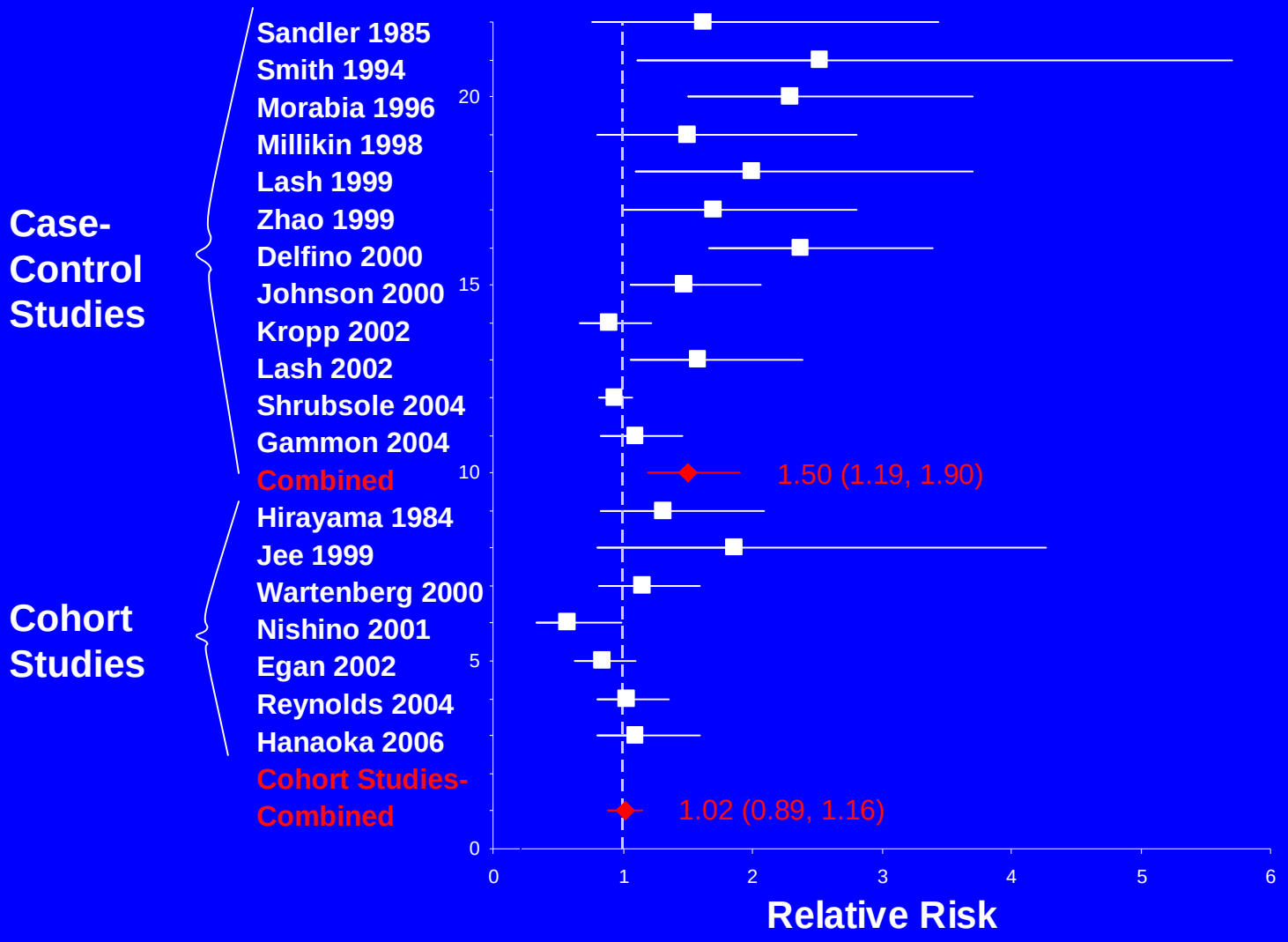
Lash 1999
Sandler 1985b
Marcus 2000
Morabia 2000
Chang-Claude 2002

Differences between IARC/ SG 2004 & CalEPA 2005 reports

Small differences in the evidence base (± several studies) do not account the differences in the conclusions of these reviews.

More important are differences in the weighting and interpretation of different types of data.

CalEPA analysis 2005:
Summary relative risks for breast cancer in women exposed to ETS vs. women who report no active smoking and no regular ETS exposure.



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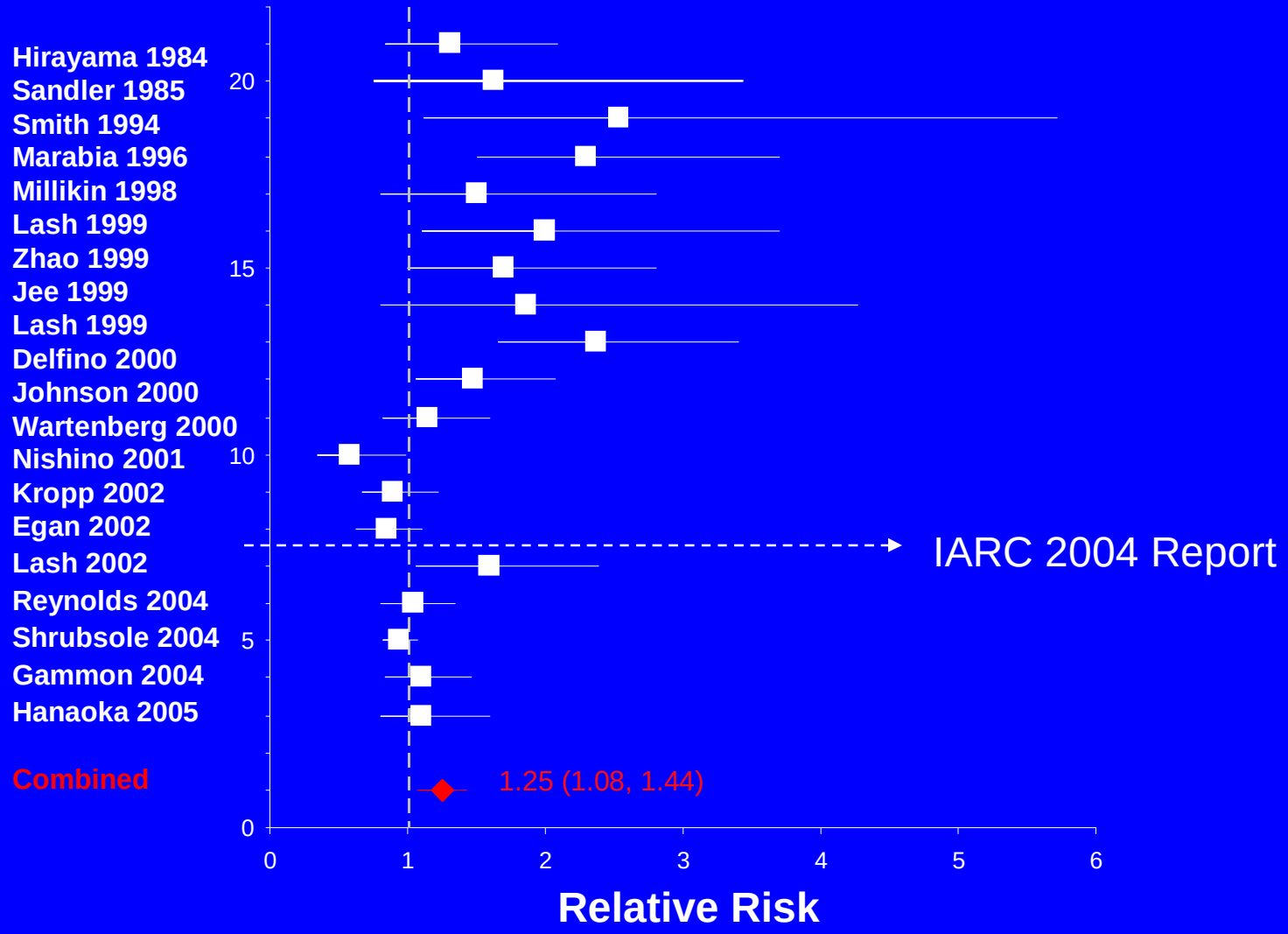
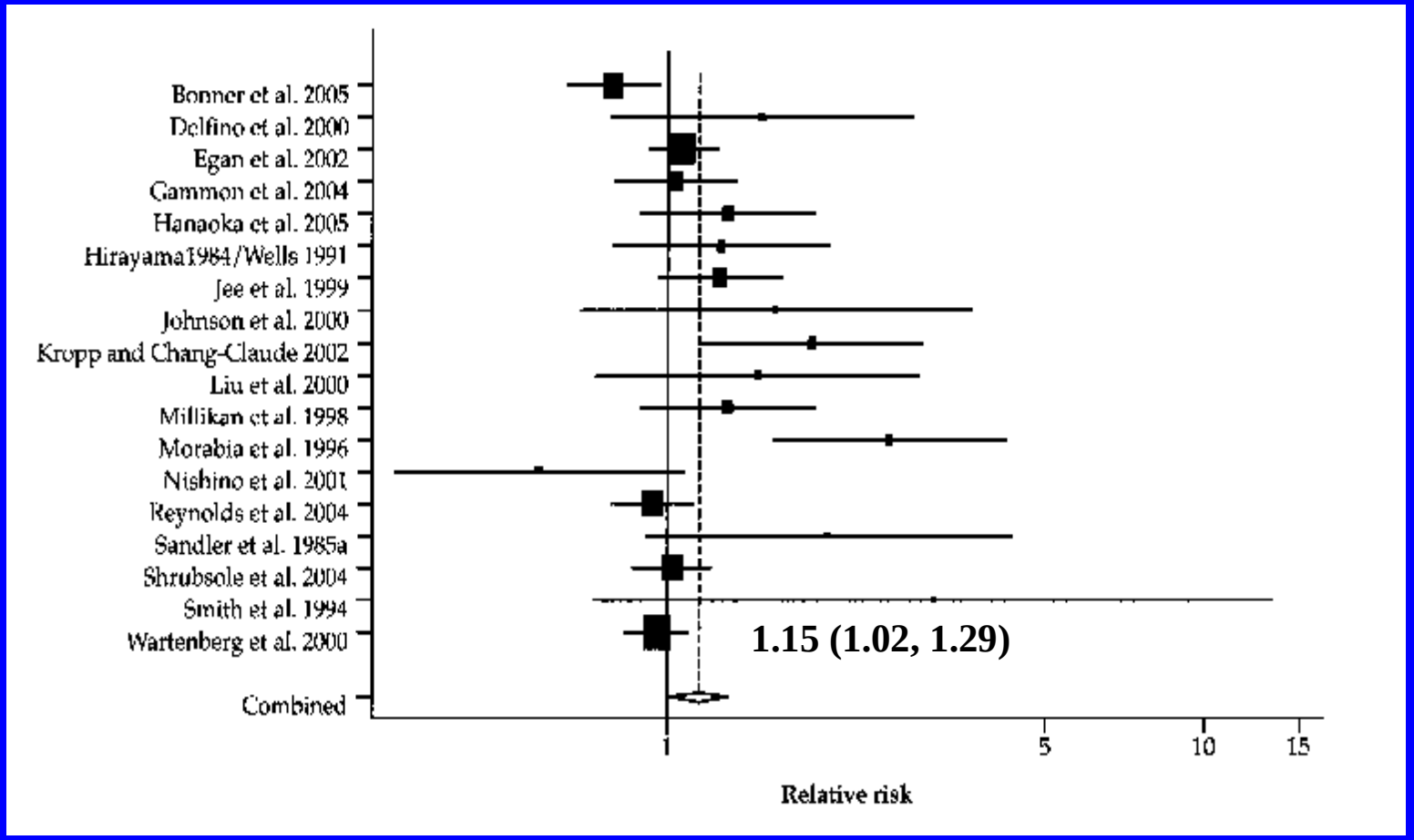
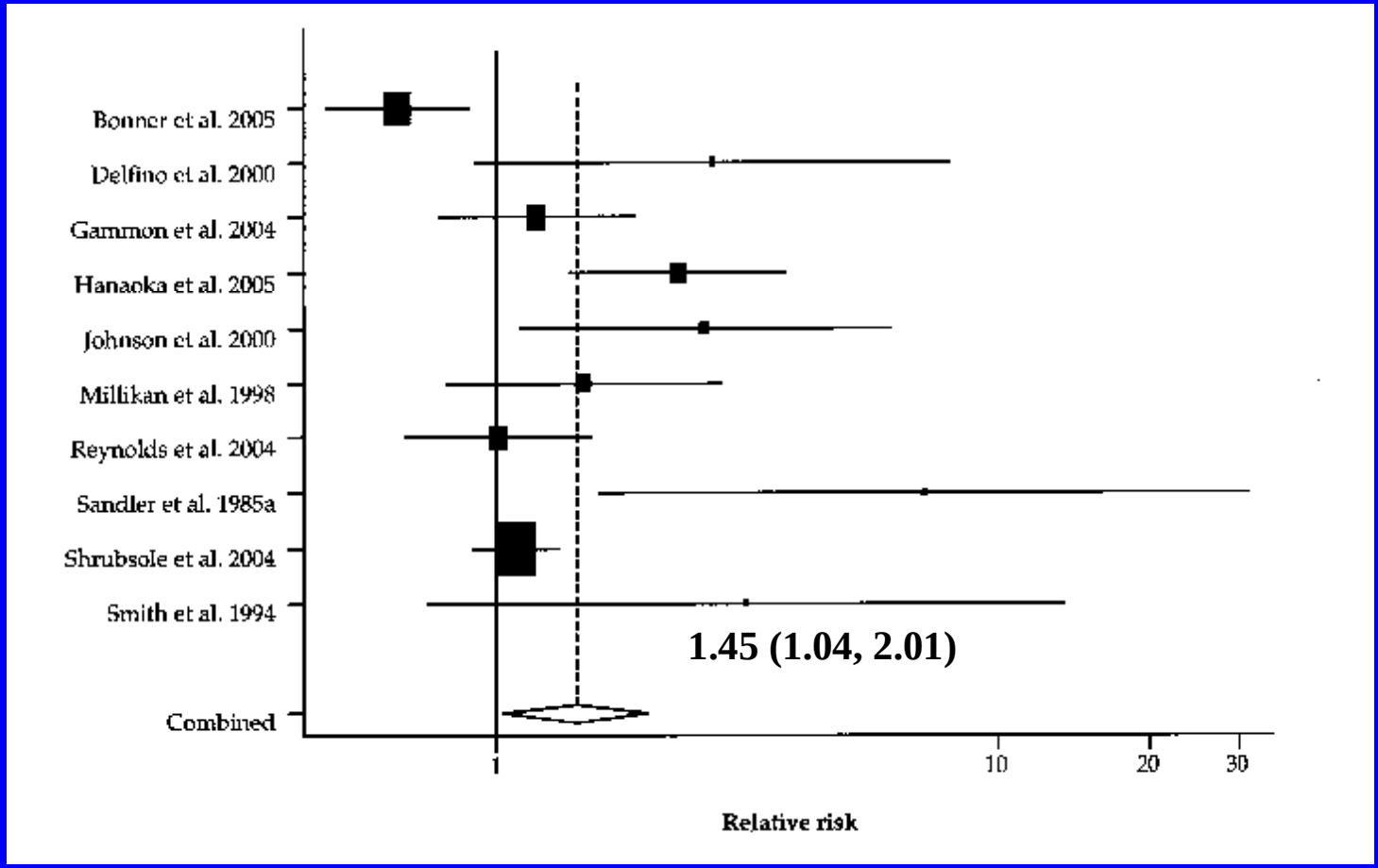


Surgeon General analysis 2006:
Relative risk (& 95% CI) of breast cancer associated with all sources of adult exposure to secondhand smoke



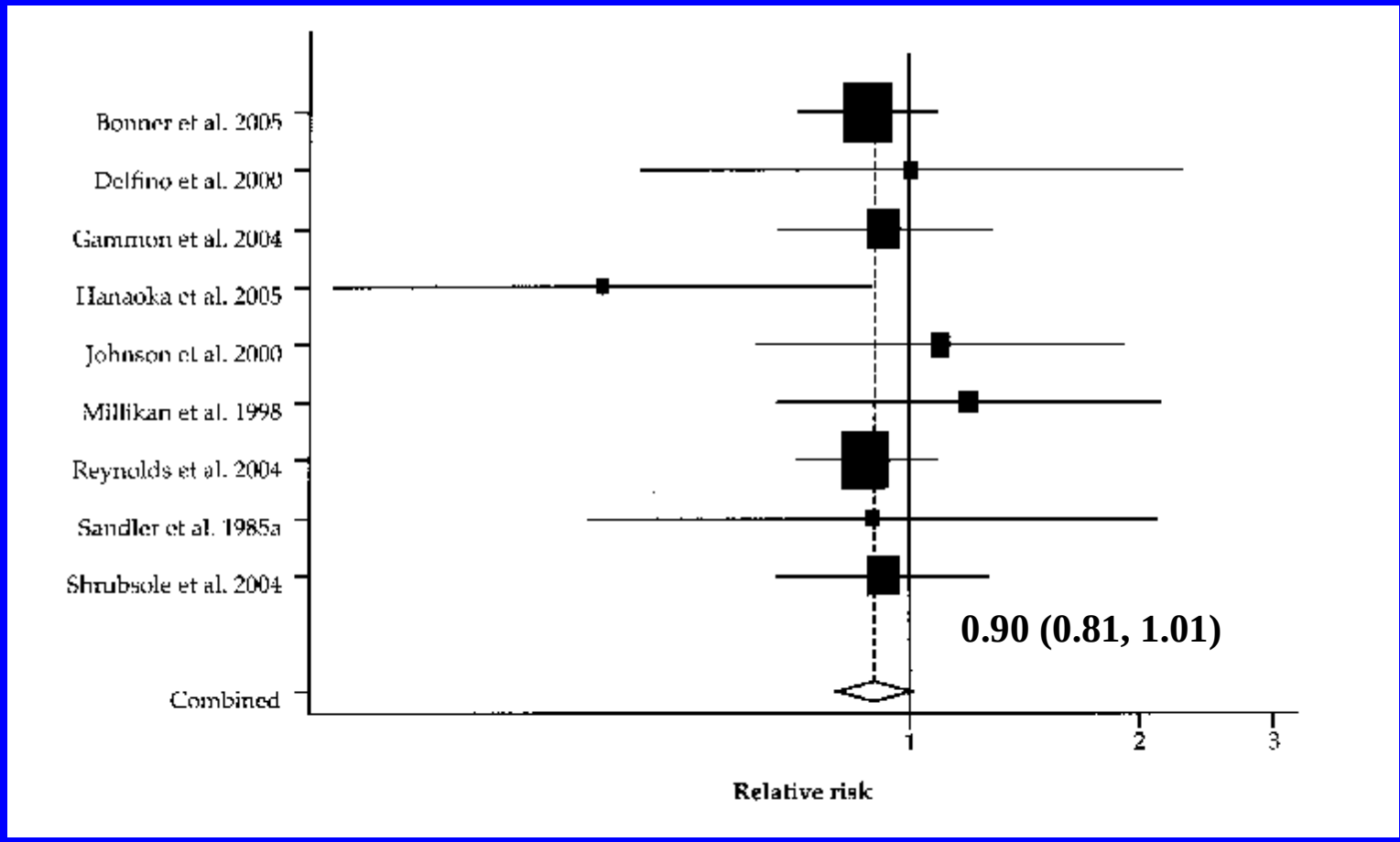
Source: The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General, 2006.

Surgeon General analyses, 2006
Finds an association between all sources of adult ETS exposure and premenopausal breast cancer



Source: The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General, 2006.

Surgeon General analyses, 2006
Finds no association between all sources of adult exposure and postmenopausal breast cancer



Source: The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General, 2006.

CalEPA 2005

"The weight of the evidence … is consistent with a causal association between ETS and breast cancer in younger, primarily premenopausal, women."

How to interpret the difference in findings between pre- & post-menopausal breast cancer?

- The observed association is stronger with pre-than with post-menopausal cancer in the data available.
- This finding was not expected *a priori* and has no clear biological rationale.
- It is presently unclear whether this represents a real finding or an artifact of subgroup analysis.

IARC Monograph 100E, 200:
Recent cohort studies of active smoking and breast cancer incidence for former smokers.