

# Association Between Smoking and Primary Malignant Brain Tumors: A Population-Based Case-Control Study in China

## Smoking and brain tumors

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Abstract code: 16517

Disclosure of Interest: None Declared



**2014** | DEC  
3-6  
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# Brain Tumors in China

- **2.3% of all malignant tumors in China now**
- **< 13% of 5-year survival rate for Adult Primary Malignant Brain Tumors (PMBTs) according current China Guideline**
- **Mortality rate of 194% in 2008 vs. 1970s and 101% vs. 1990s**

# Risk factors of PMBTs

## Established

- Ionizing radiation exposure
- Unmodifiable factors such as sex, age, race, and gene

Smoking?



# Population-based studies

- **No significantly association between smoking and BT**
  - 7 cohort studies
  - 11 case-control studies
  - 1 meta



*Mandelzweig, et al. Cancer Causes Control 2009*  
*Braganza, et al. Br J Cancer 2014*

# STUDY AIM

**To explore whether there was evidence of an association between cigarette smoking and deaths due to PMBTs**

# STUDY DESIGN

- **Case-spouse control study design was raised by Chinese epidemiologists Boqi Liu et al. in 1991. The design was incorporated into a nationwide retrospective mortality survey in China from 1989 to 1991.**



# STUDY DESIGN

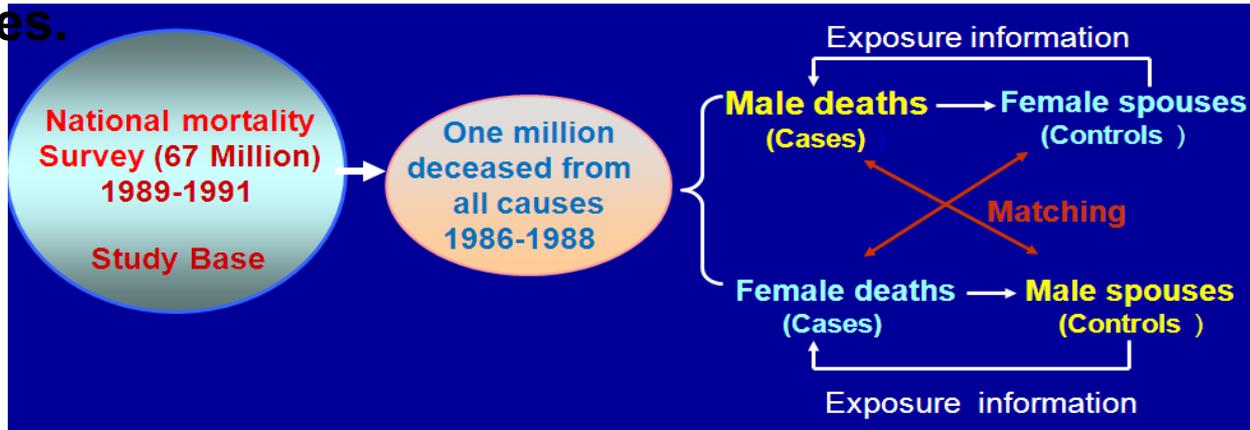
- In 1989-1991, a nationwide retrospective mortality survey was conducted in China, which involved 103 study areas and approximately 1,000,000 adult deaths from all causes during the years 1986-1988.



- **24 major cities** which were chosen to represent a wide geographical spread
- **79 rural counties** were selected through stratified random sampling among the 2,000 counties
- **Base population** including 67 million populations

# STUDY DESIGN

- Within the study base, all deceased aged 35 or over were identified. For those who died of causes related to smoking were taken as cases, whereas surviving spouses of those who died from any conditions during the same year were taken as controls. Exposure information for both cases and controls was provided by living spouses.

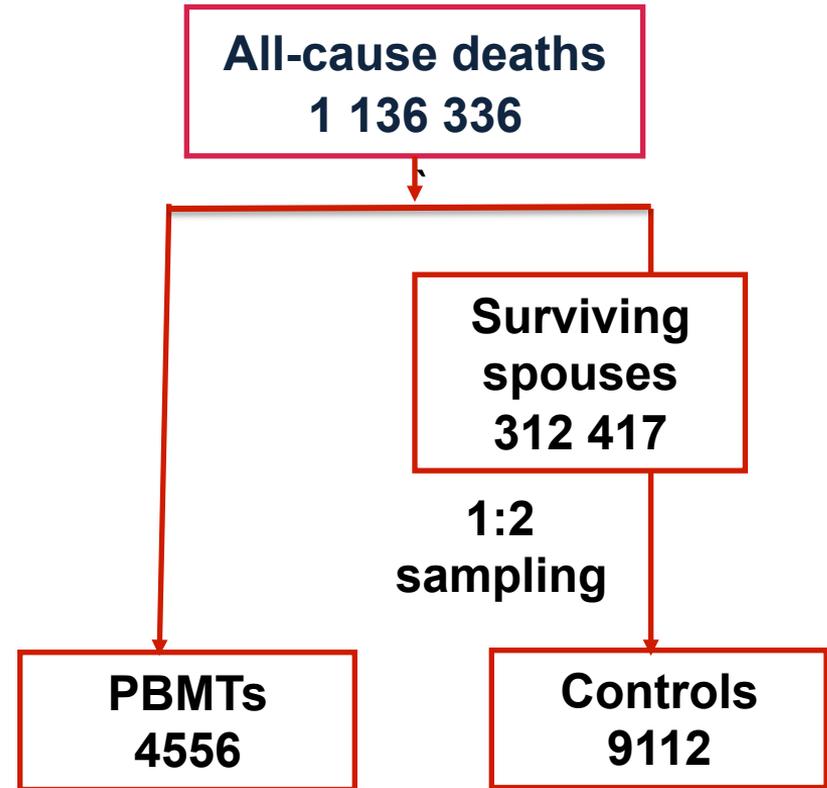


# STUDY DESIGN

- **The theoretical thinking of selecting controls**
  - **The distribution of all causes of deaths in the base population is approximately at random, so is the spouse population.**
- **Assumptions in selection of controls**
  - **Individuals in the control group had smoking habits that were similar to those of the study base.**
  - **There is no significant relationship in tobacco use between couples**

# Case and Control in This Study

- Cases defined as underlying cause of PMBT deaths (ICD-9 code 191.0–191.9)
- Controls defined as sex and age-matched surviving spouses of all-cause deaths.
- Excluded with missing data or other malignant tumors

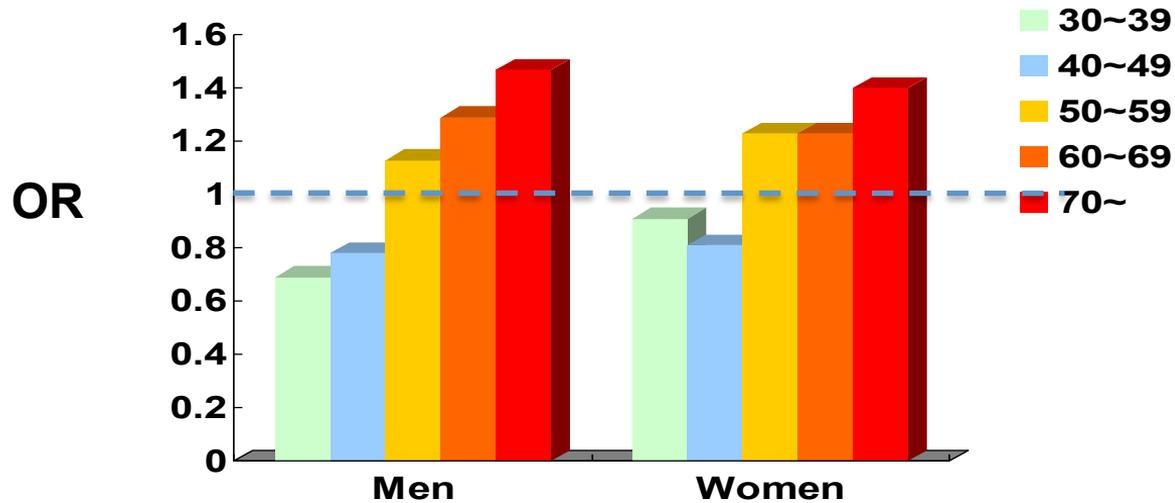


# **RESULTS** Population characteristics

- **57.1% vs 42.9% for men and women**
- **82.1% vs 17.9% for urban and rural areas**
- **41.3% vs 39.2% for the prevalence of smoking in the case and control group**
- **37.4% pathology-based diagnosis**

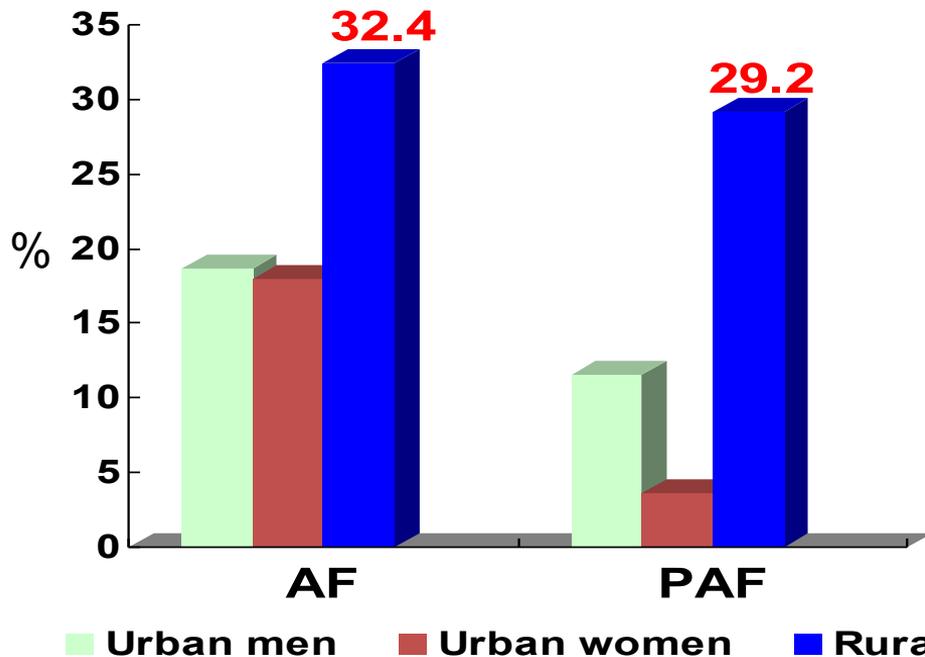
# RESULTS

- ✓ The risk from smoking increased with age



Adjusted for age and urban or rural residence

# RESULTS

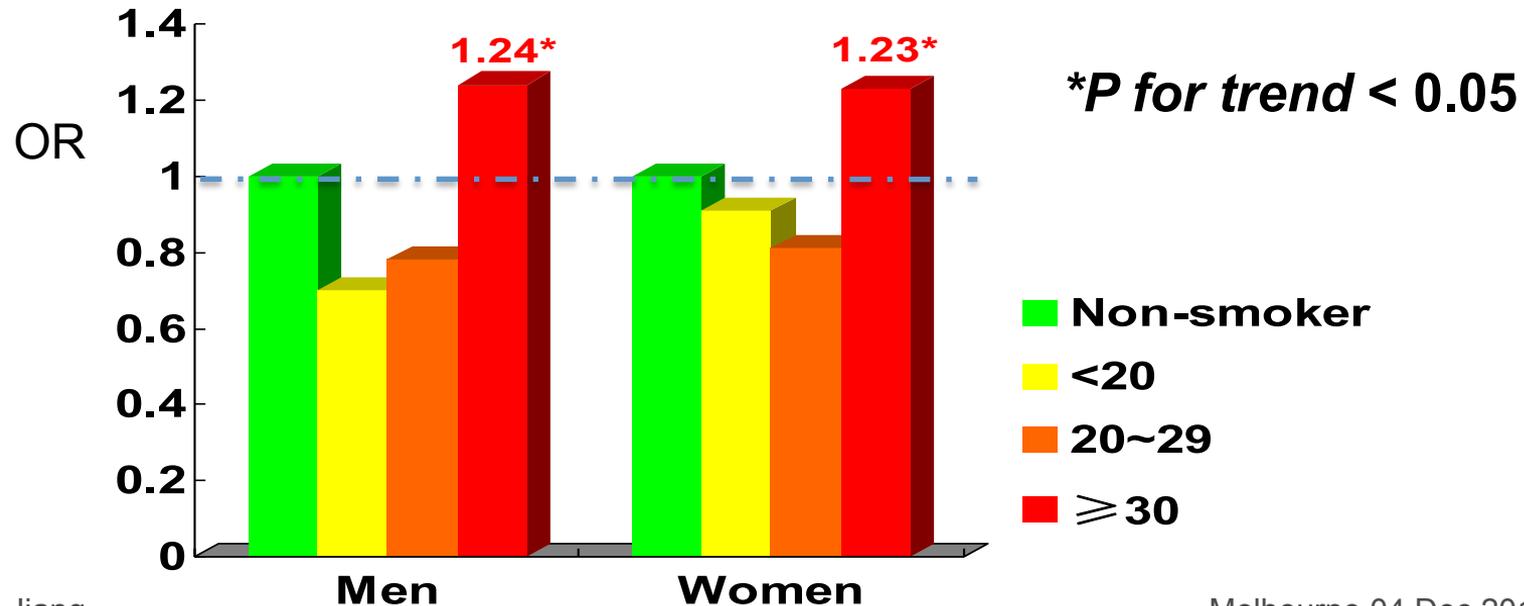


✓ A much larger AFs and PAFs among individuals aged  $\geq$  50 years

OR (95%CI): 1.23 (1.09–1.39) 1.21 (1.02–1.44) 1.50 (1.11–2.02) 1.37 (0.82–2.30)

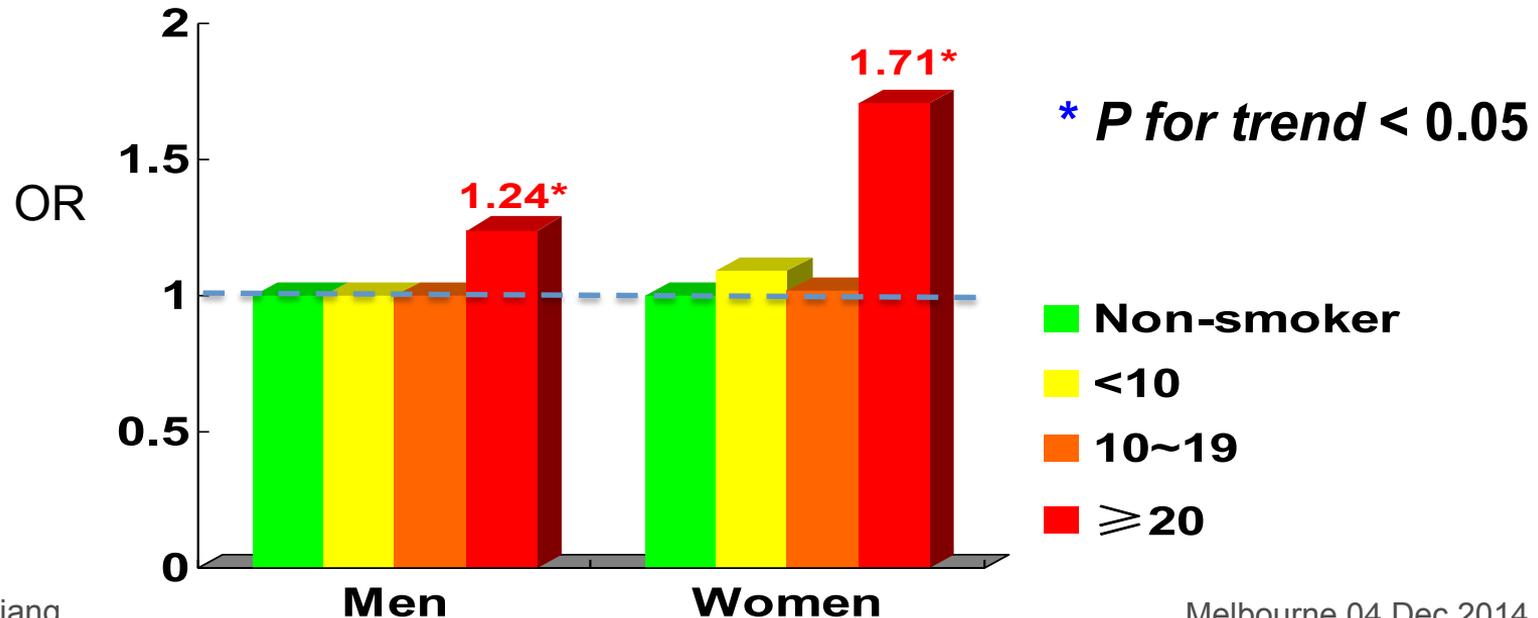
# Dose-response relationship

- The risk increased with years of smoking
  - Consistent in pathology-based comparison



# Dose-response relationship

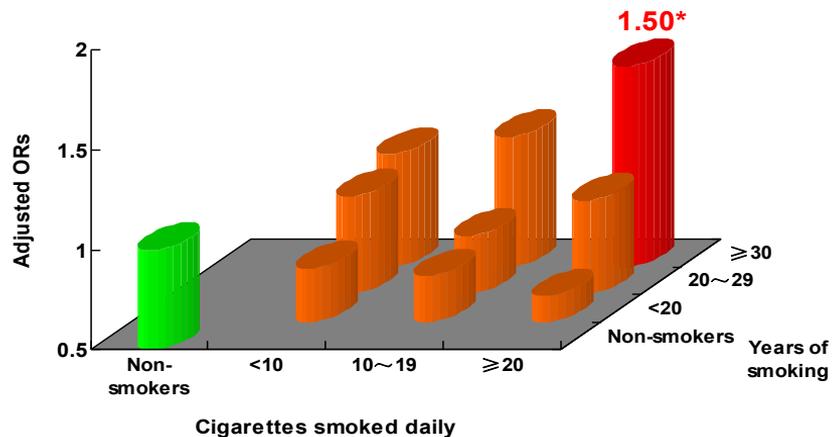
- The risk increased with cigarettes smoked daily
  - Consistent in pathology-based comparison



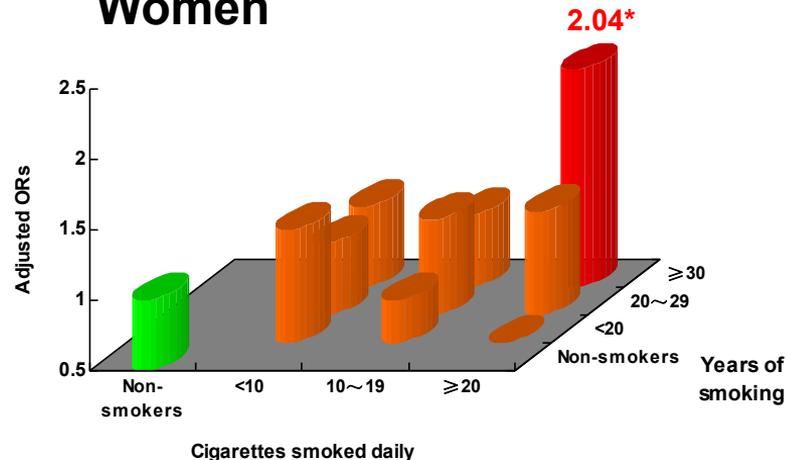
# Dose-response relationship

- Synergistic effects of years of smoking and number of cigarettes smoked daily

## Men



## Women



# DISCUSSION

- **The first study that indicates a positive association of cigarette smoking with PMBTs among both men and women worldwide.**

# DISCUSSION

- **In terms of risk factors of PMBTs, updated evidence showed that, at the cerebrovascular level and specifically at the blood-brain barrier, cigarette smoking could severely impair endothelial function by directly affecting endothelial tight junctions and the ionic homeostasis across the endothelium. More recently, an effect of nicotine on cellular proliferation, migration, signaling, and radiation sensitivity, by activating epidermal growth factor receptor and protein kinase B, has been shown in.**

# DISCUSSION

- **According to the pathophysiological and epidemiological evidence above , we hypothesized that carcinogens in cigarette smoke may act to initiate tumors in the brain, with an induction period of at least 30 years, similar to other malignant tumors. The duration and dose of exposure to tobacco were highly associated with PMBT deaths regardless of sex, age, and urban or rural residence.**

# Discussion

- **A key strength of this study is that it was a high-quality, national-level, population-based case-control study. A random sample of living spouses was selected as controls using a computer-based standardized algorithm. This approach was designed to ensure that the sample of control spouses would have similar smoking habits as those in the base population, so that differences between the recorded proportion of smokers in the case and control groups could be used to calculate unbiased**

# DISCUSSION

- **A limitation of this study lies in the multiple types of PMBTs, which are not distinguishable under ICD coding, but glioma accounts for the overwhelming majority of PMBTs defined.**
- **This study could not exclude recall bias and the measurement error from surviving spouses and survival bias from behavior change of patients after diagnosis of PMBTs such as quitting smoking, which might attenuate the association between smoking and PMBTs.**

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# Contribution in this Project

- We thank Cancer Research UK, the UK Medical Research Council, the US National Institutes of Health, the Chinese Ministry of Health, and the Chinese Academy of Medical Sciences who supported the original survey;
- We thank former minister Chen Min Zhang for his encouragement, and cooperation of local governments;
- We thank Professor Richard Peto, who gave us great support for the project;
- The thousands of doctors, nurses, and other field workers who conducted the surveys, and the million interviewees are great acknowledgments.

# Contribution in this paper

- **This work, including analysis, decision to publish, and preparation of the manuscript, has been supported by a UICC International Cancer Technology Transfer Fellowship under Contract NO ICR/13/073 / 2013 UICC**

Thanks!

