

Osler Journal Club: The Cohort Study

Mortality Attributable to Smoking in China

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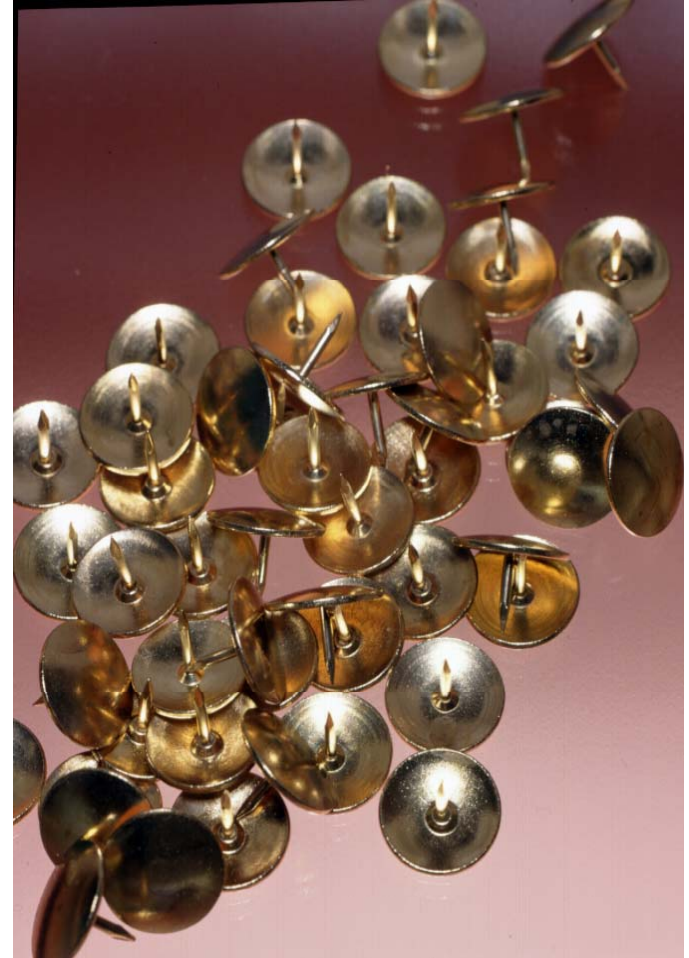
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The Cohort Study

Brass Tacks of a Cohort Study

- Groups chosen based on the basis of exposure
- Followed for the development of outcome



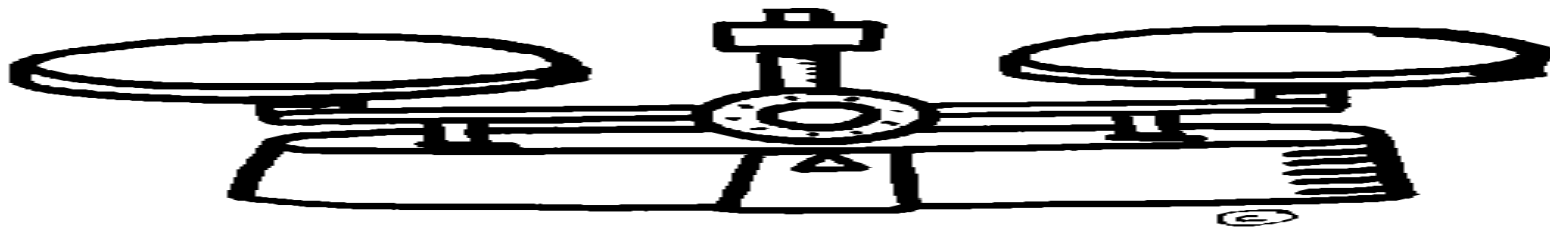
Generic Pro's and Con's of the Cohort Study

Pro's

- Time based study allows speculation of causality (Note the difference between case control)
- Observational nature allows study of toxic exposures
- Can study multiple outcomes of a specific exposure
- Intuitive
- Can Study rare exposures

Con's

- Expensive
- Time consuming and vast
- Not randomized/clean (i.e. toxic exposures often group together and health care systems change over time)
- Not good for rare diseases or outcomes with a long natural history
- Attrition



Why China... why smoking... why this article?

While smoking is on the decline in the western world, the “smoking epidemic” is in the early stages in developing countries.

The culture of smoking and overall impact of tobacco has been described as the #1 public health issue/crisis in China, but the actual attributable burden and targetable screening and populations is still not fully known.

While not terribly surprising implications about smoking as a whole, the authors sought to apply a much needed filter of generalizability to the Chinese population.



Methods

Study Population

- 1991 – China National Hypertension Survey was carried out in all 30 provinces
 - Multi-stage design of random cluster sampling designed to get a nationally representative sample of the Chinese general population > 15 yo
 - Response rate was 89.5%
- 1999-2000 – follow-up study
 - 13 provinces did not have contact information for the study subjects
 - 2 provinces did not have smoking data

Study Population

- 15 remaining provinces were evenly distributed in different geographic regions and represented various levels of economic development in China
- 15 included provinces were similar to 15 excluded provinces:
 - Age: 55.9 yo vs. 55.3 yo
 - High school education: 24.0% vs. 23.4%
 - Alcohol use: 19.8% vs. 18.7%
 - Physical inactivity: 37.0% vs. 36.6%
 - Cigarette smoking history: 37.9% vs. 36.7%
- 155,131 eligible subjects who were age ≥ 40 in 1991
 - 76,134 men, 78,997 women
 - 144,088 (92.9%) successful follow-up and inclusion in study

Baseline Examination

- Data collection in 1991
 - Single clinic visit by physician or nurse
 - Standardized methods with “stringent quality control”
 - Standard questionnaire to gather data on demographic characteristics, medical history, and lifestyle risk factors
 - Tobacco smoking definition: ≥ 1 cig/day x ≥ 1 year
 - Amount and duration of cigarette use quantified
 - Height, weight, BMI, three BP measurements, work related physical activity all assessed

Follow-up Data Collection

- 1999-2000 follow-up
 - Tracked subjects or next-of-kin to current address
 - In-depth interviews to ascertain disease status and information regarding health/death
 - Previous medical records obtained, if available
 - For deaths: information obtained from others:
 - Family (75%), PCP (12.6%), Other health care providers (3.8%), Employers, relatives, or friends (8.5%)
 - If patient died in hospital, MR obtained including:
 - Medical history, PE, labs, autopsy findings, final diagnosis
 - Photocopies made of selected sections of medical records
 - If patient died outside hospital, detailed medical history obtained from family or health care provider
 - 98.6% of deaths were verified by death certificate and/or medical records

Follow-up Data Collection

- End-point Assessment Committee
 - Reviewed medical history information and death certificates to determine final underlying cause of death with prespecified criteria
 - Two committee members independently verified diagnosis
 - Discrepancies adjudicated by discussion involving additional committee members
 - Committee members blinded to subjects' smoking history and other baseline characteristics
 - Causes of death coded according to ICD-9

IRB and Informed Consent

- Study approved by IRB at Tulane and ethics committee at Cardiovascular Institute and Fu Wai Hospital in Beijing
- Written informed consent obtained from all subjects or their proxies at follow-up

Statistical Analysis

- Mortality was primary outcome measured
- Age-standardized mortality was calculated with the use of the 5-year age-specific mortality and age distribution of the Chinese population using 2000 census data
- Relative risks calculated for subjects who had ever smoked compared with lifelong nonsmokers as reference

Statistical Analysis

- Cox-proportional-hazards models used to adjust for a variety of covariables:
 - Baseline age, level of education, alcohol consumption, level of physical activity, presence of hypertension, being overweight, self-reported diabetes, geographic regionalization, and urbanization
- Dose-response relationship of smoking measured by stratifying smokers into 3 groups:
 - <16.1 PYH, 16.1-30.3 PYH, and > 30.3 PYH

Statistical Analysis

- Multivariable-adjusted relative risks of death associated with smoking were obtained stratified by level of urbanization (urban vs. rural), sex, and age (40-54, 55-64, ≥ 65)
 - These estimates used to calculate the population attributable risk (PAR) and 95% CIs for each subgroup using the following standard equation (P = proportion of smokers, RR = relative risk):
 - $PAR = (P \times [RR-1]) \div (P \times [RR - 1] + 1)$
 - Overall relative risks or population attributable risks of death associated with smoking were weighted according to the size of the Chinese population in 2005
- All p-values were two-sided and not adjusted for multiple testing

Results

Baseline Characteristics

Table 1. Baseline Characteristics of the Subjects, According to Smoking Status.*

Variable†	Men		Women	
	Lifelong Nonsmoker	Former or Current Smoker	Lifelong Nonsmoker	Former or Current Smoker
No. of subjects‡	28,191	47,943	68,198	10,799
Age (yr)	57.3±11.1	54.6±10.0	55.7±11.0	59.5±9.6
High-school education (%)	38.8	26.6	18.5	9.5
Alcohol consumption (%)	19.1	48.2	1.8	9.1
Physical inactivity (%)	46.9	34.8	34.2	39.1
Overweight status or obesity (%)	27.2	17.6	26.3	25.1
Hypertension (%)	32.2	25.9	27.9	32.7
Self-reported diabetes (%)	2.7	1.7	2.1	2.6

* Plus-minus values are means ±SD. P values for comparisons between current or former smokers and lifelong nonsmokers were calculated by chi-square tests or t-tests. P<0.001 for all comparisons between the two groups, with the exception of P=0.01 for the comparison between the two groups of women with respect to overweight status or obesity.

† High-school education was defined as having 9 or more years of schooling. Alcohol consumption was defined as drinking alcohol on at least 12 occasions during the past 12 months. Work-related physical activity was assessed on the basis of subjects' occupation; office work was defined as physical inactivity. Overweight status or obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or more. Hypertension was defined as a mean systolic blood pressure of 140 mm Hg or more, a diastolic blood pressure of 90 mm Hg or more, or the use of an antihypertensive medication.

‡ The numbers of subjects were 153,507 for the analysis of educational status, 155,126 for the analysis of overweight status or obesity, and 155,117 for the analysis of hypertension.

Dose-Related Response

Table 2. Relative Risk of Death from Any Cause among Former or Current Smokers, as Compared with Lifelong Nonsmokers, According to the Number of Pack-Years.*

Variable	Pack-Years				P Value for Trend
	0	0.1–<16.1	16.1–<30.3	≥30.3	
Men					
No. of deaths	3841	1297	1785	3108	
Person-yr of follow-up	198,936	96,420	113,587	115,382	
Age-standardized rate per 100,000 person-yr	1278.8	1487.8	1607.2	1740.0	<0.001
Age-adjusted relative risk (95% CI)†	1.00	1.10 (1.03–1.17)	1.20 (1.13–1.27)	1.29 (1.23–1.35)	<0.001
Multivariable-adjusted relative risk (95% CI)†‡	1.00	1.10 (1.03–1.17)	1.18 (1.12–1.23)	1.26 (1.20–1.33)	<0.001
Women					
No. of deaths	6195	644	457	418	
Person-yr of follow-up	493,303	39,221	21,206	15,661	
Age-standardized rate per 100,000 person-yr	1121.5	1380.5	1553.1	1585.7	<0.001
Age-adjusted relative risk (95% CI)†	1.00	1.22 (1.13–1.33)	1.33 (1.21–1.46)	1.42 (1.28–1.57)	<0.001
Multivariable-adjusted relative risk (95% CI)†‡	1.00	1.22 (1.13–1.33)	1.29 (1.17–1.42)	1.38 (1.25–1.53)	<0.001

* Data for 2706 subjects (21,701 person-years and 118 deaths) were excluded because of missing pack-year data.

† Relative risk was estimated from Cox proportional-hazards models.

‡ Variables included age at baseline, level of education, geographic region (north vs. south), urbanization (rural vs. urban), and the presence or absence of hypertension, overweight status or obesity, alcohol consumption, and physical inactivity; the presence or absence of diabetes was considered as a time-dependent covariate.

Population Attributable Risk

Table 3. Relative Risk, Prevalence of Smoking, Population Attributable Risk, and the Absolute Number of Deaths Attributable to Smoking in China in 2005.

Age Group	Relative Risk (95% CI)		Prevalence of Smoking*	Population Attributable Risk	Absolute No. of Deaths Attributable to Smoking (95% CI)
	Age-Adjusted	Multivariable-Adjusted†			
			<i>percent</i>		<i>thousands</i>
Men					
40–54 yr	1.33 (1.20–1.48)	1.20 (1.07–1.34)	72.1	12.7	55.6 (17.3–93.8)
55–64 yr	1.26 (1.16–1.36)	1.25 (1.15–1.36)	70.6	15.0	82.4 (51.3–113.6)
≥65 yr	1.17 (1.11–1.23)	1.19 (1.12–1.26)	67.8	11.2	400.2 (315.8–484.6)
Total	1.28 (1.23–1.33)	1.21 (1.16–1.26)	71.1	12.9	538.2 (455.8–620.6)
Women					
40–54 yr	1.50 (1.26–1.80)	1.36 (1.13–1.63)	7.8	2.7	7.6 (0–15.7)
55–64 yr	1.33 (1.19–1.49)	1.31 (1.17–1.47)	11.4	3.4	12.7 (3.3–22.1)
≥65 yr	1.28 (1.18–1.37)	1.27 (1.18–1.37)	15.3	4.0	114.6 (79.4–149.8)
Total	1.41 (1.33–1.49)	1.33 (1.25–1.41)	9.9	3.1	134.8 (108.9–160.8)

* Data regarding prevalence are from the International Collaborative Study of Cardiovascular Disease in Asia, 2000–2001.⁷

† Data were adjusted for the age at baseline, educational level, geographic region (north vs. south), urbanization (rural vs. urban), and the presence or absence of hypertension, overweight status or obesity, alcohol consumption, and physical inactivity; the presence or absence of diabetes was considered as a time-dependent covariate.

Disease-Specific Risk

Table 4. Relative Risk, Population Attributable Risk, and Absolute Number of Deaths Attributable to Smoking in China, According to Sex and Cause of Death.*

Cause of Death	Men			Women		
	Multivariable-Adjusted Relative Risk (95% CI)†	Population Attributable Risk %	Absolute No. of Deaths Attributable to Smoking (95% CI) <i>thousands</i>	Multivariable-Adjusted Relative Risk (95% CI)†	Population Attributable Risk %	Absolute No. of Deaths Attributable to Smoking (95% CI) <i>thousands</i>
Cancer						
Any	1.55 (1.41–1.70)	28.0	240.4 (198.8–282.0)	1.62 (1.42–1.85)	5.7	27.8 (15.8–39.9)
Lung	2.44 (2.01–2.96)	50.6	113.0 (93.6–132.5)	2.76 (2.18–3.49)	14.8	16.0 (9.6–22.5)
Liver	1.36 (1.11–1.66)	20.3	37.2 (17.2–57.3)	1.44 (0.99–2.11)	NA	NA
Stomach	1.52 (1.23–1.89)	27.0	40.6 (23.3–58.0)	1.05 (0.71–1.56)	NA	NA
Esophageal	1.34 (1.03–1.75)	19.4	19.2 (5.2–33.3)	1.24 (0.75–2.05)	NA	NA
Colon and rectal	1.02 (0.71–1.48)	NA	NA	1.21 (0.73–1.99)	NA	NA
Other	1.26 (1.03–1.55)	15.6	24.5 (5.3–43.7)	1.42 (1.12–1.80)	4.0	6.3 (0–13.0)
Respiratory disease						
Any	1.14 (1.02–1.26)	8.8	48.6 (13.7–83.5)	1.43 (1.25–1.65)	4.1	18.2 (6.6–29.9)
Chronic obstructive pulmonary disease	1.19 (1.05–1.35)	12.1	47.3 (18.0–76.5)	1.61 (1.37–1.89)	5.6	17.1 (7.1–27.1)
Cardiovascular disease						
Any	1.17 (1.09–1.26)	10.7	126.6 (75.6–177.7)	1.21 (1.10–1.34)	2.1	19.6 (3.6–35.5)
Stroke	1.17 (1.07–1.28)	10.8	82.5 (41.7–123.4)	1.18 (1.03–1.34)	1.7	9.8 (0–22.1)
Coronary heart disease	1.21 (1.03–1.42)	12.9	30.4 (6.7–54.1)	1.41 (1.15–1.71)	3.8	7.3 (0–15.2)

* Causes of death were coded according to the *International Classification of Diseases, Ninth Revision*. NA denotes not applicable.

† Data were adjusted for the age at baseline, educational level, geographic region (north vs. south), urbanization (rural vs. urban), and the presence or absence of hypertension, overweight status or obesity, alcohol consumption, and physical inactivity; the presence or absence of diabetes was considered as a time-dependent covariate.

DISCUSSION



Conclusions

- The results of this study involving a nationally representative sample of Chinese adults indicate that tobacco smoking is a major preventable cause of death in China.
 - There was a significant, dose-response association between pack-years smoked and death.
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Conclusions

- ❑ The number of deaths attributable to smoking was much greater among men than among women.
 - ❑ Lung cancer was the leading cause of death attributable to smoking in men.
 - ❑ COPD was the leading cause of death attributable to smoking in women.
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Discussion

- Results are troublesome because the prevalence of tobacco smoking has been continuously high in adult men in China.
- The average age of smoking initiation in China has been dropping during recent decades.

Chin Med J (Engl) 1987; 100:886-92.

Zhonghua Liu Xing Bing Xue Za Zhi 2005; 26:77-83

Discussion

- Unlike studies in Western populations, this study shows that the numbers of deaths from any cause were similar among former and current smokers.
- Smoking cessation has been relatively uncommon in China.
- Most smokers quit because of chronic illness.

Discussion

- This study reported a lower relative risk associated with smoking than did studies in Western populations.
- The magnitude of the relative risks probably reflects the lower numbers of cigarettes smoked in the past and the later age of smoking initiation in subjects currently dying from smoking-related diseases.

Tobacco control policy analysis in China: economics and health.
Singapore: World Scientific Publishing 2008: 13-31.

Study Limitations

- ❑ Since smoking history was assessed by questionnaire, there may have been a small bias to deny or minimize smoking exposure.
 - ❑ Hospital records were available for 71% of subjects who died. Therefore, the classification of cause of death may be less accurate for subjects without hospital records.
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Study Limitations

- The mortality follow-up was conducted during the 1990s, which reflects the patterns of health care and disease burden at that time. Smoking-related diseases, such as cancer and cardiovascular disease, are now more common causes of death in China. Therefore, the study may underestimate current deaths attributable to smoking.
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Study Limitations

- Despite the adjustment for several potentially confounding factors in the multivariable analyses, smokers and nonsmokers may still differ with respect to other factors that contribute to disease risk.
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Study Limitations

- ❑ The authors estimated the number of deaths attributable to smoking, not the number of deaths that could be prevented by smoking cessation.
 - ❑ The study does not address passive exposure to smoking.
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