



MASTER'S COURSE IN: INTERNATIONAL MEDICINE-HEALTH CRISIS MANAGEMENT

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RN: 2010017

WARNING
YOU'RE NOT THE ONLY ONE SMOKING THIS CIGARETTE
The smoke from a cigarette is not just inhaled by the smoker, it becomes second-hand smoke, which contains more than 50 cancer causing agents.
Health Canada

Il fumo danneggia gravemente te e chi ti sta intorno

احترس التدخين يدمر الصحة ويسبب الوفاة

Roken is dodelijk Fumer tue Rauchen ist tödlich

あなたの健康を損なうおそれがありますので吸いすぎに注意しましょう喫煙マナーをまもりましょう

Yasal Uyarı: Sağlığa Zararlıdır.

Fumar puede matar

Rökning skadar allvarligt dig själv och personer i din omgivning.

Tupakoivat kuolevat nuorempina Rökare dör i förtid

Rauchen kann tödlich sein

Rygning kan dræbe

การสูบบุหรี่ทำลายสุขภาพได้

O Ministério da Saúde Adverte FUMAR NA GRAVIDEZ PREJUDICA O BEBÊ

Fumer tue

吸烟有害健康

Fumer nuit gravement à votre santé et à celle de votre entourage

Estimation du nombre de décès au Canada, 1996

Meurtres - 510
Alcool - 1 900
Accidents de la route - 2 900
Suicides - 3 900
Tabac - 45000

AVERTISSEMENT
CHAQUE ANNEE, L'ÉQUIVALENT DE LA POPULATION D'UNE PETITE VILLE MEURT DES SUITES DU TABAGISME

تنبيه هام : التدخين مضر بالصحة

CIGARS ARE NOT A SAFE ALTERNATIVE TO CIGARETTES
Health Authority Warning

[PASSIVE SMOKING AND LUNG CANCER]

Review Article June 2011

Summary in Greek

Το παθητικό κάπνισμα είναι ένας εδραιωμένος παράγοντας κινδύνου για την ανάπτυξη του καρκίνου του πνεύμονα. Η έρευνα έδειξε ότι μη καπνιστές, οι οποίοι διαμένουν με έναν καπνιστή, εμφανίζουν 20-30% αύξηση του κινδύνου ανάπτυξης καρκίνου του πνεύμονα σε σύγκριση με τους μη καπνιστές που δεν κατοικούν με έναν καπνιστή. Υπολογίζεται ότι 3.400 θάνατοι από καρκίνο του πνεύμονα που εμφανίζονται κάθε χρόνο στις ΗΠΑ, οφείλονται στο παθητικό κάπνισμα.

Ο εισπνεόμενος και εκπνεόμενος από τους καπνιστές καπνός (καπνός κεντρικής ροής) και κυρίως ο καπνός που εξέρχεται από την άκρη του τσιγάρου μεταξύ δύο εισπνοών (καπνός περιφερικής ροής), έχει αρνητικές επιπτώσεις στην υγεία και των μη καπνιστών. Μόλις το 26% των προϊόντων και υποπροϊόντων καπνού μένει μέσα στο τσιγάρο (φίλτρο), το 28% εισπνέεται από τον καπνιστή και το 46% σκορπίζεται στον αέρα. Περισσότερες από 50 καρκινογόνες ουσίες έχουν ταυτοποιηθεί στον καπνό του τσιγάρου που απελευθερώνεται στον αέρα. Στα ούρα και στο αίμα των ατόμων που εκτέθηκαν σε παθητικό κάπνισμα εντοπίζονται νικοτίνη, κοτίνη (το μεταβολικό της προϊόν) και άλλες καρκινογόνες ουσίες.

Οι πρώτες έρευνες που αναφέρουν αυξημένο κίνδυνο εμφάνισης καρκίνου του πνεύμονα σε μη καπνιστές λόγω παθητικού καπνίσματος έγιναν το 1981 στην Ιαπωνία (Hirayama) και στην Ελλάδα (Τριχόπουλος). Τα αρχικά ποσοστά μιλούσαν για διπλάσιο σχετικό κίνδυνο. Ακολούθησαν πολλές εργασίες με αντικρουόμενα συμπεράσματα. Τέθηκαν προβληματισμοί για τη στατιστική εγκυρότητα των εργασιών, αλλά και για πιθανή πίεση που ασκούνταν από Καπνοβιομηχανίες για αντίθετα αποτελέσματα από τα επιστημονικά. Ήταν, άλλωστε, γνωστό ότι η ενοχοποίηση του παθητικού καπνίσματος θα επιδρούσε αρνητικά στο εμπόριο καπνού περισσότερο μάλιστα και από το «ενεργητικό» κάπνισμα.

Τελικά, το 2002 συγκεντρώθηκαν 39 ειδικό επιστήμονες από 12 χώρες υπό την αιγίδα του Παγκόσμιου Οργανισμού Υγείας, μελέτησαν όλες τις δημοσιευμένες εργασίες που αναφέρονταν στο κάπνισμα και στον καρκίνο και συνέταξαν την αναφορά τους, σύμφωνα με την οποία: «Οι μετα-αναλύσεις καταδεικνύουν ότι υπάρχει στατιστικά σημαντική συσχέτιση ανάμεσα στην εμφάνιση καρκίνου του πνεύμονα σε μη-καπνιστές που ζουν με καπνιστές (στο σπίτι ή στην εργασία) και στο παθητικό κάπνισμα».

Η τελευταία μετα-ανάλυση (2011) περιγράφει 27% υψηλότερο κίνδυνο εμφάνισης καρκίνου του πνεύμονα σε γυναίκες αν είχαν παντρευτεί κάποιον καπνιστή.

Για να καταλήξει η επιστημονική κοινότητα σε αυτά τα συμπεράσματα είχε προηγηθεί τεράστια διαμάχη με τις καπνοβιομηχανίες. Το 2003 δημοσιεύθηκαν δύο εργασίες (που αργότερα κατηγορήθηκαν ότι ήταν υποκινούμενες από την καπνοβιομηχανία), στις οποίες δεν εμφανιζόταν στατιστικά σημαντική συσχέτιση του παθητικού καπνίσματος με τον καρκίνο του πνεύμονα. Όλα είχαν, βέβαια, ξεκινήσει το 1998, όταν διέρρευσαν στον τύπο στοιχεία από μια εργασία που διενεργούσε ο Παγκόσμιος Οργανισμός Υγείας. Πριν δημοσιευθεί η εργασία, διέρρευσαν στοιχεία που παρουσίαζαν ως αδύναμη επιστημονικά τη δόσο-εξαρτώμενη

συσχέτιση του παθητικού καπνίσματος με τον καρκίνο του πνεύμονα. Λίγο αργότερα ο Παγκόσμιος Οργανισμός Υγείας διέψευσε τα στοιχεία, αλλά η εργασία που ετοιμάζε δε δημοσιεύθηκε ποτέ. Ακολούθησαν δικαστικές διαμάχες για να φτάσουμε σήμερα στο σημείο να θεωρείται το παθητικό κάπνισμα ως καρκινογόνο (group A).

Όλα τα παραπάνω καταδεικνύουν ότι η μελέτη εργασιών πρέπει να γίνεται πάντα με περίσκεψη καθώς ο συγγραφέας του άρθρου μπορεί να έχει οικονομικά οφέλη από το αποτέλεσμα που εξάγεται. Μεγάλη περίσκεψη πρέπει να διέπει τη μελέτη μας και για τα στατιστικά σφάλματα που πολλές φορές υπεισέρχονται.

Abstract

Objective: To determine whether the review articles associate passive smoking with lung cancer, the biologic background of secondhand smoke and lung cancer and the controversy on this topic.

Data sources: Review articles published from 1990 were identified through electronic searches of GOOGLE SCHOLAR and UPTODATE with the Keywords: "Passive Smoking", "Environmental Tobacco Smoke", "Secondhand Smoke", "Lung cancer", "Smoking bans" and from a database of symposium proceedings on passive smoking.

Article Selection: An article was included if its stated or implied purpose was to review the scientific evidence that passive smoking is associated with 1 or more health outcomes. Articles were excluded if they did not focus specifically on the health effects of passive smoking or if they were not written in English, German, or French.

Outcome: The study estimated that living or working in a place where smoking is permitted increases the non-smokers' risk of developing lung cancer by 20-30%. In multiple logistic regression analyses controlling for article quality, peer review status, article topic, and year of publication, the only factor associated with concluding that passive smoking is not harmful was whether an author was affiliated with tobacco industry.

Conclusion: As a consequence of the health risks associated with passive smoking, smoking bans in indoor public places, including restaurants, cafes and nightclubs have been well introduced at national or local level, as well as some outdoor open areas.

(Picture of cover adapted without permission by World Health Organization International Agency for Research on Cancer, 2004)

Introduction

Passive smoking is defined as the inhalation of smoke, called also secondhand smoke (SHS) or environmental tobacco smoke (ETS), from tobacco products which are used by others. It happens when tobacco smoke fills any environment and is inhaled by people within that environment. It is estimated that over 50% of children worldwide are exposed to SHS in their homes. Scientific evidence shows that exposure to secondhand tobacco smoke can cause disease, disability, cancer and even death. (California Environmental Protection Agency, 2005, World Health Organization, 2003, U.S. Department of Health and Human Services, 2006, World Health Organization International Agency for Research on Cancer, 2004) The health risks of SHS are a matter of scientific discussion. (United States District Court for the District of Columbia, 2006, Tong and Glantz, 2007) This topic requires attention, because it is one of the major motivations for smoking bans in workplaces and indoor public places, such as restaurants, bars and night clubs, as well as some open public spaces.

In the early 1970s, a number of research findings began to suggest that exposure to ETS had deleterious health consequences for non-smokers. The tobacco industry understood from the outset the threat that the passive smoking issue represented to its interests, (Diethelm and McKee, 2006) and viewed this "secondary issue" as even more dangerous than the "primary issue", as it internally and euphemistically called the health effects of active smoking.

Effects

Research has generated scientific evidence that Secondhand smoke (that is, in the case of cigarettes, a mixture of smoke released from the smoldering end of the cigarette and smoke exhaled by the smoker) causes many of the same problems as active smoking, including cardiovascular diseases, lung cancer and respiratory diseases.

These diseases include:

- **Cancer:** The International Agency for Research on Cancer concluded in 2004 that "Involuntary smoking is carcinogenic to humans" (World Health Organization International Agency for Research on Cancer, 2004)
- **Lung cancer:** The effect of passive smoking on lung cancer has been extensively studied.
- **Breast cancer:** There is conflicting information regarding statistically significant increased relative risk of breast cancer. (Lissowska et al., 2007, Roddam et al., 2007)
- **Renal cell carcinoma:** A recent study shows an increased relative risk among never smokers with home or work exposure to passive smoking. (Theis et al., 2008)

- Pancreatic cancer: Passive smoking does not appear to be associated with pancreatic cancer. (Hassan et al., 2007)
- Brain tumor: The risk in children increases significantly with higher amount of passive smoking. (Filippini et al., 1994)
- Ear, nose and throat: SHS exposure is associated with hearing loss in non-smoking adults and ear infections. (Fabry et al., 2010)
- Circulatory system: Passive cigarette smoking increases the risk of atherosclerosis, heart disease, reduced heart rate variability and higher heart rate. (Felber Dietrich et al., 2007)
- Lung problems: It causes high risk and worsening of asthma.
- Cognitive impairment and dementia. (Llewellyn et al., 2009)
- During pregnancy: Low birth weight, smaller head circumferences, congenital abnormalities, premature birth when women are exposed to ETS while pregnant. (Salmasi et al., 2010)
- Risk to children: The evidence is sufficient to infer a causal relationship between exposure to SHS and sudden infant death syndrome, (McMartin et al., 2002, Milerad et al., 1998) asthma, (Vork et al., 2007) bronchiolitis, lung infections, (Spencer and Coe, 2003, de Jongste and Shields, 2003, Dybing and Sanner, 1999, DiFranza et al., 2004) Crohn's disease, (Mahid et al., 2007) learning difficulties, (Strachan and Cook, 1997) developmental delays, skin disorders (Lee et al., 2011) and neurobehavioral effects.

Passive smoking is estimated to kill 53,000 nonsmokers per year in the U.S., (Glantz and Parmley, 1991, Taylor et al., 1992) making it the 3rd leading cause of preventable death and 603,000 deaths a year worldwide, which represents 1% of the world's death. (Cheng, 2010)

Lung cancer

Lung cancer is the leading cause of cancer death worldwide, causing over one million deaths per year. (Parkin et al., 2005) Exposure to tobacco smoke is the primary etiologic factor responsible for lung cancer, and its importance is illustrated by the decline in lung cancer incidence and mortality in the U.S. that has accompanied the decline in smoking. (Jemal et al., 2001, Jemal et al., 2005)

In the U.S. lung cancer is the most commonly diagnosed cancer with an estimates of up to 219,440 new cases in 2009. The most important risk factor for lung cancer is long term exposure to inhaled tobacco smoke. Almost 87% of lung cancer cases are caused by cigarette smoking although only 20% of smokers will eventually get lung cancer. The risk is much more dependent on duration of smoking rather than consumption. Other risk

factors of lung cancer include: i) exposure to industrial carcinogens; ii) respiratory diseases; and iii) family history and genetic background.

The majority of lung tumors are classified into four major types: squamous cell carcinomas, adenocarcinomas, large cell carcinomas and small cell carcinomas. For practical therapeutic reasons epithelial tumors are divided in two main categories: small cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs) with account for approximately 75% of lung tumors and include squamous cell carcinomas, adenocarcinomas and large cell carcinomas. Squamous cell carcinoma is the most frequent lung cancer pathology in Europe. The great percentage of squamous cell carcinomas (75%) usually occurs as central masses while the remaining carcinomas are normally located peripherally. Adenocarcinomas are usually present as peripheral nodules and are quite often heterogeneous containing more than one subtype. They are characterized by early development of metastases and are associated with smoking in a lesser extend compared to squamous cell carcinomas. (Daskalos et al., 2009) Adenocarcinoma is more common in never smokers, light smokers, and former smokers while squamous cell carcinoma and small cell lung cancer are seen with a higher incidence in heavy smokers. (Sun et al., 2007, Subramanian and Govindan, 2007, Toh et al., 2006, Wakelee et al., 2007)

Lung cancer patients present a variety of symptoms that may be associated with the primary tumor or mediastinal spread of the tumor, metastasis or paraneoplastic syndrome. Symptoms include dyspnoea, cough, haemoptysis, chest pain, loss of appetite and weight loss. Lung cancer primary tumors can metastasize in many different sites including the brain, bone, liver, pleural cavity and skin.

Treatment differs for NSCLC and SCLC. Surgery is the main curative treatment for NSCLC patients, although the tumor may not be operable in many cases. Depending on the stage of disease and patient's general health status, radical radiotherapy may be used instead if surgery but with a poorer outcome. In contrast, surgery for SCLC is rarely an option. Combined chemotherapy is the main treatment option with active drugs including cisplatin, etoposide, carboplatin and others while chest radiotherapy may also be applied in certain patients. The 5-year survival rates are at 16% for 1996-2004 diagnoses.

Genetic studies in lung cancer tissues and cell lines have shown that the key events causing lung carcinogenesis, as in all cancers, include (proto)oncogene activation and tumor-suppression gene inactivation. (Daskalos et al., 2009) Contemporary advances in the understanding of the molecular biology of lung cancer have led to the identification of substantial differences between never smokers compared to smokers with lung cancer. One of the most apparent differences between lung cancer in never smokers versus current and former smokers is in the expression and mutations of the epidermal growth factor receptor (EGFR). Mutations in the EGFR gene are more common in lung tumors from never smokers compared to smokers. (Sonobe et al., 2005, Kosaka et al., 2004, Tsao et al., 2005, Pao et al., 2004, Pham et al., 2006, Tam et al., 2006) An

extensive effort to identify other biomarkers of importance in lung cancer of never smokers is ongoing in a multi-institutional effort funded by the National Cancer Institute's Early Detection Research Network and the Canary Foundation. This project was launched in May of 2009.

Evidence

Involuntary smoking involves exposure to the same numerous carcinogens and toxic substances that are present in tobacco smoke produced by active smoking, which is the principal cause of lung cancer. Most experts believe that moderate, occasional exposure to Secondhand Smoke (SHS) presents a small but measurable cancer risk to nonsmokers. More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been published during the last 25 years. These studies have been carried out in many countries and most of them showed an increased risk, especially for persons with higher exposure. To evaluate the information collectively, in particular from those studies with a limited number of cases, meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together.

In 1981, the first two studies reporting elevated rates of lung cancer among nonsmoking women married to smokers in Japan (Hirayama, 1981) and Greece (Trichopoulos et al., 1981) cited a nearly doubled risk of lung cancer associated with passive smoking. These initial findings were greeted with skepticism because it was not commonly believed that Environmental Tobacco Smoke (ETS) exposures by nonsmokers typically would be sufficient to double cancer risk. Subsequent studies (Hackshaw et al., 1997, Boffetta et al., 1998) have indicated that the initial risk estimates were indeed too high. Of course, there may be instances where exceptionally heavy ETS exposure may double the risk of lung cancer; however, in the typical spousal- and workplace-exposure situations, the excess risk is probably modest.

Because a small increase in risk of disease can be accounted for by subtle biases in study design, conduct, or analysis or by confounding by other risk factors associated with the exposure of interest, there has been intense debate about whether the increased risk of lung cancer observed among nonsmokers exposed to ETS is in fact due to the ETS exposure. It has been noted that nonsmokers married to smokers may differ from nonsmokers married to nonsmokers in ways that could influence lung cancer risk (e.g. the former group may have lower intakes of fruits and vegetables). (Matanoski et al., 1995)

A series of studies from the USA from 1986-2003, (National Research Council, 1986, United States Environmental Protection Agency, 1993) the UK in 1998 (Hackshaw, 1998) and Australia in 1997 have consistently shown a significant increase in relative risk among those exposed to passive smoke. (Alberg and Samet, 2003) In 2002, a group of

29 experts from 12 countries convened by the Monographs Program of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), Lyon, France, reviewed all significant published evidence related to tobacco smoking and cancer and in 2004 they concluded:

"These meta-analyses show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk is of the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Furthermore, other published meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at the workplace have found a statistically significant increase in risk of 12-19%. This evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer in never smokers." (World Health Organization International Agency for Research on Cancer, 2004)

Subsequent meta-analyses have confirmed these findings (Taylor et al., 2007, Stayner et al., 2007) additional studies have found that high overall exposure to passive smoke even among people with non-smoking partner is associated with greater risks than partner smoking. (Whincup et al., 2004) The overall risk depends on the effective dose received over time. The risk level is higher if non-smokers spend many hours in an environment where cigarette smoke is widespread, such as a business where many employees or patrons are smoking throughout the day or a residential care facility where residents smoke freely. (Boffetta et al., 1998)

In May 2006, the U.S. Centers for Disease Control issued its first new study on SHS in 20 years. Surgeon General Richard Carmona summarized:

"The health effects of SHS exposure are more pervasive than we previously thought. The scientific evidence is now indisputable: SHS is not a mere annoyance. It is a serious health hazard that can lead to disease and premature death in children and nonsmoking adults." The study estimated that living or working in a place where smoking is permitted increases the non-smokers' risk of developing heart disease by 25-30% and lung cancer by 20-30%.

Results of a meta-analysis including 52 studies prepared for the 2006 Surgeon General's report showed that the relative risk of lung cancer among male and female nonsmokers who were ever exposed to SHS from the spouse was 1.21 (95% CI 1.13-1.30). The magnitude of the effect was comparable for men and women, with no significant difference by geographic area.

A meta-analysis of 25 studies of lung cancer and exposure to SHS in the workplace prepared for the 2006 Surgeon General's report estimated a pooled relative risk of 1.22 (95% CI 1.13-1.33). (U.S. Department of Health and Human Services, 2006) A more

recent meta-analysis, involving 55 studies, found that women had 27 percent increase in risk if married to a smoker.

In most individual studies and meta-analyses the estimated (or pooled) RR is between 1.2 and 1.4, a level where the possibility of confounding and different types of bias should be carefully explored.

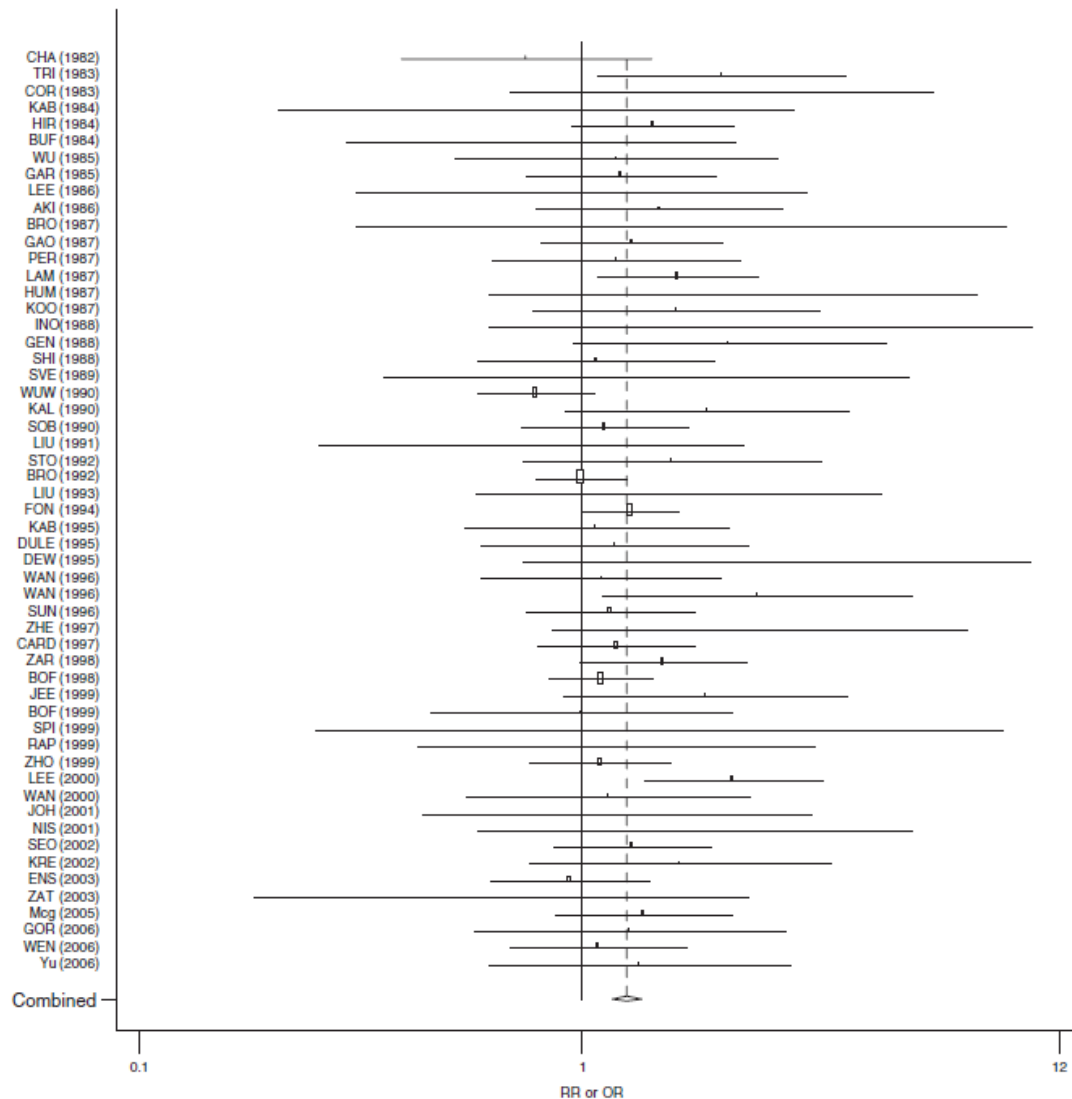


Figure 1 Forest plot of odds ratios and relative risks of lung cancer (and 95% CI) from studies of never smoking women exposed to smoking spouses, 1981-2006. (Figure adapted without permission by Taylor et al., 2007)

By restricting the data to exposure to ETS among never-smoking women, they have minimized some of the difficulties of previous meta-analyses especially in relation to misclassification bias. It could be expected that the final estimated risk may be confounded by various factors. Indeed, a household in which one spouse is a smoker may differ in some aspects from those in which neither is a smoker. Indoor air pollution and lifestyle (such as diet) are two important features in which smoking and non-smoking households may differ. For example, it has been documented that non-smokers living

with smokers have a lower intake of micronutrients, cholesterol and beta carotene. It has been estimated that the confounding effect of these dietary variables is modest. Except for specificity, the association between passive smoking and lung cancer fulfils all other criteria for causation. The strength of association (even after consideration of bias and confounding), consistency of findings across domestic and workplace primary studies, dose-response relationship and dosimetric extrapolation and biological plausibility are important criteria which indicate a causal relationship between passive smoking and lung cancer. (Taylor et al., 2007)

The next table shows the main results of published meta-analyses on the risk for lung cancer in never smokers associated with exposure to SHS from the spouse, including an indication of whether any adjustment was made for bias and confounding. All the pooled estimates show an increased risk (relative risks of 1.1-1.6), despite using different combinations of studies and methodology. (World Health Organization International Agency for Research on Cancer, 2004)

Reference	No. of studies	Sex of subjects	Pooled relative risk (95% CI)	Pooled estimate adjusted for			Adjusted pooled relative risk
				Misclassification bias	Exposure to secondhand smoke other than from the spouse	Dietary confounding	
National Research Council (1986)	13	Men and women	1.34 (1.18–1.53)	Yes	Yes	No	1.42
Wald <i>et al.</i> (1986)	13	Women	1.32 (1.16–1.53)	No	No	No	
Fleiss & Gross (1991)	9 (USA only)	Men and women	1.35 (1.19–1.54)	Yes	Yes	No	1.53
Lee (1992)	28	Women	1.12 (0.95–1.30)	No	No	No	1.08
	28	Men	1.20 (1.09–1.31)	No	No	No	
	11	Women	1.18 (1.07–1.30)	No	No	No	
Tweedie & Mengersen (1992)	26	Men	1.39 (0.97–1.99)	Yes	Yes	No	1.59
US Environmental Protection Agency (1992)	11 (USA only)	Women	1.17 (1.06–1.28)	Yes	Yes	No	1.59
Hackshaw (1998)	37	Women	1.19 (1.04–1.35)	Yes	Yes	Yes	1.26
	9	Men	1.24 (1.13–1.36)	No	No	No	
Zhong <i>et al.</i> (2000)	40	Women	1.34 (0.97–1.84)	No	No	No	1.17
Lee <i>et al.</i> (2001)	47	Women	1.20 (1.12–1.29)	Yes	No	No	1.17
Boffetta <i>et al.</i> (2002)	45	Women	1.23 (1.12–1.36)	No	No	No	1.17
	9	Men	1.25 (1.14–1.38)	No	No	No	
			1.25 (0.95–1.65)				

Figure 2 Summary results of selected published meta-analyses of the risk for lung cancer in never-smokers exposed to secondhand smoke from the spouse (Figure adapted without permission by World Health Organization International Agency for Research on Cancer, 2004)

A population based-prospective study in Japan reported a HR of 2.03 (95% CI 1.07-3.86) for development of lung adenocarcinoma for never-smoking women who lived with a smoking husband as compared to never-smoking women who lived with a non-smoking husband. (Kurahashi et al., 2008) In a report based upon the largest sample, analysis from a case-control study in Europe of 520,000 people, has estimated that the proportion of lung cancer related to SHS was 16 to 24 percent in non-smokers. (Vineis et al., 2007)

Pathophysiology

Sidestream smoke contains more than 4,000 chemicals, including 69 known carcinogens such as formaldehyde, lead, arsenic, benzene and radioactive polonium 210. The tobacco companies' own research has shown several well-established carcinogens to be present at higher concentrations in sidestream smoke than in mainstream smoke. (Schick and Glantz, 2005)

Environmental tobacco smoke can be evaluated either by directly measuring tobacco smoke pollutants found in the air or by using biomarkers, an indirect measure of exposure. As of 2005, Nicotine, cotinine, thiocyanates and proteins are the most specific biological markers of tobacco smoke exposure:

Cotinine, the metabolite of Nicotine, is measured in the blood, saliva and urine. Hair analysis has recently become a new, noninvasive measurement technique. Cotinine levels found in the urine only reflect exposure over the preceding 48 hours. (Metz-Favre et al., 2005) Cotinine accumulates in hair during hair growth, which results in a measure of long-term, cumulative tobacco exposure over the previous three months. Cotinine is a much more reliable biomarker of ETS than surveys, because certain groups of people are reluctant to disclose their smoking status and exposure to tobacco smoke, especially pregnant women and parents of young children, due to their smoking being socially unacceptable. Also, recall of tobacco smoke exposure may be difficult. (Florescu et al., 2009) In a nationally representative sample in the U.S., the mean serum level of cotinine was nearly twenty-fold higher among children exposed to SHS in the home, as compared with those not exposed in the home. (Marano et al., 2009) Cotinine measurements and particularly cotinine levels of the skin, such as the hair and nails, are therefore more reliable biomarkers.

A significant amount of biological levels of nicotine from SHS exposure are equivalent to nicotine levels from active smoking and levels that are associated with behavior changes due to nicotine consumption. (Okoli et al., 2007) Mainstream smoke, sidestream smoke and SHS contain largely the same components; however the concentration varies depending on type of smoke.

In an experiment conducted by the Italian National Cancer Institute, three cigarettes were left smoldering, one after the other, in a 60 m³ garage with a limited air exchange. The cigarettes produced particulate-matter (PM) pollution exceeding outdoor limits, as well as PM concentrations up to 10-fold that of an idling engine. (Invernizzi et al., 2004)

Mean concentrations of airborne nicotine measured in workplaces that allow smoking generally range from 2 to 6 mcg/m³ in offices and from 3 to 8 mcg/m³ in restaurants, which compares with mean nicotine concentrations from 1 to 3 mcg/m³ that have been measured in the homes of smokers. (U.S. Department of Health and Human Services, 2006)

Exposure to tobacco smoke for 30 minutes significantly reduces coronary flow velocity reserve in healthy nonsmokers. (Otsuka et al., 2001) Furthermore, genotoxic activity, the ability to damage DNA, has been demonstrated for many components of SHS. (Löfroth, 1989, Claxton et al., 1989)

The lung continues to grow from birth to adulthood and most lung growth is over by age 18, but lung volume continues to expand to 25, suggesting additional growth may occur. (Wang et al., 1993) Exposure of target organs to carcinogens during periods of rapid cell division or childhood is known to increase the risk of cancer and elevated exposure to carcinogens has been associated with higher levels of both DNA-adducts and somatic aberrations in cancer cells and may lead to genetic abnormalities that result in the development into cancer. (Hecht, 1999, Wiencke et al., 1999) If the SHS exposure took place during the critical period of growth, in the earlier part of life (0 to 25 years of age) the risk of lung cancer is greater compared to an exposure occurring after age 25. (Asomaning et al., 2008)

The risk for the development of lung cancer in response to SHS may be influenced by genetics. One study found a significant increase in polymorphisms in the gene glutathione S-transferase M1 (*GSTM1*) among 51 nonsmoking women with exposure to SHS who developed lung cancer compared with 55 nonsmoking women with lung cancer who had no ETS exposure. (Bennett et al., 1999) In another population-based study among never smokers, in those with SHS exposure, *GSTM1* and *GSTP1* polymorphisms were associated with over a 4-fold increased risk of developing lung cancer. (Wenzlaff et al., 2005) *GST* is believed to play a role in detoxifying carcinogens in tobacco smoke; thus, mutations which decrease its activity could serve to promote tumor genesis.

"Third-hand-smoke"

The term "third-hand smoke" was recently coined to identify the residual tobacco smoke contamination that remains after the cigarette is extinguished and secondhand smoke has cleared from the air. It refers to smoke components and their metabolic by-products from contact with surfaces that have absorbed smoke. The smoke leaves a residue of nicotine and other toxic substances in household dust and on surfaces. Although not yet well studied, there is concern that contact with thirdhand smoke will result in absorption of toxins through the skin or ingestion from contamination of the hands. Inhalation of resuspended dust is another potential route for entry into the body. Although direct health effects from thirdhand smoke have not been established, many of the toxins that are deposited on surfaces are group 1 carcinogens, raising concerns about chronic exposure even if it is at low levels. The persistence of these substances in the home environment represents an unappreciated health hazard through dermal exposure, dust inhalation, and ingestion. Discussion of this exposure risk may be a further incentive for families to adopt home non-smoking policies. (Winickoff et al., 2009, Sleiman et al., 2010)

More than 126 million nonsmoking Americans continue to be exposed to secondhand smoke in homes, vehicles, workplaces, and public places. Most exposure to tobacco smoke occurs in homes and workplaces. Almost 60% of U.S. children aged 3-11 years—or almost 22 million children—are exposed to secondhand smoke. (U.S. Department of Health and Human Services, 2006)

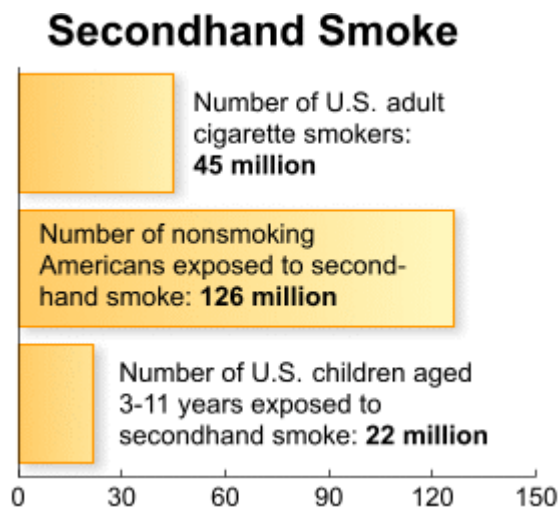


Figure 3 (Figure adapted without permission by Centers for Disease Control and Prevention, 2007)

In 2008, there were more than 161,000 deaths attributed to lung cancer in the U.S. Of these deaths, an estimated 10% to 15% were caused by factors other than first-hand smoking; equivalent to 16,000 to 24,000 deaths annually. Lung cancer in nonsmokers may well be considered one of the most common cancer mortalities in the U.S. Clinical epidemiology of lung cancer has linked the primary factors closely tied to lung cancer in nonsmokers as exposure to second-hand tobacco smoke. (Samet et al., 2009)

Opinion of public health authorities

The link between passive smoking and health risks is accepted by every major medical and scientific organization, including:

- The World Health Organization (World Health Organization International Agency for Research on Cancer, 2004)
- The U.S. National Institutes of Health (U.S. Department of Health and Human Services. Public Health Service, 2005)
- The Centers for Disease Control (Centers for Disease Control and Prevention, 2011)
- The U.S. Surgeon General (U.S. Department of Health and Human Services, 2006)
- The U.S. National Cancer Institute (National Cancer Institute, 2007)
- The U.S. Environmental Protection Agency has classified SHS as a Group A carcinogen, that is, a known human carcinogen (U.S. Environmental Protection Agency, 2010, US Environmental Protection Agency (EPA), 1992)

- The American Lung Association (American Lung Association, 2007) and American Cancer Society (American Cancer Society, 2010)
- The American Medical Association (American Medical Association, 2006)
- The Australian National Health and Medical Research Council (National Public Health Partnership, 2010)
- The U.K. Scientific Committee on Tobacco and Health (U.K. Scientific Committee on Tobacco and Health, 1998)

The governments of 168 nations have signed and currently 170 have ratified the World Health Organization Framework Convention on Tobacco Control, which states that "Parties recognize that scientific evidence has unequivocally established that exposure to tobacco smoke causes death, disease and disability." (World Health Organization, 2003)

On the other hand, there is a minority of epidemiologists who debate the magnitude of the increased risk of passive smoking: "Regular smoking only increases the risk of cardiovascular disease by 75%, so how could second-hand smoke, which is much more dilute, have an effect one-third that size?" The doses of carcinogens received from SHS exposure are far less than with active smoking. Nevertheless, exposure to SHS can begin in childhood and extend across the full lifespan. Household exposure to SHS during childhood and adolescence specifically increases the long-term risk for lung cancer in a dose-response relationship in some studies: In a population based, case-control study, household exposure to 25 or more smoker-years during childhood and adolescence doubled the risk of lung cancer, whereas exposure to fewer than 25 smoker-years did not increase the risk. (Janerich et al., 1990) Moreover, another proposed explanation is that SHS is not simply a diluted version of mainstream smoke, but has a different composition with more toxic substances per gram of total particulate matter (PM). (Novak, 2007) The more toxic makeup of SHS was first recognized in the tobacco industry's own research, though it never published its findings. (Diethelm et al., 2005, Schick and Glantz, 2005, Schick and Glantz, 2006, Schick and Glantz, 2007)

The health benefit to non-smokers of smoking bans has also been disputed by a small number of epidemiologists. They call for a prospective trial to more accurately determine the benefit. These epidemiologists advocate indoor smoking bans, but express a concern that widespread outdoor smoking bans, which are implemented by some towns in the U.S. and Europe, may be unsupported by the evidence available thus far. (Novak, 2007)

Public Opinion

Recent major surveys conducted by the U.S. National Cancer Institute and Centers for Disease Control have found widespread public belief that SHS is harmful. (U.S. Department of Health and Human Services, 2006)

Gallop	Secondhand smoke is harmful	Not harmful at all
1992	80%	
2000		
2001	95% (to children)	
2004	86%	4%
2007	85%	5%

Controversy

In 1986, the U.S. General issued a report concluding that SHS was a cause of disease. In the same year, the International Agency for Research on Cancer and the National Research Council also released reports concluding that SHS was a cause of lung cancer. (U.S. Department of Health and Human Services, 2006) Over the subsequent 20 years, the accumulation of scientific evidence has led to a scientific consensus that passive smoking is indeed harmful to non-smokers. A U.S. District Court found that the industry had internally acknowledged the harmfulness of passive smoking even earlier. (United States District Court for the District of Columbia, 2006) Nonetheless, the tobacco industry has played a central role in generating and sustaining controversy over the effects of passive smoking.

As part of its attempt to prevent or delay tighter regulation of smoking, the tobacco industry funded a number of scientific studies, where the results cast doubt on the risk associated with passive smoking, and sought wide publicity for those results. The industry also funded libertarian think tanks, which criticized both scientific research on passive smoking and policy proposals to restrict smoking.

Enstrom and Kabat

A 2003 study by Enstrom and Kabat, published in the *British Medical Journal*, argued that the harms of passive smoking had been overstated. (Enstrom et al., 2003) Their analysis reported no statistically significant relationship between passive smoking and lung cancer. (Smith, 2003) This paper was widely promoted by the tobacco industry as evidence that the harms of passive smoking were unproven. (Tong and Glantz, 2007) The American Cancer Society (ACS), whose database Enstrom and Kabat used to compile their data criticized the paper as "neither reliable nor independent", stating that scientists at the ACS had repeatedly pointed out serious flaws in Enstrom and Kabat's

methodology prior to publication. (Sampson and Steward, 2003) Notably, the study had failed to identify a comparison group of "unexposed" persons. (Thun, 2003a)

In a 1997 letter to Philip Morris, Enstrom requested a "substantial research commitment... in order for me to effectively compete against the large mountain of epidemiologic data and opinions that already exist regarding the health effects of ETS". (Enstrom, 1997) In a U.S. racketeering lawsuit against tobacco companies, the Enstrom and Kabat paper was cited by the U.S. District Court as "a prime example of how nine tobacco companies engaged in criminal racketeering and fraud to hide the dangers of tobacco smoke". (Dalton, 2007)

World Health Organization

A 1998 report by the International Agency for Research on Cancer on ETS found "weak evidence of a dose-response relationship between risk of lung cancer and exposure to spousal and workplace". (Boffetta et al., 1998)

In March 1998, before the study was published, reports appeared in the media (Macdonald, 1998, Economist, 1998) alleging that International Agency for Research on Cancer and the World Health Organization were suppressing information. In response, the WHO published a study in the Journal of the National Cancer Institute in October of the same year, which summarized:

"When all the evidence, including the important new data reported in this issue of the Journal, is assessed, the inescapable scientific conclusion is that ETS is a low-level lung carcinogen." (Blot and McLaughlin, 1998)

With the release of formerly classified tobacco industry documents, it was found that the controversy over the WHO's alleged suppression of data had been engineered by Philip Morris, British American Tobacco, and other tobacco companies in an effort to discredit scientific findings which would harm their business interests. (Ong and Glantz, 2000) This controversy was generated by the tobacco industry as part of its larger campaign to cut the WHO's budget, distort the results of scientific studies on passive smoking, and discredit the WHO as an institute.

EPA lawsuit

In 1993, the U.S. Environmental Protection Agency (EPA) issued a report estimating that 3,000 lung cancer related deaths in the U.S. were caused by passive smoking annually. (United States Environmental Protection Agency, 1993) Philip Morris and R. J. Reynolds Tobacco Company took legal action, claiming that EPA had manipulated this study and ignores accepted scientific and statistical practices. The U.S. District Court for the Middle District of North Carolina ruled in favor of the tobacco industry in 1998, finding that the EPA had failed to follow proper scientific and epidemiologic practices. In 2002, the EPA successfully appealed this decision to the U.S. Court of Appeals for the Fourth Circuit and the EPA's appeal was upheld on the preliminary grounds that their report had

no regulatory weight and the earlier finding was vacated. (United States Court of Appeals, 2002)

In 1998, the U.S. Department of Health and Human Services, through the publication by its National Toxicology Program of the 9th Report on Carcinogens, listed ETS among the known carcinogens. (U.S. Department of Health and Human Services. Public Health Service, 2005)

Tobacco industry

The tobacco industry's role in funding scientific research on passive smoking has been controversial. (Thun, 2003b) A review of published studies found that tobacco-industry affiliation was strongly correlated with findings exonerating passive smoking researchers affiliated with the tobacco industry were 88 times more likely than independent researchers to conclude that SHS was not harmful. (Barnes and Bero, 1998)

The passive smoking issue poses a serious economic threat to the tobacco industry. It has broadened the definition of smoking beyond a personal habit to something with a social impact. (Smith and Malone, 2007, Trotter and Chapman, 2003, Garne et al., 2005) Citing the tobacco industry's production of biased research and efforts to undermine scientific findings, the 2006 U.S. Surgeon General's report concluded that the industry had "attempted to sustain controversy even as the scientific community reached consensus... industry documents indicate that the tobacco industry has engaged in widespread activities... that have gone beyond the bounds of accepted scientific practice". (U.S. Department of Health and Human Services, 2006)

The positions of major tobacco companies on the issue of passive smoking is somewhat varied. In general, tobacco companies have continued to focus on questioning the methodology of studies showing that passive smoking is harmful. Some (such as British American Tobacco and Philip Morris) acknowledge the medical consensus that passive smoking carries health risks; while others continue to assert that the evidence is inconclusive. Imperial Tobacco describes SHS as "annoying" and "unpleasant", but denies any associated health risks. Several tobacco companies advocate the creation of smoke-free areas within public buildings as an alternative to outright smoking bans.

US racketeering lawsuit

On May 22, 2009, a three-judge panel of the Washington, D.C. U.S. Court of Appeals unanimously upheld that Philip Morris and other tobacco companies had:

- Conspired to minimize, distort and confuse the public about the health hazards of smoking;
- Publicly denied, while internally acknowledging, that SHS is harmful to nonsmokers;

- Undertook joint efforts to undermine and discredit the scientific consensus that SHS causes disease, notably by controlling research findings via paid consultants. (U.S. Department of Justice, 2007, United States Court of Appeals, 2009)

The Court also concluded that tobacco companies continue today to fraudulently deny the health effects of ETS exposure. (O'Reilly and Voris, 2009, Bartz, 2009)

Smoking bans

As a consequence of the health risks associated with passive smoking, smoking bans in indoor public places, including restaurants, cafes and nightclubs have been introduced at national or local level, as well as some outdoor open areas. The countries which have ratified the WHO Framework Convention on Tobacco Control (FCTC) have a legal obligation to implement effective legislation "for protection from exposure to tobacco smoke in indoor workplaces, public transport, indoor public places and, as appropriate, other public places". The parties to the FCTC have further adopted Guidelines on the Protection from Exposure to SHS which state that "effective measures to provide protection from exposure to tobacco smoke ... require the total elimination of smoking and tobacco smoke in a particular space or environment in order to create a 100% smoke free environment". (Framework Convention for Tobacco Control, 2007) Allowing smoking in the house, but with restrictions, does not provide maximum protection. In cross-sectional surveys of households containing smokers and infants or toddlers, urinary cotinine levels were lower among children from households where smoking was not permitted in the house than among those from households using less strict harm-reduction measures. (Blackburn et al., 2003, Spencer et al., 2005) A report by the Institute of Medicine concluded that data consistently demonstrates that SHS exposure increases the risk of coronary heart disease and heart attacks and that smoking bans reduce this risk. (Institute of Medicine of the National Academies, 2009) Nevertheless, there is no evidence that smoking bans increase the risk of lung cancer.

Studies in animals

Multiple studies have been conducted to determine the carcinogenicity of ETS to animals. To stimulate ETS, scientists expose animals to sidestream smoke, which emanates from the cigarette's burning cone and through its paper, or a combination of mainstream and sidestream smoke. The International Agency for Research in Cancer monographs conclude that mice with prolonged exposure to ETS, that is 6hrs a day, 5 days a week, for five months with a subsequent 4 month interval before dissection, have significantly higher incidence and multiplicity of lung tumors than control groups. (World Health Organization International Agency for Research on Cancer, 2004)

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