COMMENTARY

Tobacco and Cancer: Recent Epidemiological Evidence

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During the 1950s, the evidence was clearly sufficient to establish the carcinogenicity of tobacco smoking *(1)*. By the end of the 1950s, convincing evidence linking smoking with lung cancer and other cancers had been obtained from case–control and cohort studies, carcinogens had been identified in tobacco smoke, and cigarette smoke condensate had been shown to cause tumors when painted on the skin of mice. Since then, the numbers of deaths attributable to tobacco smoking have sharply increased, reflecting the heavy smoking patterns of previous decades. It has been estimated that tobacco smoking is currently responsible for approximately 30% of all cancer deaths in developed countries, and that if current smoking patterns persist, an epidemic of cancer attributable to tobacco smoking is expected to occur in developing countries *(2)*. In addition, smoking causes even more deaths from vascular, respiratory, and other diseases than from cancer, so that, in total, tobacco smoking is estimated to account for approximately 4–5 million deaths a year worldwide. This number is projected to increase to approximately 10 million a year by 2030. Thus, if current smoking patterns continue, there will be more than 1 billion deaths attributable to tobacco smoking in the 21st century compared with approximately 100 million deaths in the 20th century *(2)*. The only other causes of disease with such rapidly increasing impact are those associated with human immunodeficiency virus infection and, perhaps, obesity in Western countries *(2)*.

In this commentary, we review the evidence regarding the carcinogenicity of tobacco smoke that has accumulated during the last 16 years since the publication of Monograph 38 of the International Agency for Research on Cancer (IARC) in 1986 *(3)* to the updating of that monograph (Monograph 83) in 2002 *(4)*. The evidence now available shows that tobacco smoke is a multipotent carcinogenic mixture that can cause cancer in many different organs. In addition, exposure to secondhand tobacco smoke (i.e., involuntary or passive smoking by persons who do not smoke) is also carcinogenic for the human lung. This commentary, written by the epidemiologists who participated in the 2002 IARC Working Group for the preparation of the IARC Monograph 83 *(4)*, is based on the substantial body of evidence reviewed for that purpose. It represents, however, solely the views of the authors.

Tobacco Smoke is a Multiple Organ Site Carcinogen

In 1986, the IARC Working Group *(3)* found that there was sufficient evidence that active tobacco smoking was carcinogenic in humans, and concluded that tobacco smoking caused cancers not only of the lung, but also of the lower urinary tract including the renal pelvis and bladder; upper aero-digestive tract including oral cavity, pharynx, larynx, and esophagus; and pancreas. The assessment of the evidence was based on well-established principles for evidence evaluation and an application of criteria of causality. These principles include consideration of lack of any bias or plausible confounding factors that could explain the observed associations, strength of association, dose–response relationships, biologic plausibility, and the consistency of findings across investigations, study designs, and countries. The criteria used by the 2002 IARC Working Group for causality assessment are described in Table 1.

Cancer can be caused by smoking cigarettes, pipes, cigars, or bidis (which consist of a small amount of tobacco wrapped in the leaf of another plant, and are commonly used in South Asia). Since 1986, further evidence has been published that showed that smoking tobacco can also cause cancer of the nasal cavity, paranasal sinuses, and nasopharynx; stomach; liver; kidney; cervix uteri; and adenocarcinoma of the esophagus and myeloid leukemia. We consider the currently available evidence equivocal for cancer of the large bowel. The evidence was found to weigh against causality for cancer of the breast, in agreement with a recent meta-analysis *(5)*, and for cancer of the prostate *(6,7)*. For both breast and prostate the average relative risk is approximately 1.0, the positive studies do not outweigh the negative studies in overall quality, and biologic plausibility is

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Table 1. Criteria of the IARC monographs for the evaluation of the evidence relevant to carcinogenicity from studies in humans*

Evidence of carcinogenicity	Definition
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
Limited	A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
Inadequate	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.
Evidence suggesting lack of carcinogenicity	There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

*More detailed information regarding the IARC monographs can be found at the website http://monographs.iarc.fr/monoeval/preamble.html.

weak. We found that the evidence suggested an inverse relationship of tobacco smoking with endometrial cancer *(8)*.

In this commentary, we briefly review the evidence that underlies the conclusions of the 2002 IARC Working Group, and summarize the numbers of studies available and the order of magnitude of relative risks for each site with sufficient evidence of carcinogenicity (Table 2). The following site-specific sections are for those sites for which we now believe there to be sufficient evidence, since the 1986 monograph *(3)*, to conclude that smoking is a cause of cancer. (Note: although much of the evidence is based on cigarette smoking, many of the papers also contained information on other forms of tobacco smoking. Consequently, we use the generic term "tobacco" to include all forms of smoking. In addition, the term "non-smokers" as used by the authors, usually means the more appropriate term "never smokers.")

Cancers of Nasal Cavity, Paranasal Sinuses, and Nasopharynx

The 1986 IARC Working Group evaluation specifically included oro- and hypopharynx as cancer sites causally associated with tobacco smoking, but did not include cancer of the nasopharynx. As members of the 2002 IARC Working Group, we found that an increased risk of sinonasal cancer and nasopharynx cancer among cigarette smokers has been consistently reported in several case–control studies, with a positive dose–response trend associated with the amount and duration of smoking *(9,10)*. When histologic data were available, the relative risk was increased more clearly for squamous-cell carcinoma of the nasal sinuses than for adenocarcinoma *(9,11)*.

Table 2. Cancer sites for which there is "sufficient" evidence of carcinogenicity of tobacco smoking according to the International Agency for Research on Cancer Working Group*

Cancer site	No. of studies evaluated		Avg relative risk
	Case–control	Cohort	
Lung	>100	37	15.0–30.0
Urinary tract	50	24	3.0
Upper aero-digestive tract:			
Oral cavity	16	3	4.0–5.0
Oro-and hypopharynx	12	3†	4.0–5.0‡
Oesophagus (SCC or NOS)	35	19§	2.0–5.0
Larynx	25	5	10.0‡
Esophagus (adenocarcinoma)	10	NA	1.5–2.5
Pancreas	38	27	2.0–4.0
Nasal cavity, paranasal sinuses	9	1	1.5–2.5
Nasopharynx	19	2	1.5–2.5
Stomach	44	27	1.5–2.0
Liver	29	29	1.5–2.5
Kidney	13	8	1.5–2.0
Uterine cervix	49	14‖	1.5–2.5
Myeloid leukemia	Not reviewed	12	1.5–2.0

*SCC = squamous cell carcinoma; NOS = not otherwise specified; CIS = carcinoma *in situ;* CIN = cervical intraepithelial neoplasia; NA = not available.

†Also considers studies on pharynx in general, which may include nasopharynx.

‡Wide range of relative risks after adjustment for alcohol use.

§Cancer of the esophagus, regardless of histologic type.

‖Includes studies on CIS and CIN.

Stomach Cancer

We considered the many cohort and case–control studies that have examined the relationship between tobacco smoking and stomach cancer. The risk of stomach cancer is 50%–60% higher, on average, in smokers than in non-smokers (relative risk [RR] = 1.5–1.6), and in several studies more than 100% higher (relative risks greater than 2) in current smokers than in never smokers. The associations are generally consistent among both cohort and case–control studies, demonstrating positive dose–response relationships with the number of cigarettes smoked and the duration of smoking *(12–14)*. Current smoking is associated with increased risks of both cardia and non-cardia stomach cancer.

Studies that have stratified the observations by intake of alcoholic beverages or by chronic *Helicobacter pylori* infection of the stomach (two potential confounders) have found an independent association with tobacco smoking, although the absolute risk tended to be higher among smokers who were *H. pylori* seropositive than among smokers who were *H. pylori* seronegative. Worldwide it has been estimated that the proportion of stomach cancer attributable to smoking is 11% among men and 4% among women in developing countries, and 17% among men and 11% among women in developed countries *(15)*.

Liver Cancer

We found that an association between tobacco smoking and an increased risk of liver cancer is consistently seen in nearly all cohort studies and in most case–control studies, particularly the largest ones from Asia *(16,17)*, the United States *(18)*, and Greece *(19)*, with relative risks ranging from 1.5 to 2.5.

Heavy (e.g., approximately more than six glasses of alcohol per day), although not moderate, intake of alcoholic beverages is an important risk factor for liver cancer *(20)*, and one that could confound the association with tobacco smoking because smokers tend to drink more than non-smokers. However, there are now a large number of studies that have adequately controlled for this potential confounder, and consequently have excluded alcohol as an explanation for the association between smoking and liver cancer. Compared with individuals who do not drink or smoke, individuals who do not drink but do smoke have an increased risk of liver cancer *(19,21,22)*. Additional supportive evidence is provided by the association between smoking and liver cancer observed among Chinese *(16)* and Japanese *(23)* women, in whom heavy alcohol drinking is extremely rare.

Hepatitis B virus (HBV) infection causes the majority of liver cancers worldwide, although hepatitis C virus (HCV) infection accounts for a large fraction of the disease in Japan, north Africa, and southern Europe *(24)*. To distinguish the strong effect of HBV and HCV [relative risk of approximately 20 *(24)*] from the association with smoking, stratification and/or adjustment for hepatitis B surface antigen and anti-HCV antibodies have been made in several studies *(18,19,25)*. The association between smoking and liver cancer was not generally weakened by adjustments for HBV and HCV infection. With respect to the possible action of tobacco smoking on liver carcinogenesis, smokers do not seem to have an increased risk of chronic infection with hepatitis viruses *(26)*, but they may have a greater risk of progression from chronic HBV and HCV infection to liver cancer *(18,27)* than non-smokers.

Kidney Cancer

The 1986 IARC report *(3)* classified transitional carcinoma of the renal pelvis among the cancers that could be caused by smoking, but not adenocarcinoma of the renal parenchyma. In the 2002 IARC Working Group, we found that many case–control and cohort studies evaluating the association between tobacco smoking and adenocarcinoma of the renal parenchyma have been published subsequently and have shown consistently a risk of the disease in heavy smokers (i.e., of more than 20 cigarettes/day) of 1.5–2.0 times that observed in never smokers *(28,29)*. This association cannot be explained by confounding by body mass index or hypertension, both of which are known risk factors for adenocarcinoma of the renal parenchyma. Indeed, the opposite is true for body mass index, which is positively associated with an increased risk of this form of cancer and negatively associated with smoking.

Cancer of the Uterine Cervix

Cancer of the uterine cervix has been consistently associated with cigarette smoking in many studies but the association has not previously been classified as causal because potential confounding by sexual activity and related exposure to sexually transmitted viruses could not be excluded as an alternative explanation. Several cohort studies and many case–control studies provide information about the association of cigarette smoking with the incidence of invasive squamous-cell cervical cancer, and many cohort and case–control studies evaluated the association of tobacco exposures with preinvasive neoplasms such as cervical intraepithelial neoplasia and cancer *in situ*. Most studies in which risk estimates were not adjusted for infection with specific types of human papillomavirus (HPV) reported a relative risk of approximately 2.0, i.e., a doubling of the risk among smokers compared with never smokers. Women who smoked a large number of cigarettes or who smoked for a long duration generally had the highest risk of cervical cancer. Proper consideration of the presence of HPV infection is extremely important when evaluating the association between tobacco smoke exposure and invasive cervical cancer because it is widely recognized that persistent HPV infection is the main (and perhaps a necessary) etiologic factor for invasive and preinvasive cervical cancer worldwide. High-risk types of HPV, i.e., those types of HPV associated with oncogenic transformation, have been identified in 99% of invasive cervical cancer tissue specimens *(30)* and are associated with 100-fold increased risk of invasive cervical cancer relative to women without HPV infection *(31)*.

Earlier studies controlled for HPV infection by adjustment in the data analysis, whereas more recent studies controlled for HPV infection by restricting analyses to HPV-positive case and control subjects. This method is preferable when dealing with a risk factor that may modify the effect of smoking. In the IARC multicenter pooled analysis of invasive cervical cancer, Plummer et al. *(32)* examined smoking as a co-factor with human papillomavirus infection by restricting the analysis to HPV DNA–positive study participants. This restriction did not substantially alter the relationship between smoking and risk. The relative risk was 2.17 (95% confidence interval [CI] = 1.46 to 3.22) for HPV-positive case subjects compared with HPV-positive control subjects. The association between smoking and cervical cancer was also not notably reduced after adjusting for a woman's reported number of lifetime sexual partners, age at first intercourse, or other potential confounding factors. Furthermore, in cross-sectional studies, HPV cervical infection has not been found to be associated consistently with smoking *(33)*. Thus, we conclude that HPV infection cannot explain the association between cervical cancer and smoking, that the effect of smoking was unlikely to represent only a surrogate marker of a woman's sexual behavior, and that the association of tobacco smoke with invasive squamous cell cervical cancer therefore indicates a causal relationship.

Myeloid Leukemia

Tobacco smoke contains one established leukemogen (i.e., a chemical able to induce leukemia in humans), benzene. Smokers have much higher levels of benzene in their blood than non-smokers. Six of eight cohort studies with men, or men and women combined, showed greater than expected risks (average relative risk = 1.6) for myeloid leukemia among current cigarette smokers and also a positive dose–response relationship between the risk of myeloid leukemia and the number of cigarettes smoked *(34–36)*. According to Korte et al. *(37)*, linear extrapolation from the known effects of high doses of benzene suggests that benzene in cigarettes is responsible for about one-third of smoking-induced acute myeloid leukemia. We concluded that there is sufficient evidence that smoking causes myeloid leukemia, but that there is no association between smoking and the risk of lymphatic leukemia.

Cancer of the Large Bowel

Less than half of the studies that have examined the relationship between smoking and cancer of the large bowel have recorded a statistically significant increased risk of the disease among smokers. The increased risk is, however, generally less than twofold. We are uncertain whether this reflects causality or confounding with alcohol, low physical activity, high intake of dietary fat, low intake of vegetables, or other factors that are associated with an increased risk of this disease.

Other Forms of Tobacco

Most of the studies reporting information on forms of tobacco other than cigarettes have been published during the last 16 years. Although the number of lung cancer cases is usually sufficiently large to assess causality, we found that for other sites the numbers are generally too small to establish a cause–effect relationship with other forms of tobacco, with the exception of the sites mentioned below.

Bidi Smoking

Bidi smoking is the most common form of tobacco smoking in India and is predominantly a habit of men. Although bidis are smaller than cigarettes and contain much less tobacco, they deliver higher amounts of nicotine per gram of tobacco and comparable or greater amounts of tar *(38)*. On the basis of case–control studies, we found that bidi smoking can cause cancers of respiratory and digestive sites, including mouth, oropharynx, larynx, lung, esophagus, and stomach *(39–44)*. In almost all studies a dose–response relationship was found. In the studies that collected covariate information, the risk was persistently increased after adjustment for cigarette smoking or tobacco chewing, diet, alcohol use, and education level.

Cigar and Pipe Smoking

We found that cigar and/or pipe smoking is strongly and causally related to cancers of the oral cavity, oropharynx, hypopharynx, larynx, esophagus, and lung *(45–47)*. The magnitude of risk is similar to that from cigarette smoking. A clear dose–response relationship has been found with the amount of tobacco smoked, and for upper aero-digestive tract cancers, a synergistic interaction between alcohol and cigar/pipe use has been shown.

Mechanistic Supportive Evidence

The causal nature of the associations reported above, and of those already recognized as causal in the 1986 IARC Monograph *(3)*, is supported by mechanistic evidence. Developments in biochemistry and molecular biology have allowed researchers to measure metabolites of tobacco smoke in different body fluids and organs, to measure carcinogen–protein and carcinogen–DNA adducts, and to identify genetic damage (mutations or chromosome aberrations) related to smoking. These investigations have confirmed the multistage nature of tobacco carcinogenesis, which is already suggested by epidemiologic evidence.

Lung Cancer

For lung cancer, at least two lines of mechanistic evidence complement the epidemiologic findings. First, polycyclic aromatic hydrocarbons (PAH), carcinogenic compounds present in tobacco smoke, induce mutations in the p53 gene, which is crucial for cell cycle dysregulation and carcinogenesis. G to T transversions within the p53 gene have been linked to a molecular signature of tobacco mutagens in smoking-associated lung cancers for the following reasons: 1) PAHs are a major class of carcinogens in tobacco smoke that produce predominantly G to T transversions; 2) PAH adducts are present in DNA extracted from human tissues exposed to tobacco smoke; 3) the frequency of G to T transversions in lung cancers from smokers is increased relative to the frequency in lung cancers from non-smokers; 4) a nontranscribed strand bias of G to T transversions can be attributed to the preferential repair of adducts on the transcribed strand *(48)*. Second, the N-nitroso compounds are another major group of chemicals found in tobacco smoke, several of which are potent animal carcinogens. N-nitroso compounds are found in the urine of smokers. In particular, compounds known as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL-Gluc are very useful biomarkers because they are derived from the carcinogen 4-(methylnitros amino)-1-(3-pyridyl)-1-butanone (NNK), which is specific to tobacco products *(49)*. Cotinine is probably the best marker of exposure to tobacco smoke, but it is not directly relevant to carcinogenesis.

Other Cancers

The mechanistic evidence related to tobacco smoking and bladder carcinogenesis has focused on arylamines, in particular the potent carcinogen 4-aminobiphenyl, which is present in tobacco smoke. 4-Aminobiphenyl has been shown to form DNA-adducts in exfoliated bladder cells and bladder biopsy specimens from smokers *(50, 51)*. Hemoglobin adducts formed by 4-aminobiphenyl are markedly increased in smokers, particularly in smokers of black tobacco. Indeed, smokers of black tobacco have more than a twofold risk of bladder cancer than smokers of blonde tobacco *(52)*.

Evidence from studies evaluating smoking-associated DNA adduct formation also provides some support for the epidemiologic observations related to tobacco smoking and cancer of the uterine cervix. Benzo[a]pyrene metabolites have been found in the cervical mucus and as DNA adducts in cervical tissues of smokers *(53)*.

Cytogenetic damage in cells from patients with myeloid leukemia has been consistent with the effects of benzene contained in cigarette smoke. Lebailly et al. *(54)* identified six cytogenetic groups among 472 patients with acute myeloid leukemia and found that smokers had increased odds ratios for 8:21 chromosome translocations (ever smokers, OR = 4.77, 95% CI = 1.77 to 12.85; current smokers, OR = 7.07, 95% CI = 2.64 to 18.95) compared with non-smokers, compatible with an effect of benzene. The same translocations have been found, in fact, among workers exposed to benzene.

The high level of coherence between the results of mechanistic and epidemiologic studies adds strength to the causal interpretation of the associations between tobacco smoking and carcinogenesis repeatedly observed in the large body of epidemiologic evidence.

Involuntary Smoking

Non-smokers who breathe other people's smoke (i.e., involuntary smoking) inhale the same carcinogens as active smokers, though at much lower doses *(4)*. Because smoking is an established cause of lung cancer in smokers, it follows that there must also be some risk of lung cancer to lifelong non-smokers exposed to involuntary smoking *(3)*. There is also likely to be some additional risk deriving from involuntary smoking to individuals who are now non-smokers but who used to be smokers, compared with ex-smokers not exposed to involuntary smoking.

Most of the more than 50 studies evaluating involuntary smoking (or environmental tobacco smoke) and risk of lung cancer in never smokers compared risks for spouses of smokers with risks for spouses of non-smokers. These studies have been carried out in many countries and, in general, indicate an increased risk, especially for persons with high exposure (Table 3). To evaluate the information collectively, in particular from those studies with a limited number of case subjects, meta-analyses *(55)* have been conducted in which the relative risk estimates from the individual studies were pooled. Non-smokers have a statistically significant greater risk of lung cancer if their spouses are smokers than if their spouses are non-smokers. The increase in risk remains after controlling for bias and potential confounding *(55)*. From an updated meta-analysis in the IARC Monograph *(4)*, the risk is approximately 25% greater than expected for women (based on data from 46 studies that included 6257 lung cancer case subjects) and 35% greater than expected for men (based on data from 11 studies that included 442 lung cancer case subjects). In addition, there are several studies that evaluated the risk of lung cancer among non-smokers exposed to involuntary smoking at the workplace. An updated meta-analysis in the IARC Monograph *(4)* based on 19 studies of women who did not smoke (including 3588 lung cancer case subjects) shows that the risk of lung cancer was approximately 20% greater than expected.

Table 3. Relative risk (RR) of lung cancer among women who did not smoke but who have the highest exposure to involuntary smoking from a spouse who smoked compared with women who did not smoke and who had spouses that did not smoke*

Reference	Exposure	RR† (95% CI)
No. of cigarettes per day smoked by the spouse		
Garfinkel (1981) *(57)*	≥20	1.1 (0.8 to 1.6)
Kabat et al. (1995) *(58)*	>10	1.1 (0.5 to 2.3)
Humble et al. (1987) *(59)*	≥21	1.2 (0.3 to 5.2)
Koo et al. (1987) *(60)*	≥21	1.2 (0.5 to 3.0)
Boffetta et al. (1998) *(61)*	>18	1.3 (0.8 to 2.2)
Wang et al. (1996) *(62)*	≥20	1.4 (0.8 to 2.6)
Zhong et al. (1999) *(63)*	>20	1.4 (0.7 to 2.6)
Jee et al. (1999) *(64)*	≥20	1.5 (0.7 to 3.3)
Du et al. (1993) *(65)*	>20	1.6‡ (0.8 to 3.2)
Kalandidi et al. (1990) *(66)*	≥41	1.6 (0.5 to 4.6)
Hirayama (1984) *(67)*	≥20	1.7 (1.1 to 2.7)
Cardenas et al. (1997) *(68)*	≥40	1.9 (1.0 to 3.6)
Trichopoulos et al. (1983) *(69)*	≥31	1.9 (0.7 to 5.0)
Akiba et al. (1986) *(70)*	≥30	2.1 (1.7 to 2.6)
Garfinkel et al. (1985) *(71)*	≥20	2.1 (1.1 to 4.0)
Lam et al. (1987) *(17)*	≥21	2.1 (1.1 to 4.0)
Geng et al. (1988) *(72)*	≥20	2.8 (1.9 to 4.1)
Liu et al. (1993) *(73)*	≥20	2.9 (1.2 to 7.3)
Pershagen et al. (1987) *(74)*	≥16§	3.2 (1.0 to 9.5)
Inoue and Hirayama (1988) *(75)*	≥20	3.4 (1.2 to 9.7)
No. of years of marriage to a smoker		
Buffler et al. (1984) *(76)*	≥33	0.9 (0.4 to 2.3)
Sun et al. (1996) *(77)*	≥35	0.9 (0.5 to 1.7)
Boffetta et al. (1998) *(61)*	≥43	1.0 (0.7 to 1.7)
Cardenas et al. (1997) *(68)*	≥30	1.1 (0.6 to 2.1)
Wang et al. (1996) *(62)*	≥41	1.1 (0.4 to 3.1)
Zhong et al. (1999) *(63)*	≥36	1.1 (0.7 to 1.8)
Du et al. (1993) *(65)*	≥30	1.2 (0.6 to 2.3)
Fontham et al. (1994) *(78)*	≥31	1.2 (0.9 to 1.7)
Akiba et al. (1986) *(70)*	≥40	1.3 (0.6 to 2.8)
Zaridze et al. (1998) *(79)*	>15	1.4 (1.0 to 2.1)
Gao et al. (1987) *(80)*	≥40	1.7 (1.0 to 2.9)
Kalandidi et al. (1990) *(66)*	≥40	1.9 (0.8 to 4.3)
Wu et al. (1985) *(81)*	≥31‖	2.0 Not available
Humble et al. (1987) *(59)*	≥27	2.1 (0.7 to 6.9)
Choi et al. (1989) *(82)*	≥41	2.3 (1.0 to 5.6)
Stockwell et al. (1992) *(83)*	≥40	2.4 (1.1 to 5.3)
Jee et al. (1999) *(64)*	≥30	3.1 (1.4 to 6.6)
Geng et al. (1988) *(72)*	≥40	3.3 (2.1 to 5.2)

*The relative risks are ranked from lowest to highest within each measure of exposure.

†Rate ratios for cohort studies and odds ratios for case–control studies.

‡Results are from an analysis using non-tumor controls.

§For ≥30 years of marriage.

‖Years of exposure for adults (partner and workplace).

The studies that report an association between lung cancer and high levels of exposure to involuntary smoking are listed in Table 3. Of the 20 studies that reported results on the number of cigarettes smoked by the spouse, none had a relative risk lower than 1.0, and seven studies reported relative risks greater than 2.0. A similar pattern of relative risks was observed when the number of years of marriage was used as the exposure variable (Table 3). Both case–control and cohort studies report positive findings for the association with lung cancer. Publication bias, i.e., the more frequent publication of positive findings than of negative findings, is not a sufficient explanation *(55)* because approximately 300 unpublished negative studies would be needed to explain the overall relative risk in the published studies, a wholly implausible assumption. Moreover, a meta-analysis *(55)* that considers several different sources of bias (particularly misclassification of exposure), finds that the results are stable and cannot be explained by bias.

The biologic plausibility of the association between the risk of lung cancer and involuntary smoking is supported by the fact that the urine of non-smokers exposed to involuntary smoking contains concentrations of carcinogenic N-nitroso compounds specific to tobacco that are 1% to 5% of the concentrations found in the urine of active smokers, i.e., approximately proportional to the increased risk found in epidemiologic studies of involuntary smoking *(49)*.

Conclusions

Considerable epidemiologic evidence of the carcinogenicity of tobacco smoke has become available since the review by IARC in 1986 *(3)*. This new evidence along with the earlier findings led us as members of the 2002 IARC Working Group to conclude that tobacco is a potent multisite carcinogen with a substantial 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, and uterine cervix, and causing myeloid leukemia. Both cigarette smoking and smoking other forms of tobacco, including bidi, pipe, and cigars, can cause cancers in multiple organs. There is high coherence for causality between the epidemiologic evidence and the mechanistic or biologic evidence involving measurements of carcinogenic metabolites of tobacco compounds, the formation

of DNA or protein adducts, and the spectrum of gene mutations in cancers developed by smokers.

The worldwide consequences of tobacco smoking are dramatic and are likely to worsen in the near future. Tobacco smoking is currently responsible for approximately 30% of cancer deaths in developed countries, and for an increasing proportion of the cancer deaths in developing countries. Furthermore, smoking causes more deaths from vascular, respiratory, and other diseases than it does from cancer. Of all lifetime users of tobacco, half will die because of their habit, and half of these individuals will die in middle age. If current smoking patterns persist, then in the 21st century there will be more than 1 billion deaths attributed to smoking.

Measures that substantially prevent young individuals from starting smoking could avoid much of the future disease burden. Although 1 billion people worldwide already smoke and more will start, individuals who stop smoking reduce their smoking-related cancer risks effectively. A balanced public health strategy is therefore needed that not only prevents young individuals from starting to smoke, but also helps adults stop smoking. Although the beneficial effects of smoking cessation were first observed for lung cancer, evidence is now available that smoking cessation has similar effects of reducing risk for the other main tobacco-related cancers and for the main non-neoplastic diseases caused by smoking. Much evidence has been accumulated in the last 16 years. For example, Fig. 1 shows that continued smoking is associated with an exponential increase of the cumulative lung cancer mortality with age *(56)*. Compared with smokers who continue to smoke, the increase in lung cancer mortality is lower for individuals who quit smoking by age 50 years and even lower for individuals who quit smoking by age 30 years. Never smokers have the lowest cumulative lung cancer mortality. Among ever smokers, the estimated cumulative risks of death from lung cancer by age 75 years are 16% for men who continue to smoke cigarettes, 6% for men who stop smoking by age 50 years, and 2% for men who stop smoking by age 30 years. The pattern is similar among women. In other words, the earlier an individual stops smoking, the lower the risk of lung cancer. The extent to which young people become cigarette smokers over the next few decades will strongly affect mortality in the middle and second half of the 21st century. Mortality in the first half of the century, however, will chiefly be affected by the number of current smokers who stop.

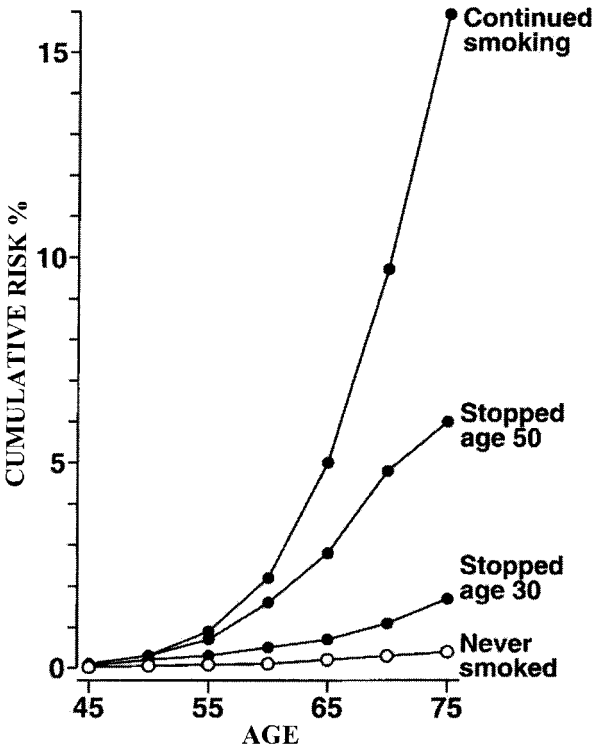

Fig. 1. Cumulative risk of lung cancer mortality among men in the United Kingdom who smoke, according to the age when they stopped smoking. [Figure adapted from the original by permission of the *British Medical Journal (56)*].

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NOTES

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