Chapter 5
Reproductive and Developmental Effects from Exposure to Secondhand Smoke

Introduction

This chapter concerns adverse effects on reproduction, infants, and child development from exposure to secondhand smoke. Previous Surgeon General's reports have not comprehensively addressed the relationship between secondhand smoke exposure and reproductive outcomes, infant mortality, or child development. The 2001 Surgeon General's report (*Women and Smoking*) did summarize the literature on developmental and reproductive outcomes in relation to secondhand smoke exposure, focusing on the specific outcomes of fertility and fecundity, fetal growth and birth weight, fetal loss and neonatal mortality, and congenital malformations (U.S. Department of Health and Human Services [USDHHS] 2001). The effects of active smoking by the mother during pregnancy were comprehensively reviewed in the 2004 report (USDHHS 2004). This new report reviews the possible effects of secondhand smoke exposure on reproductive and developmental outcomes, incorporates the substantial amount of evidence that has emerged since the 1986 Surgeon General's report (*The Health Consequences of Involuntary Smoking*, USDHHS 1986), and expands upon the 2001 report.

Conclusions of Previous Surgeon General's Reports and Other Relevant Reports

The early literature on secondhand smoke exposure and child health focused on adverse respiratory effects. Initial relevant reports were first published in the 1960s (Cameron et al. 1969), followed by larger studies in the 1970s (Colley 1974; Colley et al. 1974). The first summary report to comprehensively address reproductive and perinatal effects of secondhand smoke exposure was prepared by the California Environmental Protection Agency and released in 1997 (National Cancer Institute [NCI] 1999). These topics were also addressed by a number of other agencies and groups, including the United Kingdom Department of Health (1998), the World Health Organization (WHO 1999), and the University of Toronto (2001). Table 5.1 summarizes the conclusions for reproductive and perinatal outcomes from these reports.

Literature Search Methods

The authors identified most of the literature on secondhand smoke exposure and adverse reproductive and perinatal effects through a systematic search of the National Library of Medicine's indexed journals, which date back to 1966. The relevant Medical Subject Headings (MeSH) terms and text terms were used to search PubMed. Text terms were used because many of the relevant MeSH terms were not introduced into the PubMed key wording scheme until some time after 1966. For example, the MeSH term "Tobacco Smoke Pollution" was not introduced until 1982. The following text terms were also used in the search for articles: environmental, tobacco, smoke, secondhand smoke, paternal smoking, and passive smoking. By combining these text terms and MeSH terms using "or" as the Boolean connector, nearly 4,500 citations were identified. The authors also used this strategy to identify relevant research on outcomes. The results

Table 5.1 Findings on secondhand smoke exposure and reproductive and perinatal effects

Report	Outcome	Conclusion
Report of the Scientific Committee on Tobacco and Health (United Kingdom Department of Health 1998)	Sudden infant death syndrome	"Sudden infant death syndrome. . .is associated with exposure to environmental tobacco smoke. The association is judged to be one of cause and effect." (p. 10)
Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency (National Cancer Institute 1999)	Low birth weight/small for gestational age	"Taken together. . .[the studies] support a slight increase in LBW [low birth weight] or IUGR [intrauterine growth retardation] in association with ETS [environmental tobacco smoke, equivalent to secondhand smoke] exposure." (p. 102)
	Preterm delivery	"There was little evidence found for an association with preterm birth." (p. 102)
	Spontaneous abortion	". . .there is some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion. . . ." (p. 113)
	Congenital malformations	". . .it is not possible at this time to determine whether there is an association of ETS exposure with birth defects." (p. 119)
	Sudden infant death syndrome (SIDS)	There is "sufficient evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS." (p. 139)
	Childhood cognition and behavior	"The evidence that ETS exposure of a nonsmoking pregnant woman can result in neuropsychologic deficits in the child. . .is inconclusive." (p. 154)
		"No conclusions regarding causality can be made on the basis of these studies, but they do provide suggestive evidence that [postnatal] ETS exposure may pose a neuropsychological developmental hazard." (p. 155)
	Postnatal physical development	". . .there is little to no epidemiological evidence that ETS exposure has a significant effect on height growth of children." (p. 162)
	Female fertility and fecundability	". . .the data are inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability." (p. 178)
	Other female reproductive effects	". . .there is a paucity of data on the association of ETS exposure and lowered age at menopause or other measures of menstrual cycle dysfunction, and conclusions regarding causal associations cannot be reached." (p. 179)
	Male reproductive toxicity	". . .due to the paucity of data it is not possible to determine whether there is a causal association between ETS exposure and male reproductive dysfunction." (p. 180)
	Childhood cancers	". . .the evidence for a role of parental smoking and childhood cancers is inconclusive." (p. 282)

Table 5.1 Continued

Report	Outcome	Conclusion
International Consultation on Environmental Tobacco Smoke (ETS) and Child Health: Consultation Report (World Health Organization 1999)	Low birth weight	"ETS exposure among nonsmoking pregnant women can cause a decrease in birth weight…" (p. 4)
	SIDS	". . .infant exposure to ETS may contribute to the risk of SIDS." (p. 4)
	Neurodevelopment	". . .the effects of prenatal and postnatal ETS exposure on cognition and behaviour remain unclear." (p. 9)
	Childhood cancer	". . .there is suggestive evidence linking exposure to tobacco smoke and childhood cancer." (p. 10)
Women and Smoking: A Report of the Surgeon General (U.S. Department of Health and Human Services 2001)	Low birth weight/small for gestational age	". . .maternal exposure to ETS appears to be causally associated with detrimental effects on fetal growth." (p. 364)
	Fertility, spontaneous abortion, perinatal mortality	"Studies of ETS exposure and the risks for delay in conception, spontaneous abortion, and perinatal mortality are few, and the results are inconsistent." (p. 372)
Protection from Second-Hand Tobacco Smoke in Ontario: A Review of the Evidence Regarding Best Practices (University of Toronto 2001)	SIDS	"Exposure to second-hand smoke causes the following diseases and conditions. . . Sudden infant death syndrome. . ." (p. v)
	Low birth weight/ small for gestational age	"Exposure to second-hand smoke causes the following diseases and conditions… Fetal growth impairment including low birth-weight and small for gestational age. . ." (pp. v–vi)
	Spontaneous abortion	"Exposure to second-hand smoke has also been linked to other adverse health effects. The relationships may be causal. These include. . . Miscarriages. . ." (p. vi)

of each outcome-relevant search were then combined with the secondhand smoke-relevant search using "and" as the Boolean connector. These citations were imported into a database. Using title and abstract information, the authors selected the relevant articles for review. Finally, the references in the articles were reviewed for additional citations that were not identified through the PubMed searches.

Critical Exposure Periods for Reproductive and Developmental Effects

Assessing exposures to secondhand smoke in studies of fertility, fetal development, infant development, and child health and development is complex. For each of the three biologically relevant periods—preconception, pregnancy, and postdelivery—a number of potentially different biologic mechanisms of injury exist from exposure to secondhand smoke. Even within the nine months of pregnancy, vulnerability to the effects of secondhand smoke may change, reflecting differing mechanisms of injury as fetal

organs develop and the fetus grows. Moreover, there are multiple environments where the woman or child is exposed to secondhand smoke (e.g., workplace, home, and day care), as well as multiple sources of secondhand smoke exposure for each of these environments (e.g., household members, day care providers, and coworkers). Finally, because of the potential impact of active maternal smoking (USDHHS 2004), active smoking before and during pregnancy needs to be taken into account when assessing the potential independent effects of exposure to secondhand smoke. Maternal smoking has well-characterized adverse effects for several outcomes, such as fertility, sudden infant death syndrome (SIDS), and child growth and development. Thus, the effects of exposure to secondhand smoke may be confounded by those of maternal smoking.

Secondhand smoke exposure may have adverse effects potentially throughout the reproductive and developmental processes (Table 5.2). During the preconception period, maternal exposure to secondhand smoke can potentially affect female fertility by altering the balance of hormones that affect oocyte production, including growth hormone, cortisol, luteinizing hormones, and prolactin (Mattison 1982; Daling et al. 1987; Mattison and Thomford 1987), or by reducing motility in the female reproductive tract (Mattison 1982; Daling et al. 1987). However, separating the potential effect of secondhand smoke exposure on the mother's reproductive process and the effect of active paternal smoking on the father's reproductive process is very difficult. Although the evidence is mixed, active smoking has been shown to affect sperm morphology, motility, and concentration (Rosenberg 1987; USDHHS 2004). Cigarette smoke may also lead to infertility through a combined effect of decreased sperm motility with active paternal smoking and decreased tubal patency with active maternal smoking and secondhand smoke exposure.

During pregnancy, maternal exposure to secondhand smoke could potentially affect the pregnancy by increasing the risk for spontaneous abortion or by interfering with the developing fetus through growth restrictions or congenital malformations (NCI 1999; WHO 1999). During gestation, windows of susceptibility exist when the developing embryo or fetus is vulnerable to various intrauterine conditions or exposures. Organogenesis occurs mainly during the embryonic period (weeks three through eight of gestation), which is also the time when major malformations are most likely to develop. During weeks 9 through 38 of gestation, susceptibility decreases and insults are more likely to lead to minor malformations or functional defects (Sadler 1990).

Finally, secondhand smoke exposure in the postpartum period could affect the developing infant and child, resulting in a number of adverse health outcomes. Given the developmental processes in progress, infants and children are considered to be more vulnerable to the effects of environmental exposures than are adults (Goldman 1995; Dempsey et al. 2000). Mechanisms that could lead to compromised physical and cognitive development as a result of exposure to secondhand smoke may be similar to the processes that affect fetal development, such as hypoxia (USDHHS 1990; Lambers and Clark 1996). One review of the impact of prenatal exposure to nicotine summarized numerous animal studies that demonstrated the effects of nicotine on cognitive processes among exposed rats and guinea pigs, such as impeded learning abilities or increased attention or memory deficits (Ernst et al. 2001). In animal and human studies, prenatal nicotine exposure affected aspects of neural functioning such as the activation of neurotransmitter systems, which may lead to permanent alterations in the developing brain through changes in gene expression. The proposed consequences of altered gene expression included disturbances in neuronal pathfinding and in cell regulation and differentiation (Ernst et al. 2001). Other animal studies have shown that newborn rats exposed to sidestream smoke have reduced DNA and protein concentrations in the brain (Gospe et al. 1996). Ideally, researchers should have information on secondhand smoke exposures for all relevant periods that relate to the outcome under study, because different physiologic processes may be affected across developmental periods (Table 5.2). However, this information is frequently unavailable in a particular study.

Secondhand smoke exposures most commonly occur in the home or workplace, and exposures in public places tend to be more sporadic. Recent exposure assessment and monitoring studies have shown that the home tends to be a greater source of secondhand smoke exposure than the workplace (Emmons et al. 1994; Pirkle et al. 1996; Hammond 1999), particularly since workplace smoking bans have become more restrictive (Marcus et al. 1992) (Chapter 3, Assessment of Exposure to Secondhand Smoke, and Chapter 4, Prevalence of Exposure to Secondhand Smoke). In the home, the major sources of exposures to secondhand smoke have been smoking by the spouse or partner and other household members. Paternal smoking has been the most commonly

Table 5.2 Potentially relevant exposure periods for reproductive and perinatal outcomes

	Relevant exposure periods		
Outcome	**Preconception**	**Prenatal**	**Postnatal**
Fertility (female)	X		
Spontaneous abortion	X	X	
Low birth weight, small for gestational age, intrauterine growth retardation	X	X	
Congenital malformations	X	X	
Infant death (including sudden infant death syndrome)	X	X	X
Cognitive development	X	X	X
Childhood behavior	X	X	X
Height/growth	X	X	X
Childhood cancer	X	X	X

measured source of secondhand smoke in the home (USDHHS 1986), and paternal smoking status tends to be constant across the three developmental periods: preconception, prenatal, and postnatal (USDHHS 1986). Although many studies have not considered smoking in the home by other household members, some studies have documented that such smoking could be a significant source of secondhand smoke exposure for women (Pattishall et al. 1985; Rebagliato et al. 1995a; Pirkle et al. 1996; Ownby et al. 2000; Kaufman et al. 2002). Studies on workplace exposure have focused on whether or not the person was exposed, but less attention has been paid to quantifying the exposure (Misra and Nguyen 1999).

Fertility

Biologic Basis

Infertility is commonly defined as a failure to conceive after 12 months of unprotected intercourse. Infertility should not be confused with fecundability, which is defined as the probability of conception during one menstrual cycle and measured by time to pregnancy. Thus, low fecundability is delayed conception. The biologic plausibility that secondhand smoke exposure affects human fertility and fecundability is supported by both animal and human studies of active smoking, which include exposure to the same materials as involuntary smoking. In animal studies, numerous investigators have demonstrated the biologic effects of nicotine in disrupting oviduct function (Neri and Marcus 1972; Ruckebusch 1975) and in delaying blastocyst formation and implantation (Yoshinaga et al. 1979). Investigations of assisted reproduction among humans who actively smoke have also provided information on possible mechanisms of infertility and delayed conception from secondhand smoke exposure. Several studies of assisted reproductive techniques have suggested that active maternal smoking reduces the estradiol level in follicular fluid (Elenbogen et al. 1991; Van Voorhis et al. 1992), impedes ovulation induction (Van Voorhis

et al. 1992; Chung et al. 1997), reduces the fertilization rate (Elenbogen et al. 1991; Rosevear et al. 1992), and retards the embryo cleavage rate (dose-dependent) (Hughes et al. 1992). Metabolites of cigarette smoke have been measured in the follicular fluid of active smokers at assisted reproduction clinics (Trapp et al. 1986; Weiss and Eckert 1989; Rosevear et al. 1992) and in the cervical mucus of active smokers in a cervical cancer study (Sasson et al. 1985).

Together, the evidence from studies of biologic mechanisms and the findings of numerous epidemiologic studies have led to the conclusion that active maternal smoking causes reduced fertility. An early review by Stillman and colleagues (1986) of studies of natural reproduction in addition to the two most recent Surgeon General's reports (USDHHS 2001, 2004) support this conclusion of a causal association, and findings of meta-analyses have provided estimates of the magnitude of the effect of maternal smoking on fertility. Hughes and Brennan (1996) combined the results of seven studies on in vitro fertilization with gamete intrafallopian transfer. Comparing smokers and nonsmokers, the researchers obtained a combined odds ratio (OR) for conception of 0.57 (95 percent confidence interval [CI], 0.42–0.78). Similarly, Augood and colleagues (1998) pooled nine studies that compared smokers with nonsmokers and found a combined OR of 0.66 (95 percent CI, 0.49–0.88) for the number of pregnancies per cycle of in vitro fertilization. In their meta-analysis of 12 studies, Augood and colleagues (1998) compared smokers with nonsmokers and found that the overall OR for infertility was 1.60 (95 percent CI, 1.34–1.91). Several investigators found a dose-response trend between the level of active maternal smoking and decreased fertility (Baird and Wilcox 1985; Suonio et al. 1990; Laurent et al. 1992).

Although active paternal smoking could also play a role in infertility by affecting sperm quality, the 2004 Surgeon General's report found conflicting evidence on active smoking and sperm quality (USDHHS 2004). In another review, investigators performed a meta-analysis of 20 study populations (from 18 published papers) on cigarette smoking and sperm density and found a weighted estimated reduction of 13 percent in sperm density (95 percent CI, 8.0–17.1) among smokers compared with nonsmokers (Vine et al. 1994). The epidemiologic studies that have examined the effect of active paternal smoking on fertility are not as consistent in their findings as the studies that have investigated active maternal smoking and fertility (Underwood et al. 1967; Tokuhata 1968; Baird and Wilcox 1985; de Mouzon et al. 1988; Dunphy et al. 1991; Pattinson et al. 1991; Hughes et al. 1992; Rowlands et al. 1992; Bolumar et al. 1996; Hull et al. 2000). One review concluded that paternal smoking had no effect on fertility (Hughes and Brennan 1996).

Several studies that were conducted in reproductive clinics measured tobacco smoke biomarkers in nonsmoking men and women exposed to secondhand smoke. Cotinine was measurable in follicular fluid, with measurements related to dose (Zenzes et al. 1996), and benzo[*a*]pyrene adducts were found in ovarian cells (Zenzes et al. 1998). Both nicotine and cotinine were measured in semen of nonsmoking, secondhand smoke-exposed men attending a clinic specializing in infertility (Pacifici et al. 1995).

Epidemiologic Evidence

Although active maternal smoking has been causally associated with infertility (USDHHS 2004), less evidence is available on maternal exposure to secondhand smoke and fertility, and no data were found on paternal secondhand smoke exposure and fertility. Two studies specifically addressed maternal exposure to secondhand smoke in relation to infertility, although they examined different outcome measures (Chung et al. 1997; Hull et al. 2000). Chung and colleagues (1997) studied infertile patients undergoing a gamete intrafallopian transfer procedure (Table 5.3). The researchers found that a higher proportion of active smokers had anovulation and required significantly higher amounts of human menopausal gonadotropins (hMG) to stimulate ovulation than did nonsmokers. However, the investigators found no significant differences in these same parameters when they compared unexposed nonsmokers and secondhand smoke-exposed nonsmokers, defined as having at least one household member who smoked. Among the unexposed nonsmokers, 3.0 percent had anovulation and required an average of 26 vials of hMG. Among the exposed nonsmokers, 7.8 percent

had anovulation and required an average of 24 vials of hMG. The two groups also did not differ in pregnancy rates (45.5 percent in the unexposed group and 46.2 percent in the exposed group) or birth rates (33.3 percent versus 23.1 percent, respectively). This study included only 98 patients, of whom 13 were secondhand smoke-exposed only. Hull and colleagues (2000) assessed secondhand smoke exposures from the workplace and the home among more than 8,000 women with a planned pregnancy (Table 5.3). Nonsmoking women with any secondhand smoke exposure (n = 1,987) had an increased risk for conception delay of more than six months compared with unexposed nonsmoking women (n = 4,133) (adjusted OR = 1.17 [95 percent CI, 1.02–1.37]). In this study, the investigators also included an analysis of active paternal smoking (adjusted for active maternal smoking); they found that the fathers who smoked more than 20 cigarettes per day had an increased risk for conception delay of more than six months compared with nonsmoking fathers (OR = 1.39 [95 percent CI, 1.14–1.68]).

Two other studies examined maternal exposure to secondhand smoke in addition to active maternal smoking in relation to fertility (Table 5.3) (Baird and Wilcox 1985; Olsen 1991). Using regression analysis, Baird and Wilcox (1985) adjusted for active maternal smoking to examine the impact of active paternal smoking among 678 pregnant women. No effect was found after adjusting for active maternal smoking, although the data were not presented ($\chi^2 = 0.000$, $p = 0.953$). Olsen (1991) analyzed only nonsmoking women without a history of infertility treatments. Olsen's analysis categorized paternal smoking as 1 to 9, 10 to 19, and 20 or more cigarettes per day, and calculated the ORs for time to pregnancy of more than 6 and more than 12 months. There were increased risks for both time outcomes. The greatest risks were at exposures of 10 to 19 cigarettes per day for more than 6 months (OR = 1.32 [95 percent CI, 1.10–1.58]) and for more than 12 months (OR = 1.39 [95 percent CI, 1.10–1.75]).

The limited epidemiologic evidence on maternal secondhand smoke exposure and fertility does not warrant a meta-analysis of the relevant studies.

Evidence Synthesis

The observational evidence is quite limited. The four studies that directly address maternal secondhand smoke exposure and fertility differ substantially in study design and methods. For example, Chung and colleagues (1997) investigated patients who were attending a clinic for fertility-related problems and examined the success rate of assisted reproduction. Hull and colleagues (2000), on the other hand, included pregnant women and examined delayed natural conception. In the former study, the investigators did not account for potential confounders and obtained retrospective information about exposure to secondhand smoke from telephone interviews (Chung et al. 1997). Hull and colleagues (2000) relied on a self-administered questionnaire to ascertain exposure information during pregnancy, and used potential confounders in the analysis such as parental age, body mass index, and alcohol consumption. The evidence from this larger study on natural conception is consistent with the biologic framework established by the studies on active maternal smoking and fertility (Hull et al. 2000).

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Implications

As exposure of women of reproductive age to secondhand smoke continues, this topic needs further rigorous investigation. In particular, the frequency and extent of current exposures should be characterized. Further epidemiologic studies also merit consideration.

Table 5.3 Studies of secondhand smoke exposure and fertility

Study	Design/population	Source of exposure	Outcome	Exposure categories
Baird and Wilcox 1985	678 pregnant women who were not using contraceptives before conception, recruited through early pregnancy classes and obstetric practices	Husband	Time to pregnancy	Yes/no
Olsen 1991	Population-based survey conducted in Denmark between 1984 and 1987, completed by 10,866 women in their third trimester of pregnancy who had no history of infertility treatments	Father Father Father Father Father Father Father Father	Time to pregnancy	>6 months: 0 cigarettes/day 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day >12 months: 0 cigarettes/day 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day
Chung et al. 1997	98 infertile women undergoing a gamete intrafallopian transfer procedure	Home	Anovulation Pregnancy rate Birth rate	Data were not reported
Hull et al. 2000	12,106 pregnant women with due dates between April 1991 and December 1992	Work and home	Time to pregnancy	Yes/no

*OR = Odds ratio.
†CI = Confidence interval.

Findings	Comments
No effect (data were not presented) $\chi^2 = 0.000$, p = 0.953	Adjusted for maternal smoking and potential risk factors; paternal smoking did not affect fertility
>6 months: OR* = 1.16 (95% CI†, 0.95–1.41) OR = 1.32 (95% CI, 1.10–1.58) OR = 1.32 (95% CI, 0.96–1.80) >12 months: OR = 1.34 (95% CI, 1.05–1.72) OR = 1.39 (95% CI, 1.10–1.75) OR = 1.11 (95% CI, 0.72–1.71)	Results are for nonsmoking mothers
Anovulation: 3.0% in unexposed group 7.8% in exposed group Pregnancy rate: 45.5% in unexposed group 46.2% in exposed group Birth rate: 33.3% in unexposed group 23.1% in exposed group	13 were secondhand smoke-exposed only (nonsmokers); this study demonstrated that active, but not involuntary, cigarette smoking has an adverse impact on the pregnancy and live-birth rates in gamete intrafallopian transfer producers
Conceived after >6 months: OR = 1.17 (95% CI, 1.02–1.37) Conceived after >12 months: OR = 1.14 (95% CI, 0.92–1.42)	Findings are based on 4,133 unexposed and 1,987 secondhand smoke-exposed nonsmokers; trends by categories of cigarettes/day smoked by partners of nonsmoking women were not statistically significant; this study provides new evidence of delayed conception if a woman is exposed to secondhand smoke at home or in the workplace

Pregnancy (Spontaneous Abortion and Perinatal Death)

Biologic Basis

Fetal loss or spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation (Anderson et al. 1998). Because most early fetal losses are underreported and unrecognized, spontaneous abortions are extremely difficult to study. Twenty to 40 percent of all pregnancies may terminate too early to be recognized or confirmed (Wilcox et al. 1988; Eskenazi et al. 1995). Furthermore, the etiology of spontaneous abortion is multifactorial and not fully understood. Some early miscarriages result from chromosomal abnormalities in the developing embryo; others are related to factors associated with maternal age, with the pregnancy itself, or to other types of exposures (e.g., occupational exposure, alcohol consumption, or fever). Moreover, relatively few animal studies have been conducted to gain an understanding of how exposure to sidestream smoke may affect the processes of spontaneous abortion (NCI 1999). In one study of sea urchins, investigators noted that exposure to nicotine prevented the cortical granule reaction, which typically prevents the entry of additional sperm into the egg once fertilization has occurred (Longo and

Table 5.4 Studies of secondhand smoke exposure and pregnancy loss

Study	Design/population	Exposure categories	Source of exposure
Koo et al. 1988	Cross-sectional 136 nonsmoking wives Hong Kong 1981–1983	• Unexposed • Secondhand smoke only • Light (1–20 cigarettes/day) • Heavy (>20 cigarettes/day)	• Husband • Some work exposure
Ahlborg and Bodin 1991	Prospective 4,701 pregnancies Sweden (Orebo County) 1980–1983	• Unexposed • Secondhand smoke only • Active smoking (1–9 cigarettes/day, 10–19 cigarettes/day, or ≥20 cigarettes/day)	• Maternal smoking • Secondhand smoke exposure
Windham et al. 1992	Case-control 626 cases and 1,300 controls United States (Santa Clara County, California) 1986–1987	• Exposure ≥1 hour in a room where someone else was smoking • No maternal smoking • Mother smoked 1–10 cigarettes/day • Mother smoked >10 cigarettes/day • Any smoking	• Smoking behavior 1 month before pregnancy • Any smoking changes during pregnancy • Paternal smoking

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.

Anderson 1970). If this same process occurs in the human fertilized ovum as a result of nicotine exposure, this may be a mechanism by which abnormalities in the developing embryo result in spontaneous abortions (Longo and Anderson 1970; Mattison et al. 1989). Several tobacco components and metabolites are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, carbon monoxide (CO), and polycyclic aromatic hydrocarbons (Lambers and Clark 1996; Werler 1997). Finally, with regard to active smoking and spontaneous abortion, many studies have reported a greater increase in risk for smokers than for nonsmokers, and some studies have demonstrated dose-response relationships (USDHHS 2004).

Epidemiologic Evidence

Among five studies that reported on involuntary smoking and miscarriage or spontaneous abortion, three studies found an increased risk among exposed women compared with unexposed women. In a study conducted in Hong Kong, Koo and colleagues (1988) reported that if husbands were heavy smokers (>20 cigarettes per day), their wives were two times more likely to have a miscarriage or spontaneous abortion than were women whose husbands did not smoke. Windham and colleagues (1992) examined active and secondhand smoke exposures among 1,926 pregnant women and measured exposure to secondhand smoke two ways: the amount smoked by the "father of the unborn child," and maternal exposure to secondhand smoke for more than one hour per day (Table 5.4). After adjusting for maternal

Outcome	Findings	Comments
Miscarriage/abortion	Percentage with ≥1 miscarriage/abortion: Nonsmoking husband: 33% Husband was a light smoker: 43% Husband was a heavy smoker: 59% p value = 0.12 for wives with smoking husbands	Participants were interviewed in their homes by trained interviewers 44% of wives with nonsmoking husbands had been exposed to secondhand smoke at home or at work
Spontaneous abortion Preterm birth Low birth weight (LBW)	• Secondhand smoke exposure at work (RR* = 1.53 [95% CI†, 0.98–2.38]) for spontaneous abortion • Adjusted RR for active exposure from smoking 10–19 cigarettes/day = 2.18 (95% CI, 1.51–3.14) for preterm birth and 2.38 (95% CI, 1.22–4.65) for LBW • RR for active exposure from smoking ≥20 cigarettes/day = 2.30 (95% CI, 1.19–4.44) for preterm birth and 2.71 (95% CI, 0.86–8.53) for LBW	Source exposure data were self-reported (questionnaires)
Spontaneous abortion	• OR‡ = 1.31 (95% CI, 0.92–1.88) for mothers who smoked >10 cigarettes/day • OR = 1.5 (95% CI, 1.2–1.9) for mothers exposed to secondhand smoke for ≥1 hour/day • OR = 2.1 (95% CI, 0.8–6.0) for fathers who smoked 1–10 cigarettes/day • 40% of mothers smoked during pregnancy if fathers smoked (highly correlated)	Source exposure data were self-reported; there was no conclusive evidence of an association between active smoking and spontaneous abortion; a moderate association was observed with secondhand smoke exposure; findings were adjusted for maternal factors of age, race, education, marital status, prior fetal loss, tobacco use, alcohol consumption, bottled water intake, employment, insurance, and nausea

factors of age, race, education, marital status, prior fetal loss, tobacco use, alcohol consumption, bottled water intake, employment, insurance, and nausea, women exposed to secondhand smoke for one hour or more per day had an adjusted OR of 1.5 (95 percent CI, 1.2–1.9) for second trimester losses compared with nonsmokers. Windham and colleagues (1992), however, found no association for their second measure of involuntary smoking, which was paternal smoking (examined by dose). Ahlborg and Bodin (1991) examined involuntary smoking and spontaneous abortion among nonsmoking mothers in Sweden. Women who were exposed to secondhand smoke at work were at an increased risk for first trimester losses (relative risk [RR] = 2.16 [95 percent CI, 1.23–3.81]), but exposure to secondhand smoke at home was not associated with spontaneous abortion. In Finland, Lindbohm and colleagues (1991) examined paternal exposures to occupational lead and paternal smoking among 513 pregnancies (213 of which ended in spontaneous abortion). Without adjusting for potential confounding factors, the authors observed that paternal smoking did not increase the risk of spontaneous abortion (OR = 1.3 [95 percent CI, 0.9–1.9]). Windham and colleagues (1999b) conducted another prospective study that involved 5,000 women who resided in California from 1990 to 1991. The investigators examined exposure to secondhand smoke only among nonsmoking women and ascertained the number of hours per day that a woman was near others who smoked (including paternal smoking). There was little evidence for increased risks, and all ORs were an estimated 1.0.

Evidence Synthesis

The few studies that have examined the relationship between involuntary smoking and spontaneous abortion have inconsistent findings (Table 5.4). Although some studies reported an increased risk for spontaneous abortion among women exposed to secondhand smoke at work or at home, many found no association. However, for the studies that showed no associations, the study samples may have lacked adequate statistical power.

Three studies examined secondhand smoke exposures among women who were nonsmokers. Koo and colleagues (1988) examined rates of miscarriage among 136 nonsmoking wives who were part of a larger study on cancer. These 136 women were the controls in this study, which ascertained lifetime smoking histories of the husbands and reproductive histories of the wives. Social and demographic factors differed between families with smoking and nonsmoking husbands. The crude OR for more than two miscarriages among wives with husbands who smoked was 1.81 (95 percent CI, 0.85–3.85) (adjusted ORs were not reported). Ahlborg and Bodin (1991) reported on nonsmoking women who were exposed to secondhand smoke at home. Two estimates were provided, one for first trimester losses (OR = 0.96 [95 percent CI, 0.50–1.86]) and for one second or third trimester losses (OR = 1.06 [95 percent CI, 0.55–2.05]). Windham and colleagues (1999b) reported adjusted ORs for paternal smoking among women who were nonsmokers. When maternal age, prior spontaneous abortion, alcohol and caffeine consumption, and gestational age at initial interviews were taken into account, the investigators obtained an OR of 1.15 (95 percent CI, 0.86–1.55) for secondhand smoke exposure at home. The pooled estimate from these three studies (with the two estimates from Alborg and Bodin [1991] included separately) for secondhand smoke exposure in the home or from fathers who smoked and who were married to nonsmoking women was 1.18 (95 percent CI, 0.92–1.44).

Future studies not only need to ensure an adequate sample size, but they should give particular attention to the difficult issues of confounding and to accurate estimates of secondhand smoke exposures in the workplace and in the home.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Implications

As for other outcomes that have very few studies, further research is warranted (see "Overall Implications" later in this chapter).

Infant Deaths

Infant mortality is defined as the death of a live-born infant within 364 days of birth. Many of the major causes of infant deaths, such as low birth weight (LBW), preterm delivery, and SIDS, are also associated with exposure to tobacco smoke during and after pregnancy. The biologic mechanisms by which secondhand smoke exposure leads to these particular outcomes are discussed in other parts of this chapter and will not be discussed here. In 2002, the infant mortality rate for infants of smokers (11.1 percent) was 68 percent higher than the rate for infants of nonsmokers (6.6 percent) (Mathews et al. 2004). For each race and Hispanic-origin group, the infant mortality rate among infants of smokers was higher compared with the rate among infants of nonsmokers.

Epidemiologic Evidence

Numerous studies have demonstrated associations of active maternal smoking with neonatal and perinatal mortality (Comstock and Lundin 1967; Rush and Kass 1972; Cnattingius 1988; Malloy et al. 1988; Schramm 1997). Even with modern neonatal intensive care, children of smokers are at an increased risk for neonatal mortality (death of a live-born infant within 28 days) (Cnattingius 1988; Malloy et al. 1988; Schramm 1997), with reported OR estimates of 1.2 for infants of smokers compared with infants of nonsmokers. Two studies have assessed neonatal mortality among infants exposed to secondhand smoke. Comstock and Lundin (1967) examined neonatal mortality among a sample of 448 live births, 234 stillbirths, and 431 infant deaths that occurred between 1950 and 1964 in Washington County, Maryland. When comparisons were made between families with paternal smokers only and families with two nonsmoking parents, neonatal mortality rates that were adjusted for gender and paternal education were higher: 17.2 (father smoked) versus 11.9 (neither parent smoked) neonatal deaths per 1,000 live births. Yerushalmy (1971) examined active and involuntary smoking and perinatal outcomes among an estimated 13,000 births in California. After examining crude rates for neonatal mortality, Yerushalmy (1971) found (without considering maternal smoking) that rates for both Blacks and Whites were elevated among infants whose fathers smoked compared with infants of nonsmoking fathers; there were no adjustments for any other confounding factors.

Evidence Synthesis

Only two studies examined the relationship of involuntary smoking with neonatal mortality. Both studies reported associations of secondhand smoke exposure from paternal smoking with neonatal mortality. There is significantly more literature on active smoking by the mother during pregnancy and neonatal outcome. Although the strength of the relationship in these two studies was strong, causality cannot be inferred because of the small number of studies and because of inadequate controls for potential confounders.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Implications

In addition to the consistent relationship demonstrated between exposure to secondhand smoke and neonatal mortality, numerous studies have reported significant associations between active maternal smoking during pregnancy and infant mortality. Thus, the association of secondhand smoke exposure during pregnancy and infant mortality warrants further investigation. Moreover, the data cited were from older studies, and smoking patterns and levels of secondhand smoke exposure may have changed since the time some of the studies were conducted. To clarify the association between maternal smoking and infant mortality, more evidence is needed.

Sudden Infant Death Syndrome

The sudden, unexplained, unexpected death of an infant before one year of age—referred to as SIDS—has been investigated in relation to exposure of the fetus and infant to smoking by mothers and others during the preconception, prenatal, and postpartum periods. The death rate attributable to SIDS has declined by more than half during the past two decades (Ponsonby et al. 2002; American Academy of Pediatrics [AAP] Task Force on SIDS 2005). SIDS has decreased dramatically because of interventions such as the "Back to Sleep" campaign implemented in the 1990s (Gibson et al. 2000; Malloy 2002; Malloy and Freeman 2004). Numerous studies have examined the association between active smoking among mothers during pregnancy and the subsequent risk of SIDS. The evidence for active smoking has demonstrated a causal association between maternal smoking during pregnancy and SIDS (Anderson and Cook 1997; United Kingdom Department of Health 1998; USDHHS 2001). The 2004 Surgeon General's report concluded that the evidence is sufficient to infer a causal relationship between SIDS and maternal smoking during and after pregnancy (USDHHS 2004). This new 2006 Surgeon General's report considers exposure of the infant to secondhand smoke from the mother, father, or others.

Biologic Basis

Although studies have identified social and behavioral risk factors for SIDS, the biologic mechanism or mechanisms underlying sudden, unexplained, unexpected death before one year of age are still unknown (Joad 2000; AAP Task Force on SIDS 2005). Chapter 2 (Toxicology of Secondhand Smoke) reviews the animal and human studies that provide evidence on how prenatal and postnatal exposure to nicotine and to other toxicants in tobacco smoke may affect the neuroregulation of breathing, apneic spells, and risk for sudden infant death. Experimental data from animal models on the neurotoxicity of prenatal and neonatal exposure to nicotine and secondhand smoke can be related to several potential causal mechanisms for SIDS, including adverse effects on brain cell development, synaptic development and function, and neurobehavioral activity (Slotkin 1998; Slotkin et al. 2001, 2006; Machaalani et al. 2005). Stick and colleagues (1996) observed newborns in the hospital and reported reductions in respiratory function among infants of smokers compared with infants of nonsmokers. Other proposed mechanisms for postpartum reductions in respiratory function have included irritation of the airways by tobacco smoke, susceptibility to respiratory infections that increases the risk of SIDS, and a change in the ventilatory responses to hypoxia attributable to nicotine (Anderson and Cook 1997).

A diagnosis of SIDS requires supporting evidence from an autopsy so as to exclude other causes. Thus, SIDS is a difficult outcome to study. Numerous studies have examined the association between active smoking among mothers during pregnancy and the subsequent risk of SIDS. The evidence for active smoking has demonstrated a causal association between maternal smoking during pregnancy and SIDS (Anderson and Cook 1997; United Kingdom Department of Health 1998; USDHHS 2001, 2004).

Epidemiologic Evidence

Anderson and Cook (1997) and the California Environmental Protection Agency (Cal/EPA 1997, 2005) have provided systematic reviews of the effects of secondhand smoke exposure on SIDS. The 1997 Cal/EPA review identified and selected 10 epidemiologic studies with the best data that examined the relationship between secondhand smoke and SIDS. On the basis of the the results from the quantitative meta-analysis and the qualitative review of results on paternal and other smokers in the household, Anderson and Cook (1997) concluded that the epidemiologic evidence points to a causal relationship between SIDS and postnatal exposure to tobacco smoke.

The discussion that follows includes a review of the epidemiologic studies that examined the association between household secondhand smoke exposure and SIDS among postpartum infants. Consideration was given to the most appropriate study design that controlled for the confounding factors that are critical

to delineating the independent risk related to secondhand smoke exposure and SIDS among postpartum infants. Because researchers have established the causal risk of maternal smoking during pregnancy (USDHHS 2001, 2004), there are epidemiologic studies that provide appropriate controls in the study design for the analysis of prenatal maternal smoking and other potentially important confounding factors (e.g., infant's sleeping position and birth weight, parental use of drugs or alcohol, and the potentially synergistic effect of maternal smoking and bed sharing) (Lahr et al. 2005). Although self-reported information on the smoking behaviors of adults living in the household is an indirect measure of the potential for exposing a newborn to secondhand smoke, researchers evaluate analyses of postnatal secondhand smoke exposure from the father or other smokers in the household because these studies have the potential to more fully control for the possible confounding of maternal smoking during pregnancy. Table 5.5 provides a summary of the design, methods, and findings of the Anderson and Cook (1997) meta-analysis and of the nine primary studies identified in that review, which evaluated the risks of postnatal maternal or paternal smoking. Table 5.5 also includes the four epidemiologic studies that were published subsequent to the review by Anderson and Cook (1997). The methodology varied across these studies; many used autopsies to determine that SIDS was the likely cause of death. The "Comments" column of Table 5.5 provides other important methodologic aspects of each study. Only one study evaluated maternal exposure to secondhand smoke during pregnancy (Klonoff-Cohen et al. 1995), and only one study used urinary cotinine levels to biochemically validate secondhand smoke exposures among newborns (Dwyer et al. 1999). Many studies controlled for potential confounders that included sleeping position, parental bed sharing, social class, parental use of drugs or alcohol, birth weight, gestational age, and prenatal maternal smoking.

Of the 13 individual studies in Table 5.5 that examined the association between household secondhand smoke exposure and SIDS among postpartum infants, 10 studies independently examined the effects of postpartum maternal smoking. Each study found a significant association between postnatal maternal smoking and SIDS (Bergman and Wiesner 1976; McGlashan 1989; Schoendorf and Kiely 1992; Mitchell et al. 1993, 1997; Klonoff-Cohen et al. 1995; Ponsonby et al. 1995; Blair et al. 1996; Brooke et al. 1997; Dwyer et al. 1999). Two of the studies did not consider potential confounders (Bergman and Wiesner 1976; McGlashan 1989), and three studies did not adjust for maternal smoking during pregnancy (Ponsonby et al. 1995; Brooke et al. 1997; Dwyer et al. 1999). Among the four studies (and five samples, including the separate analyses for Whites and Blacks within the Schoendorf and Kiely [1992] study) with more complete adjustments for important confounders such as prenatal maternal smoking, the adjusted ORs for postnatal maternal smoking were all statistically significant. The ORs ranged from 1.65 (95 percent CI, 1.20–2.28) (Mitchell et al. 1993) and 1.75 (95 percent CI, 1.04–2.95) for White infants and 2.33 (95 percent CI, 1.48–3.67) for Black infants (Schoendorf and Kiely 1992), to 2.28 (95 percent CI, 1.04–4.98) (Klonoff-Cohen et al. 1995) and 2.39 (95 percent CI, 1.01–6.00), respectively (Ponsonby et al. 1995). In one study that controlled for prenatal maternal smoking in addition to many other factors in a multivariate model, the effect for postnatal maternal smoking was no longer significant ($p = 0.16$), possibly because of the strong correlation between maternal smoking during pregnancy and postnatal smoking (Blair et al. 1996). However, this study observed a significant OR for the additive effect of postnatal maternal smoking to the risk of smoking during pregnancy (OR = 2.93 [95 percent CI, 1.56–5.48]). The remaining three studies in Table 5.5 (Mitchell et al. 1991; Nicholl and O'Cathain 1992; Alm et al. 1998) were included because they provide additional data on paternal and other smoking in the household or on dose-response relationships.

Two studies provided data that assessed exposure of the infant to secondhand smoke with greater precision than with classification by the postpartum smoking status of the mother alone (Klonoff-Cohen et al. 1995; Dwyer et al. 1999). Dwyer and colleagues (1999) assessed urinary cotinine levels in 100 infants as part of a prospective study of more than 10,000 births in the Tasmanian Infant Health Survey. Of the 53 mothers who reported postnatal smoking, only 32 reported smoking sometimes or always in the same room as the infant. Maternal smoking in the same room significantly increased infant urinary cotinine levels ($p < 0.0001$) and the OR of the risk of SIDS (1.96 [95 percent CI, 1.01–3.80]). Klonoff-Cohen and colleagues (1995) collected more extensive interview data on sources of infant exposure to tobacco smoke from the mother, father, and other live-in adults, including data on whether the person smoked in the

Table 5.5 Studies of secondhand smoke exposure and sudden infant death syndrome (SIDS)

Study	Design/population	Exposure categories	Source of exposure
Bergman and Wiesner 1976	Case-control (56 cases, 86 controls, matched for gender, race [all Caucasian], and date of birth) United States (King county, Washington state) 1970–1974	• Mother smoked after pregnancy • Father smoked	• Mother and father
McGlashan 1989	Case-control (167 cases, 334 controls, matched for gender, born in same hospital, and proximate date of birth) Australia (Tasmania) 1980–1986	• Smoking status of parents • Cigarettes/day smoked by mother (habitual, during pregnancy, and during the infant's first year)	• Mother and father
Mitchell et al. 1991	Case-control (128 cases, 503 controls randomly selected from all births) New Zealand 1987–1988	• Cigarettes/day smoked by mother during the 2 weeks before the interview	• Mother
Nicholl and O'Cathain 1992	Case-control (303 cases, 277 controls, matched for date and place of birth) United Kingdom 1976–1979	• Prenatal and postnatal smoking status of the mother's partner	• Mother's partner
Schoendorf and Kiely 1992	Case-control (435 cases ≥2,500 grams [g], 6,098 controls ≥2,500 g) All infant deaths were from causes other than SIDS Sample was stratified by race: Black infants (103 cases, 2,423 controls) White infants (89 cases, 1,987 controls) Data from the National Maternal and Infant Health Survey United States 1988	• None (no prenatal or postnatal maternal smoking), mother smoked after pregnancy (secondhand), and mother smoked during and after pregnancy (combined) • Secondhand smoke exposure from other household members (none vs. any)	• Mother (smoked prenatally and postpartum) • Other household members (smoking status at time of survey)

Outcome	Findings	Comments
SIDS	Maternal smoking OR* = 2.42 (95% CI†, 1.22–4.82) Paternal smoking OR = 1.53 (95% CI, 0.78–3.01) Unadjusted	Exposure data were self-reported (mailed questionnaire); all cases were autopsied; OR and CI were calculated from prevalence estimates provided in the paper; exposure to secondhand smoke appears to enhance the risk of SIDS; potential confounders were not assessed
SIDS	Father was habitual smoker RR‡ = 1.73 (p = 0.05) Mother smoked during infant's first year RR = 2.20 (p <0.01) During infant's first year, mother smoked >10 cigarettes/day: RR = 2.37 (p <0.05) >20 cigarettes/day: RR = 3.11 (p <0.05)	Exposure data were self-reported (interview); all cases were autopsied; RR was based on statistical analysis of case-2 matched control "triples"; dose-response for level of paternal smoking was noted but RR was not reported; parental smoking carries a high relative risk for SIDS
SIDS	In the past 2 weeks, mother smoked 1–9 cigarettes/day: OR = 1.87 (95% CI, 0.98–3.54) 10–19 cigarettes/day: OR = 2.64 (95% CI, 1.47–4.74) ≥20 cigarettes/day: OR = 5.06 (95% CI, 2.86–8.95) Unadjusted	Exposure data were self-reported (interview); all cases were autopsied; maternal smoking is an independent risk factor for SIDS
SIDS	Neither mother nor her partner smoked during pregnancy 1.0 (reference) Mother did not smoke during pregnancy, partner did smoke prenatally and postnatally RR = 1.63 (95% CI, 1.11–2.40)	Exposure data were self-reported (interview); all cases were autopsied; adjusted for birth weight, maternal age and gravidity, and condition of the family's housing; RR for paternal smoking increased over 4 age-at-death intervals; postnatal secondhand smoke exposure from the father plays a role in the risk of SIDS
SIDS	<u>From mothers</u> Black infants Secondhand: OR = 2.33 (95% CI, 1.48–3.67) Combined: OR = 3.06 (95% CI, 2.19–4.29) White infants Secondhand: OR = 1.75 (95% CI, 1.04–2.95) Combined: OR = 3.10 (95% CI, 2.27–4.24) Adjusted for marital status and maternal age and education <u>From other household members (none vs. any)</u> Black infants (by mother's smoking category) None: OR = 1.00 (95% CI, 0.62–1.58) Secondhand: OR = 1.03 (95% CI, 0.43–2.47) All infants: OR = 0.93 (95% CI, 0.68–1.27) White infants None: OR = 1.33 (95% CI, 0.77–2.27) Secondhand: OR = 1.63 (95% CI, 0.58–4.74) All infants: OR = 1.41 (95% CI, 1.04–1.90) Adjusted for marital status and maternal age and education	Race of infant defined as Black non-Hispanic and White non-Hispanic; control variables were selected from birth certificates; survey questionnaire was completed by the mother; possible bias in self-reported smoking behaviors of case and control mothers; 92% of cases were autopsied; both intrauterine and secondhand smoke exposures are associated with an increased risk of SIDS

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Mitchell et al. 1993	Case-control (485 cases, 1,800 controls randomly selected from all births) Data from the New Zealand Cot Death Study 1987–1990	• Mother smoked during pregnancy • Father smoked during the past 2 weeks • Other household members smoked during the past 2 weeks • Cigarettes/day smoked by mother during the past 2 weeks, stratified by father's smoking status	Smoking in the past 2 weeks by • Mother • Father • Other household members
Klonoff-Cohen et al. 1995	Case-control (200 cases, 200 controls) United States (southern California) 1989–1992	• Postpartum secondhand smoking status of household members was assessed using multiple methods including any smoking, quantity smoked, smoking in same rooom as the infant, number of hours spent smoking around the infant	• Mother • Father • Other adult live-in residents • Day care providers

Outcome	Findings	Comments
SIDS	Maternal smoking OR = 1.65 (95% CI, 1.20–2.28) Paternal smoking OR = 1.37 (95% CI, 1.02–1.84) Smoking by other household members OR = 1.17 (95% CI, 0.84–1.63) Adjusted for region, time of day, infant's age, maternal marital status, infant's gender, socioeconomic status, birth weight, infant's race, season, maternal age, sleeping position, bed sharing, breastfeeding, and maternal smoking during pregnancy; also adjusted for either maternal smoking during pregnancy, paternal smoking in the 2 weeks before the interview, or smoking by other household members in the past 2 weeks <u>Father did not smoke</u> In the past 2 weeks, mother smoked 0 cigarettes: 1.0 (reference) 1–19 cigarettes/day: OR = 2.56 (95% CI, 1.73–3.75) ≥20 cigarettes/day: OR = 3.43 (95% CI, 2.04–5.77) <u>Father smoked</u> In the past 2 weeks, mother smoked 0 cigarettes: OR = 1.0 (95% CI, 0.64–1.56) 1–19 cigarettes/day: OR = 4.40 (95% CI, 3.26–5.95) ≥20 cigarettes/day: OR = 7.40 (95% CI, 4.92–11.13) Unadjusted	Extended the Mitchell et al. 1991 study using similar methods; exposure data were from obstetric records and self-reports (interview); autopsies were carried out in 474/485 (97.7%) of SIDS cases; infants of smoking mothers who were breastfed had a lower risk than infants of mothers who were not; secondhand smoke exposure is causally related to SIDS
SIDS	Maternal smoking Any: OR = 2.28 (95% CI, 1.04–4.98) In same room as infant: OR = 4.62 (95% CI, 1.82–11.77) Paternal smoking Any: OR = 3.46 (95% CI, 1.91–6.28) In same room as infant: OR = 8.49 (95% CI, 3.33–21.63) Smoking by other live-in adults Any: OR = 2.18 (95% CI, 1.09–4.38) In same room as infant: OR = 4.99 (95% CI, 1.69–14.75) All combined household smoking Any: OR = 3.50 (95% CI, 1.81–6.75) In same room as infant: OR = 4.99 (95% CI, 2.35–10.99) <u>Exposure to cigarettes from all sources (mother, father, live-in adults, and day care providers</u> Total number of household smokers One: OR = 3.00 (95% CI, 1.51–5.97) Two: OR = 5.31 (95% CI, 1.94–14.54) Three–four: OR = 5.13 (95% CI, 0.72–36.61) Number smoking in same room as infant One: OR = 3.67 (95% CI, 1.66–8.13) Two–four: OR = 20.91 (95% CI, 4.02–108.7) Total daily cigarette exposure 1–10: OR = 2.40 (95% CI, 1.06–5.44) 11–20: OR = 3.62 (95% CI, 1.50–8.75) ≥20: OR = 22.67 (95% CI, 4.80–107.2)	Exposure data were self-reported (interview); all reported ORs were adjusted for birth weight (in grams), routine sleep position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy; breastfeeding was protective in nonsmokers but not in smokers; secondhand smoke exposure in the same room as an infant increases the risk for SIDS; risk of SIDS associated with secondhand smoke exposure was similar among different racial groups

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Ponsonby et al. 1995	Case-control (58 cases, 62 age- and region-matched controls, 58 age-, region-, and birth weight-matched controls) Australia (Tasmania) 1988–1991	• Postpartum smoking status of mother	• Mother
Blair et al. 1996	Case-control (195 cases, 780 controls, 4 per case matched for age) United Kingdom (Southwest, Yorkshire, and Trent) 1993–1995	• Smoking status of mother, father, and others in household • Number of smokers in household • Number of cigarettes smoked daily in household	Postpartum exposure from • Mother • Father • Other household members
Anderson and Cook 1997	Meta-analysis Systematic qualitative review of epidemiologic evidence (studies were identified by electronically searching EMBASE[§] and Medline) 39 relevant studies were assessed (43 papers)	• Maternal prenatal and postnatal smoking	• Mother

Outcome	Findings	Comments
SIDS	Mother smoked postnatally (full multivariate model) OR = 2.39 (95% CI, 1.01–6.00) Mother smoked postnatally (multivariate model excluding family history of asthma) OR = 3.10 (95% CI, 1.36–7.09)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for maternal age, usual sleeping position, employment status, and family history of asthma; postpartum maternal smoking is a predictor of SIDS
SIDS	<u>Parental smoking status</u> Only father smoked: OR = 3.41 (95% CI, 1.98–5.88) Only mother smoked: OR = 7.01 (95% CI, 3.91–12.56) Both parents smoked: OR = 8.41 (95% CI, 5.08–13.92) Adjusted for maternal smoking during pregnancy <u>Multivariate analysis</u> Postnatal paternal smoking, additive to maternal smoking OR = 2.50 (95% CI, 1.48–4.22) Adjusted for mother's age, mothers without partners, parity, multiple births, short gestation, socioeconomic status, sleeping position, maternal alcohol consumption, parental use of illegal drugs, parental bed sharing, breastfeeding, and birth weight Postnatal paternal smoking, additional adjustment for maternal smoking during pregnancy Nonsignificant (p = 0.1601) <u>Number of smokers at home</u> 1 smoker: OR = 2.44 (95% CI, 1.36–4.37) 2 smokers: OR = 5.15 (95% CI, 3.24–8.21) >2 smokers: OR = 10.43 (95% CI, 3.34–32.54) <u>Cigarettes/day smoked at home</u> 1–19 cigarettes/day: OR = 2.47 (95% CI, 1.29–4.73) 20–39 cigarettes/day: OR = 3.96 (95% CI, 2.40–6.55) >39 cigarettes/day: OR = 7.57 (95% CI, 4.00–14.32) <u>Infant's daily exposure to tobacco smoke (hours)</u> 1–2: OR = 1.99 (95% CI, 1.14–3.46) 3–5 : OR = 3.84 (95% CI, 1.97–7.48) 6–8: OR = 6.78 (95% CI, 3.17–14.49) >8: OR = 8.29 (95% CI, 4.28–16.05)	Exposure data were self-reported (questionnaire); multivariate analysis found nonsignificant effect for other smoking members of household; unclear if postnatal dose-response analyses adjusted for maternal prenatal smoking or other confounding factors; dose-response analyses were limited to households where smoking was allowed in the same room as the infant; exposure to secondhand smoke in the home has an independent effect on the risk of SIDS
SIDS	Prenatal maternal smoking OR = 2.08 (95% CI, 1.96–2.21) Postnatal maternal smoking OR = 1.94 (95% CI, 1.55–2.43)	Pooled adjusted ORs were calculated using a fixed effects model; calculated results are also available using a random effects model; results are also available for pooled unadjusted ORs; the relationship between maternal smoking and SIDS is almost certainly causal—maternal smoking doubled the risk

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Brooke et al. 1997	Case-control (147 cases, 276 controls, 2 controls per case from births immediately before and after index case, thus matched for age, season, and maternity unit) Scotland 1992–1995	• Smoking status of mother and father	• Mother and father
Mitchell et al. 1997	Case-control (232 cases, 1,200 population controls) New Zealand 1991–1993	• Maternal cigarettes/day and paternal smoking status when infant was 2 months old	• Mother and father
Alm et al. 1998	Case-control (244 cases, 869 controls, matched for gender, date of birth, and hospital) Denmark, Norway, and Sweden 1992–1995	• Postnatal household secondhand smoke exposure	• Mother • Father • Other household members

Outcome	Findings	Comments
SIDS	Only father smoked OR = 2.12 (95% CI, 0.99–4.55) Only mother smoked OR = 5.05 (95% CI, 1.85–13.77) Both parents smoked OR = 5.19 (95% CI, 2.26–11.91)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for sleeping position, old mattress, maternal age, deprivation score, moved under sheets, maternal marital status, social class, use of cot bumper, sleeping with parents, symptoms in previous week, gestational age, was usually swaddled in previous week, history of infant death in family, sweaty upon waking, warmth, maternal education, beastfeeding, parity, and birth weight; parental smoking is confirmed as a modifiable risk factor for SIDS
SIDS	Maternal smoking (at 2 months home visit) 0 cigarettes/day: 1.0 (reference) 1–19 cigarettes/day: OR = 4.90 (95% CI, 2.65–9.06) ≥20 cigarettes/day: OR = 21.42 (95% CI, 6.89–66.52) Paternal smoking (at 2 months home visit) No: 1.0 (reference) Yes: OR = 3.21 (95% CI, 1.81–5.71) Risks from maternal/paternal smoking combinations Nonsmoking mother Smoking father: OR = 1.54 (95% CI, 0.67–3.45) Smoking mother: Nonsmoking father: OR = 4.15 (95% CI, 2.05–8.38) Smoking father: OR = 10.09 (95% CI, 5.89–17.37) Adjusted OR (maternal smoking and bed sharing Nonsmoking/no bed sharing: 1.0 (reference) Nonsmoking/bed sharing: OR = 1.03 (95% CI, 0.21–5.06) Smoking/no bed sharing: OR = 1.43 (95% CI, 0.58–3.51) Smoking/bed sharing: OR = 5.02 (95% CI, 1.05–24.05) Adjusted for maternal age, marital status, age mother left school, number of previous pregnancies, infant's gender, ethnicity of infant, birth weight, sleep position, breasfeeding, and the combination of bed sharing and maternal smoking	Exposure data were self-reported (interviews conducted at postpartum and at 2 months postpartum); maternal smoking and bed sharing increase risk; maternal smoking is a significant risk factor for SIDS
SIDS	Maternal postnatal smoking OR = 3.7 (95% CI, 2.5–5.5) Paternal postnatal smoking OR = 1.2 (95% CI, 0.8–1.9) Smoking by other household members (after pregnancy) OR = 1.2 (95% CI, 0.6–2.2)	Exposure data were self-reported (questionnaire); all cases were autopsied; adjusted for age, maternal age, and maternal education; exposure to secondhand smoke is an independent risk factor for SIDS

Table 5.5 Continued

Study	Design/population	Exposure categories	Source of exposure
Dwyer et al. 1999	Nested case-control study with prospective cohort study (35 cases, 9,765 controls); urinary samples for cotinine analysis were collected from 105 infants (August–October 1995) Australia (Tasmania) 1988–1995	• Postnatal household secondhand smoke exposure	• Mother • Other household members

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.
§EMBASE = Excerpta Medica Database.

same room as the infant and the number of hours the adult spent smoking in the presence of the infant. Although the researchers did not report the proportion of smoking mothers who smoked in the same room as the infant, the OR for any maternal postpartum smoking was 2.28 (95 percent CI, 1.04–4.98), adjusted for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and prenatal maternal smoking. The adjusted OR increased to 4.62 (95 percent CI, 1.82–11.77) when limited to mothers who reported smoking in the same room as the infant.

Of the 10 studies that independently evaluated postnatal maternal smoking, researchers observed a significant dose response in risk with the level of postnatal maternal smoking in the unadjusted ORs from 5 studies (Bergman and Wiesner 1976; McGlashan 1989; Mitchell et al. 1993, 1997; Dwyer et al. 1999), and in other measures of overall household postnatal smoking levels (maternal, paternal, and/or other) from 2 studies (Klonoff-Cohen et al. 1995; Blair et al. 1996). One study examined the risk of SIDS associated with increasing levels of postnatal exposure to cigarettes from all sources in three ways: total number of household smokers, total cigarette exposure per day, and the number of adults smoking in the same room as the infant (Klonoff-Cohen et al. 1995). Using these three approaches to classify increasing exposures of newborns to secondhand smoke, the investigators estimated unadjusted and adjusted ORs (controlling for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy). Although the OR was decreased slightly for one measure (total number of household smokers) by adjustment for other factors, the adjusted ORs for the other two measures were somewhat stronger than the unadjusted measures. The adjusted ORs were 3.67 (95 percent CI, 1.66–8.13) if one adult smoked in the same room as the infant, and 20.91 (95 percent CI, 4.02–108.7) if two to four adults smoked in the same room as the infant compared with infants from nonsmoking households. Using the total cigarette exposure per day as the measure of exposure, the OR for 1 to 10 cigarettes in comparison with nonsmoking households was 2.40 (95 percent CI, 1.06–5.44), which increased to 22.67 (95 percent CI, 4.80–107.2) for 21 or more cigarettes per day.

Nine studies examined paternal smoking as a source of exposure to secondhand smoke (Bergman and Wiesner 1976; McGlashan 1989; Nicholl and O'Cathain 1992; Mitchell et al. 1993, 1997; Klonoff-Cohen et al. 1995; Blair et al. 1996; Brooke et al. 1997; Alm et al. 1998). Three of the nine (McGlashan 1989;

Outcome	Findings	Comments
SIDS	Postnatal smoking Maternal postnatal smoking (breastfed infants) OR = 5.29 (95% CI, 1.16–24.11) Maternal postnatal smoking (bottle-fed infants) OR = 2.35 (95% CI, 0.73–7.62) Smoking by other household members OR = 0.69 (95% CI, 0.34–1.40) Dose-response of maternal postnatal smoking None (no maternal postnatal smoking): OR = 1.0 1–10 cigarettes/day: OR = 2.80 (95% CI, 1.08–7.27) 11–20 cigarettes/day: OR = 3.01 (95% CI, 1.22–7.42) ≥21 cigarettes/day: OR = 5.31 (95% CI, 2.04–13.81)	Exposure data are from self-reports (interview) and from urinary cotinine measures (results from n = 100); all cases were autopsied; adjusted for breastfeeding, birth weight, and smoking in same room as infant; analyses of postnatal smoking among 34 cases and 9,464 controls; cotinine data provide estimates of exposure levels by self-reported categories; there is a positive association between maternal smoking and SIDS, but cannot separate risks from prenatal and postnatal smoking

Mitchell et al. 1997; Alm et al. 1998) observed a significant risk for SIDS from paternal smoking without adjustment for several potential confounding factors, including maternal smoking during pregnancy. Four of the remaining six studies reported significantly higher risks of SIDS among infants whose fathers were smokers compared with infants whose fathers were nonsmokers (Nicholl and O'Cathain 1992; Mitchell et al 1993; Klonoff-Cohen et al. 1995; Blair et al. 1996). The fifth and sixth studies reported an association of borderline significance (OR = 1.76, $p < 0.20$) (Bergman and Wiesner 1976) and (OR = 2.12 [95 percent CI, 0.99–4.55]) (Brooke et al. 1997). Across the five studies with controls for maternal smoking, ORs ranged from 1.37 to 3.46, with the higher OR in the study with the stronger assessment of infant exposure to paternal smoking (Klonoff-Cohen et al. 1995). This study also reported an OR of 8.49 (95 percent CI, 3.33–21.63) for infants of fathers who smoked in the same room compared with infants of nonsmoking fathers, after adjustment for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy (Klonoff-Cohen et al. 1995). Five studies that measured paternal smoking provided the opportunity to examine secondhand smoke among families where the mothers were nonsmokers. Of the four studies that evaluated households with smoking fathers and nonsmoking mothers compared with nonsmoking households, two studies reported significant ORs and one study reported a borderline significance for the risk of SIDS. Blair and colleagues (1996) reported an OR of 3.41 (95 percent CI, 1.98–5.8); Nicholl and O'Cathain (1992) reported an OR of 1.63 (95 percent CI, 1.11–2.40); and Brooke and colleagues (1997) reported an adjusted OR of 2.12 (95 percent CI, 0.99–4.55). In the study with nonsignificant results for paternal smoking (OR = 1.54 [95 percent CI, 0.67–3.45]), smoking by both parents significantly increased the risk above maternal smoking only (OR = 10.09 [95 percent CI, 5.89–17.37] versus 4.15 [95 percent CI, 2.05–8.38]) (Mitchell et al. 1997). In a case-control study, Alm and colleagues (1998) reported that when the mother did not smoke during pregnancy but the father smoked after pregnancy, the OR was 1.2 (95 percent CI, 0.8–1.9) compared with nonsmoking parents. The results reported by Mitchell and colleagues (1997) and Alm and colleagues (1998) suggest that postnatal paternal exposure has a stronger effect if it augments the effect of prenatal maternal smoking. However, the significant effects for paternal smoking noted by

Mitchell and colleagues (1993), Klonoff-Cohen and colleagues (1995), and Blair and colleagues (1996), adjusting for prenatal maternal smoking and compared with households with nonsmoking mothers, indicate a likely effect from exposure to postnatal paternal smoking that is independent of prenatal maternal smoking. In addition, as noted above for maternal smoking, data from the two studies that provided more complete assessments of the infant's exposure (Klonoff-Cohen et al. 1995; Dwyer et al. 1999) suggest that using the smoking status of the father as an indirect indicator for exposure of the infant to tobacco smoke may result in a misclassification that would bias the estimated risk downward. Specifically, Klonoff-Cohen and colleagues (1995) reported that the adjusted OR for paternal smoking increased from 3.46 (95 percent CI, 1.91–6.28), based on the postpartum smoking status of the father, to 8.49 (95 percent CI, 3.33–21.63) when the father smoked in the same room as the infant.

Assessments of postnatal exposures from "other" smokers in the household are likely subject to more misclassification errors and may thus provide a weaker measure of exposure. In addition, sometimes these "other" exposures were reported for "other than maternal," thus including paternal smoking. Of the six studies that examined such "other" smoker estimates of postnatal exposure, two included smoking fathers in the "other" category and found nonsignificant overall effects (Schoendorf and Kiely 1992; Dwyer et al. 1999). But one of the studies that limited the "other" category to "mother's partner or other adult sometimes or always smokes while in the same room as infant" reported an OR of 1.96 (95 percent CI, 1.01–3.80) (Dwyer et al. 1999, p. 596). Four studies excluded postnatal parental smoking in the assessment of smoking by other adult residents (Klonoff-Cohen et al. 1995; Blair et al. 1996; Mitchell et al. 1997; Alm et al. 1998). Each of these studies observed a statistically significant effect without adjustment for other confounders; three of the studies provided adjusted ORs. The one study without adjustment found a weak dose-response effect for the amount smoked by others, but found an unadjusted OR of 4.12 (95 percent CI, 1.85–9.08) for 20 or more cigarettes per day smoked by other members of the household (excluding the parents) (Blair et al. 1996). Of the three studies with adjusted ORs, two were nonsignificant: 1.17 (95 percent CI, 0.84–1.63) (Mitchell et al. 1997) and 1.2 (95 percent CI, 0.6–2.2) (Alm et al. 1998); one remained significant: 2.18 (95 percent CI, 1.09–4.38) (Klonoff-Cohen et al. 1995). In this study by Klonoff-Cohen and colleagues (1995), the OR for other live-in adults who smoked in the same room as the infant was 4.99 (95 percent CI, 1.69–14.75), adjusted for birth weight, routine sleeping position, medical conditions at birth, prenatal care, breastfeeding, and maternal smoking during pregnancy.

A recent report by the European Concerted Action on SIDS (ECAS) provides additional supportive evidence (Carpenter et al. 2004). ECAS conducted a multicenter case-control study involving 745 SIDS cases (all with autopsies) and two or more live-birth controls per case (n = 2,411) matched by age and survey area. The multivariate analysis confirmed a significant increase in risk for SIDs after adjusting for sleeping position, older maternal age, more previous live births, and lower birth weight. The multivariate analysis of maternal smoking and household postnatal smoking (controlling for sleeping position, maternal age, number of previous live births, birth weight, and other variables) found no significant increase in risk for SIDs associated with bed sharing among mothers who did not smoke (OR = 1.56 [95 percent CI, 0.91–2.68]), but a highly significant risk associated with bed sharing among mothers who smoked (OR = 17.7 [95 percent CI, 10.3–30.3]). Among mothers who did not bed share, postnatal maternal smoking (unadjusted for prenatal smoking) significantly increased the risk of SIDs (<10 cigarettes per day, OR = 1.52 [95 percent CI, 1.10–2.09]; ≥10 cigarettes per day, OR = 2.43 [95 percent CI, 1.76–3.36]). In the multivariate analysis (adjusting for all of the above factors including maternal smoking but not prenatal smoking directly), researchers observed a risk associated with postnatal smoking by others in the household that increased from an OR of 1.07 (95 percent CI, 0.71–1.61) for 1 to 9 cigarettes per day to 1.54 (95 percent CI, 1.11–2.14) for 10 to 19 cigarettes per day, 1.73 (95 percent CI, 1.21–2.48) for 20 to 29 cigarettes per day, and 3.31 (95 percent CI, 1.84–5.96) for 30 or more cigarettes per day. These data provide additional evidence that postnatal smoking by other adults in the household independently increases the risk of SIDS.

Three studies used a case-control design to evaluate nicotine or cotinine as a biomarker of exposure at postmortem examinations in relation to the risk for SIDS. Rajs and colleagues (1997) measured nicotine and cotinine in pericardial fluid of SIDS and non-SIDS victims, all younger than one year of age at the time of their death. Mean values were similar in the two groups, but the children who died from SIDS included a greater proportion with cotinine values above 30 ng/mL. In a 1998 report based on a study with a similar design, Milerad and colleagues (1998) documented higher cotinine levels in children younger than seven years of age who had died suddenly compared with controls who had died of an infection. Because involuntary smoking increases the risk for childhood respiratory infection, the use of this control group may have underestimated the association of cotinine with a risk for sudden death. In addition, the inclusion of children up to seven years of age extends well beyond the traditional newborn period associated with SIDS. Finally, McMartin and colleagues (2002) compared lung tissue concentrations of nicotine and cotinine in deceased SIDS and non-SIDS infants who were younger than one year of age when they died. Both nicotine and cotinine concentrations were higher in the lungs of the SIDS victims.

Evidence Synthesis

The biologic evidence, especially from animal models, indicates multiple mechanisms by which exposure to secondhand smoke could cause SIDS (Chapter 2, Toxicology of Secondhand Smoke). The evidence for secondhand smoke exposure and the risk of SIDS consistently demonstrates an association between postpartum maternal smoking and SIDS (Table 5.5). The 1997 meta-analysis of 39 relevant studies produced an adjusted OR for postnatal maternal smoking of 1.94 (95 percent CI, 1.55–2.43), a level of risk that the authors concluded was almost certainly causal (Anderson and Cook 1997). Data from the four studies in Table 5.5 published since the 1997 meta-analysis add additional support for this conclusion. Nine of the thirteen studies in Table 5.5 more fully controlled for the major potential confounders (e.g., maternal smoking during pregnancy and routine sleeping position), and many controlled for a broad range of other relevant factors including maternal age, birth weight, and bed sharing. The nine studies all observed significant positive associations between postpartum maternal smoking and SIDS. Moreover, several studies demonstrated a dose-response relationship for secondhand smoke exposure attributable to postpartum maternal smoking, with increasing ORs for higher levels of postpartum maternal smoking. Finally, among the studies of postnatal maternal smoking with better adjustment for confounding, the adjusted ORs are sufficiently large, all greater than 1.5 and three of the five greater than 2.0. These ORs make it unlikely that this association is attributable to any residual confounding from unmeasured factors.

The epidemiologic evidence for secondhand smoke exposure from postpartum maternal smoking associated with the risk of SIDS is consistent and strong, and demonstrates a dose-response relationship. Evidence for secondhand smoke exposures from fathers and "other" smokers (as well as higher concentrations of nicotine and cotinine in children who die from SIDS compared with children who die of other causes) provides additional supporting evidence that secondhand smoke exposure increases the risk of SIDS. Although measures of paternal and "other" smokers in the household are not typically considered to be a comprehensive indicator of the infant's exposure to secondhand smoke, designs that can evaluate paternal smoking have the potential to more fully control for the possible confounding of maternal smoking during pregnancy. However, when considering evidence that supports an association between SIDS and paternal and "other" smokers, researchers also recognize the possible misclassification of actual infant exposures to tobacco smoke from these sources (Klonoff-Cohen et al. 1995; Dwyer et al. 1999). Despite this methodologic challenge, researchers observed an elevated OR in all nine studies of paternal smoking, ranging from 1.4 to 3.5, with many estimates around 2 or higher. Of these nine studies, five observed an elevated OR for households where the fathers smoked compared with households where neither parent smoked, and an OR of 8.5 for infants of fathers who smoked in the same room as the infant, adjusting for maternal smoking during pregnancy, routine sleeping position, and other factors. Also, out of the nine studies that examined paternal smoking, five found a statistically significant association between paternal smoking and SIDS after adjusting for maternal smoking during

pregnancy. Despite the potential for misclassification bias linking paternal smoking to an actual exposure of the infant to secondhand smoke, the pooled risk estimate was 1.9 (95 percent CI, 1.01–2.80) from the five studies of paternal smoking with stronger designs that used meta-analytic approaches and random effects modeling. Finally, all of the studies of "other" smokers in the household observed an elevated OR; however, the results that adjusted for maternal smoking during pregnancy and other important confounders were more mixed. The one study with the strongest assessment of infant exposures from "other" smoking residents (i.e., live-in adults smoking in the same room as the infant) reported an OR of 4.99 (95 percent CI, 1.69–14.75), with adjustment for multiple risk factors including maternal smoking during pregnancy and routine sleeping position (Klonoff-Cohen et al. 1995).

Researchers have established prenatal maternal smoking as a major preventable risk for SIDS (USDHHS 2001, 2004; AAP Task Force on SIDS 2005). Evidence indicates that exposure of infants to secondhand smoke from postpartum maternal smoking has a significant additive effect on risk if the mother smoked during pregnancy. In studies that accounted for maternal smoking during pregnancy, evidence indicates that postpartum maternal smoking, particularly in proximity to the infant, significantly increases the risk of SIDS. In addition, epidemiologic evidence indicates that postnatal exposure of infants to secondhand smoke from fathers or other live-in smokers can also increase the risk of SIDS. Thus, the full range of biologic and epidemiologic data are consistent and indicate that exposure of infants to secondhand smoke causes SIDS.

Conclusion

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Implications

On the basis of the epidemiologic risk data, researchers have estimated that the population attributable risk of SIDS associated with postnatal exposure to secondhand smoke is about 10 percent (Cal/EPA 2005). Therefore, the evidence indicates that these exposures are one of the major preventable risk factors for SIDS, and all measures should be taken to protect infants from exposure to secondhand smoke.

There is a need for additional research to further characterize the risk of SIDS associated with prenatal and postnatal exposure to secondhand smoke, and to evaluate the relationship between maternal smoking and infant sleeping positions and bed sharing. Future research should also focus on better assessments of actual exposures of infants to secondhand smoke using biochemical assessments and/or more detailed interviews, rather than indirect assessments based on the smoking status of household adults. Because of the continuing and significant racial disparities in infant mortality from SIDS (Malloy and Freeman 2004), there is a need to study the preventable risks factors that could be involved.

Preterm Delivery

Biologic Basis

Pregnancy complications, including premature labor, placenta previa, abruptio placentae, and premature membrane rupture may lead to preterm delivery (<37 completed weeks of gestation). Although the underlying mechanisms are not yet fully characterized, maternal active smoking is associated with these pregnancy complications (U.S. Department of Health, Education, and Welfare [USDHEW] 1979b; USDHHS 1980, 2001; Andres and Day 2000). Preterm delivery is also associated with active maternal smoking (USDHEW 1979a; USDHHS 1980, 2001; van den Berg and Oechsli 1984; Andres and Day 2000). Smoking cessation during pregnancy appears to reduce the risk for preterm delivery (van den Berg and Oechsli

1984; Li et al. 1993; Mainous and Hueston 1994b; USDHHS 2001), placenta previa (Naeye 1980), abruptio placentae (Naeye 1980), and premature membrane rupture (Harger et al. 1990; Williams et al. 1992); but the risk remains high for those who continue to smoke throughout pregnancy. Tobacco-specific nitrosamines and cotinine have been measured in the cervical mucus of women who were active smokers and women who were nonsmokers (McCann et al. 1992; Prokopczyk et al. 1997). Given that active maternal smoking is associated with preterm delivery, this finding provided further support for the biologic plausibility that secondhand smoke has a role in the injurious processes leading to preterm delivery. Although the biologic pathway from active maternal smoking to preterm delivery is not clear, the evidence for this association is strong enough to infer that maternal secondhand smoke exposure may also lead to preterm delivery.

Epidemiologic Evidence

Few data are available on the effects of maternal secondhand smoke exposure on preterm delivery, and published findings are inconsistent across studies. Four studies did not find a statistically significant association between maternal secondhand smoke exposure and preterm delivery (Table 5.6) (Martin and Bracken 1986; Ahlborg and Bodin 1991; Mathai et al. 1992; Fortier et al. 1994), but several others did report significantly increased risks with exposure to secondhand smoke (Ahluwalia et al. 1997; Hanke et al. 1999; Windham et al. 2000; Jaakkola et al. 2001). Hanke and colleagues (1999) reported an adjusted OR of 1.86 (95 percent CI, 1.05–3.45) for preterm delivery among nonsmoking mothers who were exposed to secondhand smoke for at least seven hours per day compared with unexposed mothers. Using the same secondhand smoke exposure category—exposed for at least seven hours per day—Windham and colleagues (2000) found an adjusted OR of 1.6 (95 percent CI, 0.87–2.9) for exposed, nonsmoking mothers compared with unexposed mothers. The risk increased to 2.8 (95 percent CI, 1.2–6.6) among women aged 30 or more years. Similarly, Ahluwalia and colleagues (1997) classified secondhand smoke exposure dichotomously as yes/no and also found an increased risk among nonsmoking women aged 30 or more years for preterm delivery when exposed to secondhand smoke (OR = 1.88 [95 percent CI, 1.22–2.88]), but the risk was not observed among nonsmoking women younger than 30 years of age (OR = 0.92 [95 percent CI, 0.76–1.13]). Jaakkola and colleagues (2001) used the hair nicotine level, a biologic measure of exposure to secondhand smoke among nonsmoking women. Those with the highest hair concentrations of nicotine (≥4.0 μg/gram [g]) had an adjusted OR of 6.12 (95 percent CI, 1.31–28.7) for preterm delivery when compared with women with the lowest or undetectable concentrations of hair nicotine. The limited epidemiologic evidence on maternal secondhand smoke exposure and preterm delivery currently does not warrant a meta-analysis of the relevant studies.

Evidence Synthesis

The few studies that have evaluated the association between secondhand smoke exposure and preterm delivery have shown inconsistent findings. Of the four studies that found significant associations, two studies documented that the risk was significant only for women aged 30 years or older. Jaakkola and colleagues (2001) provided the strongest evidence for an association using hair nicotine measurements, which reduce the probability of exposure misclassification. There is a biologic basis for considering this association to be causal.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Implications

Further research should be carried out, although studies of substantial size will be needed.

Table 5.6 Studies of secondhand smoke exposure and preterm delivery

Study	Design/population	Source of exposure	Outcome	Exposure categories
Martin and Bracken 1986	3,891 antenatal women seen between 1980 and 1982	Home and work, ≥2 hours/day	Preterm delivery	Yes/no
Ahlborg and Bodin 1991	4,687 prenatal women between October 1980 and June 1983	Home only Work only Both	Preterm delivery	Yes/no
Mathai et al. 1992	994 nonsmoking women receiving obstetric care at a hospital between January and May 1990	Home	Preterm delivery	Yes/no
Fortier et al. 1994	Sample of 4,644 women delivering between January and October 1989	Home only Work only Both	Preterm delivery	Yes/no
Ahluwalia et al. 1997	17,412 low-income women who received services from public maternal and child health clinics	Household members	Preterm delivery	Yes/no
Hanke et al. 1999	1,751 nonsmoking women from a randomly selected group of women who gave birth between June 1996 and May 1997	Home Work Other	Preterm delivery	No exposure 0–1 hour/day 2–3 hours/day 4–6 hours/day ≥7 hours/day
Windham et al. 2000	4,454 pregnant women in their first trimester at their first prenatal appointment through a health plan	Home and work	Preterm delivery Very preterm (<35 weeks)	No exposure: 0 to <0.5 hour/day Moderate exposure: 0.5–6.5 hours/day N = 625 High exposure: ≥7 hours/day N = 134
Jaakkola et al. 2001	389 nonsmoking women who gave birth between May 1996 and April 1997	Home and work	Preterm delivery	Hair nicotine concentrations: <0.75 μg/g[Δ] 0.75 to <4.0 μg/g ≥4.0 μg/g

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.
§AOR = Adjusted odds ratio.
Δμg/g = Micrograms per gram.

Findings	Comments
4.64% in unexposed nonsmokers 4.66% in exposed nonsmokers	No change in crude findings using regression analysis (data were not presented); secondhand smoke exposure showed no effect on preterm delivery
RR* = 0.49 (95% CI†, 0.23–1.06) RR = 1.86 (95% CI, 1.0–3.48) RR = 0.84 (95% CI, 0.53–1.33)	Adjusted; secondhand smoke exposure in the workplace was weakly associated with preterm birth
3.8% in unexposed nonsmokers 5.8% in exposed nonsmokers	Not statistically significant (data were not presented)
OR‡ = 0.93 (95% CI, 0.58–1.51) OR = 0.92 (95% CI, 0.64–1.31) OR = 0.98 (95% CI, 0.56–1.73)	Adjusted; secondhand smoke exposure was not related to preterm birth
Nonsmokers aged <30 years OR = 0.92 (95% CI, 0.76–1.13) Nonsmokers aged ≥30 years OR = 1.88 (95% CI, 1.22–2.88)	The association between secondhand smoke exposure and adverse pregnancy outcomes appears to be modified by maternal age
AOR§ = 0.54 (95% CI, 0.77–4.45) AOR = 1.24 (95% CI, 0.68–2.27) AOR = 1.73 (95% CI, 0.86–3.19) AOR = 1.86 (95% CI, 1.05–3.45)	Urine cotinine was measured in 71 women to verify nonsmoking status; maternal secondhand smoke exposure lasting ≥7 hours was a significant risk factor for preterm delivery; adjusted for maternal age, height, parity, employment, and marital status
Nonsmokers, high secondhand smoke exposure Preterm: AOR = 1.6 (95% CI, 0.87–2.9) Very preterm: AOR = 2.4 (95% CI, 1.0–5.3) Aged <30 years, high secondhand smoke exposure Preterm: AOR = 1.1 (95% CI, 0.46–2.6) Very preterm: AOR = 2.2 (95% CI, 0.75–6.6) Aged ≥30 years, high secondhand smoke exposure Preterm: AOR = 2.8 (95% CI, 1.2–6.6) Very preterm: AOR = 2.7 (95% CI, 0.74–9.7)	High secondhand smoke exposure was moderately associated with preterm birth and most strongly associated with very preterm birth; adjusted by logarithmic regression for prior pregnancy history, race, body mass index, life events, and education
AOR = 1.30 (95% CI, 0.30–5.58) AOR = 6.12 (95% CI, 1.31–28.7)	Adjusted for gender, birth order, maternal age, body mass index before pregnancy, marital status, socioeconomic status, alcohol consumption during pregnancy, and employment during pregnancy; results suggest an increase in the risk of preterm delivery

Low Birth Weight

Biologic Basis

Low birth weight (LBW), defined as less than 2,500 g or less than 5.5 pounds, can result from preterm delivery or intrauterine growth retardation (IUGR), which can occur simultaneously in a pregnancy. Reduced fetal physical growth during gestation, or IUGR, can lead to a small for gestational age (SGA) infant (≤10th percentile of expected birth weight for a given gestational age) that is either preterm or full term (≥37 weeks of gestation), and may or may not be LBW. The established link between active maternal smoking and LBW is known to occur mainly through IUGR rather than through premature birth (Chamberlain 1975; Coleman et al. 1979; Wilcox 1993). Fetal growth is greatest during the third trimester, and studies of active smoking during pregnancy demonstrate no reduction of infant birth weight if smoking ceases before the third trimester (USDHHS 1990, 2004). In 2003, 12.4 percent of births among smokers were LBW (Martin et al. 2005).

A number of researchers have postulated that the limitation of fetal growth from active maternal smoking comes from reduced oxygen to the fetus, which is directly attributable to CO exposure and nicotine-induced vasoconstriction leading to reduced uterine and umbilical blood flow (USDHHS 1990, 2004; Bruner and Forouzan 1991; Rajini et al. 1994; Lambers and Clark 1996; Werler 1997; Andres and Day 2000). Studies have shown elevated nucleated red blood cell counts, a marker of fetal hypoxia, among neonates of women who actively smoked during pregnancy (Yeruchimovich et al. 1999) and among women who were exposed to secondhand smoke (Dollberg et al. 2000). Several investigators have also found elevated erythropoietin, the protein that stimulates red blood cell production and another indicator of hypoxia, in cord blood of newborns whose mothers had smoked during pregnancy (Jazayeri et al. 1998; Gruslin et al. 2000). Because erythropoietin does not cross the placenta, it most likely originated from the fetus. A number of researchers have also reported that the concentration of erythropoietin is positively correlated with the concentration of cotinine measured in cord blood ($r = 0.41$, $p = 0.04$) (Gruslin et al. 2000), the number of cigarettes smoked per day by the mother ($r = 0.26$, $p < 0.0001$) (Jazayeri et al. 1998), and fetal growth retardation (r was not presented, $p < 0.01$) (Maier et al. 1993).

Studies have detected nicotine and its metabolites perinatally in umbilical cord serum in infants born to nonsmoking mothers, and in the cervical mucus of nonsmoking women; consequently, many researchers agree that the information on active maternal smoking is directly relevant to understanding the possible association of maternal secondhand smoke exposure and preterm delivery and LBW (USDHHS 2001). More direct evidence supports the hypothesis that maternal secondhand smoke exposure, specifically to nicotine, may lead to LBW through a pathway of fetal hypoxia (Çolak et al. 2002). One would expect attenuated physiologic effects from exposures to secondhand smoke than from active smoking based on relative dose levels, but the same biologic mechanisms of effect may apply.

Epidemiologic Evidence

A large body of literature is available on secondhand smoke exposure and LBW (Table 5.7). The first studies that reported an association were conducted in the 1960s (MacMahon et al. 1965; Comstock and Lundin 1967; Underwood et al. 1967; Terris and Gold 1969). These early studies found reductions in mean birth weight that ranged from 3 g (Underwood et al. 1967) to 42 g (Comstock and Lundin 1967) (CIs were not calculated) among infants with fathers who smoked compared with infants of nonsmoking fathers. A few relevant studies were published in the 1970s (Yerushalmy 1971; Mau and Netter 1974; Borlee et al. 1978), and one showed a statistically significant association. Borlee and colleagues (1978) found that the mean birth weight of infants of nonsmoking mothers and smoking fathers was 228 g less than the mean birth weight of infants with two nonsmoking parents. This study has been criticized, however, because the study population came from a case-control study of infants with malformations, and some evidence now indicates that both LBW (Xiao 1989; Xu 1992; Lin 1993; Samuelsen et al. 1998) and paternal smoking (Knorr 1979; Davis 1991; Savitz et al. 1991; Zhang et al. 1992; Fraga et al. 1996; Wasserman et al. 1996) are associated with birth defects.

Interest in the topic of LBW and secondhand smoke grew in the 1980s after the association between active maternal smoking during pregnancy and LBW had been established (USDHHS 1980; Stillman et al. 1986). Several investigators have reported RR estimates and adjusted OR estimates from studies published in the last two decades. These estimates have ranged from an OR of less than 1.0 (Sadler et al. 1999; Matsubara et al. 2000) to an OR of 2.31 (Mainous and Hueston 1994a) and, as a whole, have suggested that having a LBW infant is associated with maternal exposure to secondhand smoke. Some investigators have compared mean birth weights of infants whose mothers were exposed to secondhand smoke with infants of unexposed mothers. The results from these studies showed reductions in birth weights among the exposed groups that ranged from 1 g (Sadler et al. 1999; Haug et al. 2000) to 253 g (Luciano et al. 1998). In a 1998 meta-analysis of 11 studies, Peacock and colleagues (1998) found that the mean birth weight for infants of secondhand smoke-exposed mothers was 31 g less (95 percent CI, 19–44) than infants of unexposed mothers. Similarly, in a 1999 meta-analysis of secondhand smoke and LBW literature (19 studies), the summary estimates were an OR of 1.2 for LBW at term or SGA (95 percent CI, 1.1–1.3), and a difference in mean adjusted birth weights of -28 g (95 percent CI, -41 to -16) for infants of nonsmoking mothers exposed to secondhand smoke compared with infants of unexposed mothers (Windham et al. 1999a). The 1999 meta-analysis included most of the studies that were in the earlier 1998 analysis, plus a retrospective study of 992 nonsmoking pregnant women contacted by Windham and colleagues. The estimated reductions for the meta-analysis in mean birth weight were statistically significant in both meta-analyses, but a reduction of 30 g (approximately 1.24 ounces) would not be clinically significant to individual infants at low risk. On a population level, however, a slight shift in the birth weight distribution could put infants already at risk into greater risk for complications associated with LBW.

Some investigators have evaluated dose-response associations using cotinine or nicotine measures (Haddow et al. 1988; Nafstad et al. 1998), self-reported levels of exposure to secondhand smoke (Zhang and Ratcliffe 1993; Mainous and Hueston 1994a), or both (Rebagliato et al. 1995b). Of the five studies that examined these trends, findings in two studies (Haddow et al. 1988; Mainous and Hueston 1994a) suggested that a dose-response relationship exists between secondhand smoke exposure and birth weight. Haddow and colleagues (1988) measured maternal serum cotinine during the second trimester and found higher levels among nonsmoking mothers whose infants had lower mean birth weights. The adjusted mean birth weights were 3,535 g, 3,531 g, and 3,481 g for low, medium, and high cotinine levels, respectively. These results led Haddow and colleagues (1988) to "suggest that the linear model may not best reflect the true dose-response relationship" (p. 484). The difference in adjusted mean birth weights between the low- and high-exposure groups was statistically significant ($p < 0.001$). Mainous and Hueston (1994a) obtained secondhand smoke exposure information from the 1988 National Health Interview Survey and found statistically significant trends between increasing levels of maternal secondhand smoke exposure and an increase in proportions of LBW infants ($p = 0.01$) and a decrease in mean birth weights ($p = 0.007$).

Although the other three studies that evaluated dose-response relationships did not find any trends, two of those studies did find evidence of an association between maternal secondhand smoke exposure and reduced birth weight. Nafstad and colleagues (1998) measured hair nicotine levels and found that nonsmoking mothers whose nicotine levels were within the two middle quartiles were at an increased risk for having a SGA child compared with nonsmoking mothers whose nicotine levels were within the lowest quartile (OR = 3.4 [95 percent CI, 1.3–8.6]). For nonsmoking mothers with hair nicotine levels in the highest quartile, the estimated risk of having a SGA child was 2.1 (95 percent CI, 0.4–10.1). Zhang and Ratcliffe (1993) used paternal smoking as a measure of exposure to secondhand smoke and found that, compared with infants from the unexposed group, the exposed group had a mean birth weight that was 30 g lower. The mean birth weights did not decrease in a linear or monotonic manner with increasing exposure levels. Rebagliato and colleagues (1995b) also examined dose-response associations and did not find any significant trends with exposures at home, at work, from the partner, from all reported sources combined, or with measured cotinine levels. Increases in maternal exposures to secondhand smoke in public places, however, did show a significant dose-response trend with decreases in mean birth weights ($p = 0.028$).

Another means of looking for an exposure-response trend is by dividing exposure sources into home and work. One would expect that

Table 5.7 Summary of published literature on secondhand smoke and low birth weight (LBW)

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
MacMahon et al. 1965 United States	Cohort	12,192	Husband	NR*	• Mean birth weight difference: -0.7 ounces (oz.) in boys • Mean birth weight difference: -0.8 oz. in girls • No association
Comstock and Lundin 1967 United States	Cohort	448	Husband	NR	• Mean birth weight difference: -42 g† • No association
Underwood et al. 1967 United States	Cohort	24,674	Husband	NR	• Mean birth weight difference: -3 g • No association
Terris and Gold 1969 United States	Case-control	197 197	Husband	NR	• No significant difference • No association
Yerushalmy 1971 United States	Cohort	13,000	Husband	NR	• Significant association with LBW among Whites but not among Blacks • Possible association
Mau and Netter 1974 Germany	Cohort	3,696	Husband	NR	• RR = 1.2 for IUGR‡ • RR = 1.4 for LBW • No significant association
Borlee et al. 1978 Belgium	Cohort	238	Husband	NR	• Mean birth weight difference: -228 g (statistically significant) • Significant association
Hauth et al. 1984 United States	Cohort	163	All (serum thiocyanate)	NR	• No difference in birth weights for infants of involuntary smokers compared with those of nonsmokers • No association
Magnus et al. 1984 Norway	Cohort	3,130	Husband	NR	• Mean birth weight difference: -4.9 (standard deviation = 9.3) per 10 cigarettes/day • No association
Karakostov 1985 Bulgaria	Cohort	NR	NR	NR	• Mean birth weight difference: -84 g • Mean height difference: -0.5 cm§ • No significant association
Martin and Bracken 1986 United States	Cohort	4,186	Both home and work	NR	• Mean birth weight difference: -23.5 g (95% CI△, -59.9–12.8) • RR¶ = 2.17 (95% CI, 1.05–4.50)
Rubin et al. 1986 Denmark	Cohort	500	Husband	NR	• Mean birth weight difference: -120 g/pack/day • Mean birth weight difference: -6.1 g/cigarette/day ($p < 0.03$) • RR = 2.17 (95% CI, 1.05–4.50)

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
MacArthur and Knox 1987 Britain	Cohort	180	Husband	NR	• Mean birth weight difference: 123 g ($p < 0.02$) • No association
Schwartz-Bickenbach et al. 1987 Germany	Cohort	38	Home	Breast milk and infant's urine	• Mean birth weight difference: -200 g • Association
Campbell et al. 1988 Britain	Cohort	518	Husband	NR	• Mean birth weight difference: -113 g (95% CI, -216 to -8), $p = 0.03$ • Significant association
Haddow et al. 1988 United States	Cohort	1,231	Both home and work	Serum	• Mean birth weight difference: -108 g ($p < 0.0001$) • 29% had LBW • Sufficient evidence for an association (possible nonlinear dose-response)
Brooke et al. 1989 Britain	Cohort	1,018	Home	NR	• -0.5% in birth weight ratio ($p = 0.56$) • Mean birth weight difference: -18 g • No association
Chen et al. 1989 China	Cohort	1,058	Home	NR	• Mean birth weight difference: -15 g ($p = 0.92$) • 0.7% had LBW ($p = 0.67$) • No association
Ueda et al. 1989 Japan	Cohort	259	Both home and work	Maternal urine, umbilical cord blood	• No specified findings • Significant association
Lazzaroni et al. 1990 Italy	Cohort	1,002	Both home and work	NR	• Mean birth weight difference: -16 g/hour/day of secondhand smoke exposure ($p < 0.07$); -38.16 g (95% CI, -106.9–30.7) overall birth weight • -0.26 cm (95% CI, -5.6–0.03) overall length • Possible association
Mathai et al. 1990 Britain	Cohort	300	Home	Urine	• Mean birth weight difference: -66 g (questionnaire) • Nonsignificant association
Ahlborg and Bodin 1991 Sweden	Cohort	4,687	Both home and work	NR	• RR = 0.99 (95% CI, 0.45–2.21) for both home and work • RR = 0.69 (95% CI, 0.21–2.27) for home only • RR = 1.09 (95% CI, 0.33–3.62) for work only • RR = 1.83 (95% CI, 0.53–6.28) for work in the third trimester • Nonsignificant association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Ogawa et al. 1991 Japan	Cohort	5,336	Both home and work	NR	• Mean birth weight difference: -24 g (95% CI, -5 to -54) • RR for IUGR = 1.0 (95% CI, 0.7–1.5) • No association
Saito 1991 Japan	Cohort	3,025	Husband	NR	• RR = 1.21 • Significant association
Mathai et al. 1992 India	Cohort	994	Both home and work	NR	• Mean birth weight difference: -63 g (95% CI, -114 to -12) • Significant association
Pan 1992 China	Cohort	253	Husband	NR	• Higher SGA** rate in the exposed group • No specified association
Zhang and Ratcliffe 1993 China	Cohort	1,785	Husband	NR	• Mean birth weight: -30 g (95% CI, -66–7) • LBW: 0.17% • SGA: 0.20% • Possible association
Fortier et al. 1994 Canada	Cohort	4,644	Both home and work	NR	• OR†† = 0.94 (95% CI, 0.60–1.49) for both home and work • OR = 0.98 (95% CI, 0.67–1.44) for home only • OR = 1.18 (95% CI, 0.90–1.56) for work only • Nonsignificant association/inconclusive
Mainous and Hueston 1994a United States	Cohort	3,253	Both home and work	NR	• Mean birth weight difference: -84 g • 3.6% had LBW • OR for LBW = 1.59 (95% CI, 0.92–2.73) • OR for LBW in non-Whites = 2.31 (95% CI, 1.06–4.99) • Association with high exposure (threshold effect)
Martinez et al. 1994 United States	Cohort	1,219	Husband	Cord serum	• Mean birth weight difference: -88 g • Significant association
Chen and Petitti 1995 United States	Case-control	111 124	Both home and work	NR	• OR = 0.50 (95% CI, 0.14–1.74) • No association
Eskenazi et al. 1995 United States	Cohort	3,896	NR	Serum	• Mean birth weight difference: -42 g • RR for LBW = 1.35 (95% CI, 0.60–3.03) • Nonsignificant association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Rebagliato et al. 1995b Spain	Cohort	710	Both home and work	Saliva	• Mean birth weight difference: -88 g (measured by cotinine); -41 g (questionnaire) • Nonsignificant association
Roquer et al. 1995 Spain	Cohort	76	Both home and work	NR	• Mean birth weight difference: -192 g • Association
Jedrychowski and Flak 1996 Poland	Cohort	1,165	NR	Serum	• Mean birth weight difference: -73.1 g • Significant association
Ahluwalia et al. 1997 United States	Cohort	17,412	Home	NR	• Mothers aged <30 years Mean birth weight difference: -8.8 g (95% CI, -43.7–26.1) • Mothers aged ≥30 years Mean birth weight difference: 90.0 g (95% CI, -0.8–180.9) • Inconclusive for SGA • Association for LBW in the group aged ≥30 years
Dejin-Karlsson et al. 1998 Sweden	Cohort	872	Both home and work	NR	• OR for SGA = 2.3 (95% CI, 1.1–4.6) • OR for LBW = 1.3 (95% CI, 0.7–2.5) • SGA crude OR in nonsmokers = 2.4 (95% CI, 1.02–5.8)
Luciano et al. 1998 Italy	Cohort	112	Both home and work	NR	• Mean birth weight difference: -253.5 g
Nafstad et al. 1998 Norway	Case-control	58 105	Both home and work	Hair	• OR in nonsmokers = 1.4 (95% CI, 0.4–4.4)
Hanke et al. 1999 Poland	Cohort	1,751	Both home and work	NR	NR
Sadler et al. 1999 United States	Cohort	2,283	Both home and work	NR	• OR for SGA = 0.82 (95% CI, 0.51–1.33) • Mean birth weight difference: -1.2 g (95% CI, -43.3–41.0)
Windham et al. 1999a United States	Cohort	992	Husband	NR	• OR for LBW = 1.8 (95% CI, 0.64–4.8) • OR for SGA = 1.4 (95% CI, 0.79–2.5)
Haug et al. 2000 Norway	Cohort	34,799	Husband	NR	• Mean birth weight difference: -1 g • No association
Matsubara et al. 2000 Japan	Cohort	7,411	Husband Both home and work	NR	Husband RR for LBW = 0.92 (95% CI, 0.71–1.20) RR for IUGR = 0.95 (95% CI, 0.72–1.26) Both home and work RR for LBW = 0.99 (95% CI, 0.77–1.30) RR for IUGR = 0.95 (95% CI, 0.71–1.26) No association

Table 5.7 Continued

Study Location	Design	Population size	Source of secondhand smoke	Cotinine measure	Findings
Windham et al. 2000 United States	Cohort	4,454	Both home and work	NR	• Adjusted OR for LBW = 1.8 (95% CI, 0.82–4.1) • Moderate association
Jaakkola et al. 2001 Finland	Cohort	389	Both home and work	Postpartum maternal hair nicotine	• OR for LBW = 1.06 (95% CI, 0.96–1.17) • OR for SGA = 1.04 (95% CI, 0.92–1.19) • Nonsignificant association

*NR = Data were not reported.
†g = Grams.
‡IUGR = Intrauterine growth retardation.
§cm = Centimeters.
ΔCI = Confidence interval.
¶RR = Relative risk.
**SGA = Small for gestational age.
††OR = Odds ratio.

combined exposures from both sources would lead to greater risks of LBW than would exposure from only one of the two sources, but Ahlborg and Bodin (1991) did not find this to be the case. The adjusted RR for LBW among nonsmokers with any secondhand smoke exposure either at home or at work was 0.99 (95 percent CI, 0.45–2.21), but the risks with exposure in the home only and in the workplace only were 0.69 (95 percent CI, 0.21–2.27) and 1.09 (95 percent CI, 0.33–3.62), respectively. Similarly, Fortier and colleagues (1994) did not find any exposure-response trend for SGA when risks were estimated for secondhand smoke exposure in the home only (OR = 0.98 [95 percent CI, 0.67–1.44]), at work only (OR = 1.18 [95 percent CI, 0.90–1.56]), and at both home and work (OR = 0.94 [95 percent CI, 0.60–1.49]). For any exposure either at home or at work, the estimated risk for SGA was 1.09 (95 percent CI, 0.85–1.39).

Evidence Synthesis

The risk estimates for secondhand smoke exposure and LBW have generally been small and have been consistent with the expectation that exposure to secondhand smoke should produce a smaller effect than exposure to active smoking. Most studies show a reduction in the mean birth weight and an increased risk for LBW among infants whose mothers were exposed to secondhand smoke. Across the studies, diverse potential confounding factors have been considered. Despite the lack of statistical significance in many of the studies, the consistencies seen in the literature have been summarized in several published reviews and have provided the strongest argument for an association between secondhand smoke and LBW. There are several plausible mechanisms by which secondhand smoke exposure could influence birth weight. Three comprehensive reviews of the literature on secondhand smoke and LBW that were published in the past decade all found a small increase in risk for LBW or SGA associated with secondhand smoke exposure (Misra and Nguyen 1999; Windham et al. 1999a; Lindbohm et al. 2002). Based on all of the studies that reported on LBW at term or SGA and secondhand smoke exposure, a meta-analysis provided a weighted pooled risk estimate of 1.2 (95 percent CI, 1.1–1.3) for this association (Windham et al. 1999a). Given the published review and meta-analysis by Windham and colleagues (1999a), an updated meta-analysis of the relevant studies on maternal secondhand smoke exposure and birth weight currently is not warranted.

Conclusion

1. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Implications

Secondhand smoke exposure represents an avoidable contribution to birth weight reductions. Women, when pregnant, should not smoke or be exposed to secondhand smoke.

Congenital Malformations

Biologic Basis

Because of the direct fetal effects observed with exposure to tobacco smoke and because of the chemically complex and teratogenic nature of cigarette smoke, researchers have addressed the association between exposure to tobacco smoke and congenital malformations. Most of this literature has focused on active smoking during pregnancy by the mother, but a few studies have examined secondhand smoke exposure. The etiology of most congenital malformations is not fully elaborated (Werler 1997), and no studies have been conducted to identify the mechanisms by which exposure to secondhand smoke may result in congenital malformations in humans. The few studies that have assessed the effects of sidestream smoke in animals have produced little evidence to support an association of secondhand smoke exposure and malformations (NCI 1999). Some recent studies suggest that susceptibility to some malformations may depend in part on the presence of genes that increase susceptibility to tobacco smoke (Wyszynski et al. 1997). Other proposed mechanisms include teratogenic effects of high concentrations of carboxyhemoglobin and nicotine, or malformations that are the result of exposure to some yet unidentified component of the tobacco plant shown to be teratogenic if ingested by animals (Seidman and Mashiach 1991).

The evidence on the relationship between maternal smoking during pregnancy and congenital malformations is inconsistent. Most studies have reported no association between maternal smoking and congenital malformations as a whole. However, for selected malformations, particularly oral clefts, several studies have reported positive associations with active smoking during pregnancy by the mother (Little et al. 2004a,b; Meyer et al. 2004). In fact, recent studies on gene-environment interactions have furthered the etiologic understanding of oral clefts and the role of smoking (Hwang et al. 1995; Shaw et al. 1996; van Rooij et al. 2001, 2002; Lammer et al. 2004).

Epidemiologic Evidence

Of six studies that collected data on involuntary smoking and congenital malformations, two had very large sample sizes (Table 5.8). Holmberg and Nurminen (1980) examined occupational exposures among parents of infants born with congenital malformations and of control infants matched for date of birth and geographic area in Finland from 1976 to 1978. The researchers found that the distribution of paternal smoking around the time that the woman became pregnant was similar in the cases with CNS defects and their matched controls. Savitz and colleagues (1991) analyzed data collected between 1964 and 1967 on children five years of age from the Child Health and Development Studies (N = 14,685). The researchers examined 33 different malformations in relation to paternal smoking and 4 malformations—cleft lip with or without cleft palate, hydrocephalus, ventricular septal defect, and urethral stenosis—for dose-response relationships. Although prevalence ORs were 2.0 or greater for selected outcomes, the lower 95 percent confidence limits reached below 1.0 once adjustments for potential confounders were made for maternal smoking, maternal age, maternal race, and maternal education. These selected outcomes were hydrocephalus (OR = 2.4 [95 percent CI, 0.06–9.3]), ventricular septal defect (OR = 2.0 [95 percent CI, 0.9–4.3]), and urethral stenosis (OR = 2.0 [95 percent CI, 0.6–6.4]). Strabismus (OR = 0.7 [95 percent CI, 0.5–0.9]) and pyloric stenosis (OR = 0.2 [95 percent CI, 0.2–0.8]), however, occurred in significantly fewer infants with smoking fathers compared with infants of nonsmoking fathers.

Table 5.8 Studies of secondhand smoke exposure and congenital malformations

Study	Design/population	Exposure categories	Source of exposure
Holmberg and Nurminen 1980	Case-control (200) Children who were reported to the national birth defects registry and matched controls Finland	NR*	• Paternal secondhand smoke • Mothers were nonsmokers
Seidman et al. 1990	Retrospective cohort (17,152) Women on first or second postpartum day Israel	0 packs/day <1 pack/day ≥1 pack/day	• Maternal prenatal
Savitz et al. 1991	Prospective longitudinal (14,685) Children enrolled in Child Health and Development Studies between 1964 and 1967 in the San Francisco East Bay area of California United States	<20 cigarettes/day ≥20 cigarettes/day	• Paternal secondhand smoke
Zhang et al. 1992	Case-control (2,024) Birth defects were identified in the Shanghai Municipality during October 1986–September 1987 China	Nonsmokers 1–9 cigarettes/day 10–19 cigarettes/day ≥20 cigarettes/day	• Paternal
Shaw et al. 1996	Population-based case-control study Mothers of infants with orofacial cleft (731) and nonmalformed controls (734)	0 cigarettes/day 1–19 cigarettes/day ≥20 cigarettes/day	• Paternal periconceptional

Outcome	Findings	Comments
Congenital defects of the CNS[†]	• No significant association was found between smoking and CNS defects	All data were self-reported through maternal interviews; smoking was not the primary aim of the study; no adjustments were made except for maternal smoking status
Congenital anomalies	• No correlation was found between smoking behaviors and malformations of the cardiovascular, gastrointestinal, and CNS, or incidence of hypospadias • Slightly higher but not statistically significant incidence of cleft palate, cleft lip, spina bifida, and genitourinary system anomalies • Together with increased age (>35 years), smoking increased the risk of congenital malformations ($p < 0.002$) • Maternal age alone was associated with congenital malformations ($p < 0.005$)	Reproductive histories were self-reported through maternal interviews; maternal smoking may be a preventable risk factor for congenital anomalies among mothers aged ≥35 years
Congenital anomalies	• Urethral stenosis (POR[‡] = 2.4 [95% CI, 0.7–8.5]), cleft lip, and cleft palate (POR = 1.9 [95% CI, 0.5–7.3]) were more commonly seen in children of fathers who were heavy smokers	Source exposure data were reported through maternal intake interviews; assessment of paternal age, smoking, and alcohol consumption on fetal birth outcomes; outcomes were assessed independently by two physicians; this study does not strongly support the hypothesis that paternal smoking behavior is associated with birth defects
Congenital anomalies	• A modest relationship was detected between overall birth defects and paternal smoking behavior (OR[§] = 1.21 [95% CI, 1.01–1.45]) • Higher overall ORs (not broken down by the amount of exposure) for parental smoking and anencephalus (OR = 2.1), spina bifida (OR = 1.9), pigmentary anomalies of the skin (OR = 3.3), and varus/valgus deformities of the feet (OR = 1.8)	Source exposure data were reported through maternal interviews; a paternally mediated effect of smoking on birth defects is suggested and further research is encouraged
Orofacial cleft	• OR = 2.1 (95% CI, 1.3–3.6) for cleft lip with or without cleft palate and OR = 2.2 (95% CI, 1.1–4.5) for isolated cleft palate when mothers smoked ≥20 cigarettes/day • Clefting risks were even greater for infants with the transforming growth factor α (TGFα), ranging from 3-fold to 11-fold across phenotypic groups in White infants • Paternal smoking was not associated with clefting among the offspring of nonsmoking mothers • Secondhand smoke exposures were associated with slightly increased risks	Parental smoking information was obtained from telephone interviews with mothers; DNA was obtained from newborn screening blood spots and genotyped for the allelic variants of TGFα; controlling for the potential influence of other variables did not reveal substantially different results

Table 5.8 Continued

Study	Design/population	Exposure categories	Source of exposure
Wasserman et al. 1996	Case-control Mothers of infants with conotruncal heart defects (207), neural tube defects (264), limb deficiencies (178), and live-born controls (481)	0 cigarettes/day 1–19 cigarettes/day ≥20 cigarettes/day	• Maternal prenatal and postnatal • Paternal prenatal and postnatal • Home environment • Work environment • Any environment

*NR = Data were not reported.
†CNS = Central nervous system.
‡POR = Prevalence odds ratio.
§OR = Odds ratio.

Seidman and colleagues (1990) conducted immediate postpartum interviews with mothers of 17,152 infants from the three largest obstetrics units in Jerusalem; the data yielded crude ORs that showed no significant associations between paternal smoking and major anomalies (e.g., chromosomal anomalies, CNS anomalies, heart defects, cleft lip with or without cleft palate, omphalocele, diaphragmatic hernia, bowel atresias, hermaphroditism, and conjoined twins). Zhang and colleagues (1992) studied 1,012 infants with birth defects and 1,012 infants without birth defects (control group) from 10 urban districts and 29 hospitals in Shanghai. Mothers were interviewed while in the hospital. Although no adjustments were made for potential confounding variables, the investigators noted that the sample had very few families with characteristics pointing to potential confounders and that the two mothers who smoked were eliminated from the sample. In age-adjusted analyses, the investigators found that paternal smoking was associated with a slightly elevated risk among infants with birth defects (OR = 1.2 [95 percent CI, 1.01–1.45]). The researchers also investigated 25 types of malformations and observed that selected malformations were associated with paternal smoking when dose-response relationships were examined. Infants with pigmentary anomalies of the skin were more likely to have fathers who were moderate smokers (10 to 19 cigarettes per day, OR = 4.1 [95 percent CI, 1.2–14.7]); infants with spina bifida were more likely to have fathers who were heavy smokers (≥20 cigarettes per day, OR = 3.2 [95 percent CI, 1.1–9.2]); and infants with multiple defects were more likely to have fathers who smoked 1 to 9 cigarettes per day (OR = 1.74 [95 percent CI, 1.16–2.61]). Most malformations, however, were not associated with involuntary smoking.

Using maternal interviews, Shaw and colleagues (1996) assessed the association between secondhand smoke exposure during pregnancy and oral clefts. There were conflicting results for nonsmoking mothers exposed to secondhand smoke, with very few significant associations among seemingly small numbers of observations. Wasserman and colleagues (1996) examined associations between secondhand smoke exposure among nonsmoking women and risks for

Outcome	Findings	Comments
Conotruncal heart defects Neural tube defects Limb deficiencies	• OR = 1.9 (95% CI, 1.2–3.1) for conotruncal heart defects when both parents smoked compared with neither • OR = 1.7 (95% CI, 0.96–2.9) for limb deficiencies when both parents smoked compared with neither • No significant increase in risk was associated with maternal smoking in the absence of paternal smoking • An increased risk was associated with heavy paternal smoking in the absence of maternal smoking for limb deficiencies in offspring (OR = 2.1 [95% CI, 1.3–3.6]) • For conotruncal defects, the risks associated with parental smoking differed among racial and ethnic groups • Parental smoking was not associated with increased risks for neural tube defects (Father only, OR = 1.1 [95% CI, 0.76–1.7]; Mother only, OR = 0.56 [95% CI, 0.30–1.0]; Both parents, OR = 1.0 [95% CI, 0.62–1.7])	All data were self-reported through maternal interviews; observed risks did not change substantially when adjusted for maternal vitamin use, alcohol use, and gravidity

heart malformations, neural tube defects, and limb defects. With one exception, secondhand smoke exposure was not associated with these congenital malformations. For tetralogy of Fallot, nonsmoking women exposed at work (but not at home or at "any location") had an OR of 2.9 (95 percent CI, 1.3–6.5) for exposure to secondhand smoke compared with those who were not exposed. However, given the multiple associations examined in this study, and given the inconsistent results for this malformation and the other sources of secondhand smoke, this particular association may have resulted by chance alone.

Evidence Synthesis

The evidence regarding the relationship between involuntary smoking and congenital malformations is inconsistent. The few studies that have been conducted have reported no association between involuntary smoking and specific or all congenital malformations.

Investigating congenital malformations is challenging because of the sample size that is necessary to study specific malformations. To date, few clues are available regarding the hypothesized biologic mechanisms of tobacco smoke and congenital malformations. Although two studies have reported elevated rates of neural tube defects in association with involuntary smoking, this association should be examined further in future studies.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Implications

The topic of tobacco smoke exposure and congenital malformations merits further investigation, particularly in part because of the teratogenic nature of tobacco smoke.

Cognitive, Behavioral, and Physical Development

Biologic Basis

In recent years, studies have suggested that exposure to tobacco smoke during pregnancy and childhood may affect the physical and cognitive development of the growing child. Researchers who examine the effects of these exposures on childhood outcomes need to account for potential confounding factors that reflect the various correlates of secondhand smoke exposure that also affect development. For example, factors that may affect physical and cognitive development include social class, parental education, the home environment as it relates to stimulation and developmentally appropriate exposures, and pregnancy-related factors such as voluntary and involuntary smoking and alcohol and substance use. Birth weight may also be a confounding factor because it is associated with both smoking (voluntary and involuntary) and physical and cognitive development. However, some researchers argue that adjusting for birth weight may overcontrol because it may be in the causal pathway from exposure to tobacco before birth to the time when childhood outcomes are assessed (Baghurst et al. 1992).

Another methodologic challenge lies in differentiating the effects of exposure to tobacco during and after pregnancy. This differentiation is often not possible because of the high correlation of tobacco smoke exposure for these two time periods. Studies with sufficient populations and detailed information on smoking status during both pregnancy and the postpartum period have been able to stratify participants into exposure groups: no prenatal or postpartum exposure, no prenatal but some postpartum exposure, and both prenatal and postpartum exposures. Other studies have examined the effects of secondhand smoke exposure from adults other than the mother among those children whose mothers did not smoke during pregnancy. These categories have served to partially address the timing of the exposures and, in particular, to control for exposures during pregnancy.

The mechanisms by which exposures to secondhand smoke may lead to compromised physical and cognitive development have not been fully explained and may be complex. Some of the mechanisms may be similar to those proposed for maternal smoking during pregnancy, such as hypoxia or the potentially teratogenic effects of tobacco smoke (USDHHS 1990; Bruner and Forouzan 1991; Lambers and Clark 1996; Werler 1997). Studies document that components of secondhand and mainstream smoke are qualitatively similar to those of sidestream smoke, but quantitative data for doses of tobacco smoke components that reach the fetus across the placenta from active and involuntary maternal smoking have not been available (Slotkin 1998). This consideration is particularly important for outcomes assessed after one year of age because the child's exposure will have occurred for a period of time longer than the exposure of the fetus during the nine months of pregnancy.

For cognitive development, investigators have proposed a number of effects on CNS development from smoking in general and nicotine in particular. First, the fetus may suffer from hypoxia as a result of reduced blood flow or reduced oxygen levels (USDHHS 1990; Lambers and Clark 1996). Alterations in the peripheral autonomic pathways may lead to an increased susceptibility to hypoxia-induced, short-term and long-term brain damage (Slotkin 1998). In one review of prenatal nicotine exposure, Ernst and colleagues (2001) summarized numerous animal studies that document the impact of nicotine on cognitive processes of exposed rats and guinea pigs, such as slowed learning or increased attention or memory deficits. These investigators identified animal as well as human studies that have demonstrated adverse effects of nicotine exposure on neural functioning. Exposure to nicotine alters enzyme activity and thus affects brain development, and alters molecular processes that affect neurotransmitter systems and lead to permanent neural abnormalities (Ernst et al. 2001).

Cognitive Development

Epidemiologic Evidence

Twelve studies have examined the effects of secondhand smoke exposure on cognitive development in children (Table 5.9) (Rantakallio 1983; Bauman et al. 1989, 1991; Makin et al. 1991; Baghurst et al. 1992; Roeleveld et al. 1992; Schulte-Hobein et al. 1992; Byrd and Weitzman 1994; McCartney et al. 1994; Olds et al. 1994; Fried et al. 1997, 1998). The age ranges of the children varied from infants to older

adolescents. Hence, the tools used to assess cognitive development also varied and included measures of intelligence, reading and language scores, school grade retention (staying in a grade for an additional year), and various standardized cognitive functioning tests. Four studies found no association between secondhand smoke exposure and cognitive outcomes among infants and children (Baghurst et al. 1992; Schulte-Hobein et al. 1992; McCartney et al. 1994; Fried et al. 1997); four other studies reported findings that varied across outcome measures (Bauman et al. 1991; Makin et al. 1991; Olds et al. 1994; Fried et al. 1998). For example, Makin and colleagues (1991) used standardized assessments to measure skills in the following areas: speech, language, intelligence, and visual and spatial processing. The authors examined involuntary smoking during pregnancy and controlled for potential confounders such as maternal education, maternal age, and family income. Results from 14 specific standardized tests indicated significant differences between exposed and unexposed groups in 11 of the tests. Similarly, Fried and colleagues (1997) examined the effects of prenatal and postpartum secondhand smoke exposures on 131 children aged 9 through 12 years who were given standardized reading and language assessments. For the prenatal period, the investigators considered only those mothers who were not smokers and found no association between prenatal or postpartum exposures and reading skills. For language skills, however, postpartum secondhand smoke exposures were associated with lower language levels among exposed versus the unexposed children (Fried et al. 1997). Several other investigators also reported associations with cognitive development (Rantakallio 1983; Bauman et al. 1989), mental retardation (Roeleveld et al. 1992), or school performance (Byrd and Weitzman 1994). Roeleveld and colleagues (1992) examined cigarette, pipe, and cigar smoking; only secondhand smoke exposures to pipe and cigar smoke during pregnancy and in the first six months of the infant's life were associated with an increased risk for mental retardation. Bauman and colleagues (1989) studied unexposed adolescents and adolescents who had been exposed to secondhand smoke from family members. The investigators examined overall and domain-specific California Achievement Test scores for math, language, reading, and spelling to identify differences between these two groups of adolescents. After considering several potential confounding factors, including active adolescent smoking, the investigators found that test performance decreased as smoking levels of the family increased.

Evidence Synthesis

The literature cited in this discussion examined the effects of involuntary smoking on children's cognitive development. However, it is difficult to synthesize the results of these studies because the ages of the children, the assessed exposures, and the outcomes vary across and even within studies. Moreover, some of the findings across and within studies are inconsistent. Eight of the 12 studies that examined associations between involuntary smoking and children's cognitive development reported associations between secondhand smoke exposures and reduced levels of cognitive development; these investigators had used a variety of assessments, such as performance on standardized tests, grade retention, or a diagnosis of mental retardation. The use of various cognitive measures across studies precludes an assessment of consistency with specific associations. Yet the finding that secondhand smoke exposure was associated with several different outcomes suggests that exposure may, indeed, impact the cognitive development of children. More studies are clearly needed; of the studies that have been conducted, there is a need for additional efforts to replicate findings.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Implications

Further research is needed but there are complex challenges to carrying out such studies, given the need for longitudinal design and consideration of the many factors affecting cognitive functioning.

Behavioral Development

Epidemiologic Evidence

Three studies examined associations between secondhand smoke exposures and behavioral problems among children (Table 5.10) (Makin et al. 1991; Weitzman et al. 1992; Fergusson et al. 1993). Weitzman and colleagues (1992) studied children aged 4 through 11 years and reported that after adjusting for several potential confounders, heavy maternal smoking after delivery was associated with greater behavioral problems reported by the parents.

Table 5.9 Studies of secondhand smoke exposure and cognitive development

Study	Design/population	Exposure categories	Source of exposure
Rantakallio 1983	Prospective cohort (3,392) Mothers who smoked during pregnancy and controls from two northernmost provinces in Finland	• Light smokers (<10 cigarettes/day) • Heavy smokers (≥10 cigarettes/day at end of second month of pregnancy) • Father never smoked • Father formerly smoked • Father currently smoked	• Prenatal and involuntary exposure to parental smoking
Bauman et al. 1989	Secondary data analysis (2,008) Eighth-grade students from Guilford County Public Schools in North Carolina United States	• None • 1 cigarette–1 pack/day • 1–2 packs/day • >2 packs/day • Adolescent CO* levels of ≥9 parts per million, an indication of smoking	• Secondhand smoke exposure to family smoking behaviors • Alveolar breath specimens • Adolescent reports of sibling smoking behaviors
Bauman et al. 1991	Longitudinal cohort (year 5 exam, n = 5,342; year 10 exam, n = 3,737; adolescent exam, n = 2,020) Pregnancies from 1960–1967 among women enrolled in the Kaiser Foundation Health Plan in the San Francisco East Bay area Children were all from the Child Health and Development Studies United States 1987	• Mother smoked at time of exam • Father smoked at time of exam • Average number of cigarettes smoked/day by mother and father	• Parental smoking and in utero exposure from maternal smoking during pregnancy
Makin et al. 1991	Cross-sectional (91 children) Aged 6–9 years Canada (Ottawa)	During pregnancy, mother was • Active smoker • Exposed to secondhand smoke • Nonsmoker, not exposed to secondhand smoke	• Mother • Others

Outcome	Findings	Comments
Respiratory disease School performance Retarded growth	• Children of smoking parents had the most frequent incidences of hospital admissions for respiratory illness ($p < 0.024$) • Significant height reduction among children of smokers at 6 months ($p < 0.001$), 12 months ($p < 0.004$), and 14 years of age ($p < 0.023$) • Controlling for height, children of maternal smokers had highly significantly reduced school performance ($p < 0.001$ by F-test) • Maternal and paternal sources of secondhand smoke exposures had similar associations with physiologic and performance outcomes	Source exposure data were from maternal self-reports (mailed questionnaires), school public health nurses, and hospital admission records from 5–10 years ago; these findings are a subset of overall characteristic studies within this birth cohort; school performance was based on school office reports; maternal smoking had an effect on children's physical and mental development, even when these factors were controlled with regression analysis
Test performance	• Stepwise regression identified 8 significant control variables • Pair-wise interactive analysis identified 6 interactive social and psychologic control variables • Controlling for all 14 variables, a statistically significant relationship remained overall between family smoking and CAT† scores ($p < 0.017$)	Source exposure data were from maternal self-reports; test performance was based on the CAT; CAT test scores significantly decreased as family smoking increased ($p < 0.001$); other potential variables accounting for an observed association may be active maternal smoking during pregnancy, tobacco smoke ingredients other than CO, and short-term exposures to secondhand tobacco smoke
Cognitive performance in 3 testing periods (aged 5, 9–11, and 15–17 years)	• PPVT‡ scores and RAVEN§ scores for children of nonsmoking parents were statistically significant, averaging 5.9% higher than for children of smokers ($p < 0.05$) • Analyses of covariance confirmed that parental smoking had a significant effect on PPVT and RAVEN scores at the 10-year exam • Following adjustments for covariates (e.g., age, low birth weight, race, parental education, and income), a linear dose-response relationship was observed between parental smoking and cognitive performance • No significant interactions were identified between maternal prenatal and current smoking status	Source exposure data were from maternal self-reports; cognitive measurements were made with Goodenough-Harris Drawing test, the Quick Test, PPVT, and RAVEN; husband's smoking status was not measured in one 5-year examination group and in adolescent measurements; child physiologic responses, such as middle-ear effusion and respiratory illness, were related to secondhand tobacco smoke and might influence cognitive performance; family cigarette smoking is associated with selected child cognitive performance skills, and some outcomes exhibited a dose-response relationship with exposure to smoking
Speech and language, intellectual, motor, visual/spatial, academic achievement, and behavior skills	• Children of nonsmoking, unexposed mothers performed better than children of smoking or secondhand smoke-exposed mothers on tests of speech and language skills, intelligence, visual/spatial abilities, and on mother's rating of behavior	Source exposure data were self-reported (interview); children of active and secondhand smoke-exposed mothers are at risk for a pattern of negative developmental outcomes

Table 5.9 Continued

Study	Design/population	Exposure categories	Source of exposure
Baghurst et al. 1992	Prospective cohort (548) Children enrolled in the Port Pine Cohort Study, aged birth to 4 years, whose mothers attended antenatal care between May 1979 and May 1982 Australia	• Nonsmokers (never smoked or smoked ≤5 cigarettes during pregnancy) • Smokers (>5 cigarettes ever)	• Prenatal and involuntary exposures to maternal smoking
Roeleveld et al. 1992	Epidemiologic (628) Cases and referent group were 0–15 years of age, selected from medical files of the Pediatric or Child Neurology Department of Nijmegen University Hospital, or from local rehabilitation centers between 1979 and 1987 Netherlands	• Average number of cigarettes/day reported by parents • Daily amount of paternal pipe or cigar smoking	• Prenatal and secondhand smoke exposures to parental smoking
Schulte-Hobein et al. 1992	Prospective longitudinal matched pair (69 cases, 69 controls) Mothers were selected soon after delivery from 3 maternity hospitals Germany (Berlin)	• Smoked >5 cigarettes/day during pregnancy • Never smoked	• Mother's milk and secondhand smoke exposures during first year of life
Byrd and Weitzman 1994	Cross-sectional data analyses (9,996) Children aged 0–17 years whose parents participated in the National Health Interview Survey, a nationally representative civilian population United States	• Household exposures to cigarette smoke at time of survey	• Maternal prenatal and involuntary exposures

Outcome	Findings	Comments
Neuropsychologic development	• Children with postnatal exposures had significantly lower scores on the MDI[Δ] ($p < 0.03$) and MSCA[¶] verbal ($p < 0.03$), perceptual performance ($p < 0.01$), and motor ($p < 0.01$) • A statistically significant inverse association was found between maternal smoking behavior and neuropsychologic development until other determinants of development were controlled (e.g., gender, mother's intelligence, birth weight, and socioeconomic status) • Children of smoking mothers performed significantly lower (2.4–4.1%) in testing sessions ($p < 0.03$) • There was no strong evidence that maternal smoking exerted an independent effect on neuropsychologic development in early childhood	Self-reports and interviews with trained nurse interviewers were used to assess postpartum secondhand smoke exposures; neuropsychologic development was measured by the BSID**, MSCA, and MDI; social and environmental factors are major confounders of the association between maternal smoking and neuropsychologic development in childhood; more precise measures of exposures to secondhand tobacco smoke and a comprehensive assessment of confounders are required for future studies
Mental and psychomotor retardation	• Paternal pipe or cigar smoking was associated with an OR[††] of 2.4 (95% CI[‡‡], 1.2–5.1) for cases to referents	Source exposure data were from parental reports obtained in a structured interview; paternal smoking before, during, and after pregnancy is a risk factor for mental retardation among offspring
Somatic development Mental development Infant cotinine levels	• 41% of children of smokers and 32% of children of nonsmoking mothers suffered from bronchitis and pneumonia • Cotinine levels present in infants of smokers were 3-fold to 10-fold higher than in infants of nonsmokers • No confirmation of mental/developmental retardation among exposed infants	Physiologic measurements (weight and head circumference) and secondhand smoke exposures were gathered through home interviews with mothers (self-reports) and from medical records (biologic markers); BSID measured development; to prevent health risks to infants, mothers should be encouraged to stop smoking during pregnancy and while nursing, and both parents should avoid smoking when children are present
History of repeating kindergarten or first grade	• OR = 1.4 (95% CI, 1.1–1.7) for children repeating kindergarten or first grade who had a history of exposures to household smoke	Source exposure data were from maternal self-reports (questionnaires); behavior problem assessments were dropped from the analyses because behavior interviews were conducted after the child had repeated kindergarten or first grade, an experience that may account for behavior; the survey was designed to assess a multitude of social and environmental exposures; smoking in the home may contribute to social and individual factors that influence the decision to retain a child in kindergarten or first grade

Table 5.9 Continued

Study	Design/population	Exposure categories	Source of exposure
McCartney et al. 1994	Longitudinal (quasi-experimental) (190) Children aged 6–10 years enrolled in the OPPS[§§] Canada	• Nonsmoking controls • Light (>0 mg[ΔΔ] nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Prenatal and postnatal secondhand smoke exposures
Olds et al. 1994	Prospective follow-up (400) Children aged 1–4 years from a semirural county in New York state participating in a home nurse visitation program United States	• 0 cigarettes/day • 1–9 cigarettes/day • ≥10 cigarettes/day	• Prenatal exposure
Fried et al. 1997	Longitudinal (131) Children aged 9–12 years enrolled in OPPS Canada	• Nonsmoking controls • Light (>0 mg nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Maternal prenatal exposure
Fried et al. 1998	Longitudinal (131) Children aged 9–12 years enrolled in OPPS Canada	• Nonsmoking controls • Light (>0 mg nicotine/day to 16 mg nicotine/day) • Heavy (>16 mg nicotine/day)	• Maternal prenatal exposure

*CO = Carbon monoxide.
[†]CAT = California Achievement Test.
[‡]PPVT = Peabody Picture Vocabulary Test.
[§]RAVEN = Raven Colored Progressive Matrices Test.
[Δ]MDI = Mental Development Index.
[¶]MSCA = McCarthy Scales of Children's Abilities.
**BSID = Bayley Scales of Infant Development.
[††]OR = Odds ratio.
[‡‡]CI = Confidence interval.
[§§]OPPS = Ottawa Prenatal Prospective Study.
[ΔΔ]mg = Milligrams.
[¶¶]WISC = Weschler Intelligence Scale for Children.

Outcome	Findings	Comments
Central auditory processing task (SCAN)	• Secondhand smoke exposures both during and after pregnancy were not significantly associated with SCAN results	Source exposure data were from maternal self-reports obtained through interviews with a woman interviewer; maternal smoking rates were averaged over the trimester interview recordings
Intellectual functioning during the first 4 years	• Children whose mothers reported smoking ≥10 cigarettes/day during pregnancy had reduced and adjusted Stanford-Binet scores by 4.35 points (95% CI, 0.02–8.68, $p < 0.049$)	Source exposure data were obtained from maternal self-reports; BSID, MDI, Cattell, and Stanford-Binet were used to measure intellectual functioning outcomes; smoking during pregnancy poses a unique risk of neurodevelopmental impairment for exposed children
Reading scores Language scores	• Maternal prenatal secondhand smoke exposure was not associated with language or reading outcomes • Postnatal exposure to secondhand smoke was associated with lower language scores • An association was observed between prenatal cigarette smoking and altered (reduced) auditory functioning among offspring	Source exposure data were obtained from maternal self-reports through interviews in the home of the participant; multiple measures used to assess reading and language abilities included the WISC[¶¶]-III, Wide Range Achievement Test—Revised, PPVT, Fluency Test, Woodcock Reading Mastery Test, Oral Cloze Task, Seashore Rhythm Test, and Regular and Exceptional Pseudoword Task; maternal smoking negatively impacts reading and language capabilities of exposed children
Cognitive performance	• After discriminant functional analysis and key covariate adjustments, a strong linear association persisted with prenatal exposures among the 3 smoking categories ($p < 0.01$) • After discriminant functional analysis and key covariate adjustments, a strong linear association persisted with postnatal secondhand smoke exposure and the 3 smoking categories ($p < 0.05$)	Source exposure data were from maternal self-reports obtained through interviews in the home of the participant; a battery of cognitive performance tests included WISC-III, Fluency Test, Auditory Working Memory, Tactual Performance Task, Category Test, Gordon Delay Task, and the Gordon Vigilance Task; there was a dose-response association between prenatal cigarette exposure and lower global intelligence scores

Table 5.10 Studies of secondhand smoke exposure and behavioral problems among children

Study	Design/population	Exposure categories	Source of exposure
Makin et al. 1991	Prospective longitudinal study (90) Children aged 6–9 years Subsample of Ottawa Prenatal Prospective Study Canada	• Nonsmokers • Involuntary smokers • Active smokers	• Maternal prenatal and postnatal secondhand smoke exposures
Weitzman et al. 1992	Longitudinal (2,256) Children aged 4–11 years participating in the National Longitudinal Survey of Youth United States	• <1 pack/day • ≥1 pack/day • Prenatal (mother smoked during pregnancy only) • Involuntary smoking (mother smoked only after pregnancy) • Prenatal and involuntary smoking (in utero and postnatal exposures to maternal smoking)	• Prenatal and involuntary exposures to parental smoking
Fergusson et al. 1993	Longitudinal (1,265) Children aged 8, 10, and 12 years born in Christchurch, New Zealand, enrolled in the Christchurch Health and Development Study	• Mean number of cigarettes smoked/day during pregnancy (reported during each trimester) • Annual questions regarding daily maternal smoking habits for the first 5 postnatal years and converted to a daily cigarette intake amount	• Maternal smoking during and after pregnancy

Outcome	Findings	Comments
Behavioral, language, and mental development	• The active smoking group demonstrated the poorest performance on the speech, language, intellectual, and behavioral battery of exams • Involuntary smokers had intermediate scores • Nonsmokers had the best scores of the 3 groups • Stepwise discriminant analysis was performed between the involuntary smoking and nonsmoking groups and identified a significant difference ($\chi^2 = 28.15$, $p < 0.001$) • Children in active and involuntary smoking groups rated higher in behavioral problems, with an apparent dose-response relationship	This study was designed to assess a spectrum of long-term consequences of active and involuntary smoking during pregnancy; secondhand smoke exposure was primarily based on the husband's smoking habits; source exposure data were obtained from maternal self-reports through controlled interviews; pregnant mothers, and other persons who may be sources of secondhand smoke, need education and factual information about the deleterious effects smoking can have on the developing fetus
Behavioral problems	• Increased rates of children's behavioral problems were independently associated with all categories of maternal smoking behaviors and with evidence of a dose-response relationship • Among children exposed during and after pregnancy, there were 1.17 additional problems associated with smoking <1 pack/day and 2.04 with ≥1 pack/day ($p < 0.001$) • Odds ratios for extreme behavioral problems = 1.41 for <1 pack/day ($p < 0.01$) and 1.54 for ≥1 pack/day ($p < 0.02$)	Source exposure data were obtained from maternal self-reports through interviews; behavioral problems were measured by the 32-item Child Behavior Problem Index and six subscales; this study suggests that increased behavioral problems among children should be added to the spectrum of adverse health conditions associated with children's prenatal and involuntary exposures to maternal smoking
Behavioral outcomes (disruptive)	• There was a consistent dose-response relationship between the amount smoked during pregnancy and mean problem behavior scores; all behavior assessment measures that compared exposures from 0 to >20 cigarettes/day were statistically significant ($p < 0.001$) • Postnatal exposures identified associations between maternal smoking during preschool years and child behavioral problems ($p < 0.01$) • Assessments of the independent influence of prenatal vs. postnatal exposures indicated that behavioral problems were typically associated with smoking during pregnancy	Source exposure data were from maternal self-reports; outcomes were adjusted for confounding factors potentially associated with maternal smoking and childhood behavioral problems; smoking during pregnancy is associated with a small but detectable increase in the risk of childhood behavioral problems; there was no association between behavioral problems and exposure to maternal postnatal smoking

Makin and colleagues (1991) also noted that compared with children of nonsmokers, children exposed to secondhand smoke had higher levels of maternal-reported behavioral problems even after considering potential confounders. Fergusson and colleagues (1993) studied behavioral problems reported by mothers and teachers of middle school children in New Zealand. After adjusting for confounders, the researchers found small but statistically detectable increases in rates of childhood problem behaviors associated with smoking during pregnancy, but did not observe any associations between exposures to maternal smoking after pregnancy and behavioral outcomes (Fergusson et al. 1993).

Evidence Synthesis

The evidence for an association between exposure to secondhand smoke and behavioral problems in children is inconsistent. Because so few studies have been carried out on this topic, more studies are clearly warranted.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Implications

Further research is needed, but the same challenges remain that confront research on other effects such as cognitive functioning.

Height/Growth

Epidemiologic Evidence

Five studies examined the association between children's growth and secondhand smoke exposure (Table 5.11) (Rona et al. 1981, 1985; Rantakallio 1983; Chinn and Rona 1991; Eskenazi and Bergmann 1995). Two of the studies (Chinn and Rona 1991; Eskenazi and Bergmann 1995) reported no association for children aged 5 years and for children aged 5 through 11 years. Eskenazi and Bergmann (1995) used biochemical confirmation of secondhand smoke exposure and proposed that the height differences between exposed and unexposed children were attributable to the effect of tobacco smoke exposure on fetal growth. After adjusting for birth weight, however, any associations between secondhand smoke exposure and height were eliminated. Rona and colleagues (1981) found that differences in height remained among children of smokers even after adjusting for birth weight. Rantakallio (1983) examined secondhand smoke exposures from fathers during pregnancy and found that after adjusting for potential confounding factors, children exposed to paternal smoking during pregnancy were shorter than were children of nonsmoking fathers. Similarly, Rona and colleagues (1985) examined height among children aged 5 through 11 years and found small decreases among children exposed to secondhand smoke. Both of these studies found relatively small differences (1 centimeter or less) even among children exposed to heavy smokers.

Evidence Synthesis

The evidence for an association between secondhand smoke exposure and children's height/growth is mixed (Table 5.11). Those studies that do report associations find relatively consistent deficits associated with secondhand smoke exposure. However, the magnitude of the effect is small and could reflect residual confounding.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Implications

The evidence suggests that any effect of secondhand smoke exposure on height is likely to be small and of little significance. Research on secondhand smoke exposure and height is complicated by the many potential confounding factors.

Childhood Cancer

Biologic Basis

Tobacco smoke contains numerous carcinogens and is a well-established cause of cancer (USDHEW 1964, 1974; USDHHS 1980, 1986; Smith et al. 1997, 2000a,b). Numerous animal studies elucidate evidence for, and mechanisms of, transplacental carcinogenesis (Rice 1979; Schuller 1984; Napalkov et al. 1989). For example, when the oncogenic compound ethylnitrosourea (ENU) was administered intravenously or intraperitoneally to pregnant rabbits, the offspring developed renal and neural cancers (Stavrou et al. 1984). Monkeys are also susceptible to transplacental carcinogenesis, with offspring developing vascular and a variety of other tumors following prenatal administration of ENU to the mother (Rice et al. 1989). The strongest human evidence that transplacental carcinogenesis is biologically plausible may be the occurrence of vaginal clear-cell adenocarcinoma among young women whose mothers were prescribed diethylstilbesterol during pregnancy (Vessey 1989).

Limited biologic evidence suggests that involuntary exposure to cigarette smoke may also lead to transplacental carcinogenesis. Maternal secondhand smoke exposure during pregnancy, as with maternal active smoking during pregnancy, can result in increased measurable metabolites of cigarette smoke in amniotic fluid (Andresen et al. 1982; Smith et al. 1982) and in fetal blood (Bottoms et al. 1982; Coghlin et al. 1991). For example, thiocyanate levels in fetal blood were less than 50 micromoles per liter (μmol/L) when the mother was not exposed to secondhand smoke during pregnancy (Bottoms et al. 1982). Among mothers who were prenatally exposed to secondhand smoke, fetal blood levels of thiocyanate were as high as 90 μmol/L, and among mothers who actively smoked, the measurements were about 170 μmol/L. Notably, however, two studies that measured thiocyanate levels in umbilical cord blood found no differences between secondhand smoke-exposed and unexposed nonsmoking women (Manchester and Jacoby 1981; Hauth et al. 1984). Hauth and colleagues (1984) found thiocyanate levels of 23 μmol/L in umbilical cord blood from unexposed infants of nonsmoking mothers and levels of 26 μmol/L in secondhand smoke-exposed infants of nonsmoking mothers (defined as living and/or working with someone who smoked at least 10 cigarettes per day). Manchester and Jacoby (1981) also found similar cord blood levels of thiocyanate in unexposed (34 ± 3 μmol/L) and secondhand smoke-exposed (35 ± 3 μmol/L) infants of nonsmoking mothers (exposure was defined as living with someone who smoked).

Studies of maternal smoking during pregnancy found enhanced transplacental enzyme activation (Nebert et al. 1969; Manchester and Jacoby 1981) and placental DNA adducts (Everson et al. 1986, 1988; Hansen et al. 1992), and several animal studies suggested that embryonic exposure to tobacco smoke components increased tumor rates (Mohr et al. 1975; Nicolov and Chernozemsky 1979). For example, diethylnitrosamine administered to female hamsters in the last days of pregnancy produced offspring that developed respiratory tract neoplasms in nearly 95 percent of the animals. Cigarette smoke condensate in olive oil that was used in another study of pregnant hamsters was injected intraperitoneally; it produced a variety of tumors in the offspring, including tumors of the pancreas, adrenal glands, liver, uterus, and lung (Nicolov and Chernozemsky 1979). Human studies document an increased frequency of genomic deletions in the *hypoxanthine-guanine phosphoribosyltransferase* gene found in the cord blood of newborns whose mothers were exposed to secondhand smoke (compared with newborns of unexposed mothers). This finding strongly supports a carcinogenic effect of prenatal secondhand smoke exposure, particularly since these mutations are characteristic of those found in childhood leukemia and lymphoma (Finette et al. 1998). Prenatal exposure to secondhand smoke may also play a role by enhancing any effect of postnatal exposure on the development of childhood cancer (Napalkov 1973), but the potential effects of prenatal and postnatal exposures are difficult to separate given the high correlation between prenatal and postnatal parental smoking. Several studies have assessed postnatal exposures by measuring cotinine and nicotine concentrations in the saliva and urine of infants. The investigators found that those infants with reported secondhand smoke exposures had significantly higher concentrations than those infants with no reported exposure in the 24 hours before measuring the concentrations (Greenberg et al. 1984; Crawford et al. 1994).

Table 5.11 Studies of secondhand smoke exposure and children's growth

Study	Design/population	Exposure categories	Source of exposure
Rona et al. 1981	Longitudinal (1,800) Children aged 5–11 years from England and Scotland who participated in the National Study of Health and Growth United Kingdom	• Children with no smokers in the home • One smoker in the home • Two or more smokers in the home	• Parental secondhand smoke exposure at home
Rantakallio 1983	Longitudinal (12,068) Finnish children (mothers enrolled during pregnancy and children followed until 14 years of age) Finland	• Maternal smoking • Paternal smoking (exposures were not clearly defined)	• Mother • Father
Rona et al. 1985	Editorial prospective (5,000–6,000) Primary school children (aged 5–11 years) from England and Scotland United Kingdom	NR*	• Prenatal and secondhand smoke exposures from parental smoking
Chinn and Rona 1991	Observational study (11,224) English and Scottish inner-city and representative children aged 5–11 years United Kingdom	• Number of cigarettes smoked by parents at home (recorded as a continuous variable) = 0, 1–4, 5–14, 15–24, 25–34, and ≥35	• Secondhand smoke
Eskenazi and Bergmann 1995	Longitudinal cohort (2,622) Children (aged 5 years ± 6 months) enrolled in Child Health and Development Studies between 1964 and 1967 in the San Francisco East Bay area United States	• Nonsmokers exposed to secondhand smoke (cotinine levels 2–10 ng/mL‡) • Unexposed nonsmokers • Serum cotinine levels of smokers: 0–79 ng/mL 80–163 ng/mL 164–569 ng/mL	• Maternal secondhand smoke exposure during pregnancy and prenatal maternal smoking • Serum cotinine sample during pregnancy

*NR = Data were not reported.
†mm = Millimeters.
‡ng/mL = Nanograms per milliliter.

Outcome	Findings	Comments
Height	• There was a strong inverse association between height and the number of household smokers ($p < 0.001$ in England and $p < 0.01$ in Scotland) • After adjusting for confounding variables such as maternal smoking during pregnancy, paternal social class, maternal and paternal heights, and the number of siblings, a significant trend remained only in the English sample ($p < 0.01$)	Source exposure data were obtained from parental self-reports through questionnaires; children's heights were measured across all 28 study areas; persons identified regarding exposures smoked ≥5 cigarettes/day at home; secondhand smoke at home seems to affect the growth of children
Height at 14 years of age	• Children of smokers were shorter at 14 years of age compared with children of nonsmokers • Regression coefficient: -0.034 (maternal smoking, $p = 0.056$) -0.032 (paternal smoking, $p = 0.072$)	Source exposure data were self-reported (questionnaire); children of smokers were shorter than children of nonsmokers
Height (in mm[†])	• Children of mothers who smoked during pregnancy and whose parents smoked at home had significantly reduced ($p < 0.01$) heights by 2 mm for children aged 5–11 years	NR
Height, respiratory illness (wheeze)	• There were no regression coefficients of height standard deviation scores on involuntary smoking; controlling for confounders was significantly different from zero • Significant usual coughs were observed in English inner-city boys and girls ($p < 0.01$ and $p < 0.05$, respectively) • Persistent wheeze was significant for Scottish boys ($p < 0.05$)	Source exposure data were from maternal self-reports (questionnaires); heights were measured by Holtian stadiometer, and respiratory symptoms were gathered from maternal reports; overall risk of respiratory conditions resulting from secondhand smoke is small but not negligible
Height	• Children of smokers and those of nonsmokers in unadjusted analyses were 0.1, 0.2, and 0.5 centimeters shorter for each smoker's cotinine tertile, respectively • Only the adjusted heights of children of mothers who smoked prenatally and postnatally were significantly different from those of nonsmokers ($p < 0.05$), but when birth weight and gestational length were added to the model, the finding was no longer significant	Source exposure data were from maternal self-reports of smoking status; secondhand smoke exposure was measured using cotinine as a biomarker; self-reported smoking status and serum cotinine levels showed good agreement in height measurements collected by trained personnel; children whose mothers were heavy smokers during pregnancy were shorter at 5 years of age compared with children of nonsmokers; this effect appears to be attributable to in utero exposure rather than to postnatal secondhand smoke exposure

Epidemiologic Evidence

In the case of active maternal smoking during pregnancy, investigators who have reviewed the evidence have not found an association between maternal smoking and a transplacental effect on childhood cancer (Pershagen 1989; Tredaniel et al. 1994; Sasco and Vainio 1999). One meta-analysis found a 10 percent increase in risk (RR = 1.10 [95 percent CI, 1.03–1.19]) for all cancers based on 12 studies, but the quality of the available studies and the diversity of the cancer types considered precluded establishing a causal relationship (Boffetta et al. 2000). In a recent monograph on involuntary smoking, the International Agency for Research on Cancer (2004) concluded that the evidence regarding exposure to parental smoking and childhood cancer is inconsistent. Similarly, two other literature reviews of secondhand smoke exposure and childhood cancer also found no strong evidence of an association (Tredaniel et al. 1994; Sasco and Vainio 1999), but a pooled risk estimate that combined studies of specific cancer sites as well as all cancer sites was 1.23 (95 percent CI, 1.14–1.33) for paternal smoking (Sorahan et al. 1997a). Another meta-analysis of paternal smoking and risk of childhood cancer yielded a statistically significant increase in risk for non-Hodgkin's lymphoma based on 4 studies (RR = 2.0 [95 percent CI, 1.08–3.98]) and for brain tumors based on 10 studies (RR = 1.22 [95 percent CI, 1.05–1.40]) (Boffetta et al. 2000). The summary estimate from the meta-analysis for acute lymphocytic leukemia (ALL), the most common type of childhood leukemia, was not statistically significant (RR = 1.17 [95 percent CI, 0.96–1.42]). A separate review of the available studies on childhood brain tumors and tobacco smoke found mixed results for maternal exposure to secondhand smoke during pregnancy (Norman et al. 1996b).

Given the relative rarity of childhood cancer, the epidemiologic evidence on secondhand smoke exposure and childhood cancer comes almost exclusively from case-control studies (Table 5.12). One cohort study that addressed cancer outcomes among offspring (including adults) who had reported at least one parent with lung cancer assumed that these offspring had been exposed to secondhand smoke (Seersholm et al. 1997). Lung cancer patients were identified using the Danish Cancer Registry and their offspring were identified through the Danish Population Registry. Records of the offspring were then linked back to the cancer registry to obtain the overall cancer rate in this cohort, which was lower than the cancer rate for the general Danish population (standardized incidence ratio 0.9, 90 percent CI, 0.6–1.2). The cohort also did not have any statistically significant excesses for any specific cancer sites.

Seven of the case-control studies on secondhand smoke exposure evaluated all cancer types together as well as some specific types of cancers (Stjernfeldt et al. 1986; John et al. 1991; Sorahan et al. 1995, 1997a,b, 2001; Ji et al. 1997). Of another nine studies that examined only CNS tumors (Preston-Martin et al. 1982; Howe et al. 1989; Kuijten et al. 1990; Gold et al. 1993; Bunin et al. 1994; Filippini et al. 1994, 2000; McCredie et al. 1994; Norman et al. 1996a), four focused on leukemias (Magnani et al. 1990; Shu et al. 1996; Brondum et al. 1999; Infante-Rivard et al. 2000)—one included non-Hodgkin's lymphoma (Magnani et al. 1990)—and two other studies analyzed soft-tissue sarcomas (Grufferman et al. 1982; Magnani et al. 1989). Four of the seven studies that examined the overall cancer risk were conducted by the same primary investigator who studied cancer deaths in the United Kingdom during four time periods: 1953–1955 (Sorahan et al. 1997a), 1971–1976 (Sorahan et al. 1997b), 1977–1981 (Sorahan et al. 1995), and 1980–1983 (Sorahan et al. 2001). All four of these studies as well as a study from China (Ji et al. 1997) found positive exposure-response trends that were also statistically significant for the amount of paternal smoking and overall cancers, with ORs ranging from 1.08 (adjusted, 95 percent CI, 1.03–1.13) (Sorahan et al. 1995) to 1.9 (adjusted, 95 percent CI, 1.3–2.7) (Ji et al. 1997).

Because of the heterogeneity in the quality of the epidemiologic evidence on maternal secondhand smoke exposure and childhood cancers, a meta-analysis of the relevant studies is not currently warranted. In addition, the level of epidemiologic evidence on individual types of childhood cancers is limited.

Leukemia

The studies that focused on childhood leukemia (Magnani et al. 1990; Shu et al. 1996; Brondum et al. 1999; Infante-Rivard et al. 2000) did not find statistically significant associations with paternal smoking. Findings from one of these studies, which also investigated the modifying effect of three polymorphisms of the *CYP1A1* gene, showed no effect of paternal smoking on childhood leukemia (nonsignificant OR of 1.0 for all levels of reported paternal smoking), but

did suggest a protective effect with postnatal paternal smoking for children with the *CYP1A1*2B* allele but not for children without it (OR = 0.2 [95 percent CI, 0.04–0.9]) (Infante-Rivard et al. 2000). Two of the studies that examined overall and specific cancers did find significantly increased risks for ALL at the highest levels of paternal smoking, with ORs of 3.8 (95 percent CI, 1.3–12.3) for five or more pack-years[1] of smoking before conception (p for trend = 0.01) (Ji et al. 1997) and 5.29 (95 percent CI, 1.31–21.30) for 40 or more cigarettes per day before the pregnancy (p trend = 0.06) (Sorahan et al. 2001).

Lymphoma

Lymphoma was significantly associated with paternal smoking in three of the studies that analyzed multiple cancer sites (Ji et al. 1997; Sorahan et al. 1997b, 2001). The highest risk was associated with 10 or more pack-years of smoking (among nonsmoking mothers) before conception and postnatally (adjusted OR = 5.7 [95 percent CI, 1.3–26.0], p for trend = 0.03) (Ji et al. 1997). One study that was based on 17 cases of non-Hodgkin's lymphoma found large, increased risks with paternal smoking before the birth of the child (overall and by levels of smoking), although these estimates had lower confidence limits of 0.9 and 1.0, respectively (Magnani et al. 1990). Using the broader category of reticuloendothelial system neoplasms, Sorahan and colleagues (2001) also found a large increased risk (RR = 3.69 [95 percent CI, 1.49–9.15]) with paternal cigarette smoking of 20 to 29 cigarettes per day when cases were compared with controls identified from the general practitioners of the cases.

Central Nervous System

Four of the nine studies that analyzed only CNS tumors found statistically significant associations with maternal secondhand smoke exposure during pregnancy ranging from 1.5 (p = 0.03) (Preston-Martin et al. 1982) to 2.2 (95 percent CI, 1.1–4.6, p for trend = 0.02) (Filippini et al. 1994). One study of multiple cancer outcomes found significant associations for neuroblastoma and CNS cancers with paternal smoking after combining three study populations from different time periods (Sorahan et al. 1997b).

Evidence Synthesis

The strongest evidence for any childhood cancer risk from maternal secondhand smoke exposure is specific to leukemias, lymphomas, and brain tumors, although the causal pathway may actually be through DNA damage to the father's sperm from active smoking rather than through maternal secondhand smoke exposure during pregnancy. Some of the epidemiologic studies suggest a slightly increased risk in childhood cancers from prenatal and postnatal secondhand smoke exposures, but most of the studies were small and did not have the power to detect statistically significant associations. In addition, most of the studies lacked exposure assessments for relevant exposure periods (preconception, prenatal, and postnatal), which may also have reduced the risk estimates because of nondifferential misclassification of exposure status. Risk estimates may be inflated by recall bias, especially since interviews to assess exposures took place up to 15 years after birth. Parents of children with cancer may be more likely to think about possible causes for their child's illness, thereby improving their recall of exposure experiences around the time of the pregnancy and birth. Parents of healthy children, however, have no particular reason to think about their exposure experiences and their recall may not be as good. Differential recall is a potential problem common to all case-control studies. If differential positive recall between cases and controls is present, it will inflate the risk estimate for childhood cancer.

Researchers have observed exposure-response trends for overall cancers as well as for leukemia, lymphoma, and brain tumors in a number of studies. Most of the studies adjusted for potentially confounding factors such as the child's date of birth, age at diagnosis, parental education level, parental age at child's birth, socioeconomic status, residence, and race by multivariate adjustment or case-control matching. Only four studies, however, considered other cancer risk factors such as maternal x-rays, drug use, and consumption of foods containing sodium nitrite (Preston-Martin et al. 1982; Howe et al. 1989; Kuijten et al. 1990; Bunin et al. 1994). Although active maternal smoking during pregnancy does not appear to be related to childhood cancer, it was not clear in some studies whether mothers who actively smoked were excluded from the various analyses that estimated risks from

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 5.12 Case-control studies of childhood cancer by cancer type

Study	Population	Exposure period	Source of exposure
		All cancers combined	
John et al. 1991	Children aged 0–14 years, diagnosed in Denver between 1976 and 1983; controls were selected by random-digit dialing	1 year before birth	Father smoked
		1 year before birth	Father smoked Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked ≥21 cigarettes/day
Sorahan et al. 1995	Cancer deaths among children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Prenatal	Father smoked <10 years Father smoked 10–19 years Father smoked ≥20 years
		Prenatal	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Prenatal	Father smoked

Risk (95% CI*)	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.2 (0.8–2.1)	Nonsmokers	Matched for age, gender, and geographic area; adjusted for paternal education	None
1.3 (0.9–2.0) 1.9 (0.9–3.9) 1.3 (0.8–2.1) 1.0 (0.6–1.8)	Smokers and nonsmokers	Matched for age, gender, and geographic area; no adjustments	
1.20 (0.81–1.78) 1.24 (0.98–1.56) 1.26 (1.05–1.50) 1.35 (1.03–1.78) 1.47 (1.07–2.01), p trend <0.001	Smokers and nonsmokers	Matched for gender and date of birth; no adjustments	None
1.41 (1.16–1.72) 1.24 (1.04–1.47) 1.10 (0.81–1.50)	Smokers and nonsmokers	Matched for gender and date of birth; no adjustments	
1.23 (0.82–1.86) 1.17 (0.92–1.49) 1.24 (1.02–1.49) 1.30 (0.98–1.73) 1.39 (1.00–1.92), p trend = 0.003	Smokers and nonsmokers	Matched for gender, date of birth, and paternal alcohol consumption; adjusted for maternal smoking and alcohol consumption	
1.37 (1.12–1.68)	Nonsmokers	Matched for gender and date of birth; adjusted for alcohol consumption, SES†, and maternal age at child's birth	

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		All cancers combined	
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed between 1985 and 1991; population-based controls were from household registry	NR‡	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoke 10–14 years Father smoked ≥15 years
		Preconception	Father smoked <5 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked 5–9 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked ≥10 years: <10 cigarettes/day 10–14 cigarettes/day ≥15 cigarettes/day
		Preconception	Father smoked ≤2 pack-years§ Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Preconception	Father smoked

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.5 (1.1–2.3) 1.1 (0.8–1.6) 1.5 (1.0–2.3), p trend = 0.07	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
1.2 (0.7–1.8) 1.1 (0.8–1.7) 1.7 (1.2–2.5), p trend = 0.007	Nonsmokers		
1.2 (0.7–2.1) 0.9 (0.5–1.9) 0.7 (0.2–2.9)	Nonsmokers		
1.2 (0.7–2.0) 1.2 (0.8–1.9) 2.4 (1.3–4.4)	Nonsmokers		
1.5 (0.9–2.5) 1.3 (0.8–2.3) 2.0 (1.2–3.4)	Nonsmokers		
1.2 (0.8–1.8) 1.3 (0.9–2.0) 1.7 (1.2–2.5), p trend = 0.006	Nonsmokers		
1.2 (0.9–1.7) 1.4 (1.0–2.0) 1.1 (0.8–1.7), p trend = 0.57	Nonsmokers		
Diagnosis at 0–4 years of age 1.8 (1.2–2.6) Diagnosis at 5–9 years of age 0.9 (0.5–1.5) Diagnosis at 10–14 years of age 1.9 (0.5–1.8)	Nonsmokers		

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		All cancers combined	
Sorahan et al. 1997a	Deaths of children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked 1–9 cigarettes/day Father smoked 10–20 cigarettes/day Father smoked >20 cigarettes/day
		Current	Father smoked
		Current	Father smoked
Sorahan et al. 1997b	Deaths of children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cases	Current	Father smoked 1–9 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Current	Father smoked
		Current	Father smoked
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Preconception	Father smoked (same as above)

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		All cancers combined	
1.03 (0.81–1.29) 1.31 (1.06–1.62) 1.42 (1.08–1.87), p trend <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported
1.13 (1.05–1.23), p <0.01	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	
1.30 (1.10–1.53), p <0.01	Nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, and obstetric radiography	
1.02 (0.78–1.34) 1.37 (1.13–1.65) 1.33 (1.13–1.55) 1.42 (1.09–1.84) 1.63 (1.23–2.15), p trend <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers
1.29 (1.10–1.51), p <0.01	Nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, and obstetric radiography	
1.09 (1.05–1.14), p <0.001	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	
General practitioner controls 0.94 (0.53–1.66) 1.63 (1.10–2.41) 1.46 (1.05–2.03) 0.95 (0.52–1.73) 1.77 (0.94–3.34), p trend = 0.02	Smokers and nonsmokers	No adjustments (nonsignificant in analysis: paternal age at child's birth, SES, and ethnic origin)	None
General practitioner controls p trend = 0.03 (risks were not reported)	Smokers and nonsmokers	Adjusted for maternal smoking	

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Acute lymphocytic leukemia	
Magnani et al. 1990	Pediatric hospital cases in Italy, diagnosed between 1974 and 1984 and still under observation (prevalent cases)	Preconception and prenatal (up to child's birth)	Father smoked Father smoked 1–15 cigarettes/day Father smoked ≥16 cigarettes/day
John et al. 1991	Children aged 0–14 years in Denver, diagnosed between 1976 and 1983; controls were selected by random-digit dialing	1 year before birth	Father smoked
		1 year before birth	Father smoked Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked ≥21 cigarettes/day
Sorahan et al. 1995	Deaths of children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked
Shu et al. 1996	Cases aged ≤18 months, diagnosed between 1983 and 1988; identified through clinical trial registries in the United States, Canada, and Australia	1 month before conception	Father smoked
		Prenatal	Father smoked
		1 month before conception	Father smoked 1–10 cigarettes/day Father smoked 11–20 cigarettes/day Father smoked >20 cigarettes/day
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed between 1985 and 1991; population-based controls were from household registry	NR	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoked 10–14 years Father smoked ≥15 years
		Preconception	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
Sorahan et al. 1997a	Deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Acute lymphocytic leukemia	
0.9 (0.6–1.5) 0.9 (0.5–1.6) 0.9 (0.6–1.5)	Smokers and nonsmokers	No adjustments (nonsignificant in analysis: years of smoking, age at smoking initiation, and cumulative cigarette smoking)	Findings did not differ when considering paternal smoking from birth to diagnosis or during the year before birth
1.4 (0.6–3.1)	Nonsmokers	Matched for age, gender, and geographic area; adjusted for father's education	None
1.9 (1.0–3.7) 2.6 (0.9–7.9) 1.6 (0.7–3.7) 1.6 (0.7–4.0)	Smokers and nonsmokers	Matched for age, gender, and geographic area; no adjustments	
1.16 (1.06–1.27)	Smokers and nonsmokers	Matched for gender and date of birth	Risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.56 (1.03–2.36)	Smokers and nonsmokers	Matched for telephone area code and exchange number; adjusted for gender, paternal age and education, and maternal alcohol consumption during pregnancy	None
1.45 (0.95–2.19)	Smokers and nonsmokers		
2.40 (1.00–5.72) 1.33 (0.79–2.34) 1.51 (0.82–2.77), p trend = 0.12	Smokers and nonsmokers		
1.5 (0.7–3.9) 0.9 (0.4–1.5) 1.9 (0.8–4.6), p trend = 0.27	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
0.9 (0.3–2.3) 1.0 (0.5–2.2) 1.7 (0.8–3.7), p trend = 0.23	Nonsmokers		
0.8 (0.2–2.5) 1.0 (0.4–2.7) 3.8 (1.3–12.3), p trend = 0.01	Nonsmokers		
1.1 (0.4–2.8) 1.8 (0.6–5.2) 1.8 (0.6–5.5), p trend = 0.33	Nonsmokers		
1.08 (0.91–1.27)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Acute lymphocytic leukemia	
Sorahan et al. 1997b	Deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Brondum et al. 1999	Children aged <15 years, diagnosed between 1989 and 1993; identified through clinical trial registries in the United States	Ever	Father smoked
		Ever	Father smoked
		1 month before conception and prenatal	Father smoked
		Father's lifetime	Father smoked <10 cigarettes/day Father smoked 10 to <20 cigarettes/day Father smoked ≥20 cigarettes/day
		Father's lifetime	Father smoked <10 years Father smoked 10 to <20 years Father smoked ≥20 years
Infante-Rivard et al. 2000	Children aged 0–9 years in Quebec (Canada), diagnosed between 1980 and 1993; identified from tertiary care centers for childhood cancers	Postnatal up to diagnosis	Father smoked 1–20 cigarettes/day Father smoked >20 cigarettes/day
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day
		Lymphoma	
Magnani et al. 1990	Non-Hodgkin's lymphoma cases admitted to a pediatric hospital in Italy, diagnosed between 1974 and 1984 and still under observation (prevalent cases)	Preconception and prenatal (up to child's birth)	Father smoked Father smoked 1–15 cigarettes/day Father smoked ≥16 cigarettes/day

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Acute lymphocytic leukemia	
1.07 (0.99–1.16)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.04 (0.90–1.20)	Smokers and nonsmokers	Adjusted for income and paternal race and education	None
1.04 (0.86–1.26)	Nonsmokers	Adjusted for income and parental race and education	
1.07 (0.91–1.25)	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.16 (0.88–1.51) 1.04 (0.83–1.31) 1.06 (0.88–1.26), p trend = 0.56	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.12 (0.91–1.38) 1.22 (1.00–1.47) 0.91 (0.72–1.14), p trend = 0.79	Smokers and nonsmokers	Adjusted for income and paternal race and education	
1.0 (0.7–1.4) 1.0 (0.7–1.3)	Smokers and nonsmokers	Matched for age and gender; adjusted for maternal age and education	None
General practitioner controls: 0.99 (0.35–2.85) 1.34 (0.62–2.91) 1.32 (0.72–2.45) 2.33 (0.71–7.63) 5.29 (1.31–21.30), p trend = 0.06	Smokers and nonsmokers	No adjustments	None
		Lymphoma	
6.7 (1.0–43.4) 6.4 (1.0–45.5) 5.6 (0.9–37.5)	Smokers and nonsmokers	No adjustments	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Lymphoma	
Sorahan et al. 1995	Deaths among children in England, Wales, and Scotland between 1977 and 1981; included less than 50% of population cancer cases	Prenatal	Father smoked
Ji et al. 1997	Children aged <15 years in Shanghai (China), diagnosed with lymphoma between 1985 and 1991; population-based controls were from household registry	NR	Father smoked <10 cigarettes/day Father smoked 10–14 cigarettes/day Father smoked ≥15 cigarettes/day
		NR	Father smoked <10 years Father smoke 10–14 years Father smoked ≥15 years
		Preconception	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
		Postnatal	Father smoked ≤2 pack-years Father smoked >2 to <5 pack-years Father smoked ≥5 pack-years
Sorahan et al. 1997a	Deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked
Sorahan et al. 1997b	Deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Sorahan et al. 2001	Children aged <15 years in the United Kingdom, diagnosed with cancer (other reticuloendothelial system cancers) between 1980 and 1983; hospital controls were acute surgical and accident patients; general practitioner controls were population based	Preconception	Father smoked <10 cigarettes/day Father smoked 10–19 cigarettes/day Father smoked 20–29 cigarettes/day Father smoked 30–39 cigarettes/day Father smoked ≥40 cigarettes/day

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Lymphoma	
1.14 (0.99–1.31)	Smokers and nonsmokers	Matched for gender and date of birth	Risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
3.4 (0.8–14.0) 1.1 (0.3–4.8) 3.8 (0.9–16.5), p trend = 0.09	Nonsmokers	For all analyses: Matched for gender and birth year; adjusted for: birth weight; income; and paternal age, education, and alcohol consumption	Data were not collected on paternal smoking during mother's pregnancy; interviews took place ≥10 years after pregnancy
1.3 (0.2–7.0) 3.4 (0.9–12.7) 3.5 (0.9–13.7), p trend = 0.05	Nonsmokers		
3.1 (0.8–11.4) 1.8 (0.4–7.8) 4.5 (1.2–16.8), p trend = 0.07	Nonsmokers		
3.9 (0.9–16.0) 2.7 (0.8–9.6) 5.0 (1.2–22.4), p trend = 0.08	Nonsmokers		
1.37 (1.02–1.83), p <0.05	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)
1.07 (0.92–1.23)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for a 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
General practitioner controls: 1.32 (0.32–5.51) 2.65 (0.83–8.46) 3.69 (1.49–9.15) 0.29 (0.03–2.56) 1.20 (0.29–5.05), p trend = 0.35	Smokers and nonsmokers	No adjustments	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Central nervous system (CNS) cancers	
Preston-Martin et al. 1982	Brain tumor cases aged <25 years, residents of Los Angeles County, diagnosed between 1972 and 1977; identified through the Los Angeles County Cancer Surveillance Program	Prenatal	Mother lived with a smoker
Howe et al. 1989	Brain tumor cases aged ≤19 years, diagnosed at two hospitals in Toronto between 1977 and 1983	Prenatal	Father smoked
Kuijten et al. 1990	Astrocytoma cases aged <15 years, diagnosed between 1980 and 1986; identified through tumor registries in 8 hospitals in Pennsylvania, New Jersey, and Delaware; controls were selected by random-digit dialing	Prenatal	Maternal exposure to secondhand smoke
Gold et al. 1993	Brain tumor cases aged <18 years, diagnosed between 1977 and 1981; identified through 8 SEER$^{\Delta}$ Program registries	During the year of child's birth 2 years before child's birth	Father smoked <1 pack/day Father smoked ≥1 pack/day Father smoked <1 pack/day Father smoked ≥1 pack/day
Bunin et al. 1994	Astrocytoma cases aged <6 years, diagnosed between 1986 and 1989; identified through clinical trial registries in the United States	Prenatal Prenatal	Maternal exposure to secondhand smoke Father smoked
Filippini et al. 1994	Brain tumor cases aged ≤15 years, diagnosed between 1985 and 1988; identified through 8 hospitals in northern Italy	3 months before conception Before mother was aware of pregnancy After mother was aware of pregnancy	Father smoked ≤2 hours/day secondhand smoke exposure >2 hours/day secondhand smoke exposure ≤2 hours/day secondhand smoke exposure >2 hours/day secondhand smoke exposure
McCredie et al. 1994	Brain tumor cases aged <15 years in New South Wales (Australia), diagnosed between 1985 and 1989; identified through the New South Wales Central Cancer Registry	Preconception Prenatal	Father ever smoked Father smoked

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Central nervous system (CNS) cancers	
1.5 (p = 0.03)	Smokers and nonsmokers	Matched for gender, race, and birth year (within 3 years)	None
1.13 (0.615–2.09)	Smokers and nonsmokers	Matched for gender; adjusted for age at diagnosis	None
0.8 (0.5–1.3)	Smokers and nonsmokers	Matched for age, race, and telephone area code and exchange	None
0.68 (0.39–1.19) 1.07 (0.79–1.45) 0.90 (0.53–1.51) 1.15 (0.85–1.56)	Smokers and nonsmokers	Matched for age, gender, and maternal race	None
0.9 (0.6–1.5) 1.0 (0.6–1.7)	Smokers and nonsmokers	Matched for race, birth year, and telephone area code and prefix; adjusted for income	None
1.3 (0.8–2.2) 1.5 (0.7–3.5) 1.7 (0.8–3.7), p trend = 0.08 1.7 (0.8–3.8) 2.2 (1.1–4.6), p trend = 0.02	Smokers and nonsmokers Nonsmokers Nonsmokers	For all analyses: Matched for birth date, gender, and area of residence; adjusted for paternal education	Mean age at diagnosis was 8.5 years, so interviews took place more than 8 years after birth
2.0 (1.0–4.1) 2.2 (1.2–3.8)	Nonsmokers Smokers and nonsmokers	Matched for age and gender; adjusted for paternal education	None

Table 5.12 Continued

Study	Population	Exposure period	Source of exposure
		Central nervous system (CNS) cancers	
Norman et al. 1996a	Brain tumor cases aged ≤19 years, diagnosed between 1984 and 1991; identified through 19 U.S. West Coast SEER Program registries	Prenatal	Father smoked
Sorahan et al. 1997a	CNS cancer deaths among children in England, Wales, and Scotland between 1953 and 1955; included 79% of population cancer cases	Current	Father smoked
Sorahan et al. 1997b	CNS cancer deaths among children in England, Wales, and Scotland between 1971 and 1976; included 51% of population cancer cases	Current	Father smoked
Filippini et al. 2000	CNS tumor cases aged ≤15 years in northern Italy, diagnosed between 1988 and 1993; cases were identified through hospital records	5 years before conception	Father smoked
		Before mother was aware of pregnancy	≤2 hours/day secondhand smoke >2 hours/day secondhand smoke
		After mother was aware of pregnancy	≤2 hours/day secondhand smoke >2 hours/day secondhand smoke
		Before mother was aware of pregnancy	Secondhand smoke
		After mother was aware of pregnancy	Secondhand smoke

*CI = Confidence interval.
†SES = Socioeconomic status.
‡NR = Data were not reported.
§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
ΔSEER = Surveillance, Epidemiology, and End Results.

Risk (95% CI)	Maternal smoking status	Confounding	Comments
		Central nervous system (CNS) cancers	
1.2 (0.9–1.5)	Nonsmokers	Adjusted for gender, age at diagnosis or selection as control participant, birth year of child, and maternal race	None
CNS cancers 1.20 (0.96–1.51) Neuroblastoma 1.48 (1.09–2.02), p <0.05	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for maternal smoking	Exposure assessment for current smoking only; time from birth to interviews was not reported; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 4 levels from <1 cigarette/day to >20 cigarettes/day)
CNS cancers 1.02 (0.93–1.11) Neuroblastoma 1.13 (0.99–1.29)	Smokers and nonsmokers	Matched for gender, date of birth, and residence; adjusted for SES, age of father and mother at child's birth, sibship position, obstetric radiography, and maternal smoking	Exposure assessment for current smoking only; median time between birth and interviews for cases was 8.5 years, and 97% of cases were interviewed before the fourth anniversary of the child's death; nonsmokers included former smokers; risk is for 1 level increase in daily amount of cigarettes smoked (e.g., 6 levels from nonsmokers to ≥40 cigarettes/day)
1.2 (0.9–1.7)	Smokers and nonsmokers	Adjusted for age, gender, and residence	Time from birth to interviews was ≤20 years
1.7 (1.1–2.7) 1.8 (1.1–2.9)	Nonsmokers		
1.7 (1.1–2.6) 1.7 (1.1–2.6)	Nonsmokers		
Astroglial: 2.0 (1.2–3.4)	Nonsmokers		
Astroglial: 1.8 (1.1–3.0)	Nonsmokers		

paternal smoking. Thus, some of the elevated risks for cancer in their offspring from paternal smoking may have been compounded by the child's postnatal exposure to active maternal smoking.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.

4. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.

5. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.

6. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.

7. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Implications

Childhood cancers are diverse in their characteristics and etiology. Although the evidence is inadequate for some sources and periods of exposure, there is some evidence indicative of associations of childhood cancer risk with secondhand smoke exposure. Further research is needed to provide a better understanding of the potential causal relationships between types of exposures to secondhand smoke and childhood cancer risks.

Conclusions

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Pregnancy (Spontaneous Abortion and Perinatal Death)

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Infant Deaths

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Sudden Infant Death Syndrome

4. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Preterm Delivery

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Low Birth Weight

6. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Congenital Malformations

7. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Cognitive Development

8. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Behavioral Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Height/Growth

10. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Childhood Cancer

11. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.

13. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.

14. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.

15. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.

16. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Overall Implications

Because infant mortality for the United States is quite high compared with other industrialized countries, identifying strategies to reduce the number of infant deaths should receive high priority. The epidemiologic evidence for the association of secondhand smoke exposure and an increased risk of SIDS indicates that eliminating secondhand smoke exposures among newborns and young infants should be part of an overall strategy to reduce the high infant mortality rate in the United States.

The available evidence for five reproductive and childhood outcomes—childhood cancer, cognitive development, behaviors, LBW, and spontaneous abortion—calls for further research with improved methodologies. The methodologic challenges and issues that were discussed in relation to exposure assessment and reproductive outcomes might act as a guide for future research on these topics. There is a need for studies that examine exposure to secondhand smoke and childhood cancers to further evaluate the risks for specific cancer types. The evidence reviewed in this chapter points to germ-cell mutations among fathers who smoke as a possible pathway. Additional studies may be warranted that focus on childhood cancer and active paternal smoking, with improved controls for maternal secondhand smoke exposure and active smoking during pregnancy and the exposure of infants to secondhand smoke. For secondhand smoke and spontaneous abortions, studies using samples with adequate statistical power are needed. For all outcomes, investigations should include biochemical measures of exposures, and these measures should be used to determine the presence of dose-response relationships—determining dose-response relationships will greatly facilitate the assessment of causality.

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