TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Sadowsky et al., 1953, U.S.A. (238).	M.	104	White patients admitted during 1938-43 to selected hospitals in New York City, Missouri, New Orleans, and Chicago.	616	White patients with illnesses other than cancer admitted to same group of hospitals during same period.	Obtained by 4 specially trained lay interviewers. 242 records out of a total of 2,847 excluded because of incomplete or questionable smoking histories.
Sanghvi et al., 1955, India (241).	M.	73	Consecutive clinic admissions to Tata memorial Hospital, Bombay.	288	Consecutive clinic admissions of patients without cancer.	By means of "detailed questionary." No other details given.
				107	Consecutive admissions of patients with cancers other than intraoral or esophagus.	
Wynder et al., 1957, Sweden (322).	M.	39	Patients admitted to Radiumhemmet, Stockholm, during 1952-55.	115	Patients admitted to same hospital with cancer of skin, head and neck region other than squamous cell cancer, leukemia, colon, and other sites. No matching.	
	F.	35		166		
Staszewski, 1960, Poland (260).	M.	24	Patients admitted to Oncological Institute during 1957-59.	912	Other patients sent to Institute with symptoms probably not etiologically connected either with smoking or with diseases of esophagus, stomach or duodenum.	No details given on method of data collection. No age adjustment or matching. Average age of cancer patients, 60.5; controls, 53.

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Schwartz et al., 1961, France (*249*).	M.	362	Admissions to hospitals in Paris and a few large provincial cities since 1954.	362	Healthy individuals admitted to same hospital because of work or traffic accidents—matched by 5 year age group and time of admission.	Interviewed by team of specially trained interviewers who interviewed the largest proportion possible of all cancer patients. Cases and matched controls interviewed by same person.
Wynder and Bross, 1961, U.S.A. (*310*).	M.	150	Cancer patients seen in Memorial Hospital, New York City, and Kingsbridge and Brooklyn VA Hospitals during 1950–59 (86% white).	150	Patients seen in same hospitals during same time period with other tumors. 64%-malignant tumor; 36%-benign conditions. Matched by age with cancer patients.	Data collected by trained interviewers.
	F.	37	Same hospitals and same time period as male patients (86% white).	37	Same as with regard to male controls. 43% had malignant and 57% benign tumors.	
Wynder and Bross, 1961, India (*310*).	M. F.	67 27	Admitted to Tata Memorial Hospital Bombay.	134	Patients with other forms of cancer except for oral cavity and lungs; as well as various benign diseases.	Interviewed by one person. 10% of male and 4% of female cancer cases histologically confirmed.
Takano et al., 1968, Japan (*272*).	M. F.	167 33	Patients with esophageal cancer.	167 33	Patients with cancerous and non-cancerous diseases of non-digestive organs.	Interviews at various hospitals. Cases and controls age-matched.

TABLE A31.—*Summary of methods used in retrospective studies of tobacco use and cancer of the esophagus (cont.)*

Author, year, country, reference	Cases			Controls		
	Sex	Number	Method of selection	Number	Method of selection	Collection of data
Bradshaw and Schonland, 1969, South Africa (*41*).	M.	98	Patients with esophageal cancer.	341	Patients with non-malignant disease.	Hospital interviews by trained African social workers.
Martinez, 1969, Puerto Rico (*183*).	M. F.	120 59	Patients with confirmed epidermoid esophageal cancer diagnosed in 1966.	360 177	120 male, 59 female patients in same hospital with non-cancerous diagnoses. 240 male, 118 female members from same community.	Interviews by trained personnel.

TABLE A31a.—*Summary of results of retrospective studies of tobacco use and cancer of the esophagus*

Author, year, country, reference		Percent nonsmokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk ratio. All smokers to nonsmokers	
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers
Sadowsky et al., 1953, U.S.A. (*233*).		3.8	13.2	—	—	—	—	4.0	—
Sangvhi et al, 1955, India (*241*).		5.5	17.3	*Average number of bidis smoked* 15.3	14.1	—	—	3.6	—
Wynder et al., 1957, Sweden (*322*).	M	13.0	24.0						
	F	(about) 85.0	(about) 92.0	—	—	—	—	2.1	—
				—	—	—	—	2.0	—
Staszewski, 1960, Poland (*260*).		—	18.0	95.8	59.0	87.5	80.0	—	—
Schwartz et al., 1961, France (*249*).		3.0	17.0	*Total amount smoked daily (cigarettes)* 16.8	10.0	39.0	38.0	6.6	—
Wynder and Bross, 1961, U.S.A. and India (*310*).	American males	5.0	15.0	48.0	33.0	—	—	3.4	4.4
	American females	41.0	78.0	27.0	16.0	—	—	5.1	3.2
	Indian males	13.0	28.0	—	—	—	—	2.6	—
	Indian females	78.0	94.0	—	—	—	—	4.5	—
Takano et al., 1963, Japan (*272*).		17.0	23.0	—	—	—	—	1.3	—
Bradshaw and Schonland, 1969, South Africa (*41*).		15.3	31.7	31.6	5.9	—	—	2.6	11.1
Martinez, 1969, Puerto Rico (*183*).		14.0	23.6	17.9	8.6	—	—	1.8	3.5

TABLE A32.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by smoking habits and age*

Atypical nuclei	Never smoked regularly		Current Cigarettes		Ex-cigarettes		Pipe, cigar		Other	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
A. All men:										
Number men	91	—	779	—	181	—	89	—	62	—
Total sections[1]	787	100.0	6,752	100.0	1,586	100.0	766	100.0	522	100.0
No atypical nuclei	733	93.1	167	2.5	770	48.5	53	6.9	195	37.4
Some but <60 percent atypical	52	6.6	5,389	79.8	765	48.3	688	89.8	317	60.7
60 percent or more atypical	2	0.3	1,196	17.7	51	3.2	25	3.3	10	1.9
B. Men under age 50:										
Number men	26	—	236	—	28	—	9	—	7	—
Total sections	223	100.0	2,059	100.0	258	100.0	77	100.0	53	100.0
No atypical nuclei	190	85.2	71	3.4	56	21.7	1	1.3	4	7.5
Some but <60 percent atypical	33	14.8	1,853	90.0	195	75.6	74	96.1	46	86.8
60 percent or more atypical	—	—	135	6.6	7	2.7	2	2.6	3	5.7
C. Men aged 50-69:										
Number men	44	—	445	—	109	—	38	—	31	—
Total sections	379	100.0	3,853	100.0	953	100.0	310	100.0	256	100.0
No atypical nuclei	373	98.4	83	2.2	461	48.4	37	11.9	74	28.9
Some but <60 percent atypical	4	1.1	2,915	75.6	452	47.4	261	84.2	178	69.5
60 percent or more atypical	2	0.5	855	22.2	40	4.2	12	3.9	4	1.6
D. Men aged 70 or older:										
Number men	21	—	98	—	44	—	42	—	24	—
Total sections	185	100.0	840	100.0	375	100.0	379	100.0	213	100.0
No atypical nuclei	170	91.9	13	1.5	253	67.4	15	4.0	117	54.9
Some but <60 percent atypical	15	8.1	621	74.0	118	31.5	353	93.1	93	43.7
60 percent or more atypical	—	—	206	24.5	4	1.1	11	2.9	3	1.4

[1] Sections with some epithelium present.

Source: Auerbach, O. et al. (15).

TABLE A33.—*Atypical nuclei in basal cells of epithelium of esophagus of males, by amount of smoking and age*

Cells with atypical nuclei	Never smoked regularly		Current cigarette smokers					
			<1 pack		1-2 packs		>2 packs	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
A. All ages	91	...	179	—	413	—	187	—
Total sections[1]	787	100.0	1,544	100.0	3,629	100.0	1,579	100.0
No atypical nuclei	733	93.1	89	5.8	39	1.1	39	2.5
Some but <60 percent atypical	52	6.6	1,341	86.8	2,957	81.5	1,091	69.1
60 percent or more atypical	2	0.3	114	7.4	633	17.4	449	28.4
B. Men under age 50:								
Number men	26	...	9	—	132	—	55	—
Total sections[1]	223	100.0	433	100.0	1,169	100.0	457	100.0
No atypical nuclei	190	85.2	48	11.1	21	1.8	2	0.4
Some but <60 percent atypical	33	14.8	382	88.2	1,089	93.2	382	83.6
60 percent or more atypical	...	...	3	0.7	59	5.0	73	16.0
C. Men aged 50–69:								
Number men	44	...	92	—	240	—	113	—
Total sections[1]	379	100.0	789	100.0	2,116	100.0	948	100.0
No atypical nuclei	373	98.4	30	3.8	18	0.9	35	3.7
Some but <60 percent atypical	4	1.1	694	87.9	1,607	75.9	614	64.8
60 percent or more atypical	2	0.5	65	8.3	491	23.2	299	31.5
D. Men aged 70 or older:								
Number men	21	...	38	--	41	—	19	-
Total sections[1]	185	100.0	322	100.0	344	100.0	174	100.0
No atypical nuclei	170	91.9	11	3.4	—	—	2	1.1
Some but <60 percent atypical	15	8.1	265	82.3	261	75.9	95	54.7
60 percent or more atypical	...	...	46	14.3	83	24.1	77	44.2

[1] Sections with some epithelium present.

Source: Auerbach, O. et al. (*15*).

TABLE A35.—*Summary of methods used in retrospective studies of smoking and cancer of the bladder*

Author, year, country, reference	Cases			Controls	
	Sex	Number	Method of selection	Number	Method of selection
Lilienfeld et al., 1956, U.S.A. (*171*).	M.	321	Admissions to Roswell Park Memorial Institute, 1945–55 over 45 years of age.	337	No disease patients.
	F.	116	Same as males	109	Benign bladder conditions.
				317	No disease patients.
Schwartz et al., 1961, France (*249*).	M.	214	Admissions to hospitals in Paris and a few large provincial cities since 1954.	214	Healthy individuals admitted to same hospitals because of work or traffic accident, matched by 5 year age group.
Lockwood, 1961, Denmark (*175*).	M.	282	All bladder tumors reported to Danish Cancer Register during 1942–56 and living at time of interview in Copenhagen and Fredericksburg. (Includes bladder papillomas).	282	A. From election rolls matched with cases according to sex, age, marital status, occupation, and residence.
	F.	87		87	B. Another control group obtained from sample of Danish Morbidity Survey (1952, 1953, and 1954) compared with respect to smoking histories.
Wynder, 1963, U.S.A. (*326*).	M.	200	First phase:	200	
	F.	50	Admission to several hospitals in New York City during January 1957–December 1960.	50	Admission to same hospitals (excluded cancer of respiratory system, upper alimentary tract, myocardial infarction) matched by sex and age.
			Second phase:		
	M.	100	Admission to same hospitals during 1961.	100	Same as above.
	F.	20		20	
Cobb and Ansell, 1965, U.S.A. (*57*).	M.	136	Patients admitted to VA Hospital in Seattle 1951–61.	342	120 patients with cancer of sigmoid colon, 222 patients with non-neoplastic pulmonary disease.

TABLE A35.—*Summary of methods used in retrospective studies of smoking and cancer of the bladder (cont.)*

Author, year, country, reference	Cases			Controls	
	Sex	Number	Method of selection	Number	Method of selection
Staszewski, 1966, Poland (*261*).	M.	150	Patients with histologically confirmed bladder carcinoma.	750	Undefined source age-matched.
Deeley and Cohen, 1966, England (*66*).	M.	127	Patients with histologically confirmed bladder carcinoma.	127	Patients in same hospital with non-cancerous or pulmonary disease matched for age.
Yoshida et al., 1968, Japan (*330*).	M. F.	163 29	Patients with bladder cancer.	163 59	"Comparison cases."
Kida et al., 1968, Japan (*144*).	M. F.	88 26	Admissions to 15 hospitals in North Fukuoka prefecture.	88 26	Selected from patients hospitalized in same region for non-urinary ailments and age-matched
Dunham et al., 1968, U.S.A. (*85*).	M. F.	334 159	Admissions to New Orleans hospitals with histologic diagnosis of bladder carcinoma.	350 177	Admissions to same hospitals with non-neoplastic diseases and diseases unrelated to genitourinary tract.
Anthony and Thomas, 1970, England (*3*).	M.	381	Patients with papilloma and cancer of bladder at Leeds betweeen 1958-67.	275	Surgical patients without cancer previously interviewed for lung cancer study.

TABLE A35a.—*Summary of results of retrospective studies of smoking and cancer of the bladder*

Author, year, country, reference	Sex	Percent nonsmokers		Percent heavy smokers		Percent cigarettes smoked		Relative risk ratio: All smokers to nonsmokers			Comments
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers	Cigarette smokers	
Lilienfeld et al., 1956, U.S.A. (*171*).	M.	15.0	29.0	...	...	61.0	44.0	2.8	...	2.7	Cigarette and other.
	F.	87.0	83.0	...	...	...	...	1.4	...	...	
Schwartz et al., 1961, France (*249*).	M.	11.0	20.0	...	...	83.0	70.0	2	...	2.2	Cigarette only.
Lockwood, 1961, Denmark (*175*).	M.	9.0	13.4	30.0	15.0	30.0	15.0	1.6	3.0	3.0	Cigarettes main mode of smoking.
	F.	56.0	66.0	4.0	4.0	...	...	1.5	1.2	...	
Wynder et al., 1963, U.S.A. (*326*).	M.	7.0	18.0	47.0	23.0	86.0	63.0	2.9	5.2	3.3	Phases A and B combined.
	F.	61.0	86.0	6.0	...	...	...	3.9	...	...	
Cobb and Ansell, 1965, U.S.A. (*57*).	M.	4.6	25.8	79.4	43.3	...	...	7.3	10.3	...	
Staszewski, 1966, Polnnd (*261*).	M.	6.7	16.0	86.7	66.7	87.1	72.2	2.7	3.1	2.9	Cigarettes only.
Deeley and Cohen, 1966, England (*66*).	M.	2.4	7.1	...	...	...	...	3.1	...	...	

TABLE A35a.—*Summary of results of retrospective studies of smoking and cancer of the bladder (cont.)*

Author, year, country, reference	Sex	Percent nonsmokers		Percent heavy smokers		Percent cigarettes smoked		Relative risk ratio: All smokers to nonsmokers			Comments
		Cases	Controls	Cases	Controls	Cases	Controls	All smokers	Heavy smokers	Cigarette smokers	
Yoshida et al., 1968, Japan (*330*).	M.	8.0	22.7	43.4	33.0	—	—	3.4	3.7	—	
	F.	62.1	86.4	—	—	—	—	—	—	—	
Kida et al., 1968, Japan (*144*).	M.	11.0	11.0	32.0	29.0	—	—	1.0	—	—	
	F.	16.0	21.0	—	—	—	—	1.4	—	—	
Dunham et al., 1968, U.S.A. (*55*).	M.	8.6	14.5	—	—	49.4	45.4	1.8	—	1.8	Cigarettes only.
	F.	62.2	61.5	—	—	32.0	28.2	1.0	—	1.1	
Anthony and Thomas, 1970, England (*3*).	F.	6.3	6.3	—	—	36.5	20.1	1.0	—	1.3	Cigarettes only. More than 15 a day.

Chapter 5

Pregnancy

Source: 1973 Report, Chapter 4, pages 97 - 149.

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Introduction

Cigarette smoking is a common habit among women of child-bearing age in the United States. In 1970, approximately one-third of American women of child-bearing age were cigarette smokers. The percentage of U.S. women who smoked throughout pregnancy is not definitely known, but is presumably lower, probably in the neighborhood of 20 to 25 percent. With a large fetal population at potential, but preventable, risk, the relationship between cigarette smoking and the outcome of pregnancy has been the focus of considerable and continuing research.

Every investigator who has examined the relationship has confirmed that the infants of women who smoke during pregnancy have a lower average birth weight than the infants of women who do not smoke during pregnancy. Much evidence indicates that cigarette smoking during pregnancy causes this reduction in infant birth weight. Several investigators have demonstrated that the fetal and neonatal mortality rate is significantly higher for the infants of smokers than for the infants of nonsmokers; other investigators have not found higher mortality for smokers' infants. Studies of the association between maternal cigarette smoking and congenital malformations have produced conflicting results.

The following is a review of work previously reported and recent studies which bear on the relationships between cigarette smoking and different outcomes of pregnancy. In addition, the chapter includes a review of the relationship between cigarette smoking and lactation.

Smoking and Birth Weight

Epidemiological Studies

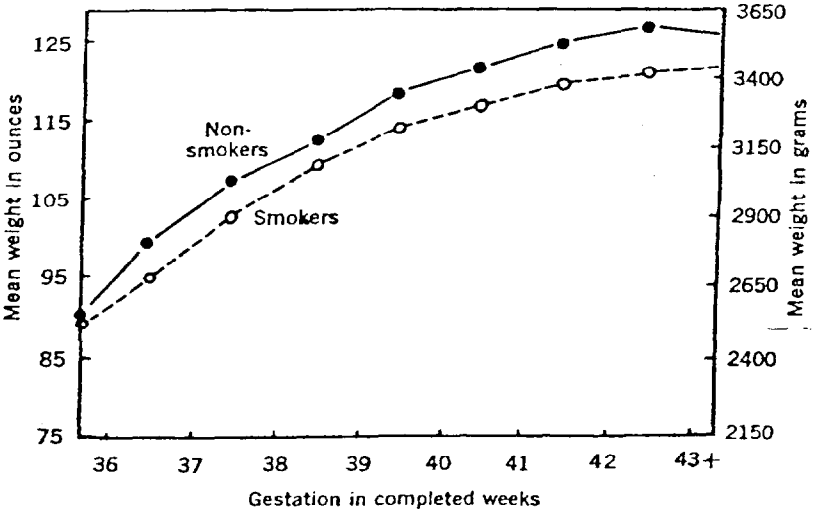
Cigarette Smoking and the Low-Birth-Weight Infant

In 1957, Simpson (*90*), using a retrospective study design, determined that among 7,499 women in San Bernardino County, Calif., the delivery of infants weighing less than 2,500 grams was nearly twice as

frequent among cigarette smokers as among nonsmokers. Subsequently, Lowe (*46*) studied 2,042 women in Birmingham, England, and demonstrated in his retrospective study that the infants of smoking mothers were delivered only slightly earlier (1.4 days on the average) than those of nonsmokers. He further noted that for gestations of 260 days and over, the infants of smokers were consistently lighter in weight during each week of gestation than those of the nonsmokers. This finding has been confirmed since, and figure 1 from the British Perinatal Mortality Study (*13*) provides illustration of this relationship.

Given the nearly constant disparity present between the birth weights of the infants of smokers and nonsmokers for gestations of 260 days and over, but absent prior to that time, and given the similar birth weights of infants of nonsmokers and of women who gave up smoking early in pregnancy and did not begin to smoke again, Lowe inferred that the influence of smoking upon birth weight might lie mainly in the later months of pregnancy. He emphasized the tentative nature of this conclusion, since the number of infants with a gestation of less than 260 days and the number of women who gave up smoking early in the pregnancy and did not begin to smoke again were both small.

Figure 1.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons.[1]



[1] This term refers to singleton births in England, Scotland, and Wales occurring during the week of March 3–9, 1958, which are included in the Perinatal Mortality Survey. These comprise 97 percent of all births notified in England and Wales or registered in Scotland during this week.

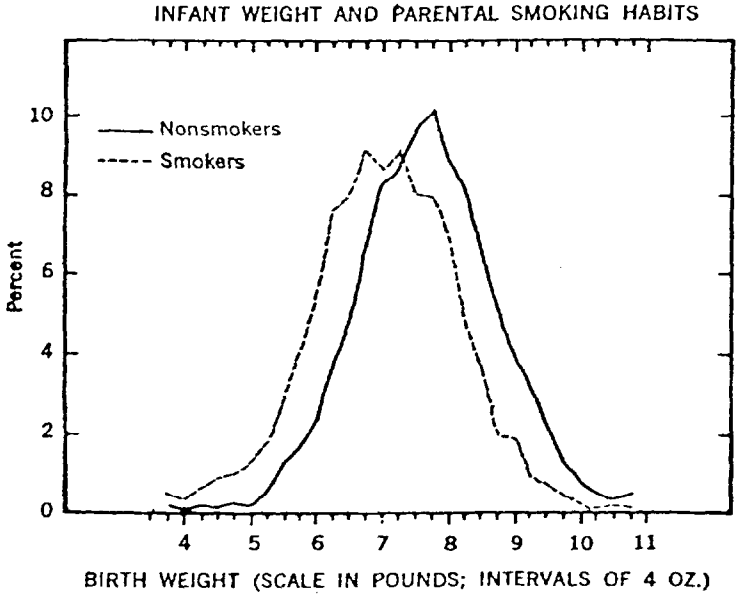
SOURCE: Butler, N. R., Alberman, E. D. (*13*).

Lowe found that the infants whose mothers smoked throughout pregnancy weighed, on the average, 170 grams less than those whose mothers did not smoke. In addition, he noted that the entire distribution of weights of infants of smokers was shifted to the left (toward lower weights) relative to that for the infants of nonsmokers. This finding, too, has been confirmed by other investigators. Figure 2 offers an illustration from MacMahon, et al. (*49*).

Given that the infants of smokers and nonsmokers differed only slightly with respect to the duration of gestation, Lowe concluded that the lower birth weight of smokers' infants must be attributed to a direct retardation of fetal growth. In other words, on the basis of his data, the infants of smokers were small-for-dates rather than truly premature.

Many investigators have subsequently confirmed this point (*12, 14, 25, 35, 65, 78, 85, 113*). Buncher (*12*), in a study of 49,897 births among U.S. naval wives, in the same population studied by Underwood, et al. (*100*), found that the infants of smokers were, on the average, delivered only 1 day earlier than those of nonsmokers. This finding accounted for only 10 percent of the discrepancy in birth weight between the two groups of infants. The remainder of the studies resulted in the detection of either similar variations in gestational length or no average difference. In a recent study, Mulcahy and Murphy (*56*),

Figure 2.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked 1 pack of cigarettes or more per day.



SOURCE: MacMahon, et al. (49).

in a sample of 5,099 Irish mothers, concluded that although the babies born to cigarette smokers were delivered slightly earlier than those of nonsmokers, independent of age and parity, the direct effect of smoking in retarding fetal growth was more significant.

The following points, based upon the results from many different studies, can be made about the relationship between cigarette smoking during pregnancy and lower infant birth weight:

1. Women who smoke cigarettes during pregnancy have a higher proportion of low-birth-weight infants than do nonsmokers. This excess of low-birth-weight infants among cigarette smokers predominantly consists of infants who are small-for-gestational age rather than gestationally premature.
2. The entire distribution of birth weights of the infants of cigarette smokers is shifted toward lower weights compared to the birth weights of the infants of nonsmokers.
3. The birth weights of the infants of cigarette smokers are consistently lighter than those of the infants of nonsmokers when the birth weights of the two sets of infants are compared within groups of similar gestational age beyond the 36th week of gestation.

The results of the studies which have been considered so far identify a relationship between cigarette smoking and lower infant birth weight and illustrate some aspects of that relationship, but do not indicate whether the association is causal or indirect. The succeeding two sections of this chapter contain evaluations of the available evidence which bears upon the nature of the association between cigarette smoking during pregnancy and the incidence of small-for-dates infants.

Evidence for a Causal Association Between Cigarette Smoking and Small-for-Dates Infants

Evidence previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) suggests that cigarette smoking is causally associated with the delivery of small-for-dates infants. The following is a summary of this evidence:

1. The results from all 30 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between maternal cigarette smoking and delivery of low-birth-weight infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker

(*3, 13, 17, 20, 25, 29, 35, 42, 43, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 78, 80, 83, 85, 90, 95, 99, 100, 113, 118*).

2. The strong association between cigarette smoking and the delivery of small-for-dates infants first demonstrated with results from studies of retrospective design (*3, 13, 17, 35, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 80, 85, 90, 95, 99, 100, 118*) has been repeatedly confirmed subsequently by data from studies of prospective design (*20, 25, 29, 42, 43, 78, 83, 113*).

3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants (*25, 43, 46, 49, 100, 113*).

4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has always been shown to be independently related to low birth weight (*1, 13, 25, 43, 46, 73, 78, 83*).

5. The association has been demonstrated in many different countries, among different races and cultures, and in different geographical settings (*13, 17, 25, 29, 36, 42, 43, 59, 73, 78, 80, 113*).

6. Previous smoking does not appear to influence birth weight if the mother gives up the habit prior to the start of her pregnancy (*25, 46, 49, 113*).

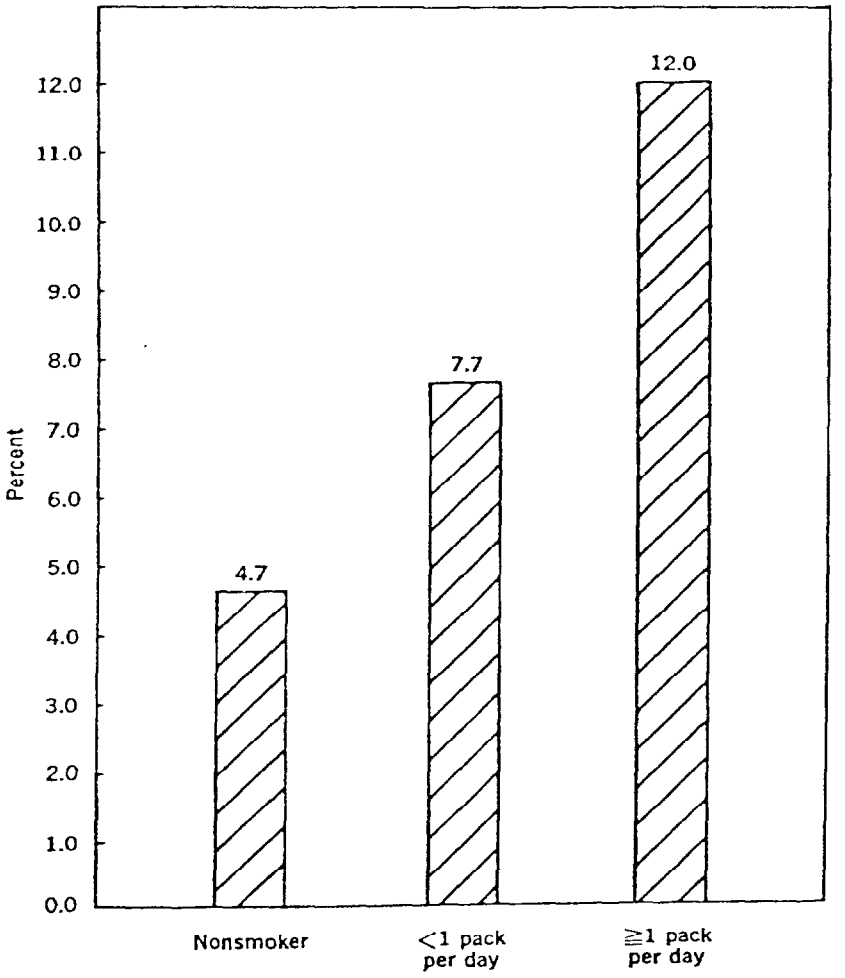
7. The infants of smokers experience an accelerated growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence (*83*).

8. Data from experiments in animals have documented that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight off-spring (*7, 8, 9, 23, 40, 87, 117*).

Several recently published studies have provided additional supporting evidence for a causal relationship between cigarette smoking and small-for-dates infants. The Ontario Perinatal Mortality Study (*66*) was conducted among 10 teaching hospitals during 1960 and 1961. The authors of this retrospective study of 50,267 births demonstrated a significant excess of infants weighing less than 2,500 grams among cigarette smokers as compared with nonsmokers ($P<0.001$). Smoking was significantly dose-related to the percentage of pregnancies terminating in the delivery of a low-birth-weight infant (fig. 3).

Niswander and Gordon (*63*) have recently reported data from the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. In this prospective study of 39,200 pregnancies, which were nearly equally divided among black and white women, the authors found a significant dose-related excess of low-birth-weight infants among smokers of both groups, compared to nonsmokers of the same race.

Figure 3.—Percentage of pregnancies with infant weighing less than 2,500 grams, by cigarette smoking category.



	Nonsmoker	<1 pack per day	≧1 pack per day
Number of infants weighing <2,500 grams:	1,322	1,186	793
Total births:	28,358	15,328	6,581

(P <0.001)

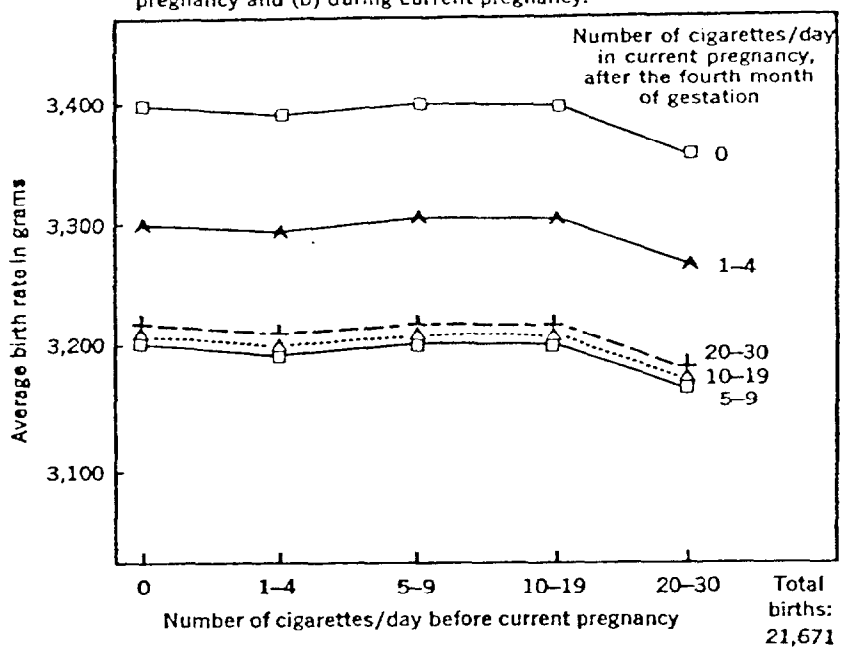
SOURCE: Ontario Department of Health (66).

Rantakallio (*76*) carried out a prospective study of 11,905 single births in Finland. Cigarette smoking mothers had significantly more infants weighing less than 2,500 grams than did nonsmokers ($P<0.001$).

Rush and Kass (*82*), in a prospective study of 1,040 pregnancies in Boston, Massachusetts; Domagala, et al. (*19*), in a retrospective study of 1,832 pregnancies in Poland; and Mukherjee and Mukherjee (*54*), in a retrospective study of 2,886 pregnancies in India, each found a significantly higher incidence of low-birth-weight infants among cigarette smokers.

Butler, et al. (*15*) have further analyzed the British Perinatal Mortality Study data. Analysis of the 16,994 questionnaires revealed that 40.8 percent of the women were cigarette smokers before pregnancy. After the fourth month, this percentage had decreased to 27.4 percent. Given the large number of women in the study, and the significant changes in smoking behavior which occurred, Butler, et al. found it possible to consider the effect of a change in smoking behavior on birth weight between the beginning of the pregnancy and the fourth month (after which smoking behavior was reportedly stable). The authors stated, "If smoking itself (rather than the type of woman who smokes) has a deleterious effect on the fetus, it would be reasonable to expect the mothers who gave up smoking during pregnancy to show differences in the birth weight and perinatal mortality of their offspring compared with those who continued to smoke." Their results are presented in figure 4. The birth weights by smoking categories were estimated by using a main effect model without mediating variables. However, the authors reported that when the mediating variables (social class, maternal age, parity, maternal height, sex of infant, gestational age, and perinatal mortality) were allowed for, the results of the analysis were very similar. The effect of cigarette smoking before pregnancy was insignificant compared to that of smoking regularly after the fourth month of gestation. The authors concluded, "The finding that a change in maternal smoking habits during pregnancy had the effect of putting the baby into a birth weight and perinatal mortality category associated with the new smoking habits points toward some kind of cause-effect relationship. * * * This finding is further strengthened by the birth weight analysis which shows that the diminution in birth weight of the offspring of smoking mothers persists and is indeed little changed when allowance has been made for a number of other social and obstetric mediating factors."

Figure 4.—Average birth weight by maternal smoking habit (a) before current pregnancy and (b) during current pregnancy.



SOURCE: Adapted from Butler, et al. (15).

Evidence for an Indirect Association Between Cigarette Smoking and Small-for-Dates Infants

Yerushalmy (*113*, *114*, *115*) has suggested that smoking is an index to a particular type of reproductive outcome and thus does not play a causal role in the production of small-for-dates infants. He has developed several lines of support for this hypothesis, from an analysis of data from the prospective investigation of 13,083 mothers in the Oakland Child Health and Development Study. He has emphasized that ineffective randomization and the phenomenon of self-selection complicate the development of appropriate inferences with regard to causality. Such difficulties do not prevent the identification of causal associations, but they demand careful and critical analysis of the data. Yerushalmy has questioned the causal nature of the relationship between cigarette smoking and small-for-dates infants because of: (a) The relationship between the smoking habit of the father and low birth weight of the infant, (b) behavioral differences between smokers and nonsmokers, and (c) comparison of the birth weights

of a woman's infants born during the periods when she smoked cigarettes and when she did not.

Yerushalmy (*114*) has stated that the smoking habit of the father could not reasonably be related to the birth weight of the infant. From preliminary data derived from the study, however, he determined that there was an increased incidence of low-birth-weight infants when the fathers smoked and, moreover, there was an apparent dose-response relationship as found for maternal smoking. However, he noted that only when both the husband and the wife smoked was the incidence of low-birth-weight babies increased. He felt that these findings supported the conclusion that smoking was a marker of types of individuals and not a causal factor for low birth weight. Other investigators have since examined this relationship (*49*, *100*), but none has confirmed an independent association for paternal smoking. The association between paternal smoking and birth weight appears to be an indirect one. Paternal and maternal smoking behavior are highly correlated and maternal smoking is strongly related to infant birth weight. Underwood, et al. (*100*) studied 48,505 women, their husbands' smoking behavior, and the relation with birth weight (table 1). If the mother was a nonsmoker, then the father's smoking had no influence on the birth weight of the infant.

TABLE 1.—*Infant birth weight by maternal and paternal smoking habits*

Cigarettes per day	Mothers			Fathers (nonsmoking mothers)		
	Number	Birthweight (grams)		Number	Birthweight (grams)	
		Mean	Difference[1]		Mean	Difference[1]
None	24,865	3,395	0	9,547	3,396	0
1 to 10	7,609	3,286	109	3,493	3,389	7
11 to 30	14,450	3,196	199	10,403	3,391	5
>30	1,570	3,182	213	1,330	3,393	3

[1] Nonsmoker minus smoker.

Source: Underwood, et al. (*100*).

Yerushalmy (*115*) pointed out that other investigators had found marked differences between smokers and nonsmokers. In his own study, he found that nonsmokers used contraceptives significantly more frequently than did smokers. Moreover, a significantly higher proportion of smokers drank coffee, beer, and whiskey. However, he did not adjust for these variables in his analysis of the association between cigarette smoking and lower infant birth weight. Other investigators have also found differences between smokers and nonsmokers. For example, Frazier, et al. (*25*) found significant differences in the distribution of parity, work history, education, and psycho-