Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking

DALE P. SANDLER, MPH, PHD, RICHARD B. EVERSON, MD, ALLEN J. WILCOX, MD, PHD, AND JAMES P. BROWDER, MD

Abstract: We obtained data on smoking by parents from 438 cancer cases and 470 controls to investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke. Cancer cases were between ages 15 and 59 at time of diagnosis. All sites but basal cell cancer of the skin were included. Cancer risk was increased 50 per cent among offspring of men who smoked. Increased risk associated with father's smoking was not explained by demographic factors, social class, or individual smoking habits, and was not limited to known smoking related sites.

Relative risk (RR) estimates associated with father's smoking tended to be greatest for smokers, males, and non-Whites. There was only a slight increase in overall cancer risk associated with maternal smoking. Mother's and father's smoking were both associated with risk for hematopoietic cancers, and a dose-response relationship was seen. The RR for hematopoietic cancers increased from 1.7 when one parent smoked to 4.6 when both parents smoked. Although they should be considered tentative, study findings suggest a long-term hazard from transplacental or childhood passive exposure to cigarette smoke. (*Am J Public Health* 1985; 75:487–492.)

Introduction

Cancer risk in adult life may be affected by transplacental and childhood exposure to cigarette smoke.[1] Data from studies in animals have demonstrated that many carcinogens are active when administered transplacentally or during early life. In some instances, effects may be produced at lower doses than are required for adults.[2–6] The tumors resulting from these transplacental and early postnatal exposures may not be apparent until adulthood.[3,7–9]

Studies in humans demonstrate that the fetus of smoking parents is exposed to components of cigarette smoke and is capable of bioactivating these chemicals.[10–20] For example, cotinine has been measured in the amniotic fluid of smokers and passive smokers[13] and thiocyanate has been measured in fetal cord blood.[14–16] Studies have also demonstrated increased activity of enzymes that metabolize benzo(a)pyrene in placentas of women who smoke,[17–19] and possibly even in placentas of women passively exposed to cigarette smoke.[20] Similar elevations may occur in the tissues of the fetus or exposed child. Finally, increased urinary excretion of mutagens has been found in passive smokers.[21]

Several epidemiologic studies have demonstrated increased risk for childhood tumors in relation to either paternal or maternal smoking,[22–24] but not all studies demonstrate an increased risk.[25,26] Even if no increased risk of childhood cancer were found, however, it would not rule out the possibility of increased cancer risk during adult life from fetal or childhood exposure. One recent study found elevated lung cancer risk for individuals whose mothers smoked.[27]

Cigarette smoke contains many known carcinogens.[28] Sidestream smoke, which is the smoke released from the cigarette between active puffs, may differ qualitatively from the mainstream smoke which is inhaled by the active smoker.[28] Some compounds occur in markedly higher concentrations in sidestream smoke, and although this smoke is diluted by the ambient air into which it is released, the passive smoker may inhale smoke which is qualitatively richer in certain compounds than mainstream smoke (Hoffman in 28). For example, the concentration of dimethylnitrosamine in sidestream smoke is 52 times that in mainstream smoke. Such qualitative differences make it difficult to predict the biologic effect of exposure to sidestream smoke.

In this study we investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke.

Methods

Our study methods have been described in greater detail elsewhere.[29] Cancer cases were selected from the hospital based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between ages 15 and 59 at time of diagnosis and included all cancer sites except basal cell cancer of the skin. Cases were restricted to age 59 and younger, since fewer than 5 per cent of women of child bearing age in 1920 were smokers.[30,31]

Cases were mailed a questionnaire for self completion, followed by a second mailing and a telephone call if needed. Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (16 per cent) either refused (n = 71) to participate or could not be contacted. Cases who died or did not respond were slightly older and were more often male or non-White; cases with respiratory cancer were more likely to have been excluded, presumably due to higher case fatality. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer and were the same race, sex, and age (± 5 years) to serve as comparison subjects. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Data were analyzed separately by control selection group and the adjusted results were nearly identical to those obtained when the control groups were combined.

Address reprint requests to Dale P. Sandler, MPH, PhD, Epidemiology Branch, Biometry and Risk Assessment Program, National Institute of Environmental Health Sciences, Mail Drop A3-02, P.O. Box 12233, Research Triangle Park, NC 27709. Drs. Everson and Wilcox are also with NIEHS; Dr. Browder is with the Department of Surgery, School of Medicine, University of North Carolina, Chapel Hill. This paper, submitted to the Journal May 1, 1984, was revised and accepted for publication October 16, 1984.

Individuals were specifically requested to supply information on natural parents. Only individuals who lived with both natural parents for all or most of the first 10 years of life are included in this report. As a result, 128 individuals were excluded (80 cases and 48 controls).

Transplacental and childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents. Subjects were asked whether parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the study subject. Subjects were also asked the usual quantity of cigarettes smoked by the parents and the frequency of smoking in the house. For this report, unless otherwise specified, exposure is classified by parental smoking in the household before the subject attained 10 years of age.

For this report, "smoking related" tumors were defined as cancer of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix.[28] Because evidence linking cervical cancer with cigarette smoking is not well documented, we also analyzed these data with cervical cancer excluded from this designation. The number of "smoking related" tumors was substantially reduced by this exclusion, but the general findings were not altered. For individual smoking status, smokers are defined to include anyone who ever smoked at least one cigarette a day for as long as six months. Nonsmokers are individuals who have never smoked.

Estimates of the relative risk (RR) in stratified analyses were obtained using the Mantel-Haenszel technique[32] for the summary odds ratio. The method of Gart[33] was used to obtain 95 per cent confidence limits for the combined estimates of RR. Estimates of the relative risk adjusted simultaneously for multiple confounding variables were obtained using a multiple logistic model.

Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, 50+) and three levels of education (<12 years, 12 years, >12 years). Age was treated as a continuous variable in the multiple logistic analysis.

Controls were matched one-to-one to cases to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are unmatched to maximize the study size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Analyses using matched pairs gave similar results.

Results

Cases and controls are distributed similarly by age, race, and sex (Table 1). Cases and controls differ only in their distribution by years of schooling with fewer cases having completed high school. However, cases and controls are similar in broad occupational categories. Cases and controls are similar with regard to their own smoking status with 45 per cent of cases and 47 per cent of controls never having smoked; the similarity is largely due to the use of friends as controls. When only cases with population controls are included, 57 per cent of cases and 47 per cent of population controls were smokers.

Maternal Smoking

There was only a small difference between cases and controls in reported exposure to maternal smoking [estimated relative risk (RR) = 1.1, 95 per cent confidence limits = 0.7, 1.6]. The RR for cancer among individuals whose mothers smoked was close to one for all measures of maternal smoking, and this lack of association persisted after adjustment for potential confounding factors including age, race, sex, education, individual smoking, and method of control selection.

Site specific relative risk estimates were calculated for 13 different sites, even though for many sites the number of cases is too small for detailed analysis. For most sites, the RR in relation to maternal smoking was close to one (Table 2). However, the RR for leukemia and lymphoma was 2.7 (95 per cent confidence limits = 1.3, 5.8). The RR for hematopoietic cancers associated with maternal smoking is greater for individuals whose fathers also smoked (2.6 vs 1.5 for nonsmoking fathers), but the RR remained elevated (RR = 2.4, 95 per cent confidence limits = 1.0, 5.5) after adjusting for father's smoking. Adjustment for age, race, sex, education, and individual smoking did not change this finding. The numbers of specific hematopoietic cancers are small precluding detailed analysis. However, the crude RR for Hodgkins disease (RR = 4.4, 95 per cent confidence limits = 1.1, 4.6), non-Hodgkins lymphomas (RR = 1.7, 95 per cent confidence limits = 0.5, 5.2) and acute leukemias (RR = 8.8, 95 per cent confidence limits = 2.0, 40.0) were greater than one.

TABLE 1—Comparisons of Cases and Controls

Factor	Cases N (%)	Controls N (%)
Total	438 (100)	470 (100)
Age (years)		
<30	83 (19)	89 (19)
30–39	72 (16)	95 (20)
40–49	117 (27)	110 (23)
50–59	166 (38)	176 (37)
Mean Age	43	43
Race		
White	325 (74)	340 (72)
Non-White	113 (26)	130 (28)
Sex		
Male	147 (34)	158 (34)
Female	291 (66)	312 (66)
Education†		
<12 years	182 (42)	164 (35)
12 years	122 (28)	171 (36)
>12 years	133 (30)	135 (29)
Occupation†		
Blue Collar	158 (39)	154 (34)
White Collar	154 (38)	183 (40)
"Housewife"	97 (24)	118 (26)
Smoking Status		
Nonsmoker	197 (45)	223 (47)
Smoker	241 (55)	247 (53)
Mother's Smoking†		
No	353 (84)	389 (85)
Yes	65 (16)	66 (15)
Father's Smoking†		
No	166 (44)	234 (53)
Yes	212 (56)	204 (47)

†Numbers reduced because of missing values.

TABLE 2—Cancer Risk from Mother's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	418*	(16)	1.1	(0.7, 1.6)
"Smoking Related"	131	(13)	0.9	(0.5, 1.6)
Not "Smoking Related"	287	(17)	1.2	(0.8, 1.8)
Lip, Oral Cavity and Pharynx	17	(12)	0.8	(0.2, 3.5)
Digestive System	31	(10)	0.6	(0.2, 2.1)
Respiratory System	22	(14)	0.9	(0.3, 3.2)
Lung	15	(13)	0.9	(0.2, 4.1)
Bone, Skin and Connective Tissue	36	(8)	0.5	(0.2, 1.8)
Breast‡	53	(15)	0.9	(0.4, 2.1)
Female Genital Tract‡	133	(17)	1.1	(0.7, 2.2)
Cervix‡	80	(15)	0.9	(0.6, 1.9)
Prostate§	10	(0)	0.0	(0.0, 3.7)¶
Testis§	5	(20)	1.8	(0.2, 16.6)
Urinary Tract	6	(0)	0.0	(0.0, 5.1)¶
Eye, Brain and Other Nervous System	37	(11)	0.7	(0.2, 2.1)
Brain	31	(13)	0.9	(0.3, 2.7)
Endocrine Glands	21	(19)	1.4	(0.5, 4.2)
Hematopoietic Tissue	41	(32)	2.7	(1.3, 5.8)
Other	6	(17)	1.2	(0.1, 10.3)

*Missing values for mother's smoking.
†For comparison 66 (15%) of 455 controls were exposed to mother's smoking.
‡Sex specific comparison: 16% of 301 female controls were exposed.
§Sex specific comparison: 12% of 154 male controls were exposed.
¶Exact confidence limits.

Paternal Smoking

There was an overall relative risk estimate of 1.5 (95 per cent confidence limits = 1.1, 2.0) for cancer among individuals whose fathers smoked in the household (Table 3). Adjusting for potential differences in age, sex, race, individual smoking status, smoking by spouse, education, maternal smoking, or method of control selection did not alter this finding (RR = 1.5). Estimates of the adjusted RR were obtained separately for the group with friend controls (RR = 1.6) and the group with population controls (RR = 1.4). The combined adjusted RR in a matched pairs analysis with a much smaller data set was also similar. The RR for cancer associated with father's smoking was greater for males than females (1.7 vs 1.4), for non-Whites than for Whites (1.7 vs 1.4), and for smokers than for nonsmokers (1.7 vs 1.2).

TABLE 3—Cancer Risk from Father's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	378*	(56)	1.5	(1.1, 2.0)
"Smoking Related"	120	(58)	1.6	(1.0, 2.5)
Not "Smoking Related"	258	(55)	1.4	(1.0, 1.9)
Lip, Oral Cavity and Pharynx	17	(53)	1.3	(0.4, 3.8)
Digestive System	30	(60)	1.7	(0.8, 3.9)
Respiratory System	22	(50)	1.1	(0.5, 2.9)
Lung	13	(62)	1.8	(0.5, 6.6)
Bone, Skin and Connective Tissue	34	(32)	0.5	(0.2, 1.2)
Breast‡	51	(51)	1.1	(0.6, 2.1)
Female Genital Tract‡	113	(60)	1.6	(1.0, 2.6)
Cervix‡	70	(61)	1.7	(1.0, 3.0)
Prostate§	9	(44)	1.0	(0.2, 4.7)
Testis§	5	(80)	5.2	(0.5, 125.9)
Urinary Tract	5	(40)	0.8	(0.1, 5.7)
Eye, Brain and Other Nervous System	30	(63)	2.0	(0.9, 4.6)
Brain	24	(67)	2.3	(0.9, 6.0)
Endocrine Glands	20	(55)	1.4	(0.5, 3.8)
Hematopoietic Tissue	37	(68)	2.4	(1.1, 5.2)
Other	5	(80)	4.6	(0.5, 108.7)

*Missing values for father's smoking.
†For comparison 47% of 438 controls were exposed to father's smoking.
‡Sex specific comparison: 48% of 288 female controls were exposed.
§Sex specific comparison: 43% of 150 male controls were exposed.

Crude estimates of relative risk for cancers at specific sites in relation to father's smoking are shown in Table 3. The RR for "smoking related" (RR = 1.6) and for "not smoking related" sites (RR = 1.4) are similar. Specific sites with elevated RR included cervix, brain, and hematopoietic tissue.

The RR of 1.7 for cervical cancer among individuals whose fathers smoked is unaffected by adjustment for age, race, sex, maternal smoking, individual smoking, or spouse smoking. The two-fold increase in risk for brain tumors in relation to paternal smoking is similarly unaffected by adjustment for potential confounding variables. Although the number of lung cancer cases with data on father's smoking is small (n = 13), the crude RR for lung cancer associated with father's smoking is 1.8, and is 2.5 after adjusting for age and individual smoking. The RR remains elevated when smoking by spouse and mother are also taken into consideration.

Leukemia and lymphoma risk is also not substantially changed by adjustment for age, sex, race, spouse smoking, and individual smoking. The adjusted RR is 2.5. However, the risk is greater for individuals whose mothers also smoked (RR = 3.1 vs 1.8 for individuals whose mothers did not smoke) and the RR is 1.9 (95 per cent confidence limits = 0.9, 4.4) after adjusting for maternal smoking. For specific hematopoietic cancers, the crude RR was elevated for Hodgkins disease (RR = 5.7, 95 per cent confidence limits = 1.2, 38.4), non-Hodgkins lymphomas (RR = 1.6, 95 per cent confidence limits = 0.6, 4.3), and for acute leukemias (RR = 4.6, 95 per cent confidence limits = 0.6, 34.2).

Individual Smoking Status

Overall and site specific relative risk estimates are shown separately for individuals who smoked and those who never smoked in Table 4. Relative risk estimates in relation to mother's smoking are similar for smokers and nonsmokers and are close to one for all sites but hematopoietic tissue. Increased cancer risk related to father's smoking is not limited to smokers or nonsmokers, although the RR for all sites combined is greater among smokers.

Dose-response

The elevated risks for all cancers combined and for most specific sites were related primarily to father's smoking. However, for leukemia and lymphoma there is an increase in risk when both parents smoked. The RR is 1.7 when one parent smoked and 4.6 if both parents smoked (Mantel-Haenszel chi for trend = 3.25, $p < 0.001$). For both mother's and father's smoking, overall cancer risk increased only slightly with reported frequency of smoking in the house. Risk also tended to increase with reported number of cigarettes smoked, but a large proportion of missing values make these data unreliable.

Discussion

We have found overall cancer risk to be increased among the offspring of men who smoked. There was only a

TABLE 4—Cancer Risk from Parental Smoking among Nonsmokers and Smokers, All Sites Combined and Selected Sites†

Site	Maternal moking						Paternal moking					
	Nonsmokers			Smokers			Nonsmokers			Smokers		
	No.	(% exposed)‡	RR	No.	(% exposed)‡	RR	No.	(% exposed)§	RR	No.	(% exposed)§	RR
All Sites	191	(12)	1.2	227	(19)	1.0	173	(49)	1.2	205	(62)	1.7
"Smoking Related"	47	(9)	0.8	84	(15)	0.8	41	(56)	1.7	79	(59)	1.5
Not "Smoking Related"	144	(13)	1.3	143	(20)	1.1	132	(46)	1.1	126	(64)	1.8
Lip, Oral Cavity, and Pharynx	0	—	—	17	(12)	0.6	0	—	—	17	(53)	1.1
Digestive System	13	(8)	0.7	18	(11)	0.6	12	(50)	1.3	18	(67)	1.7
Respiratory System	4	(25)	2.9	18	(11)	0.6	4	(50)	1.3	18	(50)	1.0
Lung	1	(0)	0.0	14	(14)	0.7	1	(100)	∞	12	(58)	1.4
Bone, Skin, and Connective Tissue	19	(11)	1.0	17	(6)	0.3	20	(30)	0.6	14	(36)	0.6
Breast‖	29	(10)	0.9	24	(21)	0.9	28	(43)	0.9	23	(61)	1.4
Female Genital Tract‖	72	(11)	1.0	61	(25)	1.2	59	(51)	1.3	54	(70)	2.2
Cervix‖	40	(8)	0.7	40	(23)	1.3	34	(56)	1.7	36	(67)	2.0
Eye, Brain and Other Nervous System	17	(6)	0.5	20	(15)	0.8	15	(53)	1.5	15	(73)	2.8
Brain	11	(9)	0.9	20	(15)	0.8	9	(56)	1.7	15	(73)	2.8
Endocrine Glands	11	(18)	1.9	10	(20)	1.1	11	(55)	1.6	9	(56)	1.3
Hematopoietic Tissue	19	(21)	2.3	22	(41)	3.1	17	(65)	2.4	20	(70)	2.4

†Sites with 15 or more cases.
‡For comparison, 11% of 220 nonsmoking controls and 18% of 235 smoking controls exposed to mother's smoking.
§For comparison, 43% of 211 nonsmoking controls and 50% of 227 smoking controls exposed to father's smoking.
‖Sex specific comparison: 45% of nonsmoking controls exposed to father's smoking and 11% exposed to mother's smoking; 52% of smoking controls exposed to father's smoking and 22% exposed to mother's smoking.

small increase in risk associated with maternal smoking. Increased risk associated with father's smoking did not appear to be explained by differences in such factors as age, race, sex, social class (as measured by education and occupation), or smoking habits of the case or control. The effect was not limited to known smoking related sites. Estimated relative risks associated with father's smoking tended to be greater for smokers, males, and non-Whites. We have previously reported an increased cancer risk for individuals married to smokers,[29] but the apparent effect of paternal smoking is not altered by adjustment for smoking by spouse.

Several findings from different sources support the plausibility of increased cancer risk from early life exposure to cigarette smoke. In addition to the experimental studies[1-9] and biochemical studies in humans,[10-21] limited support for the results of the present study can be found in other epidemiologic studies.[22-24,27] Only one of these studies, however, has reported on cancer risk during adulthood from exposure to parent's cigarette smoke.[27]

Stewart, *et al*, in a large case-control study, found a very small (RR = 1.1) increased risk for cancer in children up to age 10 whose mothers smoked.[34] An increased cancer risk related to father's smoking was not seen (RR = 1.0), but 10 years may have been too soon to detect an effect. Neutel and Buck[22] found an increased risk (RR = 1.3) in a prospective study of cancer risk through age 10 among children whose mothers smoked during pregnancy, but did not report on father's smoking.

Questions on parental smoking during pregnancy have been included in a number of case-control studies of particular childhood tumors. Our finding of a two-fold increase in risk for brain cancer among individuals whose fathers smoked is consistent with the data of Preston-Martin, *et al*.[23] In their study, which focused on exposure to nitrosamines, an increased risk of brain cancer (RR = 1.5) among children whose fathers smoked during the mother's pregnancy was seen. Sidestream cigarette smoke which is passively inhaled is one source of exposure to nitrosamines and other N-nitroso compounds.[28] Gold, *et al*, did not report on father's smoking but found a five-fold increase in risk for brain tumors among children whose mothers continued to smoke in pregnancy.[35]

Findings from a study by Grufferman, *et al*,[24] are consistent with our finding of a predominantly paternal effect. In that study, an elevated relative risk for rhabdomyosarcoma was associated only with father's smoking. Manning and Carroll reported no increased risk for childhood leukemia related to mother's smoking.[25] Father's smoking was not reported. Although the number of cases was small and dose-response data were inconsistent, Neutel and Buck did find that the offspring of smoking women had nearly twice the leukemia risk of offspring of women who did not smoke.[22]

Despite the small number of lung cancer cases included, we chose to look at lung cancer risk in relation to paternal smoking because of continued interest in passive smoking and cancer risk at this site.[27,36,37] The RR for lung cancer among individuals whose fathers smoked was 2.5 after adjusting for age and individual smoking. The adjusted RR associated with mother's smoking was 1.8, but this was based on only two smoking mothers among 15 cases. Correa, *et al*, reported an RR of 1.7 for lung cancer associated with mother's smoking, but no increased risk related to father's smoking.[27]

Our finding of a possible cervical cancer risk related to father's smoking has not been reported elsewhere. There is, however, growing support for a role of passive smoking (as measured by spouse smoking) in cervical cancer risk.[38,39]

Data on parental smoking were obtained retrospectively from offspring who may not be in a position to provide accurate histories. Parents or siblings of study subjects were

also interviewed regarding the smoking histories of the parents to validate the data obtained from subjects. We interviewed 649 relatives of subjects included in this report. Of these, 55 per cent were mothers and 40 per cent were siblings. For more than 350 subject-mother pairs, agreement on qualitative smoking questions ranged from 93 to 98 per cent and was substantially better than chance. There was also good agreement between subjects and their siblings.

Our findings are not due to any obvious recall bias. The hypothesis that parental smoking may cause cancer is not generally well known and study subjects and interviewers were told only that we were interested in smoking patterns in families. We obtained similar responses from mothers and subjects, regardless of case status, suggesting that differential recall probably did not occur.

It is difficult to distinguish transplacental and passive childhood exposures in an epidemiologic study: women who smoke during pregnancy generally continue smoking after the baby is born.[40] Father's smoking may produce transplacental as well as passive childhood exposure.[13,16,20] An effect of father's smoking on genetic material in sperm is also a possibility.[41–45] Only 16 per cent of the smoking mothers in our study began smoking after pregnancy, and no mothers smoked only during pregnancy. This made it difficult to compare cancer risks for individuals exposed in utero with risk in individuals exposed only passively in childhood. Furthermore, 94 per cent of the smoking fathers smoked both before and after the subject's birth.

Nevertheless, if an increased risk were seen for mother's but not father's smoking, a transplacental effect might be a reasonable explanation. In this study and others,[23,24] increased risks were generally related to father's smoking only. Little increased risk was associated with mother's smoking, suggesting a passive rather than a transplacental mechanism. Our failure to find a similar effect for mother's smoking might be due to the fact that they smoked fewer cigarettes than fathers or smoked different types of cigarettes. Although children may spend more time with their mothers than with their fathers, it is also conceivable that mothers do not smoke when actively engaged in child care activities.

The increasing frequency of women smoking after the 1920s should provide future studies with increasing power to detect any late effects of maternal smoking on offspring. The first sizable cohort of individuals exposed to maternal smoking is only beginning to reach the age at which cancer most commonly occurs.

REFERENCES

1. Everson RB: Individuals transplacentally exposed to maternal smoking may be at increased cancer risk in adult life. Lancet 1980; 2:123–127.
2. Druckrey H, Preussmann R, Ivankovic S: N-nitroso compounds in organotropic and tranplacental carcinogenesis. Ann NY Acad Sci 1969; 163:676–696.
3. Rice JM: Perinatal period and pregnancy: intervals of high risk for chemical carcinogens. Environ Health Perspect 1979; 29:23–27.
4. Vesselinovitch SD, Rao KVN, Mihailovich N: Neoplastic response to mouse tissues during perinatal age periods and its significance in chemical carcinogenesis. *In:* Bailar JC, Weisburger EK, Aaronson SA, *et al,* (eds): Perinatal Carcinogenesis. Nat Cancer Inst Monogr 1979; 51:239–250. DHEW Pub. No. (NIH) 79-1633. Washington, DC: Govt Printing Office, 1979.
5. Drew RT, Boorman GA, Haseman JK, McConnell EE, Busey WM, Moore JA: The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Tox Appl Pharmacol 1983; 68:120–130.
6. Wechsler W, Rice JM, Vesselinovitch SD: Transplacental and neonatal induction of neurogenic tumors in mice: comparison with related species and with human pediatric neoplasms. *In:* Bailar JC, Weisburger EK, Aaronson SA, *et al,* (eds): Perinatal Carcinogenesis. Nat Cancer Inst Monogr 1979; 51:219–226.
7. Vesselinovitch SD: Comparative studies on perinatal carcinogenesis. *In:* Tomatis L, Mohr U (eds): Transplacental Carcinogenesis. IARC Sci. Pub. No. 4. Lyon: IARC, 1973; 14–22.
8. Napalkov NP: Some general considerations on the problem of transplacental carcinogenesis. *In:* Tomatis L, Mohr U (eds): Transplacental Carcinogenesis, IARC Sci. Pub. No. 4. Lyon: IARC, 1973; 1–13.
9. Rice JM: An overview of transplacental chemical carcinogenesis. Teratology 1973; 8:113–126.
10. Lucier GW, Lui EMK, Lamartiniere CA: Metabolic activation/deactivation reactions during perinatal development. Environ Health Perspect 1979; 29:7–16.
11. Jones AH, Fantel AG, Kocan RA, Juchau MR: Bioactivation of procarcinogens to mutagens in human fetal and placental tissues. Life Sci 1977; 21:1831–1836.
12. Rifkind AB, Tseng L, Hirsch MB, Lauersen NH: Aryl hydrocarbon hydroxylase activity and microsomal cytochrome content of human fetal tissues. Cancer Res 1978; 38:1572–1577.
13. Smith N, Austen J, Rolles CJ: Tertiary smoking by the fetus (letter). Lancet 1982; 1:1252.
14. Andrews J: Thiocyanate and smoking in pregnancy. Br J Obstet Gynaecol 1973; 80:810–814.
15. Pettigrew AT, Logan RW, Willocks J: Smoking in pregnancy—effects on birthweight and on cyanide and thiocyanate levels in mother and baby. Br J Obstet Gynaecol 1977; 84:31–34.
16. Bottoms SF, Kuhnert BR, Kuhnert PM, Reese AL: Maternal passive smoking and fetal serum thiocyanate levels. Am J Obstet Gynecol 1982; 144:787–791.
17. Welch RM, Harrison YE, Conney AH, Poppers PJ, Finster M: Cigarette smoking: stimulatory effect on metabolism of 3, 4-benzpyrene by enzymes in human placenta. Science 1968; 160:541–542.
18. Nebert DW, Winker J, Gelboin HV: Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. Cancer Res 1969; 29:1763–1769.
19. Vaught JB, Gurtoo HL, Parker NB, LeBoeuf R, Doctor G: Effects of smoking on benzo(a)pyrene metabolism by human placental microsomes. Cancer Res 1979; 39:3177–3183.
20. Manchester DK, Jacoby EH: Sensitivity of human placental monooxygenase activity to maternal smoking. Clin Pharmacol Ther 1981; 30:687–692.
21. Bos RP, Theuws JLG, Henderson PT: Excretion of mutagens in human urine after passive smoking. Cancer Letters 1983; 19:85–90.
22. Neutel CI, Buck C: Effect of smoking during pregnancy on the risk of cancer in children. JNCI 1971; 47:59–63.
23. Preston-Martin S, Yu MC, Benton B, Henderson BE: N-nitroso compounds and childhood brain tumors: A case-control study. Cancer Res 1982; 42:5240–5245.
24. Grufferman S, Wang HH, DeLong ER, Kimm SYS, Delzell ES, Falletta JM: Environmental factors in the etiology of rhabdomyosarcoma in childhood. JNCI 1982; 68:107–113.
25. Manning MD, Carroll BE: Some epidemiological aspects of leukemia in children. JNCI 1957; 19:1087–1094.
26. Jaffe N, Marchetto DJ, Meadows A, Winston KR, Li FP, Scher CD: Clinical investigations of the etiology of childhood cancers. Proc Am Assoc Cancer Res 1978; 19:157.
27. Correa P, Pickle LW, Fontham E, *et al:* Passive smoking and lung cancer. Lancet 1983; 2:595–597.
28. US Department of Health and Human Services: The health consequences of smoking—cancer: a report of the Surgeon General. DHHS Pub. No. (PHS) 82-50179. Washington, DC: Govt Printing Office, 1982.
29. Sandler DP, Everson RB, Wilcox AJ: Passive smoking in adulthood and cancer risk. Am J Epidemiol 185; 121:37–48.
30. Haenszel W, Shimkin MB, Miller HP: Tobacco smoking patterns in the United States. Public Health Monogr No. 45.1956;56.
31. Harris JE: Cigarette smoking among successive birth cohorts of men and women in the United States during 1900–80. JNCI 1983; 71:473–479.
32. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies. JNCI 1959; 22:719–748.
33. Gart JJ: Point and interval estimation of the common odds ratio in the combination of 2 × 2 tables with fixed marginals. Biometrika 1970; 57:471–475.
34. Stewart A, Webb J, Hewitt D: A survey of childhood malignancies. Br Med J 1958; 1:1495–1508.
35. Gold E, Gordis L, Tonascia J, Szklo M: Risk factors for brain tumors in children. Am J Epidemiol 1979; 109:309–319.
36. Hirayama T: Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 1981; 282:183–185.
37. Trichopoulos D, Kalandidi A, Sparros L, *et al:* Lung cancer and passive smoking. Int J Cancer 1981; 27:1–4.

38. Buckley JD, Harris RWC, Doll R, *et al:* Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981; 2:1010–1015.
39. Brown DC, Pereira L, Garner JB: Cancer of the cervix and the smoking husband. Can Fam Physician 1982; 28:499–502.
40. McMahon B, Alpert M, Salber EJ: Maternal weight and prenatal smoking habits. Am J Epidemiol 1966; 82:247–261.
41. Tomatis L, Cabral JRP, Likhachev AJ, Ponomarkov V: Increased cancer incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Int J Cancer 1981; 28:475–478.
42. Nomura T: Parental exposure to X-rays and chemicals induces heritable tumours and anomalies in mice. Nature 1982; 296:575–577.
43. Evans HJ: Parental mutagenesis and familial cancer. Nature 1982; 296:488–489.
44. Evans HJ, Fletcher J, Torrance J, Hargreave TB: Sperm abnormalities and cigarette smoking. Lancet 1981; 1:627–629.
45. Grufferman S, Delzell ES, Maile MC, Michaelopoulos G: Parents' cigarette smoking and childhood cancer. Med Hypoth 1983; 12:17–20.

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Mortality Rates in Boston (and Other Large Cities), 1911

Boston's death rate for 1911 was 17.1, which is high compared with rates of most other large American cities.

The 1911 rates for the other cities having over 500,000 inhabitants were—Cleveland 13.55; Pittsburgh 14.94; Chicago 14.55; New York 15.22; St. Louis 15.36; Philadelphia 16.51; and Baltimore 18.43.

A brief analysis of these rates is desirable.

Typhoid Fever:—*From typhoid Boston had the lowest rate of all the cities. The rates per 100,000 were as follows:—Boston 9.14; Chicago 10.78; New York 10.99; Philadelphia 14.11; Cleveland 14.46; St. Louis 15.56; Pittsburgh 25.81; and Baltimore 27.28.*

Scarlet Fever:—*The rates were Baltimore 7.79; Pittsburgh 9.95; Boston 10.74; Philadelphia 11.33; New York 13.25; Chicago 21.20; St. Louis 27.26; and Cleveland 31.12.*

Diphtheria:—*The rates were Baltimore 12.05; St. Louis 16.84; Boston 18.00; Cleveland 21.94; Pittsburgh 23.60; New York 25.84; Philadelphia 31.51; and Chicago 39.11.*

Measles:—*The rates were Chicago 5.75; Cleveland 6.63; Pittsburgh 9.59; Boston 10.74; New York 13.25; Baltimore 13.63; St. Louis l5.84; and Philadelphia 19.30.*

Whooping Cough:—*The rates were Chicago 2.45; St. Louis 4.57; Philadelphia 7.34; New York 7.75; Baltimore 8.50; Cleveland 14.80; Boston 15.68; and Pittsburgh 19.54.*

Taking all these diseases together, Boston had the lowest rate with 64.30 per 100,000; the others in order were Baltimore 69.25; New York 70.88; Chicago 7.29; St. Louis 80.07; Philadelphia 83.59; Pittsburgh 88.49; and Cleveland 88.95.

Tuberculosis of the Lungs:—*The rates per 100,000 were Cleveland 121.77; Pittsburgh 130.88; St. Louis 135.29; Boston 154.88; Chicago 165.98; New York 177.39; Philadelphia 187.31; and Baltimore 205.12.*

This analysis of the communicable diseases should be extremely gratifying to the people of Boston. However, it fails to reveal the reason of Boston's higher rate. But a study of the figures for 1910, for which year more complete figures are available, will show much more. . . .

Cancer, cerebral hemorrhage, organic diseases of the heart, pneumonia and violent deaths stand out as the principal causes which have comparatively high rates in Boston. . . .

There are two reasons why Boston has such a large number of deaths of non-residents. First it has a population in its immediate suburbs greater than the population of the city itself. These people labor in Boston and when ill come to Boston hospitals. The other reason is that Boston is the recognized medical centre for all New England and attracts those afflicted with cancer, for example, a disease more prevalent in the New England States than in any of the other registration states.

Moreover in 1910 Boston had a larger percentage of its deaths over 6 years of age than any of the cities under consideration. In a word, Boston is an old city and has many old people. . . .

But in a word it may be safely said that Boston's high rate is largely due to its geographical position in the centre of populous suburbs, and to its fame as a medical centre, and not, as has been so often intimated, to the unhealthful conditions in the city.

—Davis WH: Boston's death rate. Am J Public Health 1912; 2:638–640.