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Cigarette Smoking and Down Syndrome

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SUMMARY

A matched case-control study of 100 mothers of Down syndrome children, 100 mothers of children with other defects (defect controls), and 100 mothers of children with no defects (normal controls) was carried out. All infants were born in upstate New York in 1980 and 1981. Matching was very close on maternal age for the normal controls but not for the defect controls. The risk ratios for the association of cigarette smoking around the time of conception with Down syndrome was 0.58 (90% confidence interval of 0.34–0.98) in the case-defect control comparison and 0.56 (90% confidence interval of 0.33–0.95) in the case-normal control comparison. Stratification by alcohol ingestion and maternal age did not abolish the negative trend to association. The results are contrary to that of an earlier study of others that found a positive association of older age and trisomy in spontaneous abortions. In fact, among mothers of Down syndrome cases over age 30 in this analysis, the risk ratio was lower than for younger mothers. (For case-normal control comparisons, the value was 0.39 [90% confidence interval of 0.17–0.87]). If not due to chance or confounding, the negative association in our data may be attributable to, among other factors, a selective effect of smoking upon survival or fertilizability of +21 gametes prior to conception or upon survival of +21 conceptuses after fertilization.

INTRODUCTION

A recent study of spontaneous abortions has reported an interesting pattern of association of maternal cigarette smoking and maternal age with trisomy [1]. In the data of this study, smoking was negatively associated with trisomy in younger mothers, those under 30, but positively associated with trisomy in

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older mothers. We have recently completed an extensive case-control study of instances of Down syndrome in live births in upstate New York 1980–1981. As part of that study, we have analyzed the role of cigarette smoking.

METHODS

This study was part of an investigation of an apparent "outbreak" of Down syndrome live births in counties in central New York in summer and fall of 1980. We made attempts to include all known cases of Down syndrome live births in "upstate New York" (New York State exclusive of New York City) in 1980 and the first half of 1981, both those in the region of the apparent outbreak (the cluster group) and those outside of the region (the noncluster group). We also interviewed some cases born later to bring the total cases analyzed to 100. We ascertained cases from reports on birth certificates, New York State Chromosome Registry report forms [2], and ad hoc reports from those in some areas who were concerned about an apparent increase of cases. After initial ascertainment, we contacted the physician or other reporting individual for permission to interview the mother of their case. After receiving permission, we then contacted the mother herself. There were 144 putative cases ascertained initially, of which only 100 could be included. (Reasons for exclusion were: unwillingness of physician or mother to allow an interview, inability to contact the mother, inability to obtain matched controls, erroneous original diagnosis of Down syndrome.)

Forty-one cases included in the study were born in the region of the cluster in 1980–1981, 59 were born elsewhere. For each case ascertained, we made attempts to include two controls: one, a "defect" control, had a significant malformation reported on the birth certificate; the other, a "normal" control, had no birth defect reported on the certificate. Each such triplet is denoted below as a case control "trio."

All controls were matched by race and date of birth (within 33 days). Attempts were also made to match each control by geographical area and maternal age. In general, this was only close to achievable for the normal controls. As the original thrust of the study was investigation of the cluster, the normal control was chosen from the same geographic region as the case (with four exceptions in which this was not possible). Maintaining geographic and temporal matching made it impossible to find an exact maternal-age matched normal control for each case. There were 27 cases in which maternal age was not exactly matched, but in all instances, the difference was no greater than 3 years. For the defect controls, it was not possible to match systematically on geographic region. And even though we allowed residence to vary significantly, we could not match exactly on maternal age for 76 of the defect controls. (See table 1 on some aspects of matching.)

The time span between date of birth of a case and date of interview of a mother—the "age" of a case—ranged from 137 to 744 days. The median difference in "age" between a case and control was 33 days. There were 11 cases, eight abnormal controls, and no normal controls who had died before the interview.

We attempted to set-up interviews as soon as possible after initial contact with the mother. For any case-control "trio," we sought to have a no greater time span than 14 days between the day of interview of any mother in the trio. Despite establishing "panels" of possible controls for each case before contacting any member of a trio, in several instances we were not able to complete interviews with both a defect *and* a normal control for a case. We only include in this analysis results in which complete data were obtained on all members of a case-control trio.

The interview with the mother included approximately 112 queries concerning her history and that of the child's father. Each interview lasted approximately 30–90 min. Interviewees were told they had the right not to participate and to decline to answer any particular query. A large number of variables were included in the analysis. An intensive analysis of responses revealed no evident explanation for the apparent geographic and temporal excess of cases. By 1982, the apparent outbreak had subsided.

TABLE 1

COMPARISON OF CASES AND CONTROLS ON SELECTED VARIABLES

	No.	Mean	(SEM)	Median	Range
Maternal age (yrs):					
Down syndrome	100	30.5	(0.7)	30.9	16 to 46
Defect controls	100	28.7	(0.5)	28.7	18 to 40
Normal controls	100	30.4	(0.6)	30.5	17 to 44
Case-defect control difference	100	+1.8	(0.4)	+0.8	−3 to +16
Case-normal control difference	100	+0.2	(0.1)	+0.1	−2 to +3
No. yrs smoked:					
Down syndrome	95*	4.4	(0.6)	1.2	0 to 25
Defect controls	95*	5.0	(0.6)	3.0	0 to 22
Normal controls	94*	6.6	(0.8)	3.1	0 to 25
Case-defect control difference	90*	−0.6	(0.9)	−0.1	−22 to +25
Case-normal control difference	89*	−2.2	(1.1)	−0.8	−25 to +25
Interview span in (days):					
Case-defect control difference	100	−1.5	(0.4)	−1.0	−15 to +21
Case-normal control difference	100	−1.2	(0.4)	−0.8	−14 to +16

* In some instances, smokers (or ex-smokers) could not recall the no. yrs smoked.

There were six questions included in the interview on smoking. These were:
Have you ever smoked cigarettes? ___Yes ___No
If yes:
How many years have you been smoking? _____
Were you smoking about the time of conception? ___Yes ___No
Did you smoke during the pregnancy? ___Yes ___No
What was the greatest number of cigarettes you smoked per day before the pregnancy? _____
What was the greatest number of cigarettes you smoked per day during the pregnancy? _____

In some analyses, we stratified the results by maternal age. For those instances in which cases and controls differed on maternal age, we used the maternal age of the case to make an assignment.

We could not make independent attempts to confirm the diagnosis of Down syndrome in all instances. Thirty-four of the cases included were reported to the chromosome registry with a 47, +21 karyotype. (We did not include known translocation cases.) For the remaining cases, the phenotypic diagnosis of Down syndrome had been reported by at least one medical observer. (In an additional four instances, either the physician or the mother herself indicated that the suspected diagnosis was in error. These cases were excluded from the analysis. (See also [3].)

We compared, separately, cases with the normal control group and with the defect control group. The results of these are denoted below as "normal" and "defect" comparisons, respectively.

RESULTS

Table 1 presents data on characteristics of cases and controls and indicates how close matching was on maternal age, number of years smoked, and interval between the date of control and case interviews. There were 73 exact matches on age for case-normal control pairs but only 24 exact matches for case-defect control pairs. There was a slight bias to younger age in the normal controls and a larger bias for the defect controls in comparison with cases. The interview span was very close for both case-control comparisons.

Table 2 presents data on the association of smoking (around the time of conception) with Down syndrome, stratified on maternal age. Results are presented on all case-control comparisons and those in which exact maternal-age matching was possible. While the entries in some tables are sparse, in all instances, the risk ratio is less than 1.0. For those of all ages, in three of four categories, the 90%, two-tailed (or 95% one-tailed) confidence interval excludes 1.0. For the comparison with normal controls for older mothers, in fact, the two-tailed 95% confidence interval excludes 1.0. An interesting observation is that the trends to a negative association are stronger for exact-age matched controls than for the entire group, although because of smaller numbers, these trends are of lesser statistical significance.

Table 3 presents data on smoking stratified by reports of alcohol consumption around the time of conception and by maternal age. For both the lighter and heavier drinkers, the overall trend is to a negative association with Down syndrome, but the trend is stronger and only significant at the .90 level (two-tailed) for the lighter drinkers.

We also examined trends for any reported history of maternal smoking of any amount and duration. (This is scored as positive for those who were not smoking around the time of conception but had smoked in the past.) In this analysis, the risk ratios for smoking were generally negative, but the magnitude of the effect was smaller and none of the differences were significantly different from zero. Stratification of results by alcohol ingestion in this group, however, also revealed a negative association in the normal control comparison.

Table 4 presents case-control comparisons distinguishing ex-smokers at the time of conception from nonsmokers (i.e., those who never smoked). Table 5 reveals more details about the patterns of smoking in relation to outcome and also the relationships to maternal age.

DISCUSSION

All the trends in this study with regard to older women are clearly discrepant from an earlier report of a positive association of smoking with trisomy in spontaneous abortuses in older women [1]. In fact, if anything, the trends in this study are in the opposite direction.

A report on Down syndrome live births noted as did ours no evidence for a positive association of smoking at older ages [4]. Indeed, if anything, the trend in that study was to a negative association. We have reanalyzed the data presented in [4] by Mantel-Haenszel tests. In those of all ages, the summary relative risk is 0.6 (with 95% interval of 0.3–1.0). For those under 30, the summary risk is 0.8 (with 95% interval of 0.4–1.7), and for those 30 and over, these values are 0.4 (0.2–0.9).

Thus, the results of our study and the earlier report by Kline et al. [4] of Down syndrome live births are counter to a positive association of smoking with the disorders at either younger or older ages, and, in fact, are more consistent with a negative association, particularly at the older ages. Such a result, if not attributable to chance or undetected confounding, could be attributable to inhibitory effects upon: (1) production or survival of +21 gametes,

TABLE 2

MATERNAL SMOKING AROUND TIME OF CONCEPTION

Loose Matching*: (Defect controls: no. = 100) (Normal controls: no. = 100)					Exact-age matched controls (Defect controls: no. = 24) (Normal controls: no. = 73)				
A. Down syndrome mother's age < 30									
	CONTROLS					CONTROLS			
	DEFECT		NORMAL			DEFECT		NORMAL	
CASES	+	−	+	−	CASES	+	−	+	−
+	7	10	6	11	+	3	2	5	10
−	17	11	14	14	−	6	5	13	13
Risk ratio	0.59		0.79		Risk ratio	0.33		0.77	
90% interval	(0.28–1.20)		(0.38–1.63)		90% interval	(0.06–1.49)		(0.36–1.65)	
B. Down syndrome mother's age ≥ 30									
+	4	8	5	7	+	0	0	4	2
−	14	29	18	25	−	3	5	9	17
Risk ratio	0.57		0.39		Risk ratio	0.00		0.22	
90% interval	(0.25–1.28)		(0.17–0.87)		90% interval	(0–1.7)		(0.04–0.90)	
C. All maternal ages									
+	11	18	11	18	+	3	2	9	12
−	31	40	32	39	−	9	10	22	30
Risk ratio	0.58		0.56		Risk ratio	0.22		0.55	
90% interval	(0.34–0.98)		(0.33–0.95)		90% interval	(0.04–0.90)		(0.28–1.04)	

NOTE: In each table, a "+" indicates a positive response, a "−" indicates a negative response with regard to maternal smoking around the time of conception. Thus, for mothers of all ages on the case-defect control comparison, there were 18 case "+" control "−" and 31 case "−" control "+" pairs. This indicates 18 pairs in which the case mother smoked and the control mother did not and 31 pairs with the reverse pattern. The estimated relative risk for this comparison is 18/31 or 0.58.

* Maternal age within 3 yrs in each case-normal control pair.

TABLE 3

MATERNAL SMOKING NEAR THE TIME OF CONCEPTION STRATIFIED BY ALCOHOL INGESTION NEAR THE TIME OF CONCEPTION

FREQUENCY OF ALCOHOL INGESTION BY DOWN SYNDROME MOTHERS								
≤ 1 Time per month*					≥ 2 Times per month			
A. Down syndrome mother's age < 30								
	CONTROLS					CONTROLS		
	DEFECT		NORMAL			DEFECT		NORMAL
CASES	+	−	+	−	CASES	+	−	+	−
+	5	4	3	6	+	2	6	3	5
−	12	6	8	10	−	5	5	6	4
Risk ratio	0.33		0.75		Risk ratio	1.20		0.83	
90% interval	(0.11–0.95)		(0.27–2.04)		90% interval	(0.38–3.81)		(0.26–2.60)	
B. Down syndrome mother's age ≥ 30								
+	2	5	3	4	+	2	3	2	3
−	6	22	15	13	−	8	7	3	12
Risk ratio	0.83		0.27		Risk ratio	0.38		1.00	
90% interval	(0.26–2.60)		(0.09–0.73)		90% interval	(0.10–1.29)		(0.20–5.01)	
C. All maternal ages								
+	7	9	6	10	+	4	9	5	8
−	18	28	23	23	−	13	12	9	16
Risk ratio	0.50		0.43		Risk ratio	0.69		0.89	
90% interval	(0.24–1.04)		(0.22–0.86)		90% interval	(0.31–1.52)		(0.36–2.18)	

NOTE: See footnotes to table 2 for explanation of the "+" and "−" signs.
* Includes nondrinkers.

TABLE 4

CASE-CONTROL COMPARISONS IN SMOKING STATUS ABOUT THE TIME OF CONCEPTION

	ABNORMAL CONTROLS			
	Current smokers	Ex-smokers	Nonsmokers	Total
Cases:				
Current smokers	11	4	14	29
Ex-smokers	13	7	9	29
Nonsmokers	18	6	18	42
Total	42	17	41	100
	NORMAL CONTROLS			
	Current smokers	Ex-smokers	Nonsmokers	Total
Cases:				
Current smokers	11	6	12	29
Ex-smokers	13	8	8	29
Nonsmokers	19	9	14	42
Total	43	23	34	100

(2) fertilization by +21 gametes, or (3) survival of +21 conceptuses during intrauterine life. It is of interest that the cited study of smoking and trisomy in spontaneous abortuses found a positive association at older maternal ages [1]. A smoking effect in older mothers that resulted in selective (recognized) abortion of +21 embryos and fetuses would account for this observation. If this were the case, there would be a relative dearth of +21 conceptuses surviving to live birth in this group, consistent with the observations on live birth. (This has also been hypothesized by Kline et al. [1].) Conceivably, in younger smoking mothers with Down syndrome conceptuses, a selective effect might be operative *before* the usual recognition of pregnancy accounting for the observations on abortions and live births in younger mothers reported by Kline et al. [1]. These biological considerations are speculative until direct evidence is available.

Last, the trends and inferences in our study apply to 47,+21. There were, however, 66 cases in which we did not have direct independent evidence from a laboratory that the cases had this pattern. It is possible that some of them were reported falsely by both physician and mother as instances of Down syndrome and/or had not 47,+21 but translocation Down syndrome. We cannot state unequivocally how many may have been falsely reported as affected. But the (living) children were ages 4 months to 2 years when the interviews took place, and all but seven were over 6 months. While a mistaken phenotypic diagnosis of Down syndrome is occasionally made in the newborn period [3], with increasing age, such an error is likely to be suspected and independent confirmation sought by a physician. We believe that most, if not all, mistaken

TABLE 5

MATERNAL SMOKING FOR DOWN SYNDROME CASES AND MATCHED CONTROLS BY MATERNAL-AGE QUINQUENNIA

MATERNAL AGE	DOWN SYNDROME			DEFECT CONTROLS			NORMAL CONTROLS		
	Yes	Total	Proportion	Yes	Total	Proportion	Yes	Total	Proportion
A. Any history of maternal smoking									
< 15	0	0	0	0	0	0	0	0	0
15–19	2	3	.67	2	3	.67	3	3	1.00
20–24	9	17	.53	9	15	.60	11	16	.69
25–29	19	25	.76	25	39	.64	18	27	.67
30–34	18	31	.58	18	33	.55	20	31	.65
35–39	6	13	.46	3	8	.38	9	14	.64
40–44	3	9	.33	2	2	1.00	5	9	.56
≥ 45	1	2	.50	0	0	0	0	0	0
All ages	58	100	.58	59	100	.59	66	100	.66
B. Maternal smoking near the time of conception									
< 15	0	0	0	0	0	0	0	0	0
15–19	2	3	.67	2	3	.67	3	3	1.00
20–24	5	17	.29	9	15	.60	9	16	.56
25–29	10	25	.40	19	39	.49	8	27	.30
30–34	6	31	.19	10	33	.30	16	31	.52
35–39	2	13	.15	1	8	.12	5	14	.36
40–44	3	9	.33	1	2	.50	2	9	.22
≥ 45	1	2	.50	0	0	0	0	0	0
All ages	29	100	.29	42	100	.42	43	100	.43

phenotypic diagnoses in children surviving the newborn period should have been detected by the time of interview, so the number of such instances should be close to zero. (Among the 11 cases who died before interview, the trends to a negative association with maternal smoking in case-control comparisons were even stronger than in those alive at time of interview.) With regard to translocations, perhaps 5% of the 66 cases—three or four—may have had translocation Down syndrome based upon the proportions of translocations in series to date [5].

Thus, there are reasons to expect that there are only a small proportion of cases in the series that were falsely diagnosed as having Down syndrome or which have translocations. Furthermore, instances of mistaken diagnoses or of translocation cases, in comparison with 47, +21 cases, should selectively occur more often in offspring of mothers under age 30 [3, 6]. But the trends to negative association of smoking with Down syndrome are, if anything, equal to or greater in mothers aged 30 and over than those under this age, suggesting that phenotypic false diagnoses or translocations do not contribute to the observed trends. If anything, such instances constitute "noise" in the analysis and tend to bias the results in the direction of no effect, to a relative risk of 1.0. Thus, the observed trends in this series to a negative association of maternal smoking with (presumptive) 47, +21 Down syndrome are in all likelihood, *despite*, not because of, inclusion of any such falsely diagnosed or translocation cases.

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