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AN INTERNATIONAL CASE-CONTROL STUDY ON HYPOSPADIAS THE PROBLEM WITH VARIABILITY AND THE BEAUTY OF DIVERSITY

B. KÄLLÉN*[1], E.E. CASTILLA**, E. ROBERT***, P.A.L. LANCASTER****, M. KRINGELBACH*****, O. MUTCHINICK******, M.L. MARTÍNEZ-FRÍAS******* and P. MASTROIACOVO********

Department of Embryology, University of Lund, Biskopsgatan 7, S-223 62 Lund, Sweden.

**ECLAMC/Genetica/Fiocruz - Rio de Janeiro - Brazil - and IMBICE - La Plata - Argentina.*

***Institut Européen des Génomutations - Lyon - France.*

****AIH National Perinatal Statistics Unit - University of Sydney - Australia.*

*****National Board of Health - Copenhagen - Denmark.*

******RYVEMCE - Departamento de Genética - Instituto Nacional de Nutrición Salvador Zubiran Mexico D.F. - Mexico.*

*******ECEMC - Instituto Nacional de la Salud - Universidad Complutense - Madrid - Spain.*

********IPIMC - Clinica Pediatrica - Universitá Cattolica - Rome - Italy.*

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The paper describes problems and advantages in an international cooperative study of a case-control design, aimed at investigating the possible association between exogenous hormones and hypospadias. The varying degrees of the ascertainment of specific exposures and risk factors, in spite of the use of a standardized questionnaire is illustrated. Definite support for the existence of recall or interviewer bias is presented. On the other hand, the multipopulation design offers possibilities to make use of the diversity of the populations: differences in reproductive patterns and in specific exposures such as drug use, smoking and maternal occupation.

INTRODUCTION

Multinational studies are common in the field of epidemiology of cancer or vascular disease and much insight has been gained from differences in rates and exposures between different populations. Most epidemiological studies on birth defect aetiology have been carried out within a defined population and usually within one centre. The Collaborative Perinatal Project (5) is, however, an example of a multicenter study as it was carried out in 14 American university-affiliated hospitals; studies by the EUROCAT organization are other examples (3). During the past 17 years, a number of malformation monitoring systems around the world have been collaborating in the International Clearinghouse for Birth Defects Monitoring Systems, ICBDMS (6). The main purpose has been to cooperate in the monitoring of congenital malformations but the organization has also made it possible to carry out joint studies aimed at the

[1] Corresponding author.

descriptive epidemiology of malformations (7,8) and on aetiological factors (1,9).

In this paper, a joint case-control study on hypospadias is discussed. It was carried out by eight member programs of the ICBDMS with the main purpose of studying the role of exogenous hormones in the aetiology of hypospadias. The idea was to make use of the fact that the confounders (threatened abortion, previous spontaneous abortion etc.) are probably similar in all populations but the use of sex hormones for treating these conditions varies considerably, from a very high usage in Italy, for instance, to practically no use in Australia or the Scandinavian countries.

The results pertaining to the question of the role of exogenous hormones in the aetiology of hypospadias are reported in other papers. We found an odds ratio for hypospadias after hormone therapy of 2.8 (95% confidence interval 1.2-6.9) (10) but no effect of oral contraceptive usage before or after conception (11). We also studied the relation between parental subfertility and hypospadias (12). In the study, data were collected on other exposures and other aspects. This paper focuses on a discussion of the problems involved in case-control studies in general and, specifically, studies performed as multinational efforts. The data will also be used to examine differences between the populations studied which can be useful in the planning of other studies.

MATERIALS AND METHODS

In this study, cases were singleton boys born with hypospadias (any degree of severity) but no other congenital malformation except for those directly associated with the hypospadias (undescended testicle, scrotum anomaly, etc.). Controls were the next non-malformed singleton boys born at the same hospital as the cases.

Data were collected from eight populations. Three were selected because it was known that progestins were rarely used therapeutically as pregnancy support (Australia, Denmark, Sweden) while in the other five (France, Italy, Mexico, South America and Spain) such treatments were still common.

Mothers of case and control infants were interviewed. A questionnaire was prepared and tested in a pilot study for 6 months, 134 case-control pairs distributed between the eight programs were interviewed and the questionnaire was then modified for the main study. The pilot study data were excluded. As the study was carried out in eight different programs using six different languages, the questionnaires were translated and, when completed, responses were translated back to English.

In three of the programs, ongoing case-control data collection occurs (Mexico, South America, Spain) and the present study was an extension of that: a special form was added for hypospadias cases. In these programs, the interviews were thus part of a routine procedure by the attending doctor and administered within a few days after the birth of the infant.

In four of the programs (Denmark, France, Italy, Sweden), doctors at the delivery hospitals (or personnel selected by these doctors) were asked to perform the interviews for any hypospadias case they found and also for the control, selected as described above. These interviews were also performed within a few days after the birth of the infant.

In one program (Australia), neither method could be used due to the structure of that program. Instead, two interviewers were hired who contacted the mothers of the cases (identified from the central malformation register) and the controls and interviewed them by telephone or visit. As the cases could not be identified until they had been reported to the central registry, the time elapsed between the birth of the infant and the interview was sometime long, up to one year, but similar between case and control.

In most instances, cases and controls were interviewed by the same person. Different interviewers occurred in 7% of the pairs, most coming from Italy (7%), Spain (13%), and Sweden (18%).

A total of 846 case-control pairs entered the study - their distribution between the programs is the following: Australia 117, Denmark 88, France 51, Italy 179, Mexico 32, South America 129, Spain 150, and Sweden 100. The infants which entered the study were born between September 1986 and March 1989.

Heterogeneity in frequency tables were tested using x^2 statistics. In some instances, stratification was carried out using the Mantel-Haenszel procedure. Odds ratios (OR) were calculated - their approximate 95% confidence intervals (95%CI) were estimated using Miettinen's technique. Homogeneity of OR were tested with Breslow-Day statistics. Exact tests were made using StatXact (Cytel Software Corp., Cambridge, Ma).

RESULTS AND DISCUSSION

One obvious reason to conduct a multicenter study is to increase numbers, especially when rare exposures/outcomes are studied, e.g., oral contraceptive usage in early pregnancy and hypospadias (10). The price will be an increased variability in the data collected. In the present study, different methods were utilized to minimize variability: detailed discussions of the questionnaire to be used, a pilot period during which the questionnaire was tested in all eight populations and a project plan with detailed instructions for the completion of the questionnaires.

In spite of this, variability occurred which can be demonstrated in different ways. As the majority of the interviews (with the exception of those performed in Australia) was performed by health personnel in

connection with the birth and care of the infant, a very large number of interviewers participated in the study and this may create variability. In 93% of the case-control pairs, however, the same person interviewed the case and the control mothers, usually at about the same time.

Incomplete information

In most studies based on questionnaires or interviews, a number of responses are lacking. If this number is high, it may markedly influence risk estimates. Under certain circumstances, absence of a response (or at least a written response) is equivalent to a "no" to the question. In the present study we had one central question, that on fertility problems (12), which was defined as present if the couple had tried to conceive for at least 6 months. This question was not answered in a relatively high percentage of responses from Italy and, to some extent, Spain (Table 1). Excluding these two programs, the average rate of stated fertility problems among those answering the question was 13.4%. The Italian rate was 21% if the blank questionnaires were disregarded and 13% if they were interpreted as representing no fertility problem. The corresponding figures for Spain were 17% and 15%. It therefore seems likely that blank questionnaires mean an absence of fertility problems. It can be noted that the rates of missing data among cases (36%) and controls (40%) in the Italian data are similar (X^2 = 0.58, NS). It should be stressed that although high, even the Italian rate of missing data was not remarkably high when compared with some published case-control studies (2).

Different ascertainment of events in different populations

Table 1 shows that the recorded rates of fertility problems were reasonably similar in all programs except South America, where it was only one third of that in the remaining programs. x^2 for heterogeneity between programs (based on 7 d.f.) was 29.1 when regarding blank questionnaires as "No" and 35.7 if disregarding blank questionnaires - in both instances highly statistically significant ($P < 0.001$) and completely explainable by the South American data.

Table 2 shows another example of heterogeneity: the distribution among previous pregnancies of spontaneous abortions, induced abortions, extrauterine pregnancies and deliveries reported by the mothers of cases and controls by program. The first obvious fact is that the rate of induced abortions varies tremendously: in most programs, the proportion of induced abortions among previous pregnancies varied between 14% (France) and 22% (Denmark) but in Spain the reported rate is only 2% and in Australia 9%. This obviously mirrors legislation concerning induced abortions but also, in a complex way, affects the percentage of spontaneous abortions registered. The absence of information on induced abortions in Mexico and South America does not mean that no such (illegal) abortions were made but that they were not reported. For this reason, it seemed more appropriate to remove all induced abortions from the data when the populations were compared, even if this results in a bias.

After removing induced abortions, the percentage of spontaneous abortions among all previous pregnancies varied between 18% (Denmark) to 21% (Sweden, Italy) with two exceptions: South America (10%) and Spain (15%). This heterogeneity is probably not random (x^2 = 22.0, $P < 0.01$). It could be due to different maternal age distributions because the risk of spontaneous abortion increases with woman's age. Stratification for age, using the Mantel-Haenszel procedure, and comparison with all other programs showed that this may be the explanation for the low rate in Spain (OR= 0.87, 95%CI 0.66-1.14) but hardly for that in South America (OR=0.59, 95%CI 0.44-0.78).

TABLE 1. - Started fertility problems (tried to conceive for 6 months or more) by program. Cases and controls combined. Percentages are given ± standard errors.

Program	Fertility problems			Per cent of all	Per cent of all, ecl. unknowns
	Yes	No	Unknown		
Australia	37	192	5	15.8 ± 2.4	16.3 ± 2.4
Denmark	30	141	5	17.0 ± 2.8	17.5 ± 2.9
France	12	87	3	11.8 ± 3.2	12.1 ± 3.3
Italy	47	176	135	13.1 ± 1.8	21.1 ± 2.7
Mexico	10	51	3	15.6 ± 4.5	16.4 ± 4.7
South America	10	247	1	3.9 ± 1.2	3.9 ± 1.2
Spain	46	230	24	15.3 ± 2.1	16.7 ± 2.2
Sweden	37	160	3	18.5 ± 2.7	18.8 ± 2.8
A11	229	1284	179	13.5 ± 0.8	15.1 ± 0.9

TABLE 2. - Previous pregnancies by program. Cases and controls combined.

Program	Spontan. abortions	Induced abortions	Extraut. pregnanc.	Births		Total No. of pregnan.	No. of women
				Still	Live		
Australia	51	27	0	4	206	288	234
Denmark	26	42	4	3	114	189	176
France	21	18	1	3	83	126	102
Italy	63	54	2	6	228	353	358
Mexico	16	-	0	4	64	84	64
South America	38	-	0	8	329	376	258
Spain	41	6	0	0	239	286	300
Sweden	46	46	1	5	169	276	200
A11	302	193	8	33	1432	1969	1692

Table 3 compares the distribution of women with at least one reported previous spontaneous abortion among all women with a previous pregnancy, comparing South America and the remaining programs. It can be seen that in South America, spontaneous abortions among previous pregnancies were more common among cases than controls (OR = 2.61, 95%CI 1.13-6.01, P = 0.02) but no such difference was seen among the other programs (OR=1.10, 95%CI 0.80-1.51, NS). Breslow - Day statistics give $x^2 = 3.7$, P = 0.055, indicating that this difference may be true.

The interpretation of the low rate of previous fertility problems and of previous spontaneous abortions in South America is difficult. Is the explanation a lower ascertainment, perhaps because women are less apt to report on these phenomena for cultural reasons, or are the differences real and related to less efficient pregnancy planning? In the latter case, it may be easier to demonstrate a possible relationship with hypospadias in that population than in other populations with a higher "background" of spontaneous abortions.

Different effects in different populations

In a multinational study, the effect of a specific agent may be tested on all the data or within each program's data. This can be seen with drugs used during the formative period for hypospadias (weeks 8-16). Table 4 shows these data (hormones excluded).

There is no excess of antibiotic exposure among cases compared with controls in the combined data (OR = 1.11, 95%CI 0.71-1.74) but, within individual programs cases are sometimes more often exposed than controls, and for Italy statistical significance is reached (P value = 0.03). A Breslow-Day test for the homogeneity of odds ratios results in a $x^2 = 14.9$ with 7 d.f., P = 0.04. The OR for the data from Australia, Denmark and Italy is 2.66 (95%CI 1.21-5.83, P = 0.015) and for the remaining programs OR=0.64 (95%CI 0.35-1.16, P = 0.138). The three programs specifically mentioned were selected because they had a high OR but hypothetically, a specific antibiotic or some underlying infection occurring in these populations could be a risk factor for hypospadias. In Spain and Sweden, however, the OR was below 1.0 and there was no obvious difference between Australia, Denmark, and Italy vs Spain and Sweden. Had the apparent excess risk been noted only in subtropical and tropical areas, for instance, it would have been easy to postulate that some specific infection or drug used for its treatment caused hypospadias.

Recall or interviewer bias

The question whether recall or interviewer bias is important or not in the study of the origin of birth defects has been much debated (4, 13-14). Recall bias means that the exposure information was reported differently when the infant had a birth defect versus when it was normal and that the type and degree of birth defect may influence the degree of bias. The bias may also differ between different types of exposure - "chronic" exposures are probably less biased than short-term exposures such as the temporary use of a drug. When low risks are studied, such a bias may create wrong interpretations. This is why we made a considerable effort to see whether it was present in our data. Figure 1 summarizes the estimated odds ratios (obtained by comparing the number of discordant pairs, that is, pairs where the case was exposed but not the control and vice versa) with their 95%CI. The majority lie over 1.0 and some are

TABLE 3. - Number of women with at least one previous spontaneous abortion and number of women with at least one previous pregnancy, divided into cases and controls and by program.

Program	Cases		Controls	
	Number of women		Number of women	
	with a previous spont. ab.	with a previous pregnancy	with a previous spont. ab.	with a previous pregnancy
Australia	17	71	20	86
Denmark	10	45	11	55
France	9	32	8	32
Italy	21	89	26	94
Mexico	6	12	7	15
South America	20	76	10	83
Spain	21	88	14	84
Sweden	14	64	17	64
Total	118	477	113	513
All except South America	98	401	103	430

TABLE 4. - Drug usage during weeks 8-16 (formative period for hypospadias), excluding hormones, by program and divided into cases (CA) and controls (CO).

Program	Antibiotics		Antiemetics		Sedatives		Other		Total	
	CA	CO	CA	CO	CA	CO	CA	CO	CA	CO
Australia	10	5	6	1	0	0	14	13	30	19
Denmark	7	3	0	0	1	1	9	10	17	14
France	1	1	1	1	1	0	10	7	13	9
Italy	6	0	1	1	1	1	30	28	38	30
Mexico	3	1	2	0	1	0	3	3	9	4
South America	4	6	3	0	3	1	17	11	27	18
Spain	7	13	23	14	0	1	20	18	50	46
Sweden	4	9	5	12	1	1	13	12	23	34
All	42	38	41	29	8	5	116	102	207	179

"significantly" above 1 - acute diseases other than respiratory or urinary infections, hormones during the sensitive period (10), antibiotics after the sensitive period, drugs other than antibiotics, sedatives or hormones after the sensitive period. "After the sensitive period" is defined as the drug usage that began after week 16. The mean OR for the 24 variables studied for the combined data was 1.27 ± 0.10. Among the programs, it varies from below 1.1 (Denmark, Italy, Sweden), 1.2-1.3 (Mexico, Spain) to 1.4-1.6 (Australia, France, South America). None of the factors examined had a lower confidence limit above the average OR and they may all estimate the same increased OR, at least partially an expression of recall or interviewer bias.

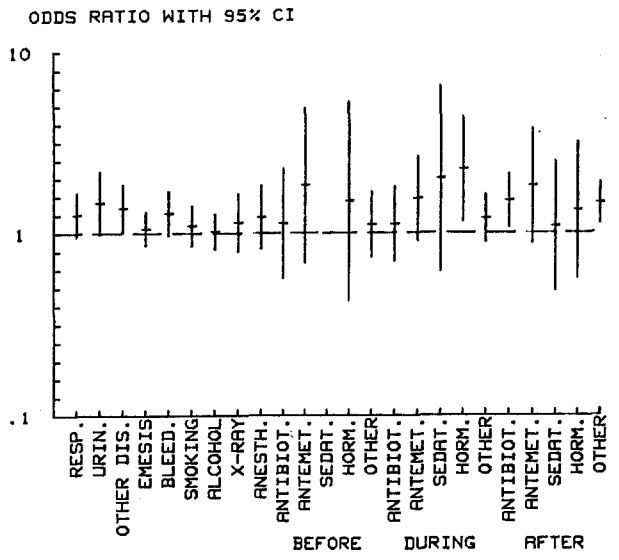

Figure 1. - Odds ratios for a number of different exposures calculated by comparison of discordant pairs (case exposed, control non-exposed vs. case non-exposed, control exposed) for the combined data. 95% confidence intervals marked with vertical lines.
RESP = respiratory tract infection; URIN = urinary tract infection; OTHER DIS = other acute disease, BLEED = bleeding during pregnancy, ANESTH = local or general anesthesia, ANTIBIOT = antibiotics, ANTIEMET = antiemetics, SEDAT = sedative, HORM = hormones. BEFORE, DURING, and AFTER refer to formative period of hypospadias (weeks 8-16).

One can suggest alternative explanations for the observation that drug usage after the formative period is associated with hypospadias. A disease or illness beginning during the formative period may cause or be associated with the malformation and result in later treatment, but a less far-fetched explanation is that the apparent difference between cases and controls is due to recall bias or interviewer bias. If so, every recorded odds ratio for a biologically plausible exogenous factor should be compared not with 1.0 but with this estimate (1.3). For example, we found an odds ratio for hormone treatment during the formative period of 2.8 (10) with a lower confidence interval which is above 1.0 but below 1.3. It could represent a high random variation of the "recall and interviewer bias" odds ratio.

Interviewer bias may well differ according to the probability of the studied factor as a causal agent. Thus, for instance, the discussion of the possible role of progestins in the aetiology of hypospadias may increase interviewer bias for that specific exposure.

The problem of interpretation of data

The main purpose of the study described in this paper was to examine the relationship between hormone exposure during the time of closure of the urethral folds and the development of hypospadias (10). The data collected indicated an odds ratio for that exposure over 2 and statistical testing, including consideration of identified confounders, showed that it was significantly increased above 1. Against this statistical "truth" there are some observations: the absence of a correlation between exposure and severity of hypospadias and the absence of a correlation between the timing of hormone exposure and the location of the urethral orifice. Furthermore, when a comparison was made between different populations with different usage of hormones, no correlation was seen between the exposure rate for hormones and the odds ratio for the main indication for hormone treatment (bleeding during pregnancy). Finally, as previously mentioned, there were strong indications of the presence of recall or interviewer bias in the data.

At one of the final meetings of the group, the interpretation of these data were extensively discussed but no consensus was reached. A closed voting was undertaken: three collaborators said that they thought the data supported the hypothesis that hormones caused hypospadias, three said the opposite, and one abstained.

There are various explanations for this divergence in interpretation. The participants had different backgrounds and different experiences, resulting in a spectrum of perspectives and opinions that were also influenced by interactions within the group during discussions of the findings. Based on the interpretation of their findings in previous studies, at least one had published a paper which incriminated hormones, another had published papers which argued against the relationship. There was probably another difference. Some of the collaborators looked upon the problem as a general health problem: was the available evidence enough to discourage the use of hormones during pregnancies? Others looked upon it from a strictly scientific point of view: was the available evidence sufficient to discard the null hypothesis that hormone exposure did not cause hypospadias?

Differences in exposures between the studied populations

So far, we have primarily discussed the problems involved in a joint study of the present type. There are, however, also advantages. In this case-control study we made use of the fact that although diseases and complaints which may act as confounders for hormone treatment reasonably are the same in all populations studied, the therapeutic traditions vary: in some programs, progestins are practically never given as pregnancy support, in others they are often used. This difference was used in order to interpret the apparent relationship between hormone treatment and hypospadias (10). If the hormones cause hypospadias, the confounders should appear more strongly related to hypospadias in populations where

progestins are given as pregnancy support than in populations where it is not. This principle - to try to separate the effect of the drug from that of the underlying disease - was used in previous multinational studies on anticonvulsants and birth defects (1,9). In spite of the fact that epilepsy probably occurs with about the same disease spectrum in different populations, specific drugs used varied markedly.

In Table 4 it can be seen that antiemetic drugs were used by 12% of the women interviewed in Spain but only by 2% of the women in the other programs. The percentage of women complaining of morning sickness is about the same (50% in Spain, 48% in the other programs, $x^2 = 0.6$, NS).

Tables 5-6 present some differences between the populations studied which may be useful in the planning of future multinational studies. It can be seen that marked differences occur in the smoking rate and also in the rate of maternal occupation and type of maternal occupation. To this should be added the likelihood that marked differences in actual exposures probably exist between programs even if the occupation is identical.

TABLE 5. - Rate of women who smoke according to program. Smoking refers to smoking during weeks 8-16, formative period of hypospadias. Cases and controls added. Per cent smoking refers to smoking at least 1 cig/day and is calculated on all with known smoking habits. Percentages are given ± standard errors.

Program	No or occasional	Cigs/day 1-9	10-19	20+	Unknown	Per cent smoking
Australia	186	21	11	12	4	19.1 ± 2.6
Denmark	101	32	35	3	5	40.9 ± 3.8
France	80	12	2	5	3	19.2 ± 4.0
Italy	264	61	16	12	5	25.2 ± 2.3
Mexico	56	5	0	0	3	8.2 ± 3.5
South America	195	15	7	4	37	11.8 ± 2.2
Spain	241	40	9	8	2	19.1 ± 2.3
Sweden	147	17	26	5	5	24.6 ± 3.1
All	1270	203	106	49	64	22.0 ± 1.0

TABLE 6. - Maternal occupation according to program (cases and controls added). Percentages ± standard errors are given. Percentage of women not working is calculated on all women; percentages of working in different professions are calculated on all working women. Health care workers are included in the professional group.

Program	Not working	Manual work	Clerk	Professional	Health care
Australia	40.3 ± 3.3	29.3 ± 3.9	36.1 ± 4.2	34.6 ± 4.1	15.8 ± 3.2
Denmark	26.1 ± 3.3	37.5 ± 4.3	25.8 ± 3.9	36.7 ± 4.3	15.6 ± 3.2
France	38.2 ± 4.8	28.6 ± 5.7	31.7 ± 5.9	39.7 ± 6.2	19.0 ± 4.9
Italy	54.6 ± 2.6	41.7 ± 3.9	33.7 ± 3.7	24.5 ± 3.4	4.9 ± 1.7
Mexico	75.0 ± 5.4	50.0	18.8	31.3	18.8
South America	77.5 ± 2.6	43.1 ± 6.5	31.0 ± 6.1	25.8 ± 5.7	not stated
Spain	69.3 ± 2.7	53.3 ± 5.2	17.4 ± 4.0	29.3 ± 4.7	9.8 ± 3.1
Sweden	16.5 ± 2.6	30.1 ± 3.6	19.9 ± 3.1	50.0 ± 3.9	31.9 ± 3.6

Concluding remarks

All participants in this study had experience with case-control studies in the individual programs and the task to carry out a joint study in order to increase numbers and to make use of the diversity between the populations studied seemed to be a relatively easy project. It was not. One principal problem with birth defect studies is that either the women have to be interviewed soon after birth and then, by necessity, a large number of interviewers is needed, or they are identified from the registries (as was the case in Australia) and interviewed at a later date when often considerable time has passed and the possibilities for misreporting of exposures increases. The structure of the society in some participating programs (South America, Mexico) makes a later follow-up nearly impossible, which also favoured the immediate-after-birth, multi-interviewer approach. The price is an increased variability in recording which was not prevented by extensive testing and standardization of the questionnaire but which, hopefully, is similar in both case and control groups.

The alternative source of bias - which may be of greater significance for the evaluation of putative exogenous agents - is recall and interviewer bias. We found definite evidence that such a bias exists by studying a number of exposures which are not biologically plausible as causing hypospadias. Our estimate of the odds ratio obtained by such bias is 1.3. It is true that it varied between different populations and it may obviously vary also between different studies. It seems wise to try to estimate the amount of such bias by including data on exposures which are implausible causes of the defect under study. The problem remains, however, that the interviewer bias especially may differ according to the biological plausibility of the exposure studied.

These lessons may be of use in the planning of future multinational studies. At the same time, data appeared in our study which demonstrated significant population differences which can be utilized in other studies, i.e., reproductive pattern, maternal smoking, or occupation. We think that the principal approach of multinational studies is sound: to make use of the diversity among populations to differentiate between the effects of various exposures and confounding factors.

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