Birthplace Differences in Stroke Rates among Coronary Heart Disease Patients: Is Variation Explained by Recognized Risk Factors?

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ABSTRACT: **Background:** The incidence of stroke varies among ethnically and culturally diverse groups.

Objectives: To examine the ethnic-geographic patterns of stroke incidence in men and women with coronary heart disease in Israel, focusing on the extent to which this variability can be explained by known differences in risk factors for stroke.

Methods: Patients with documented coronary heart disease were followed for 6–8 years for incident cerebrovascular events. Baseline medical evaluation included assessment of vascular risk factors and measurements of blood lipids. Among 15,052 patients, 1110 were identified with any incident ischemic cerebrovascular event by ICD-9 codes, of whom 613 had confirmed ischemic stroke or transient ischemic attack.

Results: A major excess of ischemic cerebrovascular events among Israeli Arab women as compared to males, and an inverse finding among Israeli born Jews, were noted. The high risk in the Arab population in Israel reflected an unfavorable risk profile, since predicted rates by multivariate analysis and observed rates were 69 and 68 per 1000, respectively. High ischemic cerebrovascular event rates were identified among patients born in the Balkan countries and North Africa (89 and 90 per 1000), but unfavorable risk factor levels of these individuals did not explain them. Most trends appeared similar in male and female patients. A comparison of observed and accepted-according-to-risk-profile rates of ischemic cerebrovascular events yielded significant differences ($P = 0.04$), consistent with an additional role of geographic/ethnic origin resulting from factors that remain unrecognized, or with variables unassessed in this study.

Conclusions: We identified an ethnic diversity in stroke risk among the Israeli born in different parts of the world beyond what could be expected on the basis of differences in known risk factors. These findings call for detailed research aimed at identifying additional differences in the risk profile of patients with atherothrombotic disease exposed to an increased risk of stroke

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Cerebrovascular disease mortality varies around the world [1]. Limited information on the incidence of stroke suggests that the latter varies as well. Migrant studies examine the role of geography, or a distinct ethnic origin, in the variation of stroke. In the landmark Ni-Hon-San comparative study among persons of Japanese origin, stroke rates were lower in Japanese men than Japanese living in San Francisco, but the latter had rates equal to United States Caucasians at least for ages 60–64 [2]. In the Israeli Ischemic Heart Disease Project the incidence of 23 year fatal ischemic stroke was considerably higher in men originating from the Middle East or North Africa, mostly from Arab countries, as compared to those of European origin. Incidence rates among the former were much higher than those predicted according to "average risk function" based on the entire sample of about 10,000 men [3].

The availability of information on stroke incidence among a large sample of 15,000 patients with coronary heart disease, screened for eligibility to a multicenter clinical trial [4], permitted us to expand the examination of the above ethnic-geographic pattern of morbidity to both men and women, using both fatal and non-fatal incidence rates. Admittedly this is restricted to persons already afflicted with CHD. Because we had assessed numerous risk factors among these patients at the screening phase, we can examine to what extent this can be explained by diverse risk profiles for stroke in these subgroups.

PATIENTS AND METHODS

Patients with documented CHD were screened to examine their eligibility for inclusion in the Bezafibrate Infarction Prevention study, a placebo-controlled secondary prevention randomized clinical trial assessing the effect of Bezafibrate [4]. These patients were examined between February 1990 and October 1992 in 18 hospitals spanning almost the entire country. Patients were 40–74 years old with a diagnosis of CHD. They were eligible for inclusion in the BIP randomized

CHD = coronary heart disease
BIP = Bezafibrate Infarction Prevention

clinical trial if they had evidence of myocardial infarction occurring between 6 months and 5 years before enrollment, or coronary insufficiency observed either at rest or during effort as manifested by typical pain and dynamic electrocardiography changes, or both. Coronary insufficiency episodes must have occurred between 6 months and 2 years before enrollment. For inclusion, specific serum lipid ranges were required as the study examined the efficacy of intervening to reduce serum triglycerides and increase high density lipoprotein-cholesterol, but we have no evidence that patients outside these limits were not screened. At the first physician visit, records were obtained on medical history, conventional risk factors and medications used, and a complete physical examination was carried out.

In our analysis of the incidence of ischemic cerebrovascular events, we excluded patients with a history of prior stroke or TIA in order to assess the risk of first-ever stroke. The total number of patients in the present analysis was 15,052. Mortality data were obtained during January 1999 from the Israel Population Registry, with cause of death coded according to ICD-9 codes. Patients in whom the underlining cause of death was ischemic cerebrovascular events were added as incident stroke to the analysis. Division into birth groups conformed with previous epidemiological large-scale studies in Israel [5], with the addition of an Israeli Arab group as most previous studies were restricted to Jewish samples. We chose to combine Jewish patients born in different areas with second-generation Israeli Jews whose parents were both born abroad, using the mother's country of birth. We ran sensitive analyses to examine whether using the father's birthplace (when different from that of the mother) affects the findings. There were negligible differences.

LABORATORY EXAMINATION

Laboratory measurements were performed in a central laboratory (Physiological and Hygiene Laboratory at the Wolfson Medical Center, Holon, Israel). All analyses were performed with a Boehringer-Hitachi 704 random-access analyzer with Boehringer diagnostic kits. Accuracy and precision were under periodic surveillance by the Centers for Disease Control and Prevention service in Atlanta, GA, USA. Blood samples were taken after 12 hours of fasting. Precipitation of low density lipoprotein and very low density lipoprotein with phosphotungstate reagent and determination of cholesterol determined HDL-C levels. Cholesterol was determined by the CHOD-PAP method (enzymatic colorimetric test). LDL-C levels were approximated by the formula of Friedewald et al. [6]. Between February 1990 and January 1994 we determined triglyceride levels by subtracting the free glycerol level, determined by using a separate enzymatic kit (Sigma Chemical), from the total triglyceride value. Since January 1994, we calculated triglyceride levels by subtracting 4.5 mg/dl (mean value of free glycerol level).

ASSESSMENT OF CEREBROVASCULAR EVENTS

We obtained computerized data files of hospitalizations with a diagnosis of any cerebrovascular disease (ICD-9 codes 430-438 or code 38.1 – carotid endarterectomy surgery). We matched the patients (based on national ID number and name) against a registry of all hospitals (except one) and the Clalit Health Services (insuring over 60% of Israelis) participating in the BIP screening process. Attainable medical records and hospital discharge summaries were systematically reviewed. Patients with intracerebral hemorrhage, subarachnoid hemorrhage or subdural hemorrhage and those not fulfilling the criteria for cerebrovascular events after review were also excluded, leaving 1110 cases for analysis. Data were collected on history, neurological examination, brain computed tomography and ancillary examinations as available, to verify the diagnosis and to determine stroke type. Two investigators including a stroke neurologist (D.T.) reviewed all classifications.

Stroke was defined according to World Health Organization criteria. Events resolving completely within less than 24 hours were diagnosed as a TIA. We classified cases as ischemic stroke on the basis of brain CT performed at the acute stage. Ischemic stroke was diagnosed if the patient had an appropriate clinical event and had a brain CT that showed a compatible low density lesion, was normal, or had findings compatible with hemorrhagic conversion of a cerebral infarct.

For the purpose of this study we assessed two endpoints. The first included all of the above 1110 patients with ischemic cerebrovascular events. The second endpoint was considered to have occurred in patients with ischemic stroke or TIA confirmed after review of their medical records, totaling 613 cases. For the remaining patients, brain CT was not performed or medical records were not available for review, so that stroke type could not be ascertained.

STATISTICAL ANALYSIS

Age-adjusted rates of ischemic cerebrovascular events incidence and by gender, in eight ethnic-geographic strata, were calculated using SPSS software version 11.0. Chi-square and ANOVA tests were used to compare the eight groups by baseline characteristics and major risk factors. Odds ratio for the incidence of ischemic cerebrovascular events and 95% confidence intervals were calculated from multivariate logistic regression for each area of birth. To estimate the "indepen-

TIA = transient ischemic attack
HDL-C = high density lipoprotein-cholesterol
LDL-C = low density lipoprotein-cholesterol

dent" contribution of area of origin to risk prediction, predicted ischemic cerebrovascular events rates were calculated by the logistic regression model and were compared to the actual number of events observed for each area of birth. The Hosmer-Lemeshow goodness-of-fit test was performed to assess overall model fit.

RESULTS

Of 15,052 patients, a total of 1110 were identified with any incident ischemic cerebrovascular event by ICD-9 codes, of whom 613 had confirmed ischemic stroke or TIA. An excess of ischemic cerebrovascular events among Israeli Arab female patients as compared to their male counterparts was noted. Adjusting only for age, the incidence rates of ischemic cerebrovascular events was high among Jews having migrated or born to migrants from North Africa (n=90) and Balkan countries (n=89) and low in their counterparts originating in East (n=73), Central (75) and other zones of Europe or South/North America (n=66), as well as among Israeli born Jews whose parents had also been born in the region subsequently becoming Israel (n=75). The results for ascertained ischemic stroke/TIA paralleled the above with one important exception – a considerably lower incidence was recorded among Israeli Arabs.

Table 1 compares major risk factors for stroke by birthplace and ethnicity. Israeli Arab patients and North African born patients depicted a considerably elevated prevalence of smoking at intake. Israeli Arabs also showed the highest prevalence of diabetes mellitus. They showed, however, the lowest rate of hypertension (defined as over 160/95 mmHg or reported antihypertensive medication use, as per the Joint National Committee definition at that time). The Israeli born Arab patients were the youngest group, but despite similar mean blood pressure and total serum cholesterol the Arab and Jewish subgroups showed sizeable differences in body mass index, and the fraction of cholesterol on HDL, the risk profile of the Arab patients being less favorable. Odds ratio for the incidence of ischemic cerebrovascular events are presented in Table 2.

In order to assess, with the inherent limitation, a "net" difference between what would have been expected on the basis of individual risk factor levels and the actual cases, we calculated individual probabilities to develop ischemic cerebrovascular events for each patient. The calculation applied a logistic risk function, incorporating coefficients equaling the logarithms of the following odds ratios: age 1.23 per 5 years, diabetes mellitus 2.00, hypertension 1.37, peripheral vascular disease 1.83, current cigarette smoking 1.40, and for each 5% increment in the fraction the serum cholesterol carried in HDL, 0.89. Jewish patients whose families originated in the Middle East or North Africa or in the Balkan countries exhibited comparable adjusted ischemic cerebrovascular event incidence to Israeli born Jews, while the age-adjusted odds ratios of patients originating in central Europe (OR 0.57, 95% CI 0.34–0.96) and the smaller group of those from "elsewhere in Europe" and the Americas (OR 0.55, 95% CI0.28–1.07) were consistent with

OR = odds ratio
CI = confidence interval

Table 1. Gender, age, comorbidity, habits, blood pressure, anthropometrics and lipids, by birthplace and ethnicity

Area of birth	Mid-East	North Africa	Eastern-Europe	Balkan States	Central Europe	Rest of Europe/ America	Israeli born Jews	Israeli Arabs	*P*
Male gender	2291 (84)	1798 (81)	3253 (79)	2066 (78)	901 (80)	443 (82)	466 (85)	791 (87)	‹ 0.001
Hypertension	748 (27)	666 (36)	1526 (37)	942 (36)	399 (35)	176 (33)	181 (33)	232 (26)	‹ 0.001
Diabetes mellitus	529 (19)	491 (22)	675 (16)	520 (20)	168 (15)	63 (12)	108 (20)	238 (26)	‹ 0.001
PVD	93 (3)	82 (4)	172 (4)	105 (4)	51 (5)	11 (2)	23 (4)	26 (3)	0.107
Smoking	346 (13)	320 (14)	313 (8)	218 (8)	83 (7)	57 (11)	61 (11)	169 (19)	‹ 0.001
NYHA class ›1	849 (31)	773 (35)	1192 (29)	715 (27)	270 (24)	108 (20)	165 (30)	317 (35)	‹ 0.001
Age (yrs)	58 (6.8)	58 (6.8)	61(6.9)	61 (6.4)	64 (6.9)	58 (7.1)	58 (7.1)	56 (6.8)	‹ 0.001
Systolic BP (mmHg)	134 (19)	134 (20)	136 (20)	136 (19)	136 (19)	132 (19)	133 (17)	131 (18)	‹ 0.001
Diastolic BP (mmHg)	81 (9.8)	81 (10.2)	82 (10.0)	82 (9.4)	81 (9.6)	81 (9.9)	81 (10.1)	80 (9.5)	‹ 0.001
BMI (kg/m2)	26.2 (3.6)	27.1 (3.8)	26.7 (3.4)	26.8 (3.6)	26.1 (3.2)	26.8 (3.7)	26.8 (3.2)	27.8 (3.6)	‹ 0.001
TC (mg/dl)	226 (39)	221 (40)	266 (39)	224 (39)	224 (39)	224 (39)	223 (42)	227 (41)	0.001
%HDL	16.7 (4.9)	17.3 (5.2)	17.5 (5.0)	17.4 (5.0)	18.0 (5.1)	17.3 (5.0)	16.5 (4.8)	16.1 (4.7)	‹ 0.001
Triglycerides (mg/dl)	166 (94)	160 (91)	148 (80)	154 (85)	147 (84)	153 (89)	189 (115)	162 (86)	‹ 0.001

PVD = peripheral vascular disease, smoking = current smoking, NYHA = New York Heart Association class, BP = blood pressure, BMI = body mass index, T = total cholesterol, %HDL = percent of HDL cholesterol of total cholesterol.
Numbers of patients and percentages are presented for attributes, mean (SD) for continuous variables.

Table 2. Crude rates (SD) and adjusted OR* (95% CI) for ischemic cerebrovascular disease by area of birth

Area of birth	Middle East	North Africa	Eastern-Europe	Balkan States	Central Europe	Rest Europe/ America	Israeli born Jews	Israeli Arabs
Ischemic cerebrovascular disease								
Crude rate	213 (7.8)	184 (8.3)	266 (6.5)	223 (8.2)	77 (6.8)	31 (5.8)	36 (6.5)	62 (6.8)
Age-adjusted OR	1.21 (0.84-1.74)	1.28 (0.88-1.86)	0.87 (0.60-1.24)	1.13 (0.79-1.64)	0.87 (0.58-1.32)	0.86 (0.52-1.41)	1.0 -----	1.16 (0.76-1.78)
Multivariate-adjusted* OR	1.25 (0.86-1.81)	1.30 (0.89-1.88)	0.93 (0.64-1.34)	1.20 (0.83-1.74)	0.97 (0.64-1.45)	0.99 (0.60-1.63)	1.0 ------	1.12 (0.72-1.72)
Ischemic stroke/TIA								
Crude rate	116 (4.2)	106 (4.8)	155 (3.8)	117 (4.4)	36 (3.2)	14 (2.6)	25 (4.5)	33 (3.6)
Age-adjusted OR	0.93 (0.60-1.45)	1.04 (0.67-1.63)	0.71 (0.46-1.10)	0.84 (0.54-1.31)	0.57 (0.34-0.96)	0.55 (0.28-1.07)	1.0 ------	0.89 (0.52-1.07)
Multivariate-adjusted* OR	0.96 (0.62-1.50)	1.06 (0.67-1.66)	0.77 (0.50-1.19)	0.89 (0.57-1.39)	0.63 (0.37-1.07)	0.63 (0.32-1.23)	1.0 ------	0.84 (0.49-1.44)

*Adjusted for gender, age, diabetes mellitus, New York Heart Association class, hypertension, peripheral vascular disease, current smoking, body mass index and percent of HDL-C of the total cholesterol.

lower susceptibility to develop an event. Multivariate adjustment increased the above two odds ratios to 0.63.

To examine whether the entire area-specific array of event rates is satisfactorily explained by the risk profiles of the individual patients we summed the individual probabilities in each area. Table 3 compares expected and observed rates of ischemic cerebrovascular events. The results demonstrate that had the risk factors identified in this study explained the ethnic variation fully, the variation should have been smaller than observed. The predicted incidence varied between 68 and 77 per 1000, whereas the observed rates ranged between 58 and 83 per 1000. Specifically, the predicted and observed crude rates for the Israeli Arab participants are both 68 per 1000. An approximate chi-square test of goodness-of-fit between the observed distribution of rates and that predicted by the overall risk function yields chi-square (7 d.f.) = 14.43, P = 0.04. These findings were maintained in men and women [Table 4], except where only 10 cases or fewer occurred among the female patients (for the relatively small groups of Central European born and "rest of Europe"), consistent with the absence of a modifying effect by gender on the likelihood of an individual exceeding his or her calculated risk of ischemic cerebrovascular events.

DISCUSSION

Ethnic-geographical patterns have been identified previously in CHD-free Israeli men, in terms of susceptibility to fatal stroke during the 1960s–1980s [7]. A similar variation was identified in the present study for men and women with CHD, where analysis includes both fatal and non-fatal cases. The advantage of the current study is that it is not restricted to men and to fatal stroke cases. Conversely, information relating to the

Table 3. Predicted ischemic cerebrovascular disease rates per 1000 by eight ethnic-geographic strata defined by area of birth, and actual event rates observed

Area of birth	Subjects	Predicted iCVE rates	Observed iCVE rates
Middle East	2740	70	78
North Africa	2221	72	83
Eastern Europe	4111	75	65
Balkan States	2645	77	83
Central Europe	1126	76	68
Rest of Europe/America	538	64	58
Israeli born Jews	551	72	65
Israeli Arabs	911	68	68

iCVE = ischemic cerebrovascular events

Table 4. Incidence rates of ischemic cerebrovascular events per 1000 patients predicted by 8 ethnic-geographic strata defined by area of birth, and actual event rates observed for men and women

	Male			Female		
Area of birth	No.	Predicted iCVE rates	Observed iCVE rates	No.	Predicted iCVE rates	Observed iCVE rates
Middle East	2291	69	77	449	76	80
North Africa	1798	71	81	423	75	92
Eastern Europe	3253	74	62	858	79	73
Balkan States	2066	77	84	579	76	81
Central Europe	901	77	73	225	75	49
Rest of Europe/ America	443	62	56	95	71	63
Israeli born Jews	466	71	67	85	77	59
Israeli Arabs	791	67	66	120	76	83

iCVE = ischemic cerebrovascular events

social risk factors pertinent to the risk of ischemic cerebrovascular events after CHD is missing in our study. In the present study, calculating individual probabilities of each of the Arab CHD patients to develop ischemic cerebrovascular events and adding them suggested that the excess incidence rate in this group as compared to Israeli born Jews was mostly a result of the unfavorable risk profile. In contrast, Jews born in Arab countries (in the Middle East including Iran, and in Morocco, Algeria, Libya and Tunisia) not only depicted higher rates than their European-born counterparts, but also appeared to exceed the rates predicted from risk factor levels. The question may arise whether the differences seen in a cohort identified and treated in the 1990s depend on the change in practice with regard to coronary subjects. While changes do occur over decades, the etiology of CHD and stroke does not change rapidly. Concerning treatment modalities that would presumably affect the presented associations, dyslipidemic therapy among study patients was virtually non-existent at screening and was only implemented in a large number of patients after information from the 1996 CARE study had been disseminated. Antihypertensive therapy may have taken a turn since JNC-7 redefined "hypertensive" as > 140/90 mmHg rather than 160/95 mmHg, but angiotensin-converting enzyme inhibition was just beginning to take hold and angiotensin II receptor blockers were not in use during follow-up. Invasive procedures at the acute phase of acute coronary syndrome were rare during the period of the study)

Differences in stroke rates among ethnic groups living in the same or adjacent neighborhoods have been reported among Japanese men living in Japan, Honolulu and San Francisco [2], from practices in South London [8], the "stroke belt" in southeastern U.S. [9], Finnmark County in Norway [10], New Mexico [11], and Maori, Pacific people and Europeans in Auckland, new Zealand [12]. In the latter study, Bonita and co-authors [12] identified, on the basis of 1803 strokes occurring between 1991 and 1992, an excess of one-third among the Maori and two-thirds among the Pacific Islanders over counterparts of European stock. The reasons for the higher incidence rates in Maori and Pacific people "may be related to levels of risk factors, but this requires further investigation." Clearly, major socioeconomic advantages persisted among the Auckland Europeans as compared to the two other groups.

Recently, Rodriguez et al. [13] compared the incidence of thromboembolic stroke requiring hospitalization in the Honolulu Heart project conducted among 7589 Japanese Hawaiians, aged 45–68, and 1216 male stroke-free survivors of the Framingham cohort in mainland U.S. of the same age range. Follow-up spanned the period between 1965 and 1985. They noticed markedly lower rates in the former cohort which could not be explained by the traditional risk factors. This resembles our findings in the sense that the patients of European origin, screened for BIP, had lower rates than counterparts from other areas, and the rate among the latter exceeded that calculated on the basis of risk factors. The variation in the Israeli CHD patient cohort agrees with the observations in New Zealand but presumably conflicts with the U.S. findings, since being of European origin in Israel is associated with relative protection from ischemic cerebrovascular events. However, it would be false to equate Far-Easterners (the men of Japanese origin) with those hailing from Middle Eastern or North African countries, both in terms of cultural and genetic differences.

A different approach, focusing on the issue of risk factors in diverse ethnic groups and their roles, was reflected in a case-control investigation by Sacco and colleagues [14] of race-ethnic disparities in the impact of risk factors on stroke, in the Northern Manhattan Stroke Study. On the basis of 688 first ischemic stroke and prospectively matched 1156 community controls, case-control estimates of odds ratios associated with hypertension were similar in whites (1.8), blacks (2.0) and Caribbean Hispanic (2.1), although the prevalence of hypertension varied considerably. However, diabetes mellitus appeared to carry considerably lower risk among whites (no risk at all as estimated in the particular design), whereas atrial fibrillation was more weakly associated with stroke in blacks. Varying risk factor prevalence in these three groups yielded considerable variance in etiologic fractions attributed to stroke risk factors among them. The results by Sacco et al. did not provide an estimated quantitative measure of the extent to which the ethnic origin might augment or reduce the risk beyond the risk factor level.

It is intriguing to examine what causes the extra risk among the North African born male CHD patients living in Israel. One possibility is that the social environment, comprising intrapersonal factors (depression, diet, stress, socioeconomic status), elements of social support and potential differences in awareness of risk, as well as access to care and utilization of health services play a role in affecting one segment of the population in Israel more than others. Although it is tempting to attribute the above-described "ethnic gradient" of predicted versus observed stroke rates in Israel to sociodemographic origins, precise measurement of factors known to play a role in the etiology of cerebrovascular disease is not available in this study. In an investigation of vascular risk factors in the Arab-Jewish study in the Hadera district, Kalter-Leibovici et al. [15] identified differences between Jews and Arabs in the use of health services and corresponding major differences in risk factors such as smoking and obesity. To what extent these factors played a role in our findings is difficult to gauge, since CHD patients as well as patients presenting with acute stroke [16] would putatively exhibit more uniform patterns in their access to health services. Additional parameters, which were not assessed in the current study, may vary, such as inflammatory factors and homocysteine levels.

Three important limitations should be mentioned. First, this is a study of coronary patients. Second, they are neither representative of the entire population of Israel, nor can we claim that they represent the CHD patient population. Third, we cannot fully ignore the possibility of an origin/gender interaction in presenting for medical attention for CHD with different levels of severity. Since migration in and out of the study can be almost ignored, as well as migration outside the country, little bias is suspected from migration.

Variation across ethnic and cultural groups in stroke morbidity and mortality rates may change over time. For example, during the Ni-Hon-San study, total mortality in Japanese men in Hiroshima and Nagasaki was higher than in Honolulu or San Francisco [2]. This has since changed. Also, the differences between stroke rates among diverse ethnic groups, or individuals of the same ethnic stock with different degrees of westernization, might involve a sizeable cohort effect and weaken as the period of migration becomes distant. The incompatibility of estimated risk with actual risk in diverse groups in Israel has now been confirmed both in CHD-free men in the 1960–1980s and in both male and female CHD patients during the last decade of the 20th century. Thus inherent susceptibility to the development of stroke may remain, beyond the extent to which variation can be explained by established risk factors.

In summary, we identified an ethnic diversity in stroke risk among Israeli residents born in different parts of the world, as well as between non-migrant Jews and Arabs. The differences went beyond what could be expected on the basis of known risk factors. This calls for detailed research aimed at identifying additional differences in the risk profile of patients with atherothrombotic disease exposed to an increased risk of stroke. Identifying these factors might assist in providing effective public health interventions.

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