# A Note on the Increased Risk of Polycythemia Vera in Jews

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THE APPARENTLY HIGH FREQUENCY of polycythemia vera among Jews has been first systematically approached by Reznikoff et al.[1] and subsequently confirmed by Damon and Holub[2] and by one of us.[3] It seemed therefore of interest to find out whether this excessive risk is present in Jews outside the U.S.A. and among all Jewish ethnic subgroups. The following report provides an attempt to answer both questions through a whole community study in Israel.

## METHOD

The study group comprised all Jewish patients with a diagnosis of polycythemia vera made in Israel between January 1, 1955 and December 31, 1966. Data were ascertained from the record rooms of all general hospitals in the country and all the major hematology clinics. Arab patients and hospitals were excluded from analysis because of probable under-referral, and consequently a lower reliability of data.

In order to avoid loss of cases due to difference in diagnostic criteria between the various hospitals and clinics, a screening was also made of records listed under the diagnoses of relative polycythemia, secondary polycythemia, benign erythrocytosis, erythrocytosis, and polycythemia type unspecified. Each record was carefully reviewed and allocated to the appropriate study category according to the diagnostic criteria listed below:

### *Polycythemia Vera*

(1) For males, red blood cell mass of at least 33 cc./Kg., or, in the absence of blood volume determinations, hematocrit of 55 vol. per cent, or hemoglobin of 18 Gm. per cent, and for females, red blood cell mass of 31 cc./Kg., or a hematocrit of 52 vol. per cent, or a hemoglobin of 17 Gm./per cent. (2) Presence of two out of the following four parameters, in the absence of a decreased oxygen saturation, and prior to initiation of therapy: (a) splenomegaly; (b) leukocytosis, of at least 10,000/cc.; (c) thrombocytosis, of at least 300,000/cc.; (d) leukocyte alkaline phosphatase score of 90 and above.

For treated patients, either three of the above mentioned findings, or the presence of consistent leukocytosis and thrombocytosis, independent of therapy, were required.

Patients with persistent elevations of only one of these four parameters, or with persistent splenomegaly alone were classified as probable polycythemia vera.

### *Benign Erythrocytosis*

Elevated red blood cell mass, with neither leukocytosis, thrombocytosis, nor splen-

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**Table 1.—Frequency Distribution of Cumulative (1955–1966) Israeli Jewish Population by Age, Sex and Ethnic Group**

| Age Group | Total | Europe | Asia + Africa | Israel |
|---|---|---|---|---|
| | | Males | | |
| 0– 9 | 2,789,148 | 108,586 | 275,237 | 2,405,325 |
| 10–19 | 2,317,400 | 368,847 | 774,974 | 1,173,579 |
| 20–29 | 1,586,632 | 382,913 | 736,037 | 467,682 |
| 30–39 | 1,466,125 | 702,441 | 569,875 | 193,809 |
| 40–49 | 1,398,908 | 930,404 | 393,664 | 74,840 |
| 50–59 | 1,233,414 | 884,629 | 295,816 | 52,969 |
| 60–69 | 665,057 | 455,595 | 179,953 | 29,509 |
| 70+ | 326,803 | 213,414 | 100,024 | 13,365 |
| Total | 11,783,487 | 4,046,829 | 3,325,580 | 4,411,078 |
| | | Females | | |
| 0– 9 | 2,637,473 | 102,387 | 260,191 | 2,274,895 |
| 10–19 | 2,169,310 | 349,879 | 714,561 | 1,104,870 |
| 20–29 | 1,581,548 | 417,021 | 709,799 | 454,728 |
| 30–39 | 1,544,083 | 783,007 | 563,098 | 197,978 |
| 40–49 | 1,414,010 | 939,787 | 398,394 | 75,829 |
| 50–59 | 1,127,578 | 776,150 | 297,841 | 53,587 |
| 60–69 | 638,495 | 427,278 | 180,360 | 30,857 |
| 70+ | 372,830 | 251,344 | 104,681 | 16,805 |
| Total | 11,485,327 | 4,046,853 | 3,228,925 | 4,209,549 |

omegaly, and in the absence of decreased oxygen saturation, another cause for secondary polycythemia.

### *Secondary Polycythemia*

Presence of decreased oxygen saturation, or another cause recognized as leading to secondary polycythemia, e.g., renal cyst, renal tumor, hemangioblastoma, etc.

### *Relative Polycythemia*

Elevated hematocrit or red blood cell levels, in the presence of normal red cell mass and decreased plasma volume. The latter two diagnostic categories were not included in the analysis. Population data were based on the 1961 general census and subsequent estimates (Table 1).

## Results

During the 12 years of study there were 155 newly diagnosed cases of definite and 27 of probable polycythemia vera.

The mean annual incidence was 6.7 (5.7–7.9*) per million, or 7.8 (6.9–9.0*) per million, if probable cases are included. Age specific rates by diagnostic category and sex are presented in Table 2. The male:female ratio is 1.1:1; however, beyond the age of 60, incidence is higher among females. The difference in incidence between males and females is not significant. In both sexes there is a peak incidence at the age group of 60–69.

* 95 per cent confidence interval.

**Table 2.—Mean Annual Incidence of Polycythemia Vera in Israel***

| Age Group | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Definite Cases | | All Cases | | Definite Cases | | All Cases | |
| | No. | Rate | No. | Rate | No. | Rate | No. | Rate |
| < 10 | — | — | — | — | — | — | — | — |
| 10–19 | — | — | — | — | — | — | — | — |
| 20–29 | — | — | — | — | 1 | 0.6 | 1 | 0.6 |
| 30–39 | 4 | 2.7 | 4 | 2.7 | 5 | 3.2 | 5 | 3.2 |
| 40–49 | 17 | 12.2 | 23 | 16.4 | 14 | 9.9 | 14 | 9.9 |
| 50–59 | 29 | 23.5 | 35 | 28.4 | 17 | 15.1 | 24 | 21.3 |
| 60–69 | 20 | 30.1 | 25 | 37.6 | 28 | 43.9 | 29 | 45.4 |
| 70+ | 7 | 21.4 | 8 | 24.5 | 13 | 34.9 | 14 | 37.6 |
| Total | 77 | 6.5 | 95 | 8.1 | 78 | 6.8 | 87 | 7.6 |

* (Per 1,000,000) by age, sex and diagnostic category (1955–1966).

It is of interest that the male:female ratio in the benign erythrocytosis cases, located during the study, is markedly higher, 8.2:1. Because referral to hospital in this group is probably lower, no incidence figures were derived. However, it seems unlikely that the low referral would effect the male: female ratio that much. A similar gradient in this ratio between the two diagnostic groups was observed in the aforementioned Baltimore study[3] as well as in a clinical study based on seven selected hospitals[5,6] (Table 3).

Age specific incidence rates by main ethnic groups are presented in Table 4. Asian- and African-born patients were combined because of the small number of cases. Israeli-born patients were excluded due to the very small population size of Israeli-born Jewish residents in advanced age groups.

In both sexes, incidence is outstandingly higher among European-born patients, as compared to Asian- and African-born. The ratio of age adjusted rates is 2.2:1 among males and 3.1:1 among females. These differences are statistically significant at the 0.04 level for males ($X^2$ 2d.f=7.24) and at the 0.001 level for females ($X^2$ 3d.f=21.78). If all patients, rather than only these with a definite diagnosis are examined, the same effect is noted.

There were no differences in the incidence of polycythemia vera between the newly arrived and veteran European-born residents. The small number of Afro-Asian born patients did not allow a similar comparison in the latter group.

## Discussion

To the best of our knowledge, the incidence of polycythemia vera has been studied only once before.[3] A comparison of the present study and the

**Table 3.—Comparison of Sex Ratio in Polycythemia Vera and in Benign Erythrocytosis in Three Studies**

| Source of Data | Polycythemia Vera | | | Benign Erythrocytosis | | |
|---|---|---|---|---|---|---|
| | Males | Females | Ratio | Males | Females | Ratio |
| Israel | 95 | 87 | 1.1:1 | 142 | 17 | 8.2:1 |
| Baltimore | 30 | 25 | 1.2:1 | 58 | 10 | 5.8:1 |
| Seven selected hospitals | 295 | 217 | 1.4:1 | 109 | 20 | 5.5:1 |

**Table 4.—Mean Annual Incidence of Polycythemia Vera in Israel (per 1,000,000), by Age, Sex and Ethnic Origin 1955–1966***

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Europe | | Asia and Africa | | Europe | | Asia and Africa | |
| Age Group | No. | Rate | No. | Rate | No. | Rate | No. | Rate |
| < 10 | — | — | — | — | — | — | — | — |
| 10–19 | — | — | — | — | — | — | — | — |
| 20–29 | — | — | — | — | 1 | 2.4 | — | — |
| 30–39 | 3 | 4.3 | 1 | 1.8 | 5 | 6.4 | — | — |
| 40–49 | 13 | 13.9 | 3 | 7.6 | 14 | 14.9 | — | — |
| 50–59 | 24 | 27.1 | 5 | 16.9 | 14 | 18.0 | 3 | 10.1 |
| 60–69 | 17 | 37.3 | 2 | 11.1 | 23 | 53.7 | 4 | 22.2 |
| 70+ | 6 | 28.1 | 1 | 10.1 | 11 | 43.8 | 2 | 13.1 |
| Total † | 63 | 8.4 | 12 | 3.8 | 68 | 9.7 | 9 | 3.2 |

* (Definite cases only excluding Israeli-born patients).
† Age adjusted, direct method, using Segi's theoretical population.[4]

previous one reveals that the incidence in Israel is higher, by about 35 per cent as compared with Baltimore City—6.7/1,000,000 versus 4.9/1,000,00. However, the higher incidence in Israel is limited to European-born residents only. Furthermore, there is no significant difference in the disease incidence between European-born Israelis and Baltimore Jews (Table 5). Thus, one may conclude that polycythemia vera is not necessarily a "Jewish Disease," but that it is more prevalent among Jews of European extraction, independent of residence. This fact is further supported by the lack of correlation between incidence and length of stay in Israel.

Any study of this kind has the drawback of retrospectively obtained information, as well as the high reliance on hospital data and on the quality of registration. Nevertheless, because both the criteria and the method of case ascertainment were similar in the two community studies discussed, it is hard to conceive that the comparison is biased. In addition, the identical sex ratio in the polycythemia vera group in both studies, and particularly the similar gradient between the sex ratios of these patients versus patients with benign erythrocytosis are helpful in validating the results.

The reason for the relatively high incidence among Jews of European extraction is unknown. It could reflect a high tendency for visits to physicians, in line with the findings of MacMahon and Koller in Brooklyn,[7] but, in the

**Table 5.—Comparison of Age Adjusted Rates of Polycythemia Vera in Israeli Jews and Baltimore Residents, by Ethnic Group***

| Israel | | Baltimore | |
|---|---|---|---|
| European born | 8.4 | Jews | 10.8 |
| Asian and African born | 3.4 | White, non-Jews | 3.6 |
| | | Nonwhite | 2.3 |

* Direct method, on the basis of Segi's theoretical population;[4] the Jewish population of Baltimore is based on an estimate.[3] It is assumed that the age distribution of Baltimore Jews is similar to that of Baltimore's total white population.

current set-up of medical care patterns in Israel, selective referral of the European-born is unlikely. On the other hand, it may represent a genuine risk factor which might also be present among non-Jewish residents of the European countries from which both U.S. and Israeli Jews originated.

Available information on familial aggregation of polycythemia vera is scarce and therefore does not support genetic predetermination. On the other hand, the similarity in patterns between Israeli and Baltimore Jews, as well as the fact that length of residence in Israel does not affect the disease incidence, seem to exclude an environmental factor in the native surroundings. Nevertheless, one cannot ignore a similarity in socioeconomic gradients and in various aspects of daily life and habits among the European-born Jews in Israel and the U.S. Jews, in contrast with those of the non-European Jews in Israel. A similar study in certain European countries may shed some additional light on this problem.

## Summary

A whole community study of polycythemia vera in Israel revealed a mean annual incidence of 6.7 per million. Ratio of age adjusted rates between European and non–European-born foreign residents was 2.2 among males and 3.1 among females. A comparison with the only other community study of polycythemia shows higher incidence in Israel as compared with the city of Baltimore, but similar rates among European-born Jews in Israel and Jewish residents in Baltimore. The data indicate that the risk of developing polycythemia vera is higher among Jews of European extraction, independent of residence.

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