Mortality of Lead Smelter Workers with the Glucose-6-phosphate Dehydrogenase-deficient Phenotype

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Abstract
The mortality experience of 1345 male workers in a lead and zinc smelting plant was followed from 1973 to 1991. Information on the erythrocyte glucose-6-phosphate dehydrogenase (G6PD) phenotype was available for 1,222 (90.9%) cohort members, which provided the opportunity to compare the mortality experience of G6PD-deficient subjects to wild-type-G6PD coworkers with similar exposure to lead. A significant decrease in mortality was observed among the total cohort as well as among the subcohort of production and maintenance workers. Most deaths (27 of 31) and all cancer deaths occurred among production and maintenance workers. Lung cancer mortality was lower than expected. Two deaths from stomach cancer were observed versus 0.6 expected. Mortality from all causes and cancer mortality were lower among production and maintenance workers with the G6PD-deficient phenotype compared to coworkers with the wild-type phenotype. Although the low statistical power of this study prevents conclusive inference, lead smelter workers with the G6PD-deficient phenotype did not suffer adverse health outcomes in terms of mortality from all causes and cancer mortality compared to coworkers with the wild-type G6PD.

Introduction
Prolonged exposure to lead may affect the reduced glutathione content in erythrocytes (1). Therefore, subjects genetically deficient in G6PD activity could be more susceptible to lead toxicity, and the occurrence of hemolytic crises could be more likely among these subjects. On the other hand, earlier reports suggested a lower risk of cancer and cardiovascular diseases among G6PD-deficient individuals (2–4), although two more recent case-control studies did not confirm the hypothesis of a protection against cancer (5, 6). Because of the hemotoxicity of lead, and because of the reported increased occurrence of cardiovascular diseases, kidney failure, and kidney, stomach, and lung cancer among lead smelter workers (7), it is of interest to explore whether their mortality experience varies according to the G6PD genetic polymorphism.

Materials and Methods
Over 300 variants in the base sequence of the G6PD gene (8) have been identified. One of these variants, the Gd-Mediterranean allele, affects 12–15% of the male population in Sardinia, Italy (9, 10), and it is associated with lack of enzymatic activity, therefore providing an ideal setting to explore mortality patterns in relation to the G6PD polymorphism. A study was conducted among workers in a lead and zinc smelting plant located in southwestern Sardinia. The industry provided data on all persons employed at any time from January 1, 1973, when the plant officially started operating, to December 31, 1990. Information provided included first and last name, date and place of birth, last known address, job title and department at hire, date of hire, and date of end of employment. Subjects (1384) who spent at least 1 day at the plant were identified. Seventeen females and 4 subjects of foreign nationality who moved back to their country of origin were excluded from the study. There were 850 workers still employed at the plant on December 31, 1991, the date of the end of follow-up. Vital status of the remaining 513 employees no longer at work was searched at the municipality of residence. Only 18 subjects (1.3% of the total cohort) could not be identified because of missing or wrong data, and they were excluded from the cohort. Death certificates were provided for all deceased subjects by the Local Health Units covering the areas where death occurred.

Observed deaths were compared to the expected deaths based upon the 5-year age group and 5-year period of follow-up-specific mortality rates in the general Sardinian male population. Standardized mortality rates from all causes, all cancers, and cardiovascular diseases were also computed separately for subjects with wild-type G6PD and G6PD-deficient subjects, based on the age distribution of the 1981 Sardinian male population as the external standard. Ninety-five % CIs of the mortality rates were based on the Poisson distribution.

Information on the G6PD phenotype of cohort members was provided by the industry. The G6PD phenotype was assayed with the Beutler’s fluorescent spot test (11) in 1,222 cohort members (90.9%), and of these, 1,080 (88.4%) were production and maintenance workers and supervisors. The fluorescent spot test is a very common standard method, modified to make it suitable for screening purposes (12), which offers the advantage of greater sensitivity and specificity than other methods (11). Quality controls procedures were used regularly, including use of standard positive and negative controls for each batch of tests. Information on mean blood lead levels among all employees in 1988–1992 and on average environmental lead in production departments in 1991 was also provided by the industry.

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2 The abbreviations used are: G6PD, glucose-6-phosphate dehydrogenase; CI, confidence interval; PY, person-year.
Short Communication: G6PD Deficiency and Mortality of Lead Smelter Workers

Results

Mean age at entry in the follow-up was 30 years (SD = 7.4), and 73.9% of cohort members entered the cohort before age 35. No significant difference in mean age at hire existed whether between administrative clerks and production and maintenance workers, or between G6PD-deficient and wild-type-G6PD subjects. G6PD-deficient subjects accounted for 19.6% of the cohort members with known G6PD phenotype. This proportion was lower among administrative clerks (18.3%) than among production and maintenance workers (19.7%). Most deaths occurred among workers aged 35. No significant difference in mean age at hire existed significantly between wild-type-G6PD and G6PD-deficient workers in production and maintenance jobs. About one-half of production workers, 66% of production supervisors, and 75% of administrative clerks had been employed for 11 years or more, and only 115 workers (8.5%) had been employed for 1 year or less. Among production and maintenance workers, the proportion of G6PD-deficient subjects over the total with known G6PD phenotype varied by duration of employment: it was lowest among workers employed less than 1 year (11.9%) and highest among workers employed for 6-10 years (30.5%). G6PD-deficient subjects were 17.1% of the longest-duration group.

Average environmental lead in the various production departments in 1991 ranged from 26.8 to 161.3 μg/m³, with a peak level of 315.5 μg/m³ in the Waeltz oven area of the Imperial Smelting department. Average blood lead levels among all employees decreased slightly from 40 μg/dl in 1988 to 35 μg/dl in 1992. Among 30 newly hired male workers previously unexposed to lead, who participated in a study conducted in 1990–1991 in the same smelting plant (13), all employed in production and maintenance jobs, the average blood lead level among wild-type-G6PD subjects (n = 27) was 15.6 μg/dl (SD = 5.5) at hire, and 35.9 μg/dl (SD = 11.8) after 138–217 days of employment. The same values among the 3 newly hired G6PD-deficient subjects were 10.0 μg/dl (range, 7–15) and 32.7 μg/dl (range, 20–51). No information is available about previous industrial hygiene measurements and biological monitoring data.

Only 31 deaths occurred in the period of follow-up, significantly fewer than expected in the total cohort and among production and maintenance workers and supervisors, most likely because of the healthy-worker effect. Only four deaths (two from cardiovascular diseases and two from nonmalignant respiratory diseases) occurred among administrative clerks. Of the 27 deaths among production and maintenance workers and supervisors, 20 were observed among workers with the wild-type G6PD (expected, 33.8), 5 among G6PD-deficient workers (1 from cancer of the hemolymphatic system, 1 from cancer of ill-defined site, 1 from nonmalignant respiratory disease, 1 from digestive disease, and 1 from accidental death; total expected deaths, 7.5), and 2 among workers with unknown G6PD phenotype (1 from cardiovascular disease, 1 from disease of the nervous system; total expected deaths, 2.5).

Overall, deaths from cardiovascular diseases, nonmalignant respiratory diseases, and digestive diseases were below the expectation. No deaths attributed to urinary diseases were registered. The death certificate of a wild-type-G6PD subject reported hemolytic crisis as the underlying cause of death. The examination of medical records revealed that this worker suffered a severe hemolytic after an acute intoxication from arsine and eventually died from acute renal failure. No deaths from blood diseases were observed among G6PD-deficient workers.

No significant excess was observed for any single cancer site. Two deaths from stomach cancer (0.6 expected) occurred among workers who were still employed at the smelting plant 8–17 years after first exposure. Lung cancer mortality was lower than expected (2 observed versus 3.5 expected).

Comparing mortality rates of wild-type-G6PD and G6PD-deficient cohort members with similar occupational exposure to lead was possible only by broad groups of causes (Table 1). Overall mortality among G6PD-deficient workers was about ¾ of that observed among workers with the wild-type G6PD, but the 95% CIs of the rates overlapped. Mortality from cancer was also lower among G6PD-deficient individuals. No deaths from cardiovascular diseases occurred among G6PD-deficient individuals, but only 1.1 were expected.

Discussion

This study has several limitations, and it must be considered as a preliminary exploration of the effects of occupational exposure to lead on the mortality experience of workers with different G6PD phenotypes. The small size of the cohort, the relatively young age of cohort members, and the short (19-year) period of follow-up meant that few PYs accumulated in the older age groups. Consequently, the observed number of deaths was small, and the study lacked statistical power. This severely limited our ability to examine deaths among G6PD-deficient individuals, although they represented a slightly greater proportion (19.7%) of the exposed cohort members than the average in the Sardinian male population (12–15%; Refs. 9 and 10). Also, analyses by latency and by level of exposure, which would help clarify the present findings, require extension of the follow-up of the same occupational cohort to provide a greater number of deaths. Currently, these analyses are not feasible because of the poor statistical power.

To the best of our knowledge, this is the first cohort study comparing the mortality of G6PD-deficient individuals exposed to lead to the mortality of coworkers with the wild-type phenotype. For such a comparison to be valid, a similar exposure to lead between the two groups is crucial. Individual biomonitoring data were not available for cohort members, but a study conducted in the same smelting plant showed that G6PD-deficient workers and workers with the wild-type G6PD had similar levels of blood lead (13). This similarity would be misleading if G6PD-deficient workers left the job earlier than coworkers with the wild-type G6PD or were transferred to jobs with no exposure. We are not aware of any cohort member who left his job or was transferred from an exposed job because of his genetic condition. However, the proportion of G6PD-

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<th>Table 1</th>
<th>Standardized mortality rates (× 10^4) from large groups of causes by G6PD phenotype among production and maintenance workers</th>
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<td></td>
<td>Wild-type G6PD (No. = 867; PYs = 10,215.9)</td>
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<tr>
<td>Rate</td>
<td>(95% CI)</td>
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<tr>
<td>Deaths</td>
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<tr>
<td>All causes</td>
<td>20</td>
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<td>All cancers</td>
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deficient individuals among production and maintenance workers was slightly higher than among administrative clerks (19.7% and 18.3% of workers with known G6PD phenotype, respectively), and the differences in average and frequency distribution of duration of employment in production and maintenance jobs between G6PD-deficient and wild-type-G6PD workers do not seem large enough for this potential bias to entirely account for our findings.

The association between occupational lead exposure and stomach cancer was considered consistent across studies (7). We observed an excess among production and maintenance workers with wild-type G6PD, but it was based on 2 deaths only, which did not allow further analyses to explore a possible occupational etiology. Total cancer mortality among G6PD-deficient workers exposed to lead, although lower, was not significantly different from wild-type-G6PD coworkers. Previous case-control studies (5, 6) did not confirm a lower cancer risk among G6PD-deficient individuals suggested by earlier reports (2, 3). Further follow-up is required to test the hypothesis of a lower cancer risk associated with the G6PD-deficient phenotype.

The absence of deaths from cardiovascular diseases among G6PD-deficient subjects is intriguing, because the condition delays the endogenous synthesis of cholesterol (14, 15), and a lower prevalence of cardiovascular diseases among these subjects has been suggested previously (4). However, too few deaths were expected to draw any conclusion based on this finding.

Extending the follow-up study of this cohort will provide the necessary statistical power to confirm that, at the levels of exposure experienced by this cohort, carrying the G6PD-deficient phenotype does not negatively affect the mortality of workers exposed to lead compared to wild-type-G6PD coworkers.

References

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