Using Alternative Comparison Populations to Assess Occupation-Related Mortality Risk Results for the High Nickel Alloys Workers Cohort

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ORIGINAL ARTICLES

Using Alternative Comparison Populations to Assess Occupation-Related Mortality Risk
Results for the High Nickel Alloys Workers Cohort

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The focus of this article is to examine how the choice of comparison group affects the identification and interpretation of cause-specific health risks in occupational cohorts when different external control populations are used. The mortality experience of approximately 31,000 high nickel alloys workers is compared with the total US population and to local populations in geographic proximity to the plants. Generally, the patterns of relative risks derived for the total cohort and various subgroups are similar across the different comparison populations. Estimated elevated risks are usually lower when cohort mortality is compared with that of local populations. An overall significant 13% risk for lung cancer is noted when compared with that of the total US population. However, no significant excess is identified when local populations are used. Subset analysis identified significant excesses of colon cancer among nonwhite males (50%- 150%) and kidney cancer among white male workers employed in melting (approximately 100%), irrespective of the comparison population.

In 1978 the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, undertook a historical prospective mortality study of workers employed in the high nickel alloys industry. The main objective of the study was to evaluate the cause-specific mortality patterns for high nickel alloys workers as a whole and for workers who were employed in jobs in 11 major work areas. The cohort consisted of 28,261 individuals with work histories and vital status known through 1977. Mortality patterns were analyzed by job classification and length of employment. A more detailed review of this cohort is described elsewhere. [1] In brief, cohort mortality, when compared with that of the general US population, showed no overall statistically significant increased risk for cancers of the lung, nasal sinuses, larynx, or kidney. An approximate 20% increase in lung cancer mortality ($P < 0.05$) was found among white males with less than 20 years' work experience, but no excess was observed in those with 20+ years of employment. When data were examined by work areas, an excess lung cancer mortality of about 25% to 50% for males employed in maintenance categories was noted. It was unclear whether the greater risk was directly associated with nickel, particularly since a similar excess was not found in other occupational groupings for which nickel exposures were also present. Mortality from cancers of the liver and large intestine was statistically significantly

elevated, with relative risks of 1.8 and 2.3, respectively. Increases in risks were found primarily among longer-term workers in the industry but were not concentrated in any particular work area. No conclusion regarding a causal association with nickel was drawn for these two cancer

sites.

Continued observation of the original cohort was recommended to further delineate the original findings, since the workers were relatively young at the time of the study. Over half of the cohort was under the age of 30 and approximately three-quarters were hired after 1950. Additional follow-up was also especially crucial for very rare cancers, those with long latencies, and those that typically occur later in life. In 1989 the decision was made to update the follow-up of the original high nickel alloys cohort to a more recent time period. At that time, the cohort was expanded to include workers from an additional plant. [2] This new cohort, with 31,165 individuals, represents the majority of US workers exposed to nickel in the production and fabrication of products from high nickel alloys. Workers' exposure to nickel was likely to metallic and/or oxidized forms.

The purpose of this article is to describe the results from the update of the follow-up and to demonstrate how the choice of comparison population affects the identification and interpretation of cause-specific mortality in an occupational setting. The primary analyses compared nickel worker cause-specific mortality to gender-, race-, age-, and time-specific mortality rates of the total US population. Additional effort investigated the extent to which the conclusions of the study depend upon the use of the total US general population as the comparison group. This was accomplished by performing additional analyses utilizing an alternative comparison population specific to the geographic region of each of the 13 high nickel alloy plants. Although analyses were done for 62 different causes of death, emphasis was given to those causes having potential association with various forms of nickel, as identified in the literature or from earlier studies of this cohort. These sites included cancers of the nasal sinuses, larynx, lung, colon, and kidney, cerebrovascular disease, heart disease, and non-malignant respiratory disease.

Methods and Materials

Nickel Worker Cohort

The cohort consists of 31,165 workers from 13 high nickel alloy plants located throughout the United States. Twelve of the plants include 28,222 male and female hourly and salaried workers involved in the production of and fabrication of products from high nickel alloys reported on by Redmond. [1] Cohort eligibility required that each case employee had worked a minimum of one year within the interval between 1956 through 1967. Thirty-nine individuals from the original high nickel alloys study have been excluded from the current study because reexamination of work histories indicated that these individuals did not meet the eligibility criteria. The 13th plant consists of the subset of male workers from the Enterline and Marsh study [2] whose primary exposure is associated with the production of high nickel alloys (1,589 male workers from cohort 1 and all 1,354 males from cohort 2). Workers from cohort 1 have a minimum of one year of employment and were actively employed in 1948. Workers in cohort 2 have a minimum of one year of employment between 1948 and 1959.

Ascertainment of Vital Status and Death Certificates

Determination of vital status of the workers was made through the end of 1988. Our procedures provide positive confirmation of vital status on both alive and deceased individuals. Alive status was assigned only upon receiving definitive information that the individual was still living through the end of 1988. Sources used to accomplish this task included lists from each company indicating its active employees, retirees, and deceased workers for whom death claims had been filed; and national databases, including the Social Security Death Master File, the National Death Index, [3] the Health Care Finance Administration, Trans Union Credit Bureau, and state departments of motor vehicle registration. Telephone follow-up was initiated in instances in which status was unresolved when the preceding sources were used.

The various state offices of vital statistics were contacted to obtain a death certificate for each cohort member identified as deceased. Death certificates were coded by a single trained nosologist according to the rules and procedures of the *International Classification of Diseases, Seventh Revision* (ICD). [4]

Description of Work History and Exposure Classification

Complete work histories were available for each member of the study cohort, including the chronology of all the jobs with dates that the employee had worked. Information was available through 1977 for the 12 original plants and through 1983 for the 13th plant. No extrapolation was done for the interval for which data was not available.

All jobs across all plants were identified and coded to a department. Each department was then assigned to a work area based on the nature of activities and the types of associated occupational exposures. This effort resulted in a classification scheme of 11 work areas that included the following: cold working, hot working, melting, grinding, allocated services (which included maintenance, janitors, guards, pattern and die and other support services), foundry, powder metallurgy, administrative and technical, pickling and cleaning,

TABLE 1 -- Exposure to Airborne Nickel and Particulate Matter, by Work Area

	Total Particulate Concentration, mg/m^3		Nickel Concentration, mg/m^3	
Work Area	**Range**	**Average**	**Range**	**Average**
Cold working	0.01-68.0	1.4	0.001-2.3	0.0064
Hot working	0.01-300.0	2.2	0.001-4.2	0.111
Melting	0.01-805.0	6.4	0.001-4.4	0.083

Grinding	0.01-253.0	2.4	0.001-2.3	0.298
Allocated services	0.01-70.0	2.2	0.001-0.350	0.071
Foundry	n/a *	n/a *	0.004-0.900	0.098
Powder--metallurgy	0.03-334.0	9.6	0.001-60.0	1.5
Administrative--technical	0.01-2.60	0.6	0.001-0.015	0.008
Pickling and cleaning	0.01-0.3	0.2	0.002-0.015	0.008

* n/a, not available.

x-ray, and all other areas. These categories were the same as those used in the original high nickel alloys study [1] to maintain comparability. Only gross industrial hygiene data were available (refer to Table 1) and, therefore, the measure of cumulative time employed in the high nickel alloys industry, or in a specific work area, was used as a crude surrogate measure of cumulative exposure.

Statistical Analyses

Relative risk (RR) estimates for high nickel worker mortality were determined for 62 causes of death, using the standardized mortality ratio (SMR). [5] The SMRs were adjusted for age, race, gender, and calendar time by the indirect method, using a modified life table technique. Two-sided tests of significance and 95% and 99% confidence intervals for the SMRs were calculated under the assumption that deaths follow a Poisson distribution. [6] The primary analysis was a comparison of observed mortality with that expected, using the total US population. The secondary analysis was a comparison using mortality rates from local populations in geographic proximity to each of the individual plants. The Standard Metropolitan Statistical Areas (SMSAs) were used to define the local populations. Although some plants were located in the same state, no two plants were located in the same SMSA. As derived from 1980 census data, the population sizes for the SMSAs varied from approximately 104,000 to 4,300,000. Individual plant cohorts represent less than 1% of their respective local population for all but one plant. The one exception was less than 2%. Employment in primary metal production and fabrication was low, ranging from 1% to 6% among the different SMSAs.

A modified version of the Occupational Cohort Mortality Analysis Program (OCMAP) [7] was used to perform the necessary statistical calculations. US and local population five-year average annual age-, race-, and gender-specific mortality rates were generated using the Mortality and Population Data System (MPDS). [8] Analyses involving comparison to the local populations use the variance formulation for the ratio of two random variables in a form specific for an SMR developed by Flanders. [9] The method described by Flanders was generalized to adjust simultaneously for age, race, gender, calendar time, and plant. This estimate of the variance for the SMR was used to construct confidence intervals and to test the statistical significance of mortality risk between nickel workers and local populations.

Mortality analyses were based on the ICD. [4] Comparability ratios [10] [11] [12] [13] [14] were used to adjust the mortality rates of the US and local populations since the study observation period spans the time covered by three ICDA (ICD, adapted) revisions (seventh, eighth, and ninth). [4] [15] [16]

Estimates of relative risk derived from the US and local populations for the time period 1948 through 1988 were examined for the total cohort, gender-race-specific subgroups, plant-specific subgroups, and various subgroups defined by time since first employment and cumulative employment in selected work areas. The starting date for tabulating years at risk for specific work areas was either the date that the one-year employment criterion was met or the date the employee started working in that particular area, whichever came last. For persons whose vital status was unresolved, person-years at risk were tabulated through the last date that the person was confirmed to be alive. Noncancer mortality rates for the local populations were not available until 1960. Therefore, relative risks for nonmalignant causes of death based on local comparisons are for the period of 1960 through 1988. For these analyses, the start date for person-years at risk was the beginning of 1960 or the date when the one year employment criteria was met, whichever came last.

Results

Description of Study Cohort

Extending vital status through 1988 and adding the Enterline and Marsh cohorts [2] to the original Redmond [1]

TABLE 2 -- Observed Deaths and Relative Risks for All Causes and Select Nonmalignant Causes of Death for High Nickel Alloys Workers, Compared With the US Population, for the Time Period of 1948 Through 1988

	White Males *n*= 26,184; person-years = 673,808			Nonwhite Males *n*= 2,104; person-years = 48,204			Females *n*= 2,877; person-years = 78,360		
Cause of Death	**Obs**	**RR**	**(95% CI)**	**Obs**	**RR**	**(95% CI)**	**Obs**	**RR**	**(95% CI)**
All causes of death	9041	0.96 *	(0.94-0.98)	819	0.80 *	(0.75-0.86)	749	0.98	(0.91-1.05)
Cerebrovascular disease	481	0.86 *	(0.79-0.94)	48	0.53 *	(0.39-0.70)	52	0.79	(0.59-1.04)

All heart disease	3971	1.02	(0.99-1.06)	288	0.85 *	(0.76-0.96)	268	1.05	(0.92-1.18)
Ischemic heart disease	3439	1.04 *	(1.01-1.08)	220	0.92	(0.81-1.06)	224	1.13	(0.98-1.28)
Nonmalignant respiratory disease	540	0.85 *	(0.78-0.92)	45	0.73 *	(0.53-0.98)	43	0.98	(0.71-1.32)
Diabetes mellitus	134	0.98	(0.82-1.17)	8	0.42 *	(0.18-0.82)	18	0.92	(0.55-1.46)
Hypertensive with heart disease	157	0.98	(0.83-1.14)	42	0.81	(0.59-1.10)	10	0.51	(0.24-0.93)
Nonmalignant respiratory disease	540	0.85 *	(0.78-0.92)	45	0.73 *	(0.53-0.97)	43	0.98	(0.71-1.31)
Influenza and pneumonia	167	0.79 *	(0.67-0.92)	25	0.80	(0.52-1.19)	14	0.81	(0.44-1.36)
Bronchitis, emphysema and asthma	144	0.86	(0.73-1.02)	9	0.86	(0.39-1.64)	12	1.33	(0.69-2.32)
Cirrhosis of the liver	168	0.71 *	(0.61-0.83)	17	0.65	(0.38-1.05)	13	0.82	(0.44-1.40)
All external causes	489	0.69 *	(0.63-0.76)	44	0.46 *	(0.33-0.62)	35	1.11	(0.77-1.54)
Accidents	302	0.62 *	(0.55-0.69)	19	0.32 *	(0.19-0.50)	27	1.20	(0.79-1.74)
Suicides	154	0.80 *	(0.68-0.94)	7	1.05	(0.42-2.17)	7	0.84	(0.34-1.73)

Obs, observed deaths; RR, relative risk; CI, confidence interval.

** $P < 0.01$.

* $P < 0.05$.

cohort provided 11 more years of follow-up and approximately 340,800 additional person-years at risk for evaluation. The combined nickel cohorts consist of 31,165 individuals, of which 91% (*n* = 28,288) are males. Ninety-three percent (*n* = 28,985) of the cohort is white. Only 76 nonwhite females are in the entire cohort. In total, there are 800,373 person-years at risk contributed by the entire cohort, with white male workers accounting for 84%. Fifteen percent of the person-years (124,202 person-years) are distributed among workers with 20 or more years' cumulative employment in the high nickel alloys industry. Seventy-nine percent of the workers have been followed-up through at least 25 years since their first occupational exposure in the high nickel alloys industry.

Vital status was resolved for over 97% of the study cohort. Thirty-four percent (*n* = 10,609) of the workers were deceased by the end of the observation period. A total of 6,500 new deaths were identified, 1,724 of which were cancer deaths. A greater proportion of the males (35%; *n* = 9,860) were deceased at the conclusion of the study period, as compared with females (26%; *n* = 749). A slightly higher percentage of deaths occurred in nonwhites in contrast to whites (38% vs 34%). The small number of nonwhite females and the limited number of deaths (*n* = 13) among this group precluded an evaluation of their mortality risk separately. Death certificates were located for 99% of workers identified as deceased.

Throughout their employment, individuals could work in more than one specific work area. Over 75% of all workers had spent some time in the allocated services work area. In general, males worked in several work areas, whereas females worked predominantly in two work areas: grinding and allocated services. Nonwhite males were more likely than white males to hold jobs in melting and grinding.

Mortality Analysis Using the US Comparison

The mortality experience of the nickel workers for 62 causes of death was compared with that of the US population for the time period of 1948 through 1988. Plant-specific analyses were conducted to examine the consistency of findings throughout the industry. Results for these analyses are described only when they further delineate an overall finding. Work-area-specific analyses were conducted to investigate the relationship of mortality to aggregate exposure. Specific work-area findings are discussed when statistically significant.

Selected cause-specific results by gender and race are presented in Tables 2 and 3 . Those causes of death not presented in the tables were not statistically significantly elevated, have smaller numbers of deaths, or have wide confidence intervals. As typical of many occupational cohorts, the relative risk (RR) from "all cause" mortality for the total cohort is significantly less than one (RR = 0.95, $P < 0.01$; Table 2). This is most pronounced among nonwhite males. Generally, the number of deaths attributed to nonmalignant causes is no greater than expected. In several instances, RRs show significant

TABLE 3 -- Observed Deaths and Relative Risks for All Cancers and Select Malignant Causes of Death for High Nickel Alloys Workers, Compared With the US Population, for the Time Period of 1948 Through 1988

	White Males *n*= 26,184; person-years = 673,808			Nonwhite Males *n*= 2,104; person-years = 48,204			Females *n*= 2,877; person-years = 78,360		
Cause of Death	**Obs**	**RR**	**95% CI**	**Obs**	**RR**	**95% CI**	**Obs**	**RR**	**95% CI**
All malignant neoplasms	2228	1.04	(0.99-1.08)	243	1.08	(0.95-1.22)	203	0.88	(0.76-1.01)

Colon	197	1.01	(0.87-1.16)	29	1.92 *	(1.28-2.76)	21	0.85	(0.53-1.30)
Liver	36	0.62 *	(0.44-0.86)	4	0.47	(0.13-1.25)	0		
Respiratory system	858	1.11 *	(1.03-1.18)	82	1.06	(0.84-1.32)	47	1.31	(0.96-1.74)
Larynx	24	0.79	(0.50-1.17)	4	0.99	(0.27-2.55)	1	1.27	(0.03-7.09)
Bronchus-trachea-lung	831	1.13 *	(1.05-1.21)	78	1.08	(0.85-1.34)	46	1.33	(0.98-1.78)
All other respiratory	3	0.35	(0.07-1.02)	0			0		
Kidney	59	1.11	(0.85-1.43)	2	0.59	(0.07-2.13)	4	1.11	(0.30-2.84)
Breast	3	1.08	(0.22-3.15)	0			46	0.93	(0.68-1.24)
Prostate (males only)	139	0.93	(0.78-1.09)	34	1.35	(0.94-1.89)	n/a		
Buccal cavity and pharynx	54	0.92	(0.69-1.20)	4	0.52	(0.14-1.33)	1	0.32	(0.01-1.80)
Digestive	570	1.01	(0.93-1.10)	80	1.19	(0.94-1.48)	42	0.74	(0.54-1.01)
Esophagus	54	1.04	(0.78-1.35)	12	0.88	(0.46-1.54)	2	0.88	(0.11-3.18)
Stomach	73	0.84	(0.66-1.06)	11	0.76	(0.38-1.35)	3	0.50	(0.10-1.46)
Rectum	63	1.18	(0.91-1.52)	5	1.22	(0.39-2.84)	2	0.41	(0.05-1.49)
Pancreas	107	0.95	(0.78-1.15)	14	1.21	(0.66-2.02)	10	0.89	(0.43-1.64)
Bladder	60	1.03	(0.79-1.33)	5	1.20	(0.39-2.79)	3	1.12	(0.23-3.28)
Central nervous system	56	0.93	(0.70-1.21)	2	0.81	(0.10-2.93)	5	0.87	(0.28-2.02)
All Lymphohematopoietic	177	0.90	(0.78-1.05)	13	0.90	(0.48-1.54)	12	0.63	(0.33-1.10)
Lympho and reticular sarcoma	22	0.66 *	(0.41-0.99)	0			0		
Hodgkin's disease	19	1.10	(0.66-1.72)	1	1.00	(0.02-5.55)	0		
Leukemia and aleukemia	67	0.86	(0.66-1.09)	5	0.97	(0.32-2.27)	5	0.72	(0.23-1.69)

n/a, not applicable.

** $P < 0.01$.

* $P < 0.05$.

deficits. The only exception is that of all heart disease among white male workers. This increased risk is specific for ischemic diseases of the heart. Significant excesses are found in mortality for white males employed in grinding and allocated services. Female employees employed in grinding also have a significant excess of 22%. Examination of ischemic heart disease by length of employment and time since first employment identifies sporadic increases in mortality without any indication of a trend.

Deaths attributed to malignant causes are no greater than expected (Table 3) . Overall, the risk of kidney cancer is not increased for any of the gender/race groups. When examined by work area, a significant twofold increase among white males was noted for those employed in melting. However, further investigation revealed no association with length of employment or time since first employment.

A significant twofold excess of colon cancer, which is not present in white workers or females, is noted among nonwhite males. Plantspecific analysis revealed that more than half ($n = 18$) of the 29 colon cancer deaths observed in nonwhite males are found in one plant with a significant RR of 2.56 ($P < 0.01$). Analysis by length of time employed did not further elucidate the finding. In general, nonwhite male workers have higher colon cancer RRs than white male workers for a particular work area. In two work areas, this difference is pronounced. The RR for white males employed in grinding is 0.78 (nonsignificant), in contrast to 2.06 ($P < 0.01$) for nonwhite males. Similarly, white males employed in allocated services have a RR of 1.00 (nonsignificant) vs 1.90 ($P < 0.01$) for nonwhite male workers. The apparent lack of a consistent pattern may be attributable to the small numbers of observed deaths among nonwhite males.

Cancer of the respiratory system, specifically lung cancer, is the only site-specific cancer that is significantly elevated for the total cohort (RR = 1.13, $P < 0.01$). Within gender/race groups, statistical significance is noted only for white males (RR = 1.13, $P < 0.01$), although the risks for lung cancer among females (RR = 1.33) and for nonwhite males (RR = 1.08) are also greater than one. The observed lung cancer risk is most predominant among white males employed in allocated services, with a significant increase of 21%. None of the work areas show a significant increase in lung cancer for females. When lung cancer mortality is examined by length of employment and time since first employment, no evidence exists for a

TABLE 4 -- Observed Deaths and Relative Risks for All Causes and Select Nonmalignant Causes of Death for High Nickel Alloys Workers, Compared With the Local Populations, for the Time Period of 1960 Through 1988

Cause of Death	White Males n= 25,753; person-years = 599,960			Nonwhite Males n= 2,072; person-years = 43,794			Females n= 2,836; person-years = 70,761		
	Obs	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI
All causes of death	8679	0.93 *	(0.91-0.95)	791	0.79 *	(0.74-0.85)	733	0.92 *	(0.85-0.98)
Cerebrovascular disease	456	0.83 *	(0.76-0.91)	46	0.68 *	(0.50-0.90)	49	0.74 *	(0.56-0.98)
All heart disease	3803	0.96 *	(0.92-0.97)	278	0.80 *	(0.71-0.90)	265	0.94	(0.84-1.06)
Ischemic heart disease	3295	0.97	(0.94-1.00)	211	0.81 *	(0.71-0.93)	221	0.99	(0.86-1.13)
Nonmalignant respiratory disease	530	0.87 *	(0.80-0.95)	42	0.66 *	(0.48-0.89)	43	1.01	(0.75-1.36)
Diabetes mellitus	130	0.87	(0.73-1.04)	7	0.40 *	(0.19-0.84)	17	0.71	(0.44-1.15)
Hypertensive with heart disease	145	0.75 *	(0.64-0.88)	42	0.70 *	(0.52-0.95)	10	0.40 *	(0.21-0.74)
Nonmalignant respiratory disease	530	0.87 *	(0.80-0.95)	42	0.66 *	(0.48-0.89)	43	1.01	(0.75-1.36)
Influenza and pneumonia	162	0.82 *	(0.70-0.96)	24	0.87	(0.58-1.30)	14	0.90	(0.53-1.53)
Bronchitis, emphysema and asthma	141	0.86	(0.73-1.02)	7	0.59	(0.28-1.24)	12	1.31	(0.74-2.31)
Cirrhosis of the liver	160	0.73 *	(0.62-0.85)	17	0.69	(0.43-1.12)	13	0.84	(0.49-1.45)
All external causes	449	0.82 *	(0.75-0.90)	43	0.55 *	(0.41-0.75)	34	1.14	(0.82-1.60)
Accidents	277	0.75 *	(0.67-0.85)	18	0.44 *	(0.28-0.70)	26	1.23	(0.83-1.81)
Suicides	143	0.87	(0.74-1.03)	7	0.93	(0.44-1.97)	7	0.83	(0.40-1.75)

** $P < 0.01$.

* $P < 0.05$.

dose-response relationship for any of the work areas or gender/race groups.

To assess further the risk of lung cancer among those who worked in allocated services, analyses were done by stratifying the cohort according to whether they did or did not work in this area. The RR for workers ever employed in allocated services is 1.18 ($P < 0.01$), while for those never employed the RR is 0.95 (nonsignificant).

Only two nasal sinus cancer deaths and one mediastinum cancer death are identified. These appear as other respiratory cancers in Table 3 . None of the remaining site-specific cancers were found to be elevated in any of the gender/race or work-area analyses.

Comparison of Mortality Risk: US vs Local Populations

To compare the risk estimates based on the US comparisons to those derived from local populations, it was important to explore whether comparisons of interest would be substantively altered depending on the calendar time frame selected for the analyses. This was necessary because mortality rates for nonmalignant causes of death were unavailable for local populations during the earlier time period of 1950 through 1959. Thus an investigation was performed to determine the extent to which the mortality comparisons using each of the control populations varied with calendar time (ie, 1948 through 1988 vs 1960 through 1988).

Generally, little variation in relative risk estimates is present across differing time periods for either US or local comparison populations. Regardless of the reference population or follow-up interval selected, the RRs for "all causes" in each race-gender category remain less than one. Comparison of estimates across the different time intervals shows that the RRs generally are greater with increased length of follow-up, reflecting a diminished healthy-worker effect associated with longer follow-up interval. Relative risks derived from the US population are slightly higher overall as compared with those based on the local populations within each race-gender group.

Table 4 summarizes the relative risk estimates for all causes and selected nonmalignant causes of death based on local rates by gender and race. The findings are based on the time period of 1960 through 1988 for nonmalignant causes of death analyses and the time period of 1948 through 1988 for malignant causes of death. Cause-specific mortality risk was not significantly elevated for any of the nonmalignant causes when local populations were used as the comparison. As in the previous analyses, several causes showed significant deficits. In contrast to the findings when the US comparison population was used, mortality from ischemic heart disease was not elevated overall or in any of the gender-race-specific analyses when compared with local populations. The RR estimates are all less

than one. Among nonwhite males, the RR was significantly less than one.

Table 5 summarizes the relative risk estimates for all cancers and select nonmalignant causes of death, based on local rates by gender and race. Relative risk estimates for all malignant neoplasms combined is less when the local rates are used as the standard, both overall and within each gender-race category. There is

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Cause of Death	**Obs**	**RR**	**95% CI**	**Obs**	**RR**	**95% CI**	**Obs**	**RR**	**95% CI**
All malignant neoplasms	2228	0.96	(0.92-1.00)	243	0.90	(0.79-1.02)	203	0.82 *	(0.72-0.94)
Colon	197	0.89	(0.77-1.02)	29	1.47 *	(1.02-2.13)	21	0.77	(0.50-1.19)
Liver	36	0.58 *	(0.42-0.81)	4	0.42	(0.16-1.13)	0		
Respiratory system	858	1.00	(0.94-1.07)	82	0.82	(0.66-1.01)	47	1.24	(0.93-1.65)
Larynx	24	0.67	(0.45-1.01)	4	0.79	(0.29-2.12)	1	1.17	(0.16-8.40)
Bronchus-trachea-lung	831	1.02	(0.96-1.10)	78	0.82	(0.66-1.03)	46	1.26	(0.94-1.68)
All other respiratory	3	0.32	(0.10-1.00)	0			0		
Kidney	59	1.06	(0.81-1.37)	2	0.43	(0.11-1.74)	4	1.04	(0.39-2.78)
Breast	3	1.03	(0.33-3.23)	0			46	0.84	(0.63-1.13)
Prostate (males only)	139	0.90	(0.76-1.06)	34	1.18	(0.84-1.66)	n/a		
Buccal cavity and pharynx	54	0.82	(0.63-1.08)	4	0.43	(0.16-1.15)	1	0.31	(0.04-2.21)
Digestive	570	0.92 *	(0.85-1.00)	80	1.02	(0.81-1.27)	42	0.69 *	(0.51-0.93)
Esophagus	54	0.88	(0.67-1.16)	12	0.75	(0.42-1.33)	2	0.81	(0.20-3.25)
Stomach	73	0.80	(0.63-1.01)	11	0.73	(0.40-1.33)	3	0.48	(0.15-1.48)
Rectum	63	1.02	(0.79-1.31)	5	0.92	(0.38-2.22)	2	0.35	(0.09-1.40)
Pancreas	107	0.93	(0.77-1.13)	14	1.07	(0.63-1.82)	10	0.89	(0.48-1.66)
Bladder	60	0.95	(0.73-1.22)	5	0.98	(0.40-2.37)	3	1.01	(0.32-3.14)
Central nervous system	56	0.91	(0.70-1.18)	2	0.72	(0.18-2.90)	5	0.85	(0.35-2.04)
All lymphohematopoietic	177	0.90	(0.78-1.05)	13	0.76	(0.44-1.31)	12	0.59	(0.34-1.04)
Lympho and reticular sarcoma	22	0.65 *	(0.43-1.00)	0			0		
Hodgkin's disease	19	0.98	(0.62-1.54)	1	0.76	(0.11-5.48)	0		
Leukemia and aleukemia	67	0.87	(0.68-1.10)	5	0.82	(0.34-1.98)	5	0.68	(0.28-1.65)

** $P < 0.01$.

* $P < 0.05$.

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no evidence of an increased risk for malignant neoplasms as a group. Overall and gender-race-specific relative risks for lung cancer are lower when local population comparisons are used. In contrast to the findings using US comparisons, none of the work-area subgroup analyses produce significantly elevated risks.

There is a consistent statistically significant excess risk for colon cancer ranging from about 1.5, when the local population rates are used, to 2.0, when US population rates are used. Work-area-specific findings suggest an elevated mortality risk among nonwhite males concentrated in grinding, allocated services, and the miscellaneous category of all other work areas. There is no indication of excess mortality from colon cancer among white males or females.

The work-area-specific kidney cancer risk among white males employed in melting remains when local populations are used. Relative risk estimates are significant at $P < 0.05$ and are quite similar (RR = 2.06 US population; RR = 1.96 local population). Analysis of the remaining site-specific cancers did not reveal any significant excesses.

Analysis by duration of employment and length of time since first employment revealed no significant excess in mortality among workers for lung cancer, kidney cancer, colon cancer, and ischemic heart disease for any gender/race groups. Mortality analysis for the remaining 56 causes of death by race, gender, and time period did not show any increase in risks, regardless of the comparison group utilized.

A comparison of RRs for the primary cancers of interest derived from US and local populations is presented in Table 6 . The results reported for ischemic heart disease are based on the shorter time period; however, this curtailed period of observation still contains 96% of all deaths and 89% of the total person-years.

Discussion

For most diseases, population mortality patterns exhibit geographical variation because of the environment, lifestyle, urbanization, and genetics. The use of mortality rates based on a local general population is one method to control for geographic variation in mortality. In this instance, nickel worker mortality is indeed closer to that of local communities than to that of the general US population for several cause of death categories, particularly lung cancer and ischemic heart disease.

When local populations are used as the standard, several methodologic aspects are noteworthy. A frequent concern raised when rates from a county or groups of counties are used as standards is the unreliability associated with the smaller

TABLE 6 – Relative Risks (95% Confidence Intervals) for Selected Causes of Death for High Nickel Alloys Workers, by Comparison Population: 1948-1988 for Cancer Causes and 1960-1988 for Nonmalignant Causes

Cause of Death	Gender/Race	US Population	Local Populations
Lung cancer	White male	1.13 * (1.05-1.21)	1.02 (0.96-1.10)
	Nonwhite male	1.08 (0.85-1.34)	0.82 (0.66-1.03)
	Female	1.33 (0.98-1.78)	1.26 (0.94-1.68)
	All workers	1.13 * (1.06-1.21)	1.01 (0.95-1.08)
Colon cancer	White male	1.01 (0.87-1.16)	0.89 (0.77-1.02)
	Nonwhite male	1.92 * (1.28-2.76)	1.47 * (1.02-2.13)
	Female	0.85 (0.53-1.30)	0.77 (0.50-1.19)
	All workers	1.05 (0.92-1.19)	0.92 (0.81-1.04)
Kidney cancer	White male	1.11 (0.85-1.43)	1.06 (0.81-1.37)
	Nonwhite male	0.59 (0.07-2.13)	0.43 (0.11-1.74)
	Female	1.11 (0.30-2.84)	1.04 (0.39-2.78)
	All workers	1.08 (0.84-1.38)	1.01 (0.79-1.29)
Ischemic heart disease	White male	1.05 * (1.01-1.09)	0.97 (0.94-1.00)
	Nonwhite male	0.93 (0.81-1.06)	0.81 * (0.71-0.93)
	Female	1.13 (0.98-1.29)	0.99 (0.86-1.13)
	All workers	1.05 * (1.01-1.08)	0.96 * (0.93-0.99)

** $P < 0.01$.

* $P < 0.05$.

population size. This was not as major a problem in these analyses because each of the plants studied is located within a metropolitan area and the local populations were defined by established SMSAs. This helps to assure baseline rates with adequate precision and stability. Furthermore, we used an extension of the Flanders method, [9] which incorporates a component in the variance estimate of the relative risk. This accounts for the additional variability in the local mortality rates due to the smaller population sizes.

A second concern often expressed when local rates are used is that the occupational group of interest may constitute a large portion of the local population used as the comparison. This problem is also alleviated in the current analyses because of the location of the plants in urban areas. The nickel worker cohort comprises about 0.2% of the SMSA populations, thus assuring that nickel workers do not have a major influence on the local comparison rates.

Finally, urban industrial areas tend to have somewhat higher rates for lung and some other cancers. In this instance, utilizing the local populations provides some control for those non-occupational cancer risk factors associated with metropolitan lifestyle.

An additional comparison group that could be considered in an occupational health study is a cohort of workers from a different but related industry. Such a comparison would have the potential to control for socioeconomic factors related to risks of disease. The use of such a comparison population should theoretically offset the healthy-worker effect that is often seen in risk assessments of occupational

groups that involve a comparison to the general population. Before another industrial cohort is used as a control population, several characteristics of the potential control cohort should be considered. These include the geographic proximity of the potential industrial control cohort plants to the plants of the study cohort, the similarity of employment period of the control and study cohorts, and the similarity of the control and study cohorts follow-up period.

As part of the overall evaluation of mortality risk in this high nickel alloys cohort, analyses that involved a comparison of the nickel workers' mortality to that of a cohort of steelworkers were performed. This cohort was available from occupational risk assessments undertaken by some of the authors. [17] In retrospect, we identified several deficiencies in using this occupational group as a comparison population. First, steelworker mortality follow-up was only available through 1982. The limitation of the nickel worker cohort to this time frame would result in an analysis that excludes 35% of the nickel workers' deaths. Second, the steelworkers were not contemporaries of the nickel workers with respect to their time frame of employment. The steelworker cohort was defined as those workers who were employed in 1951 through 1955. The nickel cohort used a much broader time frame encompassing employment from the late forties to mid-1960s. Last, the geographic areas of the steel plants differed substantially from those of the nickel plants, with more than 35% of the steelworkers in one geographic area. For these reasons, we have not included discussion of findings

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based on the steelworker comparison in this report.

In this study, estimates indicating an elevated lung cancer risk depend to a large degree on which population is used as the comparison. Overall, white male nickel workers have a 13% greater risk relative to the US population and little or no excess relative to the local populations. Work-area-specific analysis identified a significant excess risk of 18% among workers employed in allocated services when compared with that of the US population, and no excess was identified when compared with that of the local populations. A similar finding is noted among workers in grinding. This pattern suggests that other non-occupational factors associated with geographic areas of residence may explain the modest increase in lung cancer mortality. The identified excess of lung cancer when compared with that of the US population is no larger than that which could be explained by some confounding factor, such as cigarette smoking.

The consistent moderate elevation of colon cancer among nonwhite males regardless of the comparison group suggests that this finding may merit further study. Because of the small numbers of nonwhite workers, it is not clear to what extent the elevated colon cancer risk may also be plant-specific. The local population comparison suggests that approximately 50% of the excess may be explained by variations in risk factors associated with people living in different geographic regions.

Overall, there is no increased risk of kidney cancer. However, among white males employed in melting, a significant twofold excess of kidney cancer is evident when both the total US and local populations are used for comparison. Because the number of deaths attributed to this cause is small, it is difficult to assess the nature of this finding further.

The elevated risk of ischemic heart disease among white males in comparison with that of the US population is not evident in analyses using the local populations. This suggests that the increased risk noted when this risk is compared with that of the US population may be due to factors related to geographic variability in mortality patterns rather than occupational exposure. Peto et al [18] noted a similar finding for cardiovascular disease in their study of nickel workers in Great Britain. Comparison of the mortality of British nickel refinery workers to national death rates indicated a significant excess of 15%. In contrast, when Peto et al used mortality rates from a population local to the plant, no increased risk for cardiovascular disease was identified.

Although analyses with an alternative comparison population do not provide the same specificity as analyses having disease-specific risk factors for each individual, they do provide some insight into the interpretation of the mortality patterns. It is recommended that investigators consider the use of alternative comparison populations when investigating mortality risk associated with occupational exposures. A reasonable choice is a population drawn from geographic regions in proximity to the study cohort plant locations, such as the SMSAs. The use of a cohort of workers from a different industry could also be considered. However, when such control populations are used, they should be populations that are similar to the study cohort in terms of geographic location of the plants, period of employment, and period of follow-up.

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