Excess Melanoma Incidence in a Cohort Exposed to High Levels of Environmental Selenium

Marco Vinceti, Kenneth J. Rothman, Margherita Bergomi, Nazzarena Borciani, Luigi Serra, and Gianfranco Vivoli

Department of Hygiene, Microbiology and Biostatistics, University of Modena Medical School, Modena, Italy 41100 [M. V., M. B., N. B., G. V.]; Section of Preventive Medicine and Epidemiology, Evans Department of Medicine, Boston University Medical Center, Boston, Massachusetts 02118-2393 [K. J. R.]; and Department of Pathology, Santa Maria Nuova Hospital, Reggio Emilia, Italy 42100 [L. S.]

Abstract

Epidemiological studies on the relation between selenium and human cancer have yielded strongly conflicting results. Prompted by the observation of a positive association between selenium intake and site-specific cancers, including melanoma, in a large cohort of nurses, we studied the 11-year melanoma incidence in an Italian cohort that consumed unusually high levels of inorganic selenium in tap water from 1975 to 1985. The setting was Reggio Emilia, an Italian municipality that provided a natural experiment relating to intake of high levels of inorganic selenium. We identified 2,065 individuals with high selenium exposure, who contributed a total of 20,179 person-years of follow-up, and we compared their experience with the 1,384,386 person-years of follow-up in the remaining population of Reggio Emilia. We included all cases of pathologically confirmed malignant melanoma, including intraocular melanoma, identified from the Reggio Emilia Hospital, the Bologna regional registry of hospital discharges, and the Milan National Cancer Institute. Eight cases of malignant melanoma occurred in the exposed cohort during the follow-up. Melanoma incidence was 3.9 times greater in the exposed than in the unexposed cohort (95% exact confidence limits, 1.8–7.4).

Introduction

Garland et al. (1) reported a moderate but imprecisely measured increased risk of melanoma, as well as of lung and colorectal cancer and all cancers, among female nurses with average or high levels of selenium in toenail samples, compared with nurses whose toenail selenium levels were low. Two other smaller studies reported slightly negative associations between serum levels of selenium and subsequent melanoma (2, 3). Selenium has anticarcinogenic effects in several animal models (4), possibly as a consequence of its powerful toxicity (5), thus generating interest for a possible chemopreventive action in humans (6). Selenium has also been shown to be a pro-oxidant and a carcinogen under other experimental conditions (5, 7–9).

Evidence from the most recent epidemiological studies is extremely conflicting, ranging from positive to inverse relations between selenium exposure and subsequent cancer incidence or mortality, despite the fact that most studies examined populations with comparable ranges of selenium intake (1, 3, 10–21). Possible explanations of these inconsistencies are the potential confounding effects of dietary variables and the different biological activity of the various chemical forms of selenium, a feature that was not taken into account in most of the published studies.

Nearly all dietary selenium comes from foods, mostly meat, fish, and, in some countries, cereals (9, 22, 23). In food, most selenium appears in its organic forms, as seleno-amino acids (24, 25). It is, therefore, highly unusual for a human population to consume substantial amounts of inorganic selenium. Nevertheless, a rare geological source of inorganic selenium in a local water supply in Reggio Emilia, in northern Italy, has allowed the creation of a natural experiment. From 1972 to 1988, several thousand residents of this community consumed municipal water drawn from two wells that contained a high concentration of inorganic selenium. Prompted by the report of Garland et al. (1), as well as by an increase in mortality from cancer of certain sites, including melanoma, in this Italian cohort (26), we have evaluated the melanoma incidence in this population by comparing it with the incidence in the remainder of the municipality.

Materials and Methods

The population of the Reggio Emilia municipality is ~135,000, constituting nearly one-third of the population of the Reggio Emilia Province. The selenium-exposed area, comprising the neighborhoods of Rivalta and part of the bordering neighborhoods, had an isolated water distribution system that tapped water from two wells with high selenium content from September 1972 through September 1988 (16, 27). The selenium, in the form of selenate, was present at a concentration of 3–13 μg/liter in the wells and ~7–9 μg/liter in tap water. Selenium levels in the municipal water of the remainder of the province was below 1 μg/liter. In 1989, the wells were completely disconnected from the municipal water supply, and the selenium content of the water dropped to below 1 μg/liter. Apart from selenium, the tap water in Rivalta was similar in composition to that supplied to the remainder of the municipality: the chemical analyses included volatile solvents, trihalomethanes, pesticides, and 41 other chemicals, including all elements with known toxicity. Recently, measured radon content in water from the well Rivalta-1 (Rivalta-2 collapsed in 1989) was...
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similar to that determined in underground water of the general Emilia Romagna Region.

It was not feasible to ascertain the addresses of residents before 1980, but the Rivalta area is characterized by residential stability. We conducted a door-to-door assessment to determine the source of water for each home, and we relied on water subscription records to learn the history of water supply to each residence. We used residential records from 1980 and 1985 to determine the identity of the residents in each housing unit in the municipality. We then traced the residential history of each exposed individual identified in both 1980 and 1985 through municipal records back through 1974, before which no information existed on water source. We considered those individuals who were continuous residents in the Rivalta area from 1975 through 1985 and whose residence received municipal water to be the exposed cohort. Using these definitions, we classified 2065 people (1021 males and 1044 females) as exposed to inorganic selenium in their drinking water. Duration of exposure was at least 11 years. In addition, the location of the residence and the source of drinking water for each case was checked individually by a personal visit or telephone call.

We attempted to identify all cases of pathologically confirmed primary invasive melanoma occurring from January 1, 1986, through December 31, 1996, among residents of the Reggio Emilia municipality. We included all melanomas, including intraocular cases, in the analysis, except for two new melanomas in persons who had already had a diagnosis of melanoma during the follow-up period. Most cases could be identified from the records of the Department of Pathology of the Reggio Emilia Hospital. We identified one additional case by reviewing the files of the Emilia Romagna Hospital Discharges Registry, a regional registry in Bologna that began in 1991, and discharges from the National Cancer Institute in Milan during the period 1986–1996.

To assess the overall comparability of the exposed cohort with the surrounding community, we also collected information on educational level and occupation for all residents from municipal records.

Results

Eight people in the exposed cohort developed a malignant melanoma during the follow-up period, whereas 128 cases were diagnosed in the remainder of the municipal population. These figures included one case of intraocular melanoma that occurred in the exposed cohort and four that occurred in the reference population. In Table 1, we show the age- and sex-specific incidence rates of melanoma for the exposed and comparison populations. The compared populations had similar distributions with respect to educational attainment and occupation (Table 2).

If the exposed population had experienced the melanoma rates of the comparison population, specific for sex, calendar-year, and 5-year categories of age, 2.06 cases would have occurred. The SMR was 3.9 [95% mid-P exact confidence limits (CL) 1.8–7.4; Ref. 28]. The SMR for males was 5.0 (95% CL, 1.6–12.0) and for females was 3.2 (95% CL, 1.0–7.7). We repeated the calculation of the SMRs after exclusion from analysis of the cases with intraocular melanoma, obtaining a value of 3.5 (95% CL, 1.5–6.9). Corresponding figures for males and females were 5.1 (95% CL, 1.6–12.2) and 2.5 (95% CL, 0.6–6.7), respectively.

We also examined the incidence rates and rate ratios for two calendar periods, 1986–1990 and 1991–1996. We standardized these measures to the overall age and sex distribution of the exposed cohort. For the first period, the standardized rate in the exposed (cases/100,000 person-years) was 40.8, compared with 34.3 for the second period. The rate ratio, using the comparison cohort as a reference, was 4.0 for the first period and 3.4 for the second period.

Discussion

This small population in the Rivalta area of Reggio Emilia offers the unusual opportunity to observe possible biological effects of inorganic selenium exposure. Unfortunately, the size...
of the population and limited resources hinder our inferences. Thus, we had little information on potential confounding factors, aside from age, sex, and community data on occupation and educational level. Nevertheless, few risk factors for melanoma are known apart from sun exposure and number of nevi (29); we do not expect that either of these factors differs substantially between the populations that we compared.

In this study, the reference group included a few exposed persons, i.e., subjects consuming the high-selenium tap water for a different (generally shorter) period than that required for the cohort membership. This misclassification would have biased the SMRs toward unity, underestimating the effect of the exposure.

Although no direct estimate of the dietary intake of selenium in Reggio Emilia residents performed, serum selenium concentrations of selenium in the local population have been shown to be similar (30) or slightly lower (31) than those determined in other Italian populations. Because dietary intake and serum levels of selenium in Italy tend to be homogeneous (22, 23, 32), the national estimate of 45–50 μg/day appears to be a reasonable estimate of the usual selenium intake in the Reggio Emilia area. We estimated that the naturally occurring supplementation of selenium through drinking water ranged from 10 to 20 μg/day, but a comparison between the absolute amount of selenium intake through diet and that through drinking water may be misleading because the limited information available on the chemical forms of selenium in foodstuffs suggest that, by far, most selenium in the diet is present as organic selenium compounds (24, 25). Furthermore, absorption and bioavailability of elements such as selenium are more effective and, therefore, potentially more toxic through drinking water than through foodstuffs (33).

Thus, the population of the Rivolta area may be unique for its high intake of inorganic selenium. The biological effects of the different chemical forms of selenium may differ markedly (5, 25); in several laboratory studies, toxicity of selenium appeared to be much higher for the inorganic than for the organic forms of this metalloid (34, 35).

In a recently published randomized trial carried out in patients with nonmelanoma skin cancer, no effect on subsequent melanoma occurrence was noted, whereas a lower incidence of other site-specific cancers was reported (17). A comparison between our study and that investigation is difficult, however, because no information was made available about the chemical form of selenium used in the trial (200 μg/day for an average of 4.5 years), the study group was not drawn from the general population, and the average follow-up was only 6.4 years, including the period of supplementation.

Despite the small numbers reported here and the conflicting literature on selenium carcinogenicity, there is some biological plausibility for a carcinogenic effect. Whereas the selenium-dependent glutathione-peroxidases, which contain the trace element as selenocysteine, have antioxidant properties, in laboratory studies inorganic selenium species have been shown to be pro-oxidants and mutagens (5, 34, 36), even at very low concentrations (37). A suppressive effect of inorganic selenium on natural killer cells activity has also been demonstrated (38). Moreover, laboratory studies have demonstrated that skin is a target organ in chronic, low-dose selenium toxicity (9), and skin lesions were observed in occupationally exposed subjects even in the absence of increased plasma levels of the element (39).

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References


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