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Cancer incidence following long-term consumption of drinking water with high inorganic selenium content

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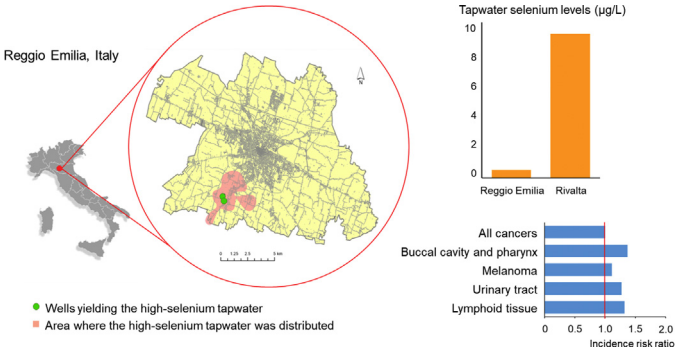
HIGHLIGHTS

- Chronic exposure to inorganic selenium via drinking water may be unsafe to the human.
- Long-term exposure to inorganic selenium may increase cancer risk.
- Selenium exposure increased melanoma and oropharyngeal, urinary and lymphoid cancer risk.
- The EU drinking water selenium standard of 10 μg/L should be reassessed.

GRAPHICAL ABSTRACT



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ABSTRACT

Selenium, a trace element to which humans are exposed mainly through diet, has been involved in the etiology of human cancer. We investigated the long-term effects of selenium exposure on cancer incidence using data from a natural experiment in Northern Italy. During the 1970s–1980s, in a part of the Italian municipality of Reggio Emilia, residents were inadvertently exposed to unusually high levels of inorganic hexavalent selenium (selenate) through drinking water. We followed the exposed residents for 28 years, generating data on incidence (when available) and mortality rates for selected cancer sites; the remaining municipal residents comprised the unexposed (reference) group. We observed no substantial difference in overall cancer incidence comparing exposed and unexposed cohorts. We detected, however, a higher incidence of cancer at some sites, and for a few of them, namely cancers of the buccal cavity and pharynx, melanoma, urinary tract and lymphoid tissue, the excess incidence was particularly evident in the first period of follow-up but decreased over time. Overall, these results suggest that consumption of water with levels of selenium in its inorganic hexavalent form close to the European standard, 10 μg/L, may have unfavourable effects on cancer incidence.

1. Introduction

In the field of nutritional epidemiology, few topics have attracted more attention than the association between dietary intake of selenium

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and cancer (Vinceti et al., 2000; Vinceti et al., 2017c; Vinceti et al., 2018), eliciting ongoing debate and controversy (Vinceti et al., 2013b). While the first laboratory studies in the 1940s indicated carcinogenic activity of selenium species, subsequent studies documented a cancer-inhibitory activity of selected selenium species, thus providing evidence for both carcinogenic and anti-carcinogenic activity of the element, depending on its chemical form (Vinceti et al., 2017c; Vinceti et al., 2018). However, it was only during the 1990s that the relation between selenium intake and cancer risk gained wide attention by the general public and the epidemiologic community. This followed the implementation of a small trial among patients with history of non-melanoma skin cancer to detect the effect of selenized yeast on cancer recurrence, following some indication from ecologic and other observational studies of a beneficial effect of selenium (Duffield-Lillico et al., 2002; Duffield-Lillico et al., 2003). Unexpectedly, selenium-supplemented participants had a lower incidence of some secondary outcomes, including colorectal, lung and particularly prostate cancers. This prompted the implementation of further experimental and non-experimental epidemiologic studies (Vinceti et al., 2017c). More recently, the pattern of the selenium-cancer association has evolved again, due to the null or detrimental effects of selenium reported in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a large randomized controlled trial carried out during the 2000s (Kristal et al., 2014; Lippman et al., 2009). The comprehensive epidemiologic literature about selenium and cancer has been recently assessed and summarized in a systematic review and meta-analysis (Vinceti et al., 2018). This review concluded that the literature does not support a beneficial effect of selenium on overall cancer risk, and that selenium supplementation may increase the incidence of high-grade prostate cancer and type 2 diabetes. An additional issue is represented by the possible use of selenium compounds in cancer therapy (Evans et al., 2017).

Despite the accumulating literature, the question of whether selenium influences cancer incidence is not entirely settled (Vinceti et al., 2017c). Among the issues still open is the possibility of specific effects of selenium on cancer risk according to the specific chemical form of the element, a key issue that could be most feasibly assessed in experimental studies that administer specific and known selenium species to its participants (Vinceti et al., 2017b; Vinceti et al., 2018). An exception to this rule is a natural experiment in a Northern Italian community, where drinking water with an unusually high content of inorganic hexavalent selenium was accidentally distributed for more than a decade (Vinceti et al., 2013b). After describing the early effects of selenium exposure (Vinceti et al., 2000) and investigating more recent effects on cancer mortality (Vinceti et al., 2016), in the present report, we investigate its long-term effects on cancer incidence. We did this to take into account cancers characterized by long induction, latent and survival periods, and to assess any waning over time of the short-term excess cancer risk detected in previous studies.

2. Material and methods

With approval of the Reggio Emilia Ethics Committee, we performed a retrospective follow-up of two cohorts of consumers of high selenium drinking water in the municipality of Reggio Emilia, Northern Italy during 1986–2013 (Fig. 1). These cohorts had been previously identified following the detection of a unique "natural experiment" involving the distribution of drinking water with high selenium levels of geologic origin for over 15 years starting from 1972 in part of the municipal territory named Rivalta, as described in more detail elsewhere (Vinceti et al., 2000). Selenium found in tap water distributed in this exposed area was in the inorganic hexavalent form, selenate (8–10 μg/L), and its overall levels were slightly below the current drinking water standard in the European Union (Vinceti et al., 2013a). The cohorts were composed by all subjects who had been continually residing in Rivalta from January 1st 1980 through December 31st 1985 (main cohort, $n = 5182$), and from January 1st 1974 through December 31st 1985 (long-term exposure cohort, $n = 2065$), provided that they had available municipal tap water in the earliest records of the Municipal Water Supply Agency, and further validated through mailed and door-to-doors surveys (Vinceti et al., 1996; Vinceti et al., 2000). Tap water distributed in Rivalta showed no other difference in its chemical composition or in physical features compared with the tap water supplied in the remaining municipal territory (Vinceti et al., 2000).

The unexposed cohort comprised all remaining 110,048 individuals who had been continually residing in the Reggio Emilia municipality since December 31, 1980 through December 31, 1985. For the comparison with the selenium long-term exposure cohort, this reference cohort was further restricted to the 95,715 people who resided in the municipality since December 31, 1974 and did not move into the Rivalta area during the 1974–1980 period.

To quantify cancer occurrence during follow-up, we used incidence data from the Reggio Emilia Cancer Registry at the Epidemiology Unit of the Local Health Authority, i.e. beginning on January 1, 1996. For the previous period, 1986–1995, we used mortality data as a proxy of incidence data, based on the death certificate directory of all residents available at the Epidemiology Unit, beginning on January 1, 1986. We linked all records by taxpayer number, the only unique identification number available for Italian residents at a nationwide level. Overall, we analyzed the difference in cancer events between exposed and unexposed cohorts based on cancer deaths (1986 to 1995) and incident cancer diagnoses (1996 to 2013).

Outcomes of interest were all malignant tumors excluding non-melanoma skin cancers, chronic myeloproliferative disorders, and myelodysplastic syndromes. We took into consideration the first incident cancer at each site during follow-up. For the all-site cancer incidence outcome, we took into consideration only the first incident cancer at any site during the follow up: so, the total amount of single site cases was higher than that of all sites. We computed incidence rate ratios (RR) for all cancers and cause-specific cancers in the exposed cohorts, using the unexposed cohorts as the referent. We adjusted for age (10 year age groups), sex and follow-up period (1986–1995, 1996–2004 and 2005–2013). To compute RRs and their 95% confidence intervals (CI), we ran multivariate Poisson models, with stratification by sex and follow-up period.

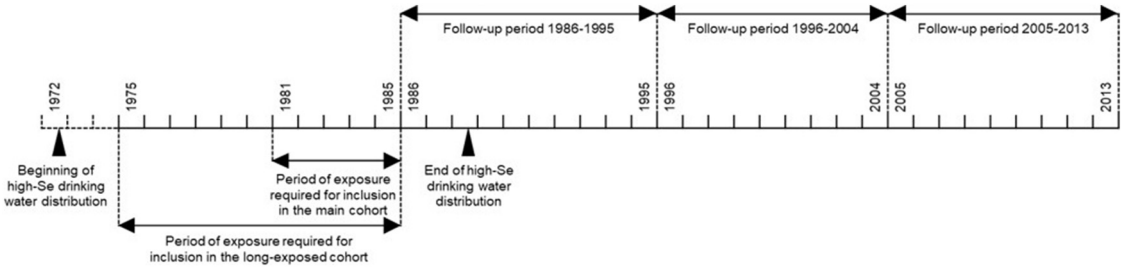

Fig. 1. Timing of the exposure to the tapwater with high content of hexavalent inorganic selenium of residents in Reggio Emilia, Northern Italy, and periods of follow-up of exposed and unexposed cohorts.