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Benzene exposure at workplace and risk of colorectal cancer in four Nordic countries

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ABSTRACT

Objective: The aim of this case-control study was to assess the effect of occupational benzene exposure on the risk of colorectal cancer, including its subtypes.

Methods: The study included 181,709 colon cancer and 109,227 rectal cancer cases diagnosed between 1961 and 2005 in Finland, Iceland, Norway and Sweden. Cases were identified from the Nordic Occupational Cancer Study (NOCCA) cohort. Five controls per case were selected from the same cohort, matched for country, birth year, and sex. Occupational benzene exposure for each study participant was estimated by linking their job titles to country specific job-exposure matrices. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by using conditional logistic regression models. The results were adjusted for physical strain at work, formaldehyde, ionizing radiation and wood dust.

Results: Increased risk was observed for all colorectal cancer (OR = 1.12, 95% CI 1.05–1.18) for the high decile of cumulative benzene exposure, indicating a statistically significant dose-response relationship. This excess risk was mainly seen in ascending colon (OR = 1.27, 95% CI 1.13–1.43), and transversal colon (OR = 1.21, 95% CI 1.01–1.41). The ORs in the highest exposure category were markedly higher in women than in men in all subsites of colon and rectum.

Conclusion: This study showed an association between workplace benzene exposure and colorectal cancer. The risk was restricted to ascending and transversal colon, and was the strongest among women.

1. Background

Benzene exposure at workplace has historically occurred via inhalation or dermal absorption of solvents, especially in the rubber, paint, printing and parts-manufacturing industries. It may also occur during chemical manufacturing and crude oil refining. Workers involved in transportation of crude oil and gasoline, dispensing of gasoline at service stations are also occupationally exposed to benzene. Drivers experience benzene exposure due to exhaust fumes from motor vehicles [1].

Benzene has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer since 1979, based on

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studies of leukemia [2]. This evaluation was reaffirmed specifically for acute myeloid leukemia and acute non-lymphocytic leukemia in 2009 [3], as well as in 2017 [4]. More recently, there have been numerous reports for benzene exposure and leukemia subtypes, non-Hodgkin lymphoma, multiple myeloma, and to a lesser extent other tumors in adults [5–7].

Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death in the world, with more than two-thirds of all cases and about 60% of all deaths occurring in countries with a high or very high human development index [8]. The incidence rates of colorectal cancers has increased in the Nordic countries over the past decades [9].

Lifestyle factors such as obesity, lack of physical activity, smoking, alcohol intake, and consumption of red and processed meat have been linked to an increased risk of colorectal cancers [10–14].

Among occupational factors, a protective effect on the risk of colon cancer was observed for physical activity at workplace in some previous studies [15–17]. Increased risk of colorectal and rectal cancers, but not colon cancer, was reported for diesel exhaust exposure in Canadian men [18]. Prolonged exposure to asbestos was linked to an elevated risk of cancer of total colon, distal colon and rectum in the Prospective Netherlands Study [19]. Some recent studies of night shift-work have also been associated with colorectal cancer [20]. Potential associations for other occupational agents were also suggested [21,22]. However, colorectal cancer was not linked to selected solvents, combustion products, metals, dusts and other occupational agents in a recent case-control study [23].

Evidence on association between benzene exposure and colorectal cancer is very limited and inconsistent. Increased incidence of cancer of colon and rectum was observed in a study of Danish seafarers exposed to substances including benzene [24], and Goldberg et al [25] observed some evidence for association between benzene and colon cancer. However, no association between benzene exposure and cancers of colon and rectum was found in a case-control study in Montreal, Canada [26].

The aim of the current study was to assess the effect of occupational benzene exposure on the risk of colorectal cancer, including its subtypes.

2. Methods

The current case-control study was nested within the Nordic Occupational Cancer Study (NOCCA) cohort. The NOCCA cohort consists of 14.9 million persons from Finland, Iceland, Norway, Sweden and Denmark [27], and it is based on a linkage between national census records and cancer registries. Persons were included into the cohort on January 1 of the year following the first available census where they participated, provided they were 30–64 years old. They were then followed up till the date of emigration, death or December 31 of the following years: in Denmark 2003, in Finland 2005, in Iceland 2004, in Norway 2003, and in Sweden 2005 [27]. Information on dates of death and emigration was obtained from Central Population Registers of these countries. Data from various registries were linked by using unique personal identification numbers used in all five Nordic countries. This method ensured a complete ascertainment of relevant events for each person included into the cohort, because the possibility of error in identifiers is extremely small [27]. Data from Denmark were not included in the present study because we did not have access to individual level records from this country.

The study included all incident colorectal cancer cases diagnosed between 1961 and 2005 in Finland, Iceland, Norway and Sweden. Categories of ascending colon, transversal colon and descending colon were separated for specific analysis. All remaining parts of colon (e.g. sigmoid colon, appendix, cecum, splenic and hepatic flexures) were combined into “other colon” category.

Five controls for each case were randomly selected from the NOCCA cohort. Cases and controls could have a previous history of cancer other than colorectal cancer before the date of diagnosis of the case (hereafter “index date”). Cases and controls were matched by country, sex and year of birth. Study participants had to be 20 years or older at index date, and had to have at least one census record before that date.

Job history information of the study participants was obtained from computerized census records from 1960 and later censuses in Sweden and Norway, and from 1970 and later censuses in Finland. In Iceland, the only computerized census record was available from 1981 census. Census questionnaires were self-administered and included questions related to economic activity, occupation, and industry. In Finland, Norway, and Sweden they were filled in by the heads of households for all members of households, whereas in Iceland each member of household who was at least 17 years old, personally filled in the questionnaire [27].

Occupational benzene exposure was estimated by linking the NOCCA job-exposure matrix (NOCCA-JEM) to job titles of study participants. The NOCCA-JEM was developed by a Nordic expert panel, including experts from each of country based on the template of the Finnish job-exposure matrix (FINJEM) [28]. It assigns prevalence of exposure (P) and annual average level (L) of exposure among the exposed persons for 28 occupational agents in more than 300 specific occupational groups in four time periods: 1945-59, 1960-74, 1975-84, 1985-94 [29].

We assigned a product of P and L of benzene exposure to each year over the duration of employment period of study participants. These values were then summed up to estimate cumulative exposure to benzene. Employment period of study participants was assumed to start at age 20 years and end at either 65 years or index date, whichever occurred first. If a person had different occupations in different censuses, we assumed that he/she changed occupation midway of known census years. The same procedure was used to estimate cumulative exposures for co-exposures.

Selection of covariates for the main effect model was based on the “purposeful covariate selection” method [30]. All occupational agents considered as potential confounders, and significantly associated (Wald test $p < 0.25$) with colorectal cancer risk in univariate logistic regression models were selected for multivariate model. In the next step, covariates were removed from multivariate model if they were not significantly contributing to the model fit. This procedure suggested that formaldehyde, ionizing radiation, wood dust and perceived physical workload could be included into the final main effect model as covariates.

We estimated odds ratios (OR) and 95% confidence intervals (CI) by using conditional logistic regression models. Cumulative benzene exposure and covariates were categorized by using 50^{th} and 90^{th} percentiles of exposure distribution among exposed controls as cut-points. Hence, the resulting exposure categories were: unexposed, ≤ 50th percentile, 50th–90th, > 90th percentile. Unexposed categories were used as a reference in all analyses. We treated ordinal levels of benzene exposure as continuous in order to test for significance of dose-response relationship (p-trend). Significance of interaction between benzene exposure and sex were assessed by using analysis of variance.

Finally, we performed sensitivity analyses to evaluate robustness of the main findings. This included analysis with 10- and 20-year lag-time, analysis with tertile categorization and analysis with adjustment for lifestyle factors. The lag-time analyses were performed under the assumption that cancer may develop over a number of years, and recent exposures may not be related to the disease risk. Therefore, in 10 and 20 years lag-time analyses, we did not count exposures occurring 10 and 20 years before the index date, respectively. Because NOCCA-JEM assigns exposure values from 1945, we also conducted sensitivity analysis including only persons who spent most part of their working career after 1945. We therefore excluded persons born before 1920 in this sensitivity analysis.

Lifestyle related factors by occupation in Finland were available