Original Article

Workplace Diesel Exhausts and Gasoline Exposure and Risk of Colorectal Cancer in Four Nordic Countries

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Abstract

Background: Evidence on associations between occupational diesel exhaust and gasoline exposure and colorectal cancer is limited. We aimed to assess the effect of workplace exposure to diesel exhaust and gasoline on the risk of colorectal cancer.

Methods: This case–control study included 181,709 colon cancer and 109,227 rectal cancer cases diagnosed between 1961 and 2005 in Finland, Iceland, Norway, and Sweden. Cases and controls were identified from the Nordic Occupational Cancer Study cohort and matched for country, birth year, and sex. Diesel exhaust and gasoline exposure values were assigned by country-specific job-exposure matrices. Odds ratios and 95% confidence intervals were calculated by using conditional logistic regression models. The results were adjusted for physical strain at work and occupational exposure to benzene, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.

Results: Diesel exhaust exposure was associated with a small increase in the risk of rectal cancer (odds ratio = 1.05, 95% confidence interval 1.02–1.08). Gasoline exposure was not associated with colorectal cancer risk.

Conclusion: This study showed a small risk increase for rectal cancer after workplace diesel exhaust exposure. However, this finding could be due to chance, given the limitations of the study.

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1. Introduction

Colorectal cancer is the third most common cancer in men and the second in women with about two-thirds of the cases occurring in countries with a high human development index [1]. The incidence rate of colorectal cancer varies widely for both sexes worldwide with the highest rates observed in Australia/New Zealand and the lowest in Western Africa [1]. The incidence rate of colorectal cancer has increased in the Nordic countries over the past decades [2]. Obesity, lack of physical activity, smoking, alcohol intake, and consumption of red and processed meat are among lifestyle
factors that have been linked to an increased risk of colorectal cancers [3–8].

Previous studies suggested associations also with occupational agents. For example, physically active work was associated with reduced risk of colorectal cancer, particularly with distal sites of the colon [9,10]. Prolonged exposure to asbestos was linked to an elevated risk of cancer of the total colon, distal colon, and rectum in the Prospective Netherlands Study [11]. Increased risk of colorectal cancer was also linked to night shift work [12], benzene exposure [13,14], and exposure to metalworking fluids [15,16].

Evidence on associations between workplace diesel exhaust and gasoline exposure and colorectal cancer is scarce. Few studies observed modest association between workplace diesel exhaust exposure and risk of the colon and rectum [13,17–19].

The aim of the present study was to assess associations between workplace diesel exhaust and gasoline exposures and colorectal cancer, including its subtypes.

2. Materials and methods

This case-control study was nested within the Nordic Occupational Cancer Study (NOCCA) cohort. The NOCCA cohort includes 15 million persons from Finland, Iceland, Norway, Sweden, and Denmark, who were aged from 30 to 64 years on January 1 of the year after the first available census where they participated [20]. They were followed up until the date of emigration, death, or 31 December of the following years: 2003 in Denmark and Norway, 2004 in Iceland, and 2005 in Finland and Sweden [20]. 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. This method ensured a complete ascertainment of relevant events for each person included in the cohort because the possibility of error in identifiers is extremely small [20]. Data from Denmark were not included in the present study because we did not have access to individual-level records from this country.

All incident colorectal cancer cases diagnosed between 1961 and 2005 in Finland, Iceland, Norway, and Sweden, and reported to the national cancer registries, were included in this study. Categories of the ascending, transversal, and descending colon were used for specific analysis. The remaining sites (e.g. sigmoid colon, appendix, cecum, splenic and hepatic flexures) were combined into the category of "other colon".

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 ("index date"). Cases and controls were matched by country, sex, and the year of birth, and the controls were living in the country on the index date. Study participants had to be 20 years or older on the index date and had to have at least one census record before that date.

Job titles of study participants were available from computerized census records from 1960, 1970, 1980, and 1990 in Sweden; from 1960, 1970, and 1980 in Norway; and from 1970, 1980, and 1990 in Finland. In Iceland, the only computerized census record was available from 1981 census [20].

Diesel exhaust and gasoline exposure values were assigned 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 country, based on the template of the Finnish job-exposure matrix [21]. 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: 1945–1959, 1960–1974, 1975–1984, and 1985–1994 [22].

We assigned a product of P and L of diesel exhaust and gasoline exposures to each year over the duration of the employment period of study participants. These values were then summed up to estimate cumulative exposures. Occupational groups exposed to diesel engine exhaust and gasoline are presented in Appendix A. The employment period of study participants was assumed to start at age 20 years (typical age at job start) and end either at age 65 years (typical retirement age) or on the 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 other occupational agents.

Selection of covariates for the main effect model was based on the “purposeful covariate selection” method [23]. Covariates with Wald test p-value less than 0.25 from univariate logistic regression models were selected as candidates for the multivariate model. In the next step, covariates were removed from the multivariate model if they were not significantly contributing to the model fit. This procedure suggested that benzene, formaldehyde, ionizing radiation, chromium, chlorinated hydrocarbons, wood dust, and perceived physical workload could be included into the final main effect model as covariates. Because none of these covariates were strongly correlated with diesel exhaust or gasoline, we included them in the same model.

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by using conditional logistic regression models. In multilevel exposure analysis, cumulative diesel exhaust and gasoline exposures were categorized by using 50th and 90th percentiles of exposure distribution among exposed controls as cutpoints. Hence, the resulting exposure categories were the following: unexposed, < 50th percentile, 50th–90th, and > 90th percentile. Unexposed categories were used as a reference in all analyses. Ordinal levels of exposure categories were used as continuous to test for significance of dose–response relationship in overall exposure analysis, unexposed category was defined as never exposed, and all other categories were combined into the ever-exposed category. Significance of interaction among diesel exhaust, gasoline, and sex were assessed by using analysis of variance.

The lifestyle-related factors by occupation and gender were available from the Finnish job-exposure matrix [21]. These data were based on the Finnish Health Behaviour and Health Among the Finnish Population surveys conducted by the Finnish Institute for Health and Welfare since 1978. The purpose of these surveys was to collect information on the health of employment-aged persons to track trends and changes over time. The main topics included in the surveys were eating habits, tobacco use, physical activity, health conditions, and alcohol consumption [24]. We controlled for the following lifestyle factors in the sensitivity analysis including only the Finnish data: the proportion of daily smokers; proportion of men drinking at least eight and women drinking less than twice a week; and proportion of those who have leisure time exercise less than twice a week; and proportion of those with a body mass index of 25 or higher [21].

Other sensitivity analyses included analyses with 10- and 20-year lag time and analysis with tertile categorization. The lag time analyses were performed under the assumption that recent exposures may not be related to cancer risk. In 10- and 20-year lag time analyses, we did not count exposures occurring 10 and 20 years before the index date, respectively.

All analyses were conducted by using R statistical software, version 3.4.1 (R Core Team. 2017: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).
3. Results

Table 1 shows numbers and proportions of cases for each cancer site by country, sex, and age at diagnosis. All proportions shown for cases in this table are the same also for controls because they were matched for these characteristics. The study included 181,709 colon cancer cases and 109,227 rectal cancer cases. There were more female than male colon cancer cases, whereas rectum cancer was more common in men than in women. Most of the cases were from Sweden, whereas only less than 1% were from Iceland. The median age at diagnosis was 71 years for colon cancer and 70 years for rectal cancer (Table 1).

Statistically significantly increased risk of rectal cancer (OR = 1.05, 95% CI 1.02-1.08) and decreased risk of cancer of the descending colon (OR = 0.88, 95% CI 0.80-0.97) were observed for overall diesel exhaust exposure (Table 2). Increased risk with the borderline significance was observed for the transversal colon (OR = 1.05, 95% CI 1.00-1.11) and all colorectal (OR = 1.02, 95% CI 1.00-1.03). Overall gasoline exposure did not seem to be associated with colorectal cancer risk (Table 2).

Analysis with categorical exposures showed similar risk pattern as in overall analysis (Table 3). However, the only significantly increased risk for rectal cancer was observed for the medium diesel exhaust category (OR = 1.07, 95% CI 1.04-1.11), whereas for other exposure categories, risk estimates were not significant (Table 3).

Analysis with adjustment for lifestyle factors in the Finnish data showed associations of diesel exhaust exposure with rectal and all colorectal cancers with significant dose–response relationship.

Table 1

| Characteristics | Ascending (n = 63,867), n (%) | Transversal (n = 26,681), n (%) | Descending (n = 8,863), n (%) | “Other colon" (n = 82,296), n (%) | All colon (n = 1,81709), n (%) | Rectum (n = 1,09227), n (%) | Colorectal (n = 2,99936), n (%) |
|----------------|-------------------------------|--------------------------------|------------------------------|----------------------------------|-----------------------------|-----------------------------|-------------------------------|
| Country        |                               |                                |                              |                                  |                             |                             |                               |
| Finland        | 11,003 (17.2)                 | 4,542 (17.0)                   | 1,452 (16.4)                 | 11,601 (14.1)                    | 28,598 (15.7)               | 19,903 (18.2)               | 48,501 (16.7)                 |
| Iceland        | 185 (0.3)                     | 77 (0.3)                       | 94 (1.1)                     | 760 (0.9)                        | 1,116 (0.6)                 | 424 (0.4)                   | 1,540 (0.5)                   |
| Norway         | 18,683 (29.3)                 | 8,493 (31.8)                   | 2,782 (31.4)                 | 20,633 (25.1)                    | 50,591 (27.8)               | 28,123 (25.7)               | 78,714 (27.1)                 |
| Sweden         | 33,996 (53.2)                 | 13,569 (50.9)                  | 4,535 (51.2)                 | 49,304 (50.9)                    | 101,404 (53.2)              | 60,777 (55.6)               | 162,181 (55.7)                |
| Sex            |                               |                                |                              |                                  |                             |                             |                               |
| Men            | 27,721 (43.4)                 | 12,556 (47.1)                  | 4,358 (49.2)                 | 40,402 (49.1)                    | 85,037 (46.8)               | 60,019 (54.9)               | 145,056 (49.9)                |
| Women          | 36,146 (56.6)                 | 14,125 (52.9)                  | 4,086 (50.8)                 | 41,896 (50.9)                    | 96,672 (53.2)               | 49,208 (45.1)               | 145,880 (50.1)                |
| Age at diagnosis |                             |                                |                              |                                  |                             |                             |                               |
| ≤ 40           | 997 (1.6)                     | 381 (1.4)                      | 181 (2.0)                    | 1,198 (1.5)                      | 2,757 (1.5)                 | 984 (0.9)                   | 3,741 (1.3)                   |
| 41–60          | 9,947 (15.6)                  | 5,044 (18.9)                   | 2,045 (23.1)                 | 16,342 (19.9)                    | 33,378 (18.4)               | 21,713 (19.9)               | 55,091 (18.9)                 |
| 61–80          | 39,254 (61.5)                 | 16,466 (61.7)                  | 5,413 (61.1)                 | 51,028 (62.0)                    | 112,161 (61.7)              | 68,909 (63.1)               | 181,070 (62.2)                |
| ≥ 80           | 13,669 (21.4)                 | 4,790 (18.0)                   | 1,224 (13.8)                 | 13,730 (16.7)                    | 33,413 (18.4)               | 17,621 (16.1)               | 51,034 (17.5)                 |
| Mean, median   | 71,73                        | 70,71                          | 68,69                       | 69,71                            | 70,71                       | 69,70                       | 70,71                        |

Table 2

| Exposure agent | Cancer location | Never | Ever | ORb | 95% CI | Never | Ever | ORb | 95% CI |
|----------------|-----------------|-------|------|-----|--------|-------|------|-----|--------|
| Diesel         | Ascending       | 57,809 | 6,058 | 1.00 | 0.97–1.04 | 61,973 | 1,894 | 1.10 | 0.95–1.18 |
|                | Transversal     | 120,187 | 23,887 | 1.00 | 0.97–1.04 | 129,391 | 25,844 | 1.09 | 0.82–1.36 |
|                | Descending      | 132,318 | 2,794 | 1.00 | 0.97–1.11 | 129,391 | 837 | 0.97 | 0.82–1.16 |
|                | “Other colon” b | 39,673 | 7,981 | 1.00 | 0.97–1.11 | 42,927 | 8,593 | 1.00 | 0.75–1.33 |
| Gasoline       | Ascending       | 369,035 | 6,832 | 0.98 | 0.95–1.01 | 396,992 | 2,617 | 1.12 | 0.89–1.08 |
|                | Transversal     | 819,041 | 163,343 | 0.99 | 0.97–1.02 | 811,301 | 176,091 | 1.01 | 0.94–1.08 |
|                | Descending      | 89,504 | 18,366 | 1.01 | 1.02–1.08 | 82,296 | 5,618 | 1.01 | 0.86–1.02 |
|                | “Other colon” b | 485,074 | 96,574 | 1.01 | 1.00–1.03 | 527,915 | 105,546 | 0.93 | 0.86–1.02 |

a OR estimates were adjusted for benzene, perceived physical workload, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.
b “Other colon” included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.
when diesel exhaust exposure was categorized using tertile cut-off points, medium and high diesel exhaust exposure levels were significantly associated with an increased rectal cancer risk with dose–response relationship (OR = 1.08, 95% CI 1.04–1.12 and OR = 1.07, 95% CI 1.02–1.11 respectively) (Appendix D).

4. Discussion

The present study showed small positive association between workplace diesel exhaust exposure and rectal cancer. This association remained increased also when adjusted for lifestyle factors, when diesel exhaust exposure was categorized using tertile cut-off points, and in analysis with 10- and 20-year lag time. Observed statistically significantly decreased overall risk of descending colon cancer is likely to be a chance finding due to multiple testing as it was not confirmed in other analyses. We did not observe association between occupational gasoline exposure and colorectal cancer.

Diesel and gasoline are most widely used fuel types in combustion engines, and their emissions consist of many carcinogens, including polycyclic aromatic hydrocarbons, nitroarenes, carbon monoxide, and 3-nitrobenzanthrone among others [25,26]. Although similar particles are emitted from both gasoline- and diesel-powered engines, the distribution and surface properties of the particles are different, suggesting potential differences in health effects associated with these exposures [27]. The main route of diesel exhaust particles administered via the gastrointestinal route and inhaled ambient air. Some of inhaled particles accumulated in the respiratory tract could be translocated to gastrointestinal tract as a result of mucociliar clearance [28]. Previous animal studies showed that diesel exhaust particles administered via the gastrointestinal route

| Exposure agent | Diesel | Gasoline |
|----------------|--------|----------|
| Cancer location | | |
| Ascending colon | | |
| Unexposed | 57,809 | 290,146 | 1.00 | 61,973 | 310,521 | 1.00 |
| Low | 3,039 | 14,600 | 1.02 | 0.97–1.06 | 903 | 4,278 | 1.07 | 0.95–1.21 |
| Medium | 2,377 | 11,687 | 0.98 | 0.93–1.03 | 779 | 3,610 | 1.03 | 0.90–1.19 |
| High | 642 | 2,902 | 1.04 | 0.94–1.15 | 212 | 926 | 1.06 | 0.88–1.27 |
| Transversal colon | | |
| Unexposed | 23,887 | 120,187 | 1.00 | 25,844 | 129,319 | 1.00 |
| Low | 1,390 | 6,637 | 1.05 | 0.98–1.12 | 414 | 2,050 | 0.95 | 0.79–1.16 |
| Medium | 1,124 | 5,232 | 1.07 | 0.99–1.15 | 337 | 1,583 | 0.99 | 0.80–1.22 |
| High | 280 | 1,349 | 1.03 | 0.89–1.19 | 86 | 381 | 1.02 | 0.77–1.36 |
| Descending colon | | |
| Unexposed | 7,981 | 39,673 | 1.00 | 8,593 | 42,927 | 1.00 |
| Low | 403 | 2,366 | 0.80 | 0.71–0.91 | 137 | 664 | 1.18 | 0.86–1.62 |
| Medium | 388 | 1,819 | 0.97 | 0.86–1.11 | 111 | 575 | 0.90 | 0.63–1.29 |
| High | 91 | 457 | 0.96 | 0.74–1.24 | 22 | 149 | 0.68 | 0.40–1.15 |
| Other colon<sup>d</sup> | | |
| Unexposed | 73,666 | 369,035 | 1.00 | 79,681 | 398,692 | 1.00 |
| Low | 4,385 | 21,215 | 1.00 | 0.97–1.04 | 1,269 | 6,431 | 0.95 | 0.86–1.06 |
| Medium | 3,364 | 17,025 | 0.95 | 0.91–0.99 | 1,039 | 5,102 | 0.96 | 0.85–1.08 |
| High | 883 | 4,215 | 1.02 | 0.94–1.11 | 309 | 1,265 | 1.15 | 0.98–1.34 |
| All colon | | |
| Unexposed | 163,343 | 819,041 | 1.00 | 176,091 | 881,531 | 1.00 |
| Low | 9,217 | 44,818 | 1.00 | 0.98–1.03 | 2,723 | 13,423 | 1.00 | 0.93–1.08 |
| Medium | 7,253 | 35,763 | 0.98 | 0.95–1.01 | 2,266 | 10,670 | 0.98 | 0.91–1.07 |
| High | 1,896 | 8,923 | 1.02 | 0.97–1.09 | 629 | 2,721 | 1.07 | 0.97–1.19 |
| Rectum | | |
| Unexposed | 96,574 | 485,074 | 1.00 | 105,546 | 527,915 | 1.00 |
| Low | 6,190 | 30,553 | 1.03 | 0.99–1.06 | 1,819 | 9,337 | 0.93 | 0.85–1.02 |
| Medium | 5,187 | 24,422 | 1.07 | 1.04–1.11 | 1,512 | 7,143 | 0.94 | 0.85–1.04 |
| High | 1,276 | 6,086 | 1.05 | 0.98–1.13 | 350 | 1,740 | 0.92 | 0.80–1.06 |
| All colorectal | | |
| Unexposed | 259,917 | 1,304,115 | 1.00 | 281,637 | 1,409,446 | 1.00 |
| Low | 15,410 | 75,382 | 1.02 | 0.99–1.04 | 4,535 | 22,732 | 0.97 | 0.92–1.03 |
| Medium | 12,441 | 60,195 | 1.02 | 0.99–1.04 | 3,784 | 18,028 | 0.97 | 0.91–1.04 |
| High | 3,168 | 14,988 | 1.04 | 0.99–1.09 | 980 | 4,474 | 1.02 | 0.94–1.11 |

Diesel and gasoline were categorized based on 50<sup>th</sup> and 90<sup>th</sup> percentile of cumulative exposure distribution among exposed colorectal cancer cases and controls.

- The low diesel exposure category was defined as ≤0.8 milligram per cubic meter (mg/m<sup>3</sup>); medium category 0.8–2.3 mg/m<sup>3</sup>; and high category >2.3 mg/m<sup>3</sup>. The unexposed category was used as a reference.
- The low gasoline exposure category was defined as ≤1.9 parts per million (ppm)-years; medium category 1.9–4.6 ppm-years; and high category >4.6 ppm-years. The unexposed category was used as a reference.
- OR estimates were adjusted for benzene, perceived physical workload, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.
- "Other colon" included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.

(p < 0.01) (Table 4). Notably, most of the risk estimates observed in Table 3 slightly increased away from null after adjusting for lifestyle factors.

Risk of rectal cancer for categorical diesel exhaust exposure remained increased also in analyses with 10- and 20-year lag time (Appendices B, C). When diesel exhaust exposure was categorized using tertile cut-off points, medium and high diesel exhaust exposure levels were significantly associated with an increased rectal cancer risk with dose–response relationship (OR = 1.08, 95% CI 1.04–1.12 and OR = 1.07, 95% CI 1.02–1.11 respectively) (Appendix D).
can induce DNA adducts and oxidative stress resulting in DNA strand breaks in gastrointestinal epithelial cells [29,30].

Accuracy and completeness of cancer incidence data is one of the strengths of the present study. Validation studies showed high degree of completeness, comparability, accuracy, and timeliness of cancer registration in the Nordic countries [31]. Reliable occupational data from census records are another advantage of the study. Previous studies demonstrated high accuracy of occupational classifications based on census records in the Nordic countries [32,33]. Finally, by linking job histories to NOCCA-JEM, we were able to control for the effect of many concomitant agents that can be present among diesel exhaust and gasoline-exposed workers.

Potential exposure misclassification is the main limitation of the study. First, the NOCCA-JEM cannot account for exposure heterogeneity within the occupation because it assigns average exposure to all members of the occupational group. Second, the NOCCA-JEM does not separate occupations by industry. Exposure intensity and prevalence may vary by industries included into the same occupation. Third, we did not have complete job histories of study participants and therefore imputed them from available computerized census records by assuming that a person changed occupation midway between consecutive censuses. Job histories were imputed from four census records in Sweden and from three census records in Finland and Norway. In Iceland, the only available computerized census record was 1981 census. However, this is unlikely to strongly bias the main results because Icelandic population constituted only less than 1% of the overall study population (Table 1). In addition, previous studies demonstrated low occupational mobility in the Nordic countries [20,32].

We could not control for leisure time physical activity, diet, smoking, alcohol intake, and body mass index in the main analyses. These factors have been linked to colorectal cancer risk in previous studies [3,4,6–8]. However, we were able to assess on the aggregate level the effect of lifestyle factors on associations between diesel exposure and colorectal cancer in Finland.
exhaust, gasoline, and colorectal cancer in the Finnish part of the data. Adjustment for lifestyle factors slightly increased risk estimates away from the null. Therefore, if data on lifestyle factors were available, most of the associations observed in the main analysis would likely to be stronger.

Associations observed in this study are consistent but weaker than the results from studies conducted in Canada [13,18,19], which observed increased risk of rectal cancer. A recent Australian case-control study [34] reported nonsignificantly increased risk of all colorectal cancer for exposure to diesel and gasoline exhaust emissions (OR = 1.14, 95% CI 0.89–1.46 for diesel and OR = 1.07, 95% CI 0.84–1.36 for gasoline). The difference in results between our study and Canadian and Australian studies could in part be explained by the difference in the prevalence of diesel exhaust exposure. For example, any exposure to diesel exhaust was only 11% in our study population compared with 19% in an Australian study [34] and 18% and 36% in Canadian studies [18,19].

In conclusion, the present study showed a small risk increase of rectal cancer among workers occupationally exposed to diesel exhaust. However, we cannot exclude the possibility of this weak to modest association to be due to chance, given the limitations of the present study. Workplace gasoline exposure was not linked to colorectal cancer risk.

**Ethical approval**

As this study was register-based, neither ethical committee review nor informed consent from the study participants was required.

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**Conflict of interest**

Authors declare no conflict of interest.

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**Appendix**

**Appendix A**

Occupational groups exposed to diesel engine exhaust and gasoline.

| Occupation                      | 1945–1959 (P x L)b | 1960–1974 (P x L)b | 1975–1984 (P x L)b | 1985–1994 (P x L)b |
|---------------------------------|--------------------|--------------------|--------------------|--------------------|
| Diesel engine exhaustc          |                    |                    |                    |                    |
| Miners and quarrymen            | 0.03               | 0.08               | 0.33               | 0.28               |
| Asphalt workers                 | 0.10               | 0.14               | 0.13               | 0.10               |
| Construction machinery operators| 0.07               | 0.13               | 0.12               | 0.09               |
| Railway engine drivers, steam engine firemen | 0.02 | 0.10 | 0.09 | 0.05 |
| Engine room crew                | 0.10               | 0.07               | 0.07               | 0.07               |
| Road transport supervisors      | 0.07               | 0.09               | 0.08               | 0.07               |
| Harbor masters                  | 0.06               | 0.08               | 0.07               | 0.06               |
| Road and tram service personnel | 0.05               | 0.05               | 0.07               | 0.06               |
| Machine and engine mechanics    | 0.05               | 0.07               | 0.07               | 0.06               |
| Stevedores                      | 0.02               | 0.07               | 0.06               | 0.04               |
| Maintenance crews and supervisors| 0.02             | 0.06               | 0.05               | 0.04               |
| Assisting construction workers  | 0.04               | 0.06               | 0.04               | 0.02               |
| Messengers and delivery boys    | 0.02               | 0.05               | 0.05               | 0.04               |
| Forklift operators              | 0.01               | 0.05               | 0.04               | 0.03               |
| Service station attendants      | 0.03               | 0.03               | 0.05               | 0.00               |
| Motor vehicle and tram drivers  | 0.02               | 0.03               | 0.03               | 0.03               |
| Mechanical engineers            | 0.01               | 0.01               | 0.01               | 0.02               |
| Policemen                       | 0.01               | 0.01               | 0.01               | 0.01               |
| Stationary engine and machinery operators | 0.00 | 0.00 | 0.01 | 0.01 |
| Gasolineb                       |                    |                    |                    |                    |
| Service station attendants      | 0.80               | 0.80               | 0.06               | 0.00               |
| Printers                        | 0.30               | 0.00               | 0.00               | 0.00               |
| Occupation in graphics          | 0.20               | 0.00               | 0.00               | 0.00               |
| Machine and engine mechanics    | 0.10               | 0.10               | 0.02               | 0.01               |

Estimates were retrieved from the Nordic Occupational Cancer Study job-exposure matrix.

a Occupations were listed from the largest to the smallest P x L value.
b P was proportion, and L was annual average exposure in the occupational group.
c The unit of diesel engine exposure was mg/m³, and the unit of gasoline exposure was parts per million (ppm).
### Appendix B

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer from 10-year lag time analysis.

| Exposure agent | Diesel\(^a\) | Gasoline\(^b\) |
|----------------|-------------|-------------|
| Cancer location | Case, n | Control, n | OR | 95% CI | p-trend | Case, n | Control, n | OR | 95% CI | p-trend |
| Ascending colon Unexposed | 58,161 | 291,962 | 1.00 | 62,123 | 311,191 | 1.00 |
| Low | 3,524 | 16,768 | 1.02 | 0.98–1.07 | 0.98 | 783 | 3,751 | 1.04 | 0.92–1.18 |
| Medium | 1,961 | 9,535 | 0.97 | 0.91–1.03 | 0.91 | 843 | 3,847 | 1.04 | 0.91–1.19 |
| High | 221 | 1,070 | 1.01 | 0.87–1.17 | 0.95 | 118 | 546 | 0.93 | 0.74–1.17 |
| Transversal colon Unexposed | 24,027 | 120,986 | 1.00 | 25,892 | 129,667 | 1.00 |
| Low | 1,661 | 7,618 | 1.08 | 1.02–1.15 | 1.02 | 380 | 1,831 | 1.02 | 0.84–1.24 |
| Medium | 888 | 4,268 | 1.03 | 0.94–1.13 | 0.94 | 363 | 1,696 | 1.02 | 0.83–1.25 |
| High | 105 | 533 | 1.00 | 0.81–1.24 | 0.81 | 46 | 211 | 0.98 | 0.68–1.42 |
| Descending colon Unexposed | 8,042 | 40,012 | 1.00 | 8,611 | 43,043 | 1.00 |
| Low | 498 | 2,704 | 0.85 | 0.76–0.95 | 0.76 | 121 | 567 | 1.29 | 0.94–1.78 |
| Medium | 281 | 1,451 | 0.87 | 0.74–1.03 | 0.74 | 119 | 618 | 0.97 | 0.69–1.36 |
| High | 42 | 148 | 1.30 | 0.91–1.86 | 0.91 | 12 | 87 | 0.58 | 0.29–1.15 |
| All colon Unexposed | 164,391 | 824,600 | 1.00 | 176,497 | 883,522 | 1.00 |
| Low | 10,722 | 51,368 | 1.01 | 0.99–1.04 | 0.99 | 2,398 | 11,841 | 1.02 | 0.91–1.15 |
| Medium | 5,878 | 29,293 | 0.96 | 0.92–0.99 | 0.92 | 2,453 | 11,546 | 1.02 | 0.95–1.11 |
| High | 42 | 148 | 1.97 | 0.81–1.24 | 0.81 | 12 | 87 | 0.58 | 0.29–1.15 |
| Rectum Unexposed | 97,221 | 488,847 | 1.00 | 105,785 | 529,241 | 1.00 |
| Low | 7,376 | 35,083 | 1.07 | 1.04–1.10 | 1.04 | 1,631 | 8,258 | 0.96 | 0.88–1.05 |
| Medium | 4,140 | 19,934 | 1.05 | 1.00–1.10 | 1.00 | 1,604 | 7,530 | 0.97 | 0.88–1.06 |
| High | 490 | 2,271 | 1.09 | 0.99–1.21 | 0.99 | 207 | 1,106 | 0.84 | 0.71–0.99 |
| All colorectal Unexposed | 261,612 | 1,313,447 | 1.00 | 282,282 | 1,412,763 | 1.00 |
| Low | 18,098 | 86,451 | 1.04 | 1.02–1.05 | 1.02 | 4,029 | 20,099 | 0.99 | 0.93–1.05 |
| Medium | 10,018 | 49,227 | 0.99 | 0.97–1.02 | 0.97 | 4,057 | 19,076 | 1.01 | 0.95–1.07 |
| High | 1,208 | 5,555 | 1.08 | 1.01–1.15 | 1.01 | 568 | 2,742 | 0.94 | 0.84–1.04 |

*Diesel and gasoline were categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed colorectal cancer cases and controls.

\(^a\) The low diesel exposure category was defined as \( < 0.8 \) milligram per cubic meters (mg/m\(^3\)); medium category \( 0.8–2.3 \) mg/m\(^3\); and high category \( > 2.3 \) mg/m\(^3\). The unexposed category was used as a reference.

\(^b\) The low gasoline exposure category was defined as \( < 1.9 \) parts per million (ppm)-years; medium category \( 1.9–4.6 \) ppm-years; and high category \( > 4.6 \) ppm-years. The unexposed category was used as a reference.

\(^c\) OR estimates were adjusted for benzene, perceived physical workload, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.

\(^d\) Other colon included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.
# Appendix C

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer from 20-year lag time analysis.

| Exposure agent | Cancer location | Diesel<sup>a</sup> | Gasoline<sup>b</sup> |
|----------------|----------------|-------------------|---------------------|
|                | Case, n | Control, n | OR<sup>c</sup> | 95% CI | p-trend | Case, n | Control, n | OR<sup>c</sup> | 95% CI | p-trend |
| Ascending colon | Unexposed | 59,019 | 296,053 | 1.00 | | 62,428 | 312,619 | 1.00 | | |
|                 | Low | 3,535 | 16,969 | 1.01 | 0.96–1.05 | | 566 | 2,731 | 1.02 | 0.90–1.16 | |
|                 | Medium | 1,269 | 6,077 | 0.98 | 0.90–1.07 | | 776 | 3,534 | 1.03 | 0.90–1.17 | |
|                 | High | 44 | 236 | 0.91 | 0.66–1.26 | 0.92 | 97 | 451 | 0.89 | 0.69–1.15 | 0.90 |
| Transversal colon | Unexposed | 24,394 | 122,859 | 1.00 | | 26,021 | 130,326 | 1.00 | | |
|                 | Low | 1,693 | 7,701 | 1.08 | 1.02–1.15 | | 296 | 1,395 | 1.04 | 0.86–1.25 | |
|                 | Medium | 573 | 2,708 | 1.08 | 0.95–1.22 | | 328 | 1,516 | 1.01 | 0.83–1.23 | |
|                 | High | 21 | 137 | 0.78 | 0.49–1.23 | 0.04 | 36 | 168 | 0.95 | 0.63–1.43 | 0.91 |
| Descending colon | Unexposed | 8,155 | 40,661 | 1.00 | | 8,661 | 43,274 | 1.00 | | |
|                 | Low | 511 | 2,732 | 0.86 | 0.77–0.96 | 0.96 | 89 | 405 | 1.13 | 0.82–1.55 | |
|                 | Medium | 186 | 889 | 1.04 | 0.83–1.29 | 1.02 | 102 | 560 | 0.80 | 0.57–1.12 | |
|                 | High | 11 | 33 | 1.57 | 0.78–3.16 | 0.37 | 11 | 76 | 0.60 | 0.29–1.21 | 0.09 |
| "Other colon"<sup>d</sup> | Unexposed | 75,296 | 377,383 | 1.00 | | 80,297 | 401,663 | 1.00 | | |
|                 | Low | 5,127 | 24,794 | 0.99 | 0.96–1.03 | 1.02 | 820 | 4,314 | 0.92 | 0.82–1.02 | |
|                 | Medium | 1,804 | 8,980 | 0.98 | 0.91–1.05 | 1.04 | 1023 | 4,846 | 1.00 | 0.90–1.12 | |
|                 | High | 71 | 333 | 1.03 | 0.79–1.33 | 0.35 | 158 | 667 | 1.11 | 0.91–1.37 | 0.68 |
| All colon | Unexposed | 166,864 | 836,956 | 1.00 | | 177,407 | 887,882 | 1.00 | | |
|                 | Low | 10,866 | 52,196 | 1.00 | 0.98–1.03 | 1.00 | 1771 | 8,845 | 0.98 | 0.91–1.05 | |
|                 | Medium | 3,832 | 18,654 | 1.00 | 0.95–1.05 | 1.00 | 2,229 | 10,456 | 1.00 | 0.93–1.08 | |
|                 | High | 147 | 739 | 0.97 | 0.81–1.16 | 0.92 | 302 | 1,362 | 0.98 | 0.85–1.14 | 0.91 |
| Rectum | Unexposed | 98,864 | 496,883 | 1.00 | | 106,372 | 532,135 | 1.00 | | |
|                 | Low | 7,602 | 35,982 | 1.07 | 1.04–1.10 | 1.00 | 1,253 | 6,278 | 0.94 | 0.86–1.02 | |
|                 | Medium | 2,539 | 12,738 | 1.04 | 0.98–1.11 | 1.00 | 1,421 | 6,786 | 0.93 | 0.85–1.03 | |
|                 | High | 122 | 532 | 1.17 | 0.96–1.42 | <0.01 | 181 | 936 | 0.84 | 0.70–1.01 | 0.03 |
| All colorectal | Unexposed | 265,728 | 1,333,839 | 1.00 | | 283,779 | 1,420,017 | 1.00 | | |
|                 | Low | 18,468 | 88,178 | 1.04 | 1.01–1.05 | 1.00 | 3,024 | 15,123 | 0.96 | 0.91–1.02 | |
|                 | Medium | 6,471 | 31,392 | 1.02 | 0.98–1.05 | 1.00 | 3,650 | 17,242 | 0.98 | 0.92–1.04 | |
|                 | High | 269 | 1,271 | 1.05 | 0.92–1.20 | 0.01 | 483 | 2,298 | 0.93 | 0.83–1.04 | 0.16 |

Diesel and gasoline were categorized based on 50<sup>th</sup> and 90<sup>th</sup> percentile of cumulative exposure distribution among exposed colorectal cancer cases and controls.

<sup>a</sup> The low diesel exposure category was defined as ≤0.8 milligram per cubic meter (mg/m³); medium category 0.8–2.3 mg/m³; and high category >2.3 mg/m³. The unexposed category was used as a reference.

<sup>b</sup> The low gasoline exposure category was defined as ≤1.9 parts per million (ppm)-years; medium category 1.9–4.6 ppm-years; and high category >4.6 ppm-years. The unexposed category was used as a reference.

<sup>c</sup> OR estimates were adjusted for benzene, perceived physical workload, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.

<sup>d</sup> "Other colon" included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.
Appendix D
Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer.

| Exposure agent | Diesel | Gasoline |
|----------------|--------|----------|
| Cancer location | OR | 95% CI | p-trend | OR | 95% CI | p-trend |
| Ascending colon | | | | | | |
| Unexposed | 57,809 | 290,146 | 1.00 | 61,973 | 310,521 | 1.00 |
| Low | 2,089 | 9,741 | 1.05 | 1.00–1.10 | 422 | 2,026 | 1.06 | 0.92–1.23 |
| Medium | 1,959 | 9,701 | 0.98 | 0.92–1.03 | 789 | 3,728 | 1.09 | 0.96–1.24 |
| High | 2,010 | 9,747 | 0.97 | 0.92–1.04 | 683 | 3,060 | 1.02 | 0.89–1.18 |
| Transversal colon | | | | | | |
| Unexposed | 23,887 | 120,187 | 1.00 | 25,844 | 129,391 | 1.00 |
| Low | 924 | 4,439 | 1.03 | 0.95–1.11 | 179 | 987 | 0.84 | 0.67–1.05 |
| Medium | 948 | 4,359 | 1.09 | 1.01–1.17 | 356 | 1,722 | 0.99 | 0.81–1.22 |
| High | 922 | 4,420 | 1.04 | 0.95–1.14 | 302 | 1,305 | 1.09 | 0.88–1.35 |
| Descending colon | | | | | | |
| Unexposed | 7,981 | 39,673 | 1.00 | 8,593 | 42,927 | 1.00 |
| Low | 274 | 1,590 | 0.82 | 0.72–0.95 | 58 | 339 | 1.00 | 0.69–1.46 |
| Medium | 297 | 1,540 | 0.89 | 0.78–1.02 | 134 | 542 | 1.28 | 0.92–1.78 |
| High | 311 | 1,509 | 0.95 | 0.81–1.12 | 78 | 507 | 0.72 | 0.49–1.04 |
| “Other colon”d | | | | | | |
| Unexposed | 73,666 | 369,035 | 1.00 | 79,681 | 398,692 | 1.00 |
| Low | 3,024 | 14,217 | 1.03 | 0.99–1.08 | 594 | 3,014 | 0.98 | 0.87–1.11 |
| Medium | 2,745 | 14,091 | 0.94 | 0.90–0.98 | 1,113 | 5,505 | 0.99 | 0.89–1.11 |
| High | 2,863 | 14,147 | 0.97 | 0.93–1.03 | 910 | 4,279 | 0.98 | 0.87–1.10 |
| All colon | | | | | | |
| Unexposed | 163,343 | 819,041 | 1.00 | 176,091 | 881,531 | 1.00 |
| Low | 6,311 | 29,990 | 1.03 | 0.99–1.06 | 1,253 | 6,366 | 0.99 | 0.91–1.07 |
| Medium | 5,949 | 29,691 | 0.97 | 0.94–1.00 | 2,392 | 11,497 | 1.04 | 0.96–1.12 |
| High | 6,106 | 29,823 | 0.98 | 0.95–1.02 | 1,973 | 9,151 | 0.99 | 0.92–1.08 |
| Rectum | | | | | | |
| Unexposed | 96,574 | 485,074 | 1.00 | 105,546 | 527,915 | 1.00 |
| Low | 4,127 | 20,611 | 1.01 | 0.97–1.05 | 856 | 4,579 | 0.88 | 0.79–0.99 |
| Medium | 4,238 | 19,983 | 1.08 | 1.04–1.12 | 1,567 | 7,798 | 0.91 | 0.83–1.01 |
| High | 4,288 | 20,467 | 1.07 | 1.02–1.11 | <0.01 | 1,258 | 5,843 | 0.98 | 0.89–1.09 |
| All colorectal | | | | | | |
| Unexposed | 259,917 | 1,304,115 | 1.00 | 281,637 | 1,409,446 | 1.00 |
| Low | 10,400 | 50,456 | 1.02 | 0.99–1.04 | 2,969 | 15,338 | 0.94 | 0.88–1.00 |
| Medium | 10,228 | 49,851 | 1.02 | 0.99–1.04 | 3,100 | 14,914 | 1.00 | 0.94–1.07 |
| High | 10,391 | 50,258 | 1.01 | 0.99–1.04 | 3,230 | 14,982 | 1.00 | 0.94–1.07 |

Diesel and gasoline were categorized based on tertiles of cumulative exposure distribution among exposed colorectal cancer cases and controls.

a The low diesel exposure category was defined as <0.5 milligram per cubic meter (mg/m³); medium category 0.5–1.1 mg/m³; and high category >1.1 mg/m³. The unexposed category was used as a reference.

b The low gasoline exposure category was defined as <1 parts per million (ppm)-years; medium category 1–3.2 ppm-years; and high category >3.2 ppm-years. The unexposed category was used as a reference.

c OR estimates were adjusted for benzene, perceived physical workload, formaldehyde, ionizing radiation, chlorinated hydrocarbons, chromium, and wood dust.

d “Other colon” included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.

Appendix E. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2019.01.001.

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