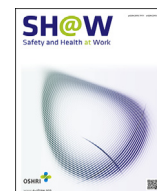




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Original Article

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

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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 cut-points. 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 five portions of alcohol weekly; proportion of those who fulfill fewer than three of the four recommended dietary habits; 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

Selected demographic characteristics of incident colorectal cancer cases in the Nordic Occupational Cancer Study cohort during 1961-2005

Characteristics	Ascending (n = 63,867), n (%)	Transversal (n = 26,681), n (%)	Descending (n = 8,863), n (%)	"Other colon" ^a (n = 82,298), n (%)	All colon (n = 1,81709), n (%)	Rectum (n = 1,09227), n (%)	Colorectal (n = 2,90936), 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 (59.9)	101,404 (55.8)	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)	4,505 (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

^a "Other colon" included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.

Table 2

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for ever vs never occupational diesel and gasoline exposures and colorectal cancer

Exposure agent Cancer location	Diesel				Gasoline			
	Case, n	Control, n	OR ^a	95% CI	Case, n	Control, n	OR ^a	95% CI
Ascending colon								
Never	57,809	290,146			61,973	310,521		
Ever	6,058	29,189	1.00	0.97-1.04	1,894	8,814	1.06	0.95-1.18
Transversal colon								
Never	23,887	120,187			25,844	129,391		
Ever	2,794	13,218	1.05	1.00-1.11	837	4,014	0.97	0.82-1.16
Descending colon								
Never	7,981	39,673			8,593	42,927		
Ever	882	4,642	0.88	0.80-0.97	270	1,388	1.00	0.75-1.33
"Other colon" ^b								
Never	73,666	369,035			796,81	398,692		
Ever	8,632	42,455	0.98	0.95-1.01	2,617	12,798	0.98	0.89-1.08
All colon								
Never	163,343	819,041			176,091	881,531		
Ever	18,366	89,504	0.99	0.97-1.02	5,618	27,014	1.01	0.94-1.08
Rectum								
Never	96,574	485,074			105,546	527,915		
Ever	12,653	61,061	1.05	1.02-1.08	3,681	18,220	0.93	0.86-1.02
All colorectal								
Never	259,917	1,304,115			281,637	1,409,446		
Ever	31,019	150,565	1.02	1.00-1.03	9,299	45,234	0.98	0.93-1.03

^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.

Table 3
Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer.

Exposure agent Cancer location	Diesel ^a					Gasoline ^b				
	Case, <i>n</i>	Control, <i>n</i>	OR ^c	95% CI	p-trend	OR ^c	95% CI	OR ^c	95% CI	p-trend
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	0.92	212	926	1.06	0.88–1.27	0.50
Transversal colon										
Unexposed	23,887	120,187	1.00			25,844	129,391	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	0.11	86	381	1.02	0.77–1.36	0.87
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	0.24	22	149	0.68	0.40–1.15	0.09
"Other colon" ^d										
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	0.09	309	1,265	1.15	0.98–1.34	0.29
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	10,870	0.98	0.91–1.07	
High	1,896	8,923	1.02	0.97–1.09	0.46	629	2,721	1.07	0.97–1.19	0.43
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	<0.01	350	1,740	0.92	0.80–1.06	0.18
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	0.05	980	4,474	1.02	0.94–1.11	0.94

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 meter (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.

($p < 0.01$) (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).

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-nitrobenzathrone 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 and gasoline exposure was inhalation of polluted ambient air. Some of inhaled particles accumulated in the respiratory tract could be translocated to gastrointestinal tract as a result of mucociliary clearance [28]. Previous animal studies showed that diesel exhaust particles administered via the gastrointestinal route

Table 4

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer in Finland.

Exposure agent Cancer location	Diesel ^a					Gasoline ^b				
	Case, <i>n</i>	Control, <i>n</i>	OR ^c	95% CI	p-trend	Case, <i>n</i>	Control, <i>n</i>	OR ^c	95% CI	p-trend
Ascending colon										
Unexposed	10,191	51,332	1.00			10,833	54,278	1.00		
Low	293	1,359	1.06	0.93–1.22		78	375	1.09	0.77–1.57	
Medium	418	1,894	1.05	0.93–1.19		77	288	1.10	0.69–1.75	
High	101	430	1.08	0.85–1.38	0.23	15	74	0.86	0.44–1.66	0.96
Transversal colon										
Unexposed	4,182	21,030	1.00			4,469	22,375	1.00		
Low	115	619	0.94	0.75–1.16		34	180	0.88	0.51–1.53	
Medium	195	828	1.14	0.95–1.38		32	127	0.94	0.47–1.89	
High	50	233	1.04	0.73–1.46	0.37	7	28	0.98	0.36–2.69	0.83
Descending colon										
Unexposed	1,335	6,727	1.00			1,432	7,150	1.00		
Low	37	221	0.85	0.58–1.24		8	52	0.91	0.32–2.62	
Medium	62	264	1.09	0.78–1.52		11	43	0.55	0.15–2.02	
High	18	48	1.79	0.97–3.32	0.22	1	15	0.16	0.01–1.72	0.16
"Other colon" ^d										
Unexposed	10,678	53,783	1.00			11,439	57,191	1.00		
Low	320	1,408	1.09	0.95–1.24		72	352	1.06	0.74–1.51	
Medium	470	2,212	1.01	0.90–1.14		69	371	0.85	0.54–1.32	
High	133	602	1.06	0.86–1.31	0.52	21	91	0.99	0.55–1.81	0.81
All colon										
Unexposed	26,386	132,872	1.00			28,173	140,994	1.00		
Low	765	3,607	1.04	0.95–1.13		192	959	1.03	0.83–1.30	
Medium	1,145	5,198	1.05	0.97–1.13		189	829	0.94	0.71–1.24	
High	302	1,313	1.09	0.95–1.26	0.07	44	208	0.87	0.58–1.29	0.57
Rectum										
Unexposed	18,180	91,690	1.00			19,606	97,985	1.00		
Low	574	2,636	1.10	1.01–1.22		145	731	0.93	0.71–1.22	
Medium	918	4,155	1.11	1.02–1.21		128	638	0.83	0.60–1.15	
High	231	1,034	1.14	0.97–1.34	< 0.01	24	161	0.65	0.38–1.10	0.10
All colorectal										
Unexposed	44,566	224,562	1.00			47,779	238,979	1.00		
Low	1,339	6,243	1.06	1.00–1.14		337	1,690	0.99	0.84–1.18	
Medium	2,063	9,353	1.08	1.02–1.14		317	1,467	0.91	0.74–1.13	
High	533	2,347	1.11	1.00–1.23	< 0.01	68	369	0.77	0.56–1.06	0.17

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 meter (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, wood dust, smoking, alcohol, BMI, diet, and physical activity.^d "Other colon" included sigmoid colon, appendix, cecum, and splenic and hepatic flexures.

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

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 ^a	1945–1959 (P × L) ^b	1960–1974 (P × L) ^b	1975–1984 (P × L) ^b	1985–94 (P × L) ^b
Diesel engine exhaust^c				
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	0.08	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
Gasoline^b				
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 × 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 Cancer location	Diesel ^a					Gasoline ^b				
	Case, n	Control, n	OR ^c	95% CI	p-trend	Case, n	Control, n	OR ^c	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		783	3,751	1.04	0.92–1.18	
Medium	1,961	9,535	0.97	0.91–1.03		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	0.91
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		380	1,831	1.02	0.84–1.24	
Medium	888	4,268	1.03	0.94–1.13		363	1,696	1.02	0.83–1.25	
High	105	533	1.00	0.81–1.24	0.13	46	211	0.98	0.68–1.42	0.83
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		121	567	1.29	0.94–1.78	
Medium	281	1,451	0.87	0.74–1.03		119	618	0.97	0.69–1.36	
High	42	148	1.30	0.91–1.86	0.16	12	87	0.58	0.29–1.15	0.24
"Other colon" ^d										
Unexposed	74,161	371,640	1.00			79,871	399,621	1.00		
Low	5,039	24,278	1.00	0.97–1.04		1,114	5,692	0.95	0.85–1.06	
Medium	2,748	14,039	0.93	0.88–0.98		1,128	5,385	1.02	0.91–1.15	
High	350	1,533	1.11	0.99–1.25	0.22	185	792	1.11	0.92–1.35	0.54
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		2,398	11,841	1.01	0.93–1.08	
Medium	5,878	29,293	0.96	0.92–0.99		2,453	11,546	1.03	0.95–1.11	
High	718	3,284	1.07	0.98–1.16	0.61	361	1,636	1.00	0.88–1.14	0.76
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		1,631	8,258	0.96	0.88–1.05	
Medium	4,140	19,934	1.05	1.00–1.10		1,604	7,530	0.97	0.88–1.06	
High	490	2,271	1.09	0.99–1.21	< 0.01	207	1,106	0.84	0.71–0.99	0.13
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		4,029	20,099	0.99	0.93–1.05	
Medium	10,018	49,227	0.99	0.97–1.02		4,057	19,076	1.01	0.95–1.07	
High	1,208	5,555	1.08	1.01–1.15	0.02	568	2,742	0.94	0.84–1.04	0.55

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 $0.8\text{--}2.3$ 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 $1.9\text{--}4.6$ 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 ^a					Gasoline ^b				
	Case, n	Control, n	OR ^c	95% CI	p-trend	Case, n	Control, n	OR ^c	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		89	405	1.13	0.82–1.55	
Medium	186	889	1.04	0.83–1.29		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" ^d										
Unexposed	75,296	377,383	1.00			80,297	401,663	1.00		
Low	5,127	24,794	0.99	0.96–1.03		820	4,314	0.92	0.82–1.02	
Medium	1,804	8,980	0.98	0.91–1.05		1,023	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		1,771	8,845	0.98	0.91–1.05	
Medium	3,832	18,654	1.00	0.95–1.05		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		1,253	6,278	0.94	0.86–1.02	
Medium	2,639	12,738	1.04	0.98–1.11		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	1.03	1.01–1.05		3,024	15,123	0.96	0.91–1.02	
Medium	6,471	31,392	1.02	0.98–1.05		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 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 meter (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 D

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for occupational diesel and gasoline exposures and colorectal cancer.

Exposure agent Cancer location	Diesel ^a					Gasoline ^b				
	Case, n	Control, n	OR ^c	95% CI	p-trend	Case, n	Control, n	OR ^c	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	0.54	683	3,060	1.02	0.89–1.18	0.40
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	0.13	302	1,305	1.09	0.88–1.35	0.32
Descending colon										
Unexposed	7,981	39,673	1.00			8,593	42,927	1.00		
Low	274	1,593	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	0.18	78	507	0.72	0.49–1.04	0.19
"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	0.06	910	4,279	0.98	0.87–1.10	0.92
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	0.18	1,973	9,151	0.99	0.92–1.08	0.53
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	0.58
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	0.14	3,230	14,982	1.00	0.94–1.07	0.63

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/m^3); medium category 0.5–1.1 mg/m^3 ; and high category > 1.1 mg/m^3 . 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>.**References**

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