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TOPIC HIGHLIGHT

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Occupational exposures and colorectal cancers: A quantitative overview of epidemiological evidence

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Abstract

A traditional belief widespread across the biomedical community was that dietary habits and genetic predisposition were the basic factors causing colorectal cancer. In more recent times, however, a growing evidence has shown that other determinants can be very important in increasing (or reducing) incidence of this malignancy. The hypothesis that environmental and occupational risk factors are associated with colorectal cancer is gaining ground, and high risks of colorectal cancer have been reported among workers in some industrial branches. The aim of this study was to investigate the epidemiologic relationship between colorectal cancer and occupational exposures to several industrial activities, by means of a scientific literature review and meta-analysis. This work pointed out increased risks of colorectal cancer for labourers occupied in industries with a wide use of chemical compounds, such as leather (RR = 1.70, 95%CI: 1.24-2.34), basic metals (RR = 1.32, 95%CI: 1.07-1.65), plastic and rubber manufacturing (RR = 1.30, 95%CI: 0.98-1.71 and RR = 1.27, 95%CI: 0.92-1.76, respectively), besides workers in the sector of repair and installation of machinery exposed to asbestos (RR = 1.40, 95%CI: 1.07-1.84). Based on our results, the estimated crude excess risk fraction attributable to occupational exposure ranged from about 11% to about 15%. However, homogeneous pattern of association between colorectal cancer and industrial branches did not emerge from this review.

Key words: Colorectal cancer; Occupational exposures; Public health; Chemical compounds; Basic metals; Meta analysis

Core tip: The hypothesis that occupational risk factors are associated with colorectal cancer is gaining ground, and high risks of colorectal cancer have been reported among workers in some industrial branches. This study investigated the epidemiologic relationship between colorectal cancer and exposures in several industrial activities, by means of a literature review and meta-analysis. Results pointed out increased risks of colorectal cancer for labourers exposed to chemical compounds, besides workers in the sector of machinery installation exposed to asbestos. Based on our results, the estimated crude excess risk fraction attributable to occupational exposure ranged from about 11% to about 15%.

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INTRODUCTION

In the world about 1234000 new colorectal cancer diagnoses were estimated in 2008[1], less than 60% of them are from developed countries. From 15% to 25% of colorectal cancer deaths can be prevented by screening using fecal occult blood test[2]. Colon cancer most commonly occurs sporadically and is estimated to be inherited in 5%-15% of cases[3-5].

Thus far, several risk factors are evaluated to be related to sporadic forms of colorectal cancer. Diet is definitely the most important exogenous factor identified up to now in the etiology of colorectal cancer. It has been estimated that 70% of colorectal cancers could be prevented by nutritional intervention[3]. Physical activity has consistently been associated with decreased risk of colon cancer in studies that have concentrated on occupational activity, leisure activity and total activity[6]. Furthermore, cigarette smoking, alcohol consumption[6] and family history[7-9], showed to increase risks of this malignancy. Approximately 20% of the large bowel cancers in men appear to be attributable to smoking[10] and individuals consuming the most alcohol had 60% greater risk of colorectal cancer compared with non- or light drinkers[11]. Moreover, disparities in the incidence of colorectal cancer by economic status and other socio-ecological parameters have been described[12,13].

As above mentioned, a minor fraction of colorectal tumors shows inherited patterns, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). FAP is thought to be the effect of a deletion in tumor suppressor genes (adenomatous polyposis coli or *APC* genes), leading in most cases to a drastically altered protein[14]. HNPCC appeared to be linked to mutated *MLH1* and *MLH2* genes, that are involved in DNA repair processes[4]. However, these inherited DNA mutations frequently did not seem to represent a sufficient condition to develop a cancer because other mutations or carcinogenic events must occur to produce malignant phenotypes[15].

Evidence also showed that risk and protective factors[16-19] are differently associated with proximal and distal colon and with gender[20].

Although colorectal cancer, as other tumors[21,22] or chronic degenerative diseases[23], is not commonly considered to be occupational in etiology, elevated risks have been reported among workers in some industrial branches such as the textile industry[24,25], automobile industry[26-28], beverage industry[29] as well as in subjects exposed to asbestos[30-33], dioxin[34], wood dust[35], organic solvents[36-38] and metal-working fluids[39].

Iron and steel workers experienced higher relative risk (RR) for colorectal cancers[40-43]. These labourers could be exposed to mineral dusts and several chemical compounds. Some evidence are available on the possible relationship between exposure to oil mist and colorectal[44] and rectal cancer[45] and solvents and colon cancer[46]. A strongly increased mortality for colon cancer was observed among copper smelters[41] and steel foundry workers employed for at least 5 years in non-oven unit[40].

Dockyard workers experienced an higher mortality for colon cancer compared to general population[47,48]. This working category was likely exposed to many carcinogenic agents (*e.g.*, asbestos, polycyclic aromatic hydrocarbons, aromatic amines, welding smokes, *etc.*). Exposure to asbestos could account for a fraction of this risk, since several evidences are piling up on this issue[33,49-53].

Also fur production workers are exposed to a wide variety of chemical compounds, considered to be carcinogenic (formaldehyde, para-phenylenediamine or others dyes and pigments) in tanning, cleaning and dyeing fur, as well as to fur dust[54]. Tannery workers are also exposed to tanning and dyeing chemical agents, including chromium[55].

Sparse evidence of increased risk for colorectal cancers is available for workers in furniture industry[56], meat workers[57-59], workers exposed to hydrazine (contained in rocket fuels) in an aerospace industry plant[60], workers occupied in production of lens and metal spectacle frames (due to exposures to abrasives or cutting oil mists or both, possibly by ingestion)[44] and printing machine operators[61].

Rodu *et al*[62] observed an higher mortality for rectal cancer in workers of a petrochemical research facility, while plastic and rubber production industries showed only statistically borderline results. Workers occupied in these industrial branches were likely exposed to several chemical compounds in manufacturing of methilmetacrylate, polyurethane foam, resins and polypropylene[63-76]. Thus, these results strongly suggest a role for chemical compounds exposures, as a whole, in increasing the risk of colorectal cancers.

Results from manufacture of beverages relied on data on brewery workers[77,78] with a personal high beer intake. Thus, this observed most likely could not be referred to an occupational exposure in a narrow sense.

Despite this evidence entailing a role of occupational and environmental exposures in colorectal cancer onset, reduction in risk was observed in crop and animal production[79,80] and in some mining and quarrying activities. Agriculture, mining and quarrying are not sedentary occupations, therefore this physical activity could account for this lower risk. Moreover, farmers often have a lower prevalence of smoking compared to general population average[79] and when results are provided by cohort studies an "healthy worker" effect could be present. In spite of this, some sparse evidence of increased risk in workers exposed to pesticide or herbicide is provided by studies focused on specific compounds, such as Dicamba[81], Imazethapyr[82], Chlorpyrifos[83] or Toxaphene[83].

Thus, a detailed exploration of the relationship between occupational exposure and colorectal cancer could improve the rational base to plan measures for risk prevention and public health protection, not to say that the interruption of hazardous exposures seemed also to have a positive impact on prognosis of cancer patients[84].

To our knowledge, no comprehensive review and meta-analysis studies were carried out to date on this specific

topic.

The aim of this study was to investigate the epidemiologic relationship between colorectal cancer and occupational exposures in several industrial branches, by means of a scientific literature review and meta-analysis.

LITERATURE SEARCH

A literature search for all manuscripts published up to June 2013 was performed by the authors. Queried databases were PUBMED (June 2013-form 1960) and EMBASE (June 2013-form 1960).

The search strategy included terms (free text or MeSH terms) for occupational exposures, both stated as industrial branch (*e.g.*, textile industry) and single chemical compound (*e.g.*, asbestos), and colon cancer, rectal cancer or colorectal cancer. Moreover, the search on PUBMED database was carried out using specific search string for the study of putative occupational determinants of diseases[85].

Authors also checked the literature cited and listed in the selected studies' references and included any that met the criteria of this study. Manuscripts were reviewed and initially selected on the basis of title and abstract.

Prospective, case-control and meta-analysis studies were eligible for this study and article had to report at least one risk or mortality estimate to be included in quantitative analysis, [standardized mortality ratio; standardised incidence ratio; hazard ratio; RR; odds ratio (OR)] and a precision estimate (95%CI) relating exposure to an industrial branch to colon, rectal, or colorectal cancer or enough data to calculate them. Articles reporting only exposure to a single chemical compound not related to a specific job task or industrial branch were not included in the quantitative analysis. When available, fully adjusted estimates were included and analyzed. Any industrial branch exposure was taken into consideration when the same article provided more than one. Moreover, industrial branches were reclassified by the authors, using the description of productive activities within the papers, according to the United Nation International Standard Industrial Classification of all economic activities Rev. 4 (ISIC rev. 4).

Data from duplicated publications or by the same authors in the same cohorts were removed and only one estimate was retained in the analysis, using the highest adjustment and largest sample size.

Data from cohort and non-cohort studies were also separately analyzed. Pooled estimates were computed when the number of studies permitted. The within-study pooled estimate of subgroups was included in the analysis when a study provided only separate risks subgroups of workers (*e.g.*, according to sex or job tasks or cancer site).

Studies that showed disaggregated estimates for gender allowed to calculate also pooled RR for colorectal, colon and rectal cancer separately in male and female.

Presence of heterogeneity between studies was assessed using the I^2 statistic. Pooled risks were calculated applying a random-effect model to compensate for potential between-study heterogeneity[86].

Given that positive studies are more likely to be published than negative ones (*i.e.*, publication bias) and the interpretation of funnel plots could be subjective and misleading[87,88], the Duval and Tweedie[89] non parametric trim-and-fill procedure was used to address the publication bias issue. This statistical method assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot, if asymmetry is found, it adjusts for the potential effect of non-published (imputed) studies. All statistical analysis were carried out using STATA/SE 11 (Stata College Statin, TX, United States) software.

RESULTS OF CASE-CONTROL AND META-ANALYSIS STUDIES

A total amount of 83 papers, from 1976 to 2012, were selected and included in the review and meta-analysis. These articles provided for 141 different risk estimates, 60 (42.6%) for colorectal cancer, 57 (40.4%) for colon cancer and 24 (17.0%) for rectal cancer. Cohort study was the most frequent used study design (68, 81.9%), while the 12 case-control studies accounted for a lower percentage (14.5%). Crop and livestock farming (ISIC code 01) were the most represented occupational branches (12 studies, 15%), followed by exposures in chemical (ISIC code 20) and rubber and plastic (ISIC code 22) industries (11, 13.8%, and 6, 7.5%, studies, respectively). Also workers exposed in glass, ceramic or cement productions (ISIC code 23) were extensively studied (8 papers, 10.0%), as well as public administration personnel (6 studies, 7.5%). Details were shown in Table 1.

Table 2 shows results of meta-analytic studies for colorectal cancer. Overall estimate underlined a slight and statistically significant increased risk, also when trim and fill adjusted result was considered. The increase in risk ranged from 12% to 19%. Taking into account only results for cohort studies, estimates were similar to overall ones and no statistical adjustment for publication bias was required. The effect size of the adjusted pooled RR carried out on non-cohort studies was close to adjusted overall results, although not statistically significant.

Taking into account results for specific industrial branches, tannery and fur industry workers (ISIC code 15) showed to have a significant increased risk (RR = 1.70, 95%CI: 1.24-2.34), while results for iron and steel workers (ISIC code 24) showed increased adjusted RR of about 30% (RR = 1.32, 95%CI: 1.07-1.65).

Manufacture of furniture (ISIC code 31), manufacture of machinery (ISIC code 28), manufacture of electronic products (ISIC code 26) and food (ISIC code 10) industries also showed significant increased RR ranging from 1.50 to 2.14, although estimates were only based on one study each.

Results underlined a pooled RR of colorectal cancer of 1.29 for brewery workers (ISIC code 11), but it seems probably due to an high personal alcohol intake more

Table 1 Articles included in the literature review and meta-analysis, by cancer site, International Standard Industrial Classification code and exposure features

Authors	Cancer site	ISIC	Exposure	Article type	Estimate
Cantor *et al*[94]	Colorectal	01 - Crop and animal production	Aerial pesticide applicators	Cohort	RR
Greenburg *et al*[95]			Pesticides applicators	Cohort	RR
Lee *et al*[83]			Farming	Cohort	RR
Lo *et al*[90]			Pesticides	Case-Control	OR
Lynch *et al*[96]			Pesticides applicators	Cohort	RR
Wiklund and Dich[97]			Agriculture	Cohort	SIR
Mikoczy and Rylander[98]		03 - Fishing and aquaculture	Fishermen	Cohort	SIR
Finkelstein[99]		08 - Other mining and quarrying	Dust	Meta-analysis	SMR
Kusiak[100]			Miners	Cohort	SMR
Gubéran *et al*[57]		10 - Manufacture of food products	Butchers	Cohort	SMR
Fritschi *et al*[58]			Meat Workers	Cohort	SMR
McLean *et al*[59]			Meat Workers	Cohort	SMR
Carstensen *et al*[77]		11 - Manufacture of beverages	Brevery workers	Cohort	RR
Thygesen *et al*[78]			Brevery workers	Cohort	SIR
Goldberg and Thériault G[101]		13 - Manufacture of textile	Synthetic textiles	Cohort	SMR
Mastrangelo *et al*[24]			Textile	Meta-analysis	RR
Vobecky *et al*[102]			Carpet production	Cohort	SMR
Guay and Siemiatycki[54]		15 - Manufacture of leather and related products	Fur industry	Cohort	SMR
Montanaro *et al*[55]			Tannery workers	Cohort	SMR
Sweeney *et al*[103]			Fur industry	Cohort	SMR
Roscoe *et al*[104]		16 - Manufacture of wood and of products of wood and cork	Automotive wood modelists	Cohort	SMR
Swanson *et al*[26]			Automobile industry	Cohort	SMR
Rodu *et al*[62]		19 - Manufacture of coke and refined petroleum products	Petroleum	Cohort	SMR
Acquavella *et al*[70]		20 - Manufacture of chemicals and chemical products	Alachlor (herbicide)	Cohort	SIR
Berger and Manz[64]			Coke gas	Cohort	SMR
Fraser *et al*[65]			Fertilisers manufacturing	Cohort	SMR
Leet *et al*[66]			Alachlor (herbicide)	Cohort	SMR
Schnorr *et al*[67]			Polyurethane foam	Cohort	SMR
Tomenson *et al*[68]			Methil-methacrylate	Cohort	RR
Walker *et al*[69]			Methil-methacrylate	Cohort	SMR
Acquavella *et al*[63]		22 - Manufacture of rubber and plastics products	Polypropylene manufacturing	Cohort	SIR
Cowles *et al*[71]			Plastic and resins	Cohort	SMR
Kaleja *et al*[72]			Polypropylene production	Cohort	SIR
Lagast *et al*[73]			Polypropylene production	Meta-analysis	RR
Lewis *et al*[74]			Polypropylene production	Cohort	SIR
Sathiakumar *et al*[75]			Rubber industry	Cohort	SMR
McMichael *et al*[76]			Rubber industry	Cohort	SMR
Albin *et al*[106]		23 - Manufacture of other non-metallic mineral products	Asbestos cement workers	Cohort	RR
Jakobsson *et al*[107]			Cement workers	Cohort	SMR
Seidman *et al*[108]			Asbestos	Cohort	SMR
Smailyte *et al*[52]			Cement workers	Cohort	SMR
Wingren[109]			Glass Workers	Cohort	SIR
Zhang *et al*[110]			Ceramic factories	Cohort	SMR
Jackobsson *et al*[43]		24 - Manufacture of basic metals	Stainless steel workers	Cohort	SIR
Redmond *et al*[40]			Steel workers	Cohort	SMR
Xu *et al*[42]			Iron and steel workers	Cohort	SMR
Wang *et al*[44]		26 - Manufacture of computer, electronic and optical products	Optical industry	Case-Control	OR
Ritz *et al*[60]		28 - Manufacture of machinery and equipment n.e.c	Aerospace workers	Cohort	RR
Delzell *et al*[111]		29 - Manufacture of motor vehicles	Motor vehicle manufacturing	Cohort	SMR
Innos *et al*[56]		31 - Manufacture of furniture	Wood dust	Cohort	SIR
Puntoni *et al*[48]		33 - Repair and installation of machinery and equipment	Shipyard	Cohort	RR
Puntoni *et al*[47]			Shipyard	Cohort	SMR
Nasterlack *et al*[112]		37 - Sewerage	Wastewater treatment	Cohort	SIR
Reynolds and Austin[113]		72 - Scientific research and development	Physics laboratory workers	Cohort	SIR
Ahn *et al*[114]		84 - Public administration and defence	Emergency responders	Cohort	SIR
Demers *et al*[115]			Firefighters	Cohort	SIR
Strand *et al*[116]			Asbestos (Military - Navy)	Cohort	SIR
Yamane[117]			United States Air Force workers	Cohort	SIR
Czene *et al*[118]		96 - Other personal service activities	Hairdressers	Cohort	SIR
Brownson *et al*[61]	Colon	01 - Crop and animal production	Agriculture	Case-control	OR
Cantor *et al*[94]			Aerial pesticide applicators	Cohort	SMR

Fredriksson *et al*[119]			Farmers	Case-Control	OR
Freedman *et al*[120]			Farmer s	Case-Control	OR
Koutros *et al*[82]			Aromatic amine pesticide	Cohort	RR
Rusiecki *et al*[121]			Pesticides	Cohort	RR
Wiklund and Dich[97]			Agriculture	Cohort	SIR
Fredriksson *et al*[119]		02 - Forestry and logging	Gardeners	Case-Control	OR
Mikoczy and Rylander[98]		03 - Fishing and aquaculture	Fishermen	Cohort	SIR
Brownson *et al*[61]		05 - Mining of coal and lignite	Coal Mining	Case-Control	OR
Tomaskova *et al*[122]			Black coal miners	Cohort	SMR
Brownson *et al*[61]		07 - Mining of metal ores	Metal mining	Case-control	OR
Gómez *et al*[123]			Mercury miners	Cohort	SMR
Brownson *et al*[61]		08 - Other mining and quarrying	Metal mining	Case-control	OR
Fredriksson *et al*[119]			Miners	Case-Control	OR
Brownson *et al*[61]		10 - Manufacture of food products	Food industry	Case-control	OR
Johnson *et al*[124]			Food industry	Case-Control	OR
Carstensen *et al*[77]		11 - Manufacture of beverages	Brevery workers	Cohort	RR
Thygesen *et al*[78]			Brevery workers	Cohort	SIR
Fredriksson *et al*[119]		14 - Manufacture of wearing apparel	Dressmakers and needle workers	Case-Control	OR
Brownson *et al*[61]		15 - Manufacture of leather and related products	Leather production	Case-control	OR
Montanaro *et al*[55]			Tannery workers	Cohort	SMR
Fredriksson *et al*[119]		16 - Manufacture of wood and of products of wood and cork	Lumberers and sawmill workers	Case-Control	OR
Roscoe *et al*[104]			Automotive wood model	Cohort	SMR
Simpson *et al*[125]			Wood dust	Case-Control	OR
Swanson *et al*[26]			Automobile industry	Cohort	SMR
Fredriksson *et al*[119]		17 - Manufacture of paper and paper products	Paper and pulp workers	Case-Control	OR
Brownson *et al*[61]		18 - Printing and reproduction of recorded media	Printing	Case-control	OR
Brownson *et al*[61]		19 - Manufacture of coke and refined petroleum products	Petroleum	Case-control	OR
Brownson *et al*[61]		20 - Manufacture of chemicals and chemical products	Chemical workers	Case-control	OR
Collins *et al*[126]			Methil-methacrylate	Cohort	SMR
Fraser *et al*[65]			Fertilisers manufacturing	Cohort	SMR
Fredriksson *et al*[119]			Chemical workers	Case-Control	OR
Schnorr *et al*[67]			Polyurethane foam industry	Cohort	SMR
Walker *et al*[69]			Methil-methacrylate	Cohort	SMR
Harrington and Goldblatt[105]		21 - Manufacture of basic pharmaceutical products and pharmaceutical preparations	Pharmaceutical industry	Cohort	SMR
McMichael *et al*[76]		22 - Manufacture of rubber and plastics product	Rubber industry	Cohort	SMR
Straif *et al*[127]			Rubber industry	Cohort	SMR
Smailyte *et al*[52]		23 - Manufacture of other non-metallic mineral products	Cement workers	Cohort	SIR
Jakobsson *et al*[107]		24 - Manufacture of basic metals	Stainless steel workers	Cohort	SIR
Redmond *et al*[40]			Steel workers	Cohort	SMR
Tokudome and Kuratsune[41]			Metal refinery	Cohort	SMR
Brownson *et al*[61]		25 - Manufacture of fabricated metal products	Metal manufacturing	Case-control	OR
Fredriksson *et al*[119]			Metal workers	Case-Control	OR
Fredriksson *et al*[119]		31 - Manufacture of furniture	Cabinet makers	Case-Control	OR
Innos *et al*[56]			Wood dust	Cohort	SIR
Fredriksson *et al*[119]		33 - Repair and installation of machinery and equipment	Mechanics	Case-Control	OR
Puntoni *et al*[48]			Shipyard	Cohort	SMR
Puntoni *et al*[47]			Shipyard	Cohort	SMR
Fredriksson *et al*[119]		49 - Land transport and transport via pipelines	Rail and road workers	Case-Control	OR
Reynolds and Austin[113]		72 - Scientific research and development	Physics laboratory workers	Cohort	SIR
Fredriksson *et al*[119]		81 - Services to buildings and landscape activities	Cleaners	Case-Control	OR
Baris *et al*[128]		84 - Public administration and defence	Firefighters	Cohort	SMR
Brownson *et al*[61]			National security	Case-control	OR
Youakim[129]			Firefighters	Cohort	RR
Fredriksson *et al*[119]		86 - Human health activities	Nurses	Case-Control	OR
Fredriksson *et al*[119]		96 - Other personal service activities	Dry Cleaners and hairdresser	Case-Control	OR
Cantor *et al*[94]	Rectum	01 - Crop and animal production	Aerial pesticide applicators	Cohort	RR
Settimi *et al*[130]			Agriculture	Case-Control	OR
Wiklund and Dich[97]			Agriculture	Cohort	SIR
Mikoczy and Rylander[98]		03 - Fishing and aquaculture	Fishermen	Cohort	SIR
Carstensen *et al*[77]		11 - Manufacture of beverages	Brevery workers	Cohort	RR
Thygesen *et al*[78]			Brevery workers	Cohort	SIR
Montanaro *et al*[55]		15 - Manufacture of leather and related products	Tannery workers	Cohort	SMR
Roscoe *et al*[104]		16 - Manufacture of wood and of products of wood and cork	Automotive wood model	Cohort	SMR
Rodu *et al*[62]		19 - Manufacture of coke and refined petroleum products	Petroleum industry	Cohort	SMR

Fraser *et al*[65]	20 - Manufacture of chemicals and chemical products	Fertilisers manufacturing	Cohort	SMR
Manuwald *et al*[131]		Dioxine compounds	Cohort	SMR
Schnorr *et al*[67]		Polyurethane foam industry	Cohort	SMR
Walker *et al*[69]		Methil-methacrylate	Cohort	SMR
McMichael *et al*[76]	22 - Manufacture of rubber and plastics product	Rubber industry	Cohort	SMR
Smailyte *et al*[52]	23 - Manufacture of other non-metallic mineral products	Cement workers	Cohort	SIR
Jakobsson *et al*[107]	24 - Manufacture of basic metals	Stainless steel workers	Cohort	SIR
Langård *et al*[132]		Ferrochromium/silicon	Cohort	SMR
Redmond *et al*[40]		Steel workers	Cohort	SMR
Malloy *et al*[133]	29 - Manufacture of motor vehicles	Metalworking fluids	Cohort	RR
Innos *et al*[56]	31 - Manufacture of furniture	Wood dust	Cohort	SIR
Puntoni *et al*[48]	33 - Repair and installation of machinery and equipment	Shipyard	Cohort	SMR
Puntoni *et al*[47]		Shipyard	Cohort	SMR
Reynolds and Austin[113]	72 - Scientific research and development	Physics laboratory workers	Cohort	SIR

SMR: Standardized mortality ratio; SIR: Standardized incidence ratio; ISIC: International Standard Industrial Classification.

than an occupational exposure. Moreover, pooled RR for colorectal cancer was increased and statistically significant for workers occupied in repair and installation of machinery (ISIC code 33, RR = 1.40, 95%CI: 1.07-1.84): this interesting results was entirely driven from two cohort studies on Italian shipyard labourers, exposed to asbestos.

Results showed also an increased risk (RR = 1.34, 95%CI: 1.12-1.61) in textile industry (ISIC code 13), mainly based on estimates of a meta-analytic study[24], while no increase in risk was observed in the adjusted cohort studies estimate. Thus, the overall result was not statistically significant, despite a two-fold increased RR.

Results of borderline significance were observed for chemical (ISIC code 20) and rubber and plastic (ISIC code 22) industries, while some mining and quarrying (ISIC code 08) and agricultural (ISIC code 01) occupations showed significant risk deficits. Moreover, the latter productive branch showed a statistically increase risk for colorectal cancer in only one case-control study on pesticide applicators[90].

Table 3 shows results of meta-analytic studies for colon cancer. Overall RR showed an increase in risk (RR = 1.13, 95%CI: 1.05-1.23) similar to adjusted colorectal cancer one.

An increased and statistically significant risk for colon cancer was observed in beverage production industry (brewery workers), steel and metal workers, and in repair and installation of machinery labourers. These results are consistent with those of colorectal cancer (Table 2).

Moreover, this analysis showed borderline results for chemical and rubber and plastic industries, also consistent with those reported in Table 2.

In addition, results showed a RR = 1.80 (95%CI: 1.20-2.70), statistically significant, for colon cancer in workers exposed in printing industry (ISIC code 18), although only based on a single case-control study.

Excluding manufacture of wood and cork industries (ISIC code 16) and metal mining (ISIC code 07), no significant risk deficits for colon cancer were observed. These decreased risks were observed only in non-cohort and cohort studies, respectively.

Table 4 shows results of meta-analytic studies for rectal cancer. Increased RR was observed in overall analysis, although the 95%CI includes the 1 value. This result is consistent with those of colon and colorectal cancer analyses.

Increased and significant risk estimates for rectal cancer were observed only in beverage industry, related to brewery workers, and in the manufacture of coke and refined petroleum product (ISIC code 19), though only based on a single cohort study each.

Risk in male did not significantly differ from risk in female, except for colorectal cancer in which the analysis showed an increased pooled estimate of borderline significance in men (Table 5).

OCCUPATIONAL EXPOSURES

Occupational exposures, in a broad sense, appear to be a risk factor for colorectal, colon and rectal cancers. Probably, a fraction of the total amount of cases of these malignancies could be explained considering occupational exposures as cofactors in the process leading to cancer.

Slight but significant increased RR were observed for colorectal and colon cancers, though the pooled estimate for rectal cancer did not reach the conventional statistical significance. Despite this issue, results were consistent each other and showed a similar effect size ranging from 12% to 15%. Consequently, a crude excess fraction of risk, attributable to occupational exposure considered as a whole, could be calculated, and its results range from 10.7% to 13.0%.

No significant difference between male and female was observed in analyses carried out by gender, although some evidences suggested a different association in the two sexes[20].

Most of the papers included in this review reported a cohort design and, limiting the analysis to this sort of studies, the effect size appeared to be stronger than the overall results, except for rectal cancer. The large amount of cohort studies could be an advantage to investigate an etiologic relationship between risk factors and cancer, thus these results firmly stressed a role of exposures in workplace in increasing the risk of colon and colorectal cancers.

Table 2 Pooled estimates for colorectal cancer, by industrial branch and study design

ISIC	Industrial branch	Cohort studies (95%CI)		Other study design[2] (95%CI)		All (95%CI)	
		Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]
1	Crop and animal production	0.86 (0.81-0.91)	-	2.6 (1.12-6.02)	-	0.86 (0.76-0.97)	-
3	Fishing and aquaculture[1]	0.98 (0.70-1.10)	-	-	-	0.98 (0.87-1.10)	-
8	Other mining and quarrying	0.8 (0.70-0.92)	-	0.84 (0.77-0.92)	-	0.83 (0.77-0.89)	-
10	Manufacture of food products	1.21 (0.76-1.92)	-	-	-	1.21 (0.76-1.92)	-
11	Manufacture of beverages	1.29 (1.19-1.40)	-	-	-	1.29 (1.19-1.40)	-
13	Manufacture of textile	2.82 (0.19-41.78)	0.73 (0.07-7.96)	1.34 (1.12-1.61)	-	2 (0.83-4.86)	-
15	Manufacture of leather and related products	1.7 (1.24-2.34)	-	-	-	1.7 (1.24-2.34)	-
16	Manufacture of wood and of products of wood and cork	1.65 (0.60-4.58)	-	-	-	1.65 (0.60-4.58)	-
19	Manufacture of coke and refined petroleum products[1]	1.21 (0.69-2.12)	-	-	-	1.21 (0.69-2.12)	-
20	Manufacture of chemicals and chemical products	1.27 (0.92-1.76)	-	-	-	1.27 (0.92-1.76)	-
22	Manufacture of rubber and plastics products	1.3 (0.94-1.79)	-	1.37 (0.86-2.18)	-	1.3 (0.98-1.71)	-
23	Manufacture of other non-metallic mineral products	1.25 (0.85-1.85)	-	-	-	1.25 (0.85-1.85)	-
24	Manufacture of basic metals	1.32 (1.07-1.65)	-	-	-	1.32 (1.07-1.65)	-
26	Manufacture of computer, electronic and optical products[1]	-	-	2.14 (1.02-4.50)	-	2.14 (1.02-4.50)	-
28	Manufacture of machinery and equipment nec[1]	2.2 (1.03-4.72)	-	-	-	2.2 (1.03-4.72)	-
29	Manufacture of motor vehicles[1]	1.27 (0.89-1.82)	-	-	-	1.27 (0.89-1.82)	-
31	Manufacture of furniture[1]	1.5 (1.21-1.87)	-	-	-	1.5 (1.21-1.87)	-
33	Repair and installation of machinery and equipment	1.4 (1.07-1.84)	-	-	-	1.4 (1.07-1.84)	-
37	Sewerage[1]	1.14 (0.47-2.77)	-	-	-	1.14 (0.47-2.77)	-
72	Scientific research and development[1]	1.18 (0.77-1.82)	-	-	-	1.18 (0.77-1.82)	-
84	Public administration and defence	0.97 (0.62-1.52)	0.87 (0.58-1.30)	-	-	0.97 (0.62-1.52)	0.87 (0.58-1.30)
96	Other personal service activities[1]	1.09 (0.98-1.21)	-	-	-	1.09 (0.98-1.21)	-
-	All industrial branches combined	1.18 (1.08-1.30)	1.18 (1.08-1.30)	1.36 (0.94-1.97)	1.13 (0.81-1.57)	1.19 (1.09-1.33)	1.12 (1.03-1.23)
	Heterogeneity (I^2)	84.1%		87.9%		84.3%	

[1]Only one study; [2]Case-control studies and meta-analyses; [3]Duval and Tweedie trim and fill method. RR: Relative risk; ISIC: International Standard Industrial Classification.

Moreover, results from this review could promote public health measures: workers exposed in industrial branches with increased risk of colorectal cancers could be effectively addressed to screening and counselling programs, in order to prevent the onset of the neoplasia or to anticipate the diagnosis, with a positive effect on the chance of cure and survival.

Adjustment by possible bias

The effect size of occupational exposures, considered as a whole, on colorectal cancers is probably lower than tobacco smoke[10] and alcohol consumption[11], though in some industrial branches such as leather, beverages, manufacture of metals, repair and installation of machinery, rubber and plastic industries, the risk could rise to levels comparable to these major risk factors.

Furthermore, not all studies provided estimates fully adjusted for well known risk or protective factors, especially those not recent, and thus a residual confounding can not be excluded.

The choice of excluding studies devoted to analyse exposure to single substances or chemical compound

Table 3 Pooled estimates for colon cancer, by industrial branch and study design

ISIC	Industrial branch	Cohort studies (95%CI)		Other study design[2] (95%CI)		All (95%CI)	
		Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]
1	Crop and animal production	1 (0.66-1.52)	-	0.98 (0.85-1.13)	-	0.96 (0.84-1.10)	-
2	Forestry and logging[1]	-	-	1.48 (0.28-7.92)	-	1.48 (0.28-7.92)	-
3	Fishing and aquaculture[1]	0.93 (0.79-1.09)	-	-	-	0.93 (0.79-1.09)	-
5	Mining of coal and lignite	0.9 (0.68-1.20)	-	1.1 (0.42-2.91)	-	0.92 (0.69-1.21)	0.9 (0.69-1.17)
7	Mining of metals	0.19 (0.05-0.71)	-	1.5 (0.65-3.64)	-	0.57 (0.08-4.30)	-
8	Other mining and quarrying[1]	-	-	0.91 (0.45-1.83)	-	0.91 (0.45-1.83)	-
10	Manufacture of food products	1.06 (0.44-2.57)	-	1.32 (0.93-1.87)	-	1.28 (0.98-1.70)	-
11	Manufacture of beverages	1.25 (1.12-1.40)	-	-	-	1.25 (1.12-1.40)	-
14	Manufacture of wearing apparel[1]	-	-	0.66 (0.20-2.20)	-	0.66 (0.20-2.20)	-
15	Manufacture of leather and related products	1.66 (0.85-3.24)	-	1.3 (0.61-2.76)	-	1.49 (0.90-2.46)	1.49 (0.90-2.46)
16	Manufacture of wood and of products of wood and cork	2.19 (0.56-8.52)	1.2 (0.35-4.16)	0.53 (0.37-0.78)	-	0.96 (0.46-1.97)	0.96 (0.46-1.97)
17	Manufacture of paper and paper products[1]	-	-	0.66 (0.17-2.61)	-	0.66 (0.17-2.61)	-
18	Printing and reproduction of recorded media[1]	-	-	1.8 (1.20-2.70)	-	1.8 (1.20-2.70)	-
19	Manufacture of coke and refined petroleum products[1]	-	-	1.3 (0.51-3.29)	-	1.3 (0.51-3.29)	-
20	Manufacture of chemicals and chemical products	1.2 (0.99-1.45)	-	1.07 (0.68-1.71)	-	1.18 (0.99-1.40)	-
21	Manufacture of basic pharmaceutical products and pharmaceutical preparations[1]	1.22 (0.58-2.24)	-	-	-	1.22 (0.58-2.24)	-
22	Manufacture of rubber and plastics products	1.31 (0.88-1.95)	-	1.16 (0.95-1.41)	-	1.19 (1.00-1.42)	1.16 (0.99-1.36)
23	Manufacture of other non-metallic mineral products[1]	0.77 (0.29-2.06)	-	-	-	0.77 (0.29-2.06)	-
24	Manufacture of basic metals	1.75 (1.16-2.65)	1.61 (1.09-2.38)	-	-	1.75 (1.16-2.65)	1.61 (1.09-2.38)
25	Manufacture of fabricated metal products	-	-	0.83 (0.55-1.24)	-	0.83 (0.55-1.24)	-
31	Manufacture of furniture	1.65 (1.24-2.20)	-	0.8 (0.27-2.36)	-	1.4 (0.77-2.54)	-
33	Repair and installation of machinery and equipment	1.91 (1.39-2.62)	1.81 (1.39-2.37)	0.99 (0.43-2.29)	-	1.75 (1.27-2.41)	-
49	Land transport[1]	-	-	2.39 (0.83-6.92)	-	2.39 (0.83-6.92)	-
72	Scientific research and development[1]	1.23 (0.72-2.11)	-	-	-	1.23 (0.72-2.11)	-
84	Public administration and defence	1.32 (0.85-2.05)	-	0.9 (0.59-1.38)	-	1.19 (0.85-1.67)	-
86	Human health activities[1]	-	-	1 (0.49-2.05)	-	1 (0.49-2.05)	-
96	Other personal service activities[1]	-	-	1.37 (0.51-3.72)	-	1.37 (0.51-3.72)	-
-	All industrial branches combined	1.23 (1.09-1.39)	1.23 (1.09-1.39)	1.03 (0.92-1.15)	1.03 (0.92-1.15)	1.13 (1.05-1.22)	1.13 (1.05-1.22)
	Heterogeneity (I^2)	70.5%		42.3%		61.4%	

[1]Only one study; [2]Case-control studies and meta-analyses; [3]Duval and Tweedie trim and fill method. RR: Relative risk; ISIC: International Standard Industrial Classification.

if not specifically related to a definite industrial branch, may be questionable, but our aim was to show quantitative estimates in several productive divisions to provide a general overview on occupational exposures at a productive branch level.

In addition, an evident between-studies heterogene-

Table 4 Pooled estimates for rectal cancer, by industrial branch and study design

ISIC	Industrial branch	Cohort studies (95%CI)		Other study design[2] (95%CI)		All (95%CI)	
		Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]	Crude RR	Adjusted RR[3]
1	Crop and animal production	0.86 (0.74-1.00)	-	1.5 (0.55-2.45)	-	0.97 (0.67-1.41)	-
3	Fishing and aquaculture[1]	1.05 (0.86-1.25)	-	-	-	1.05 (0.87-1.26)	-
10	Manufacture of food products[1]	0.75 (0.33-1.70)	-	-	-	0.75 (0.33-1.70)	-
11	Manufacture of beverages	1.45 (1.13-1.85)		-	-	1.45 (1.13-1.85)	-
15	Manufacture of leather and related products	2.06 (0.36-3.76)	-	-	-	2.06 (0.91-4.65)	-
16	Manufacture of wood and of products of wood and cork[1]	0.4 (0.06-2.53)	-		-	0.4 (0.06-2.53)	-
19	Manufacture of coke and refined petroleum products[1]	2.49 (1.02-6.07)	-	-	-	2.49 (1.02-6.07)	-
20	Manufacture of chemicals and chemical products	1.22 (0.62-2.41)	-	-	-	1.22 (0.62-2.41)	-
22	Manufacture of rubber and plastics products	0.82 (0.55-1.22)	-	-	-	0.82 (0.55-1.22)	-
23	Manufacture of other non-metallic mineral products[1]	1.25 (0.61-2.55)	-	-	-	1.25 (0.61-2.55)	-
24	Manufacture of basic metals	1.25 (0.77-2.04)	-		-	1.25 (0.77-2.04)	-
29	Manufacture of motor vehicles	1.7 (0.53-5.43)	-	-	-	1.7 (0.53-5.43)	-
31	Manufacture of furniture	1.32 (0.93-1.88)	-	-	-	1.32 (0.93-1.88)	-
33	Repair and installation of machinery and equipment	0.76 (0.42-1.38)	-	-	-	0.76 (0.42-1.38)	-
72	Scientific research and development[1]	1.1 (0.26-1.95)	-	-	-	1.1 (0.52-2.34)	-
-	All industrial branches combined	1.15 (0.99-1.34)	1.15 (0.99-1.34)	1.5 (0.55-2.45)	1.5 (0.55-2.45)	1.15 (0.99-1.34)	1.15 (0.99-1.34)
	Heterogeneity (I^2)	53.8%		-		53.8%	

[1]Only one study; [2]Case-control studies and meta-analyses; [3]Duval and Tweedie trim and fill method. RR: Relative risk; ISIC: International Standard Industrial Classification.

Table 5 Colorectal cancer risk in occupational exposures, by gender

Site	Gender	Crude RR	95%CI	Adjusted RR[1]	95%CI
Colorectal	M	1.21	1.09-1.35	1.10	1.00-1.22
	F	0.94	0.85-1.04	0.93	0.84-1.04
Colon	M	1.07	0.97-1.18	-	-
	F	0.95	0.76-1.20	-	-
Rectum	M	1.11	0.93-1.32	-	-
	F	1.53	0.47-4.93	-	-

[1]Duval and Tweedie trim and fill method. M: Male; F: Female; RR: Relative risk.

ity was observed, while the publication bias seemed to be weak. The latter issue was controlled adjusting the pooled estimates with the Duval and Tweedie[89] non parametric trim-and-fill procedure. The former was not surprisingly observed in a study collecting several different results from papers diverging in terms of study design, exposures assessment, adjustment for potential confounders, geographical area, thus this may have affected the precision of the pooled estimates.

Interaction between working activity and genetic susceptibility

The most relevant findings emerged from this review indicate that, though there is no homogeneous pattern of association between colorectal cancer and working activities (in a broad sense), risk evaluation for this disease deserves much attention in occupational setting. The exposure to some industrial branches such as that for processing animal furs and leather, or others where toxic chemicals (*e.g.*, asbestos) are used, significantly increases the risk of colorectal cancer. As reported above, also agricultural activities should enter this domain even if a reduction in risk of colorectal cancer was observed in this work maybe due to a "healthy worker" effect or to some personal habits. Evidence on colorectal malignancies of farmers is provided by investigations strictly focused on the exposure to specific agro-chemicals.

Traditionally epidemiological and experimental data on colorectal cancer supported associations with diet and familial genetic factors[7,8]. Interestingly, a genetic susceptibility was thought to be involved not only in rare familial colon cancers but in more common sporadic forms

as well[9]. Thus, a common belief in scientific community was that both dietary habits and genetic predisposition were the basic factors causing colorectal carcinogenesis[9]. In more recent times, however, a growing evidence has shown the relevant carcinogenic role played by general lifestyles (cigarette smoking, alcohol consumption, physical activity, diet, *etc.*) and much more important here - exposure to environmental chemicals, so the attention on simple mechanisms of genetic-environmental determination of disease has been strongly resized.

On the other hand, studies based on genome-wide association approaches suggested that familial predisposition to develop malignancies does not depend on mendelian patterns but to complex interactions between genomic, epigenomic and environmental conditions[91]. In many cases, misconceptions on these inherited diseases depend on the erroneous assumption that heritability means "genetic determination". Estimates on heritability of multifactorial diseases do not provide reliable information on the proportion of cases really due to simple genetic factors, furthermore these estimates cannot be used to discover how many cases are due to environmental effects[92].

Other studies on detrimental effects of the environment emphasize the essential role played by the environmental exposures on the environment residing within the organism. These studies revealed that both early and advanced stages of carcinogenesis can be promoted by means of chemical (or other) influences on the stromal micro-environment[84,93]. The nature of these dynamics is far from being clear and the relationship between micro- and macro-environment in tumor initiation and progression is only now starting to be appreciated. This picture provides strong reasons to act on environmental carcinogens by planning effective efforts to control incidence rates of colorectal and other tumors.

Despite advancements in developing tools to strengthen surveillance on occupational cancer, in Western countries still many workers are exposed to carcinogens in the workplace: a serious challenge not only for workers but also for entrepreneurs, trade unions, decision makers and health institutions. Managing the exposure to chemicals causing malignancies and other degenerative pathologies is not a mere biomedical affair but is a prerequisite for reducing the economic burden of work-related morbidity/mortality and avoiding social conflicts. In short, it is a matter of social cohesion and equity. This entails new political and economic paradigms in planning occupational safety and, especially, in addressing health expenditures. Education and public communication programs on primary prevention in the workplace will be essential. After all, innovative actions to protect human health often require solely good science, culture and common sense. Improving our environment and lifestyles is much more feasible and infinitely less expensive than improving our genetics.

To our knowledge, this article provides the largest review of papers regarding the risk of colorectal cancers in workers of several industrial branches. Our results pointed out increased risks for labourers occupied in industries with a wide use of chemical compounds, such as leather, basic metals, plastic and rubber manufacturing, besides workers in the sector of repair and installation of machinery exposed to asbestos.

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