Occupational Risk Factors for Prostate Cancer: A Meta-analysis

REVIEW

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Prostate cancer is the second most common cancer in men worldwide. There are many occupational factors that have been suggested to cause prostate cancer. Our aim was to evaluate the evidence for causality by a literature review of occupational factors. We searched literature in Medline and SCOPUS from 1966 to June 30, 2015 to identify occupational risk factors for prostate cancer. The following risk factors were selected: farmers/agricultural workers, pesticides – whole group, and separately organophosphate and organochlorine pesticides, carbamates and triazines, cadmium, chromium, cutting fluids, acrylonitrile, rubber manufacturing, whole body vibration, shift work, flight personnel, ionizing radiation, and occupational physical activity. For each factor a literature search was performed and presented as meta-analysis of relative risk and heterogeneity (Q and I^2 index). A total of 168 original studies met the inclusion criteria with 90,688 prostate cancer cases. Significantly increased risks were observed for the following occupational exposures: pesticides (metaRR = 1.15, 95% confidence interval [CI] = 1.01-1.32; I^2 = 84%), and specifically group of organochlorine pesticides (meta relative risk [metaRR] = 1.08, 95% CI = 1.03-1.14; I^2 = 0%), chromium (metaRR = 1.19, 95% CI = 1.07-1.34; I^2 = 31%), shift work (metaRR = 1.25, 95% CI = 1.05-1.49; I^2 = 78%) and pilots (metaRR = 1.41, 95% CI = 1.02-1.94; I^2 = 63%) and occupational physical activity in cohort studies (metaRR = 0.87, 95% CI = 0.81-0.94; I^2 = 0%). The literature review supports a causal association for a few of the previously suggested factors.
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Key Words: Epidemiologic studies, Work-place factors, Exposure assessment, Causal association, Literature search

INTRODUCTION

Worldwide, prostate cancer is the second most common cancer with estimated age-standardized incidence rate 31.1, and the fifth leading cause of death from cancers in men (age-standardized mortality rate 7.8) [1]. The highest prostate cancer incidence has been recorded in Australia, New Zealand and North America, and in Western and North Europe, while the lowest incidence is noted in Asia. Partly, this difference in incidence can be explained by routine prostate specific antigen (PSA) testing among older age in more developed countries. There is relatively less variation in death rates, which are higher in less developed than in more developed countries. In general, mortality rates are high in Black population and increase with age [2]. In Europe, the highest

incidence rates were estimated in Northern and Western countries, such as Norway (193.2), France (187.5), and Sweden (175.2) [3].

Known risk factors for prostate cancer include older age, heredity and race/ethnicity. Most men diagnosed with prostate cancer were older than 65 years [2]. Studies among brothers, fathers and twins indicated that family history of prostate cancer can increase the risk of developing prostate cancer substantially [4-6]. Recent genetic studies revealed that previously observed highest incidence rates of prostate cancer among African American can be partly explained by biological differences based on tumor markers [2,7,8].

Many various exposures at the work places and work environment have been studied thoroughly such as different

chemical, physical and psychological and ergonomic risk factors; however, the results are not conclusive. Therefore, the aim of this literature review is to examine the association between work-related exposures and prostate cancer and to assess the evidence for the possible relationship.

MATERIALS AND METHODS

To identify possible occupational risk factors for prostate cancer we first searched for review and meta-analysis articles published from 1966 to June 30, 2015 in Medline and SCOPUS using the following search terms "occupational risk factors and prostate cancer". A total of 182 articles were found. We excluded articles related to methological problems (n = 9), environmental and ecologic factors (n = 15), biological mechanism/genetic/molecular factors (n = 17), clinical studies (therapy and diagnosis of prostate cancer) (n = 13), reviews published in other language than English (n = 20), reviews not mentioning results for prostate cancer (n = 16) and duplicates from Medline and SCOPUS (n = 13) leaving 72 relevant reviews (Supplementary Fig. SF1). In that way we identified numerous potential occupational risk factors for prostate cancers such as: pesticides, farmers and agricultural workers, cadmium, chromium, polycyclic aromatic hydrocarbons (PAH), cutting fluids, diesel fumes, metal fabrication, metal dust, rubber, rubber industry, ionizing radiation, electromagnetic fields, shift work, night work, flight personnel, dyeing/leather processing, vehicle batteries, whole body vibration (WBV), occupational physical activity, circadian disruption and melatonin secretion, acrylonitrile, sunlight and vitamin D deficiency, dioxins and Agent Orange, zinc, lead, stress and job strains, methyl bromide, perchlorethylene, benzo(a)pyrene, methylene chloride, firefighters, sewage workers and petroleum and gasoline, and perfluorooctanoate and perfluorooctanesulfonate [9-80].

We defined the inclusion criteria for each factor as occupational exposure associated with prostate cancer reported in at least three reviews and/or meta-analysis based on epidemiologic studies. Thus, the following risk factors were selected: farmers/agricultural workers, pesticides, and separately organophosphate and organochlorine pesticides, carbamates and triazines, cadmium, chromium, cutting fluids, acrylonitrile, rubber manufacturing, WBV, shift work, flight personnel, ionizing radiation, and occupational physical activity.

The next step was to search for original articles for each selected occupational factor. For that purpose, the following search terms were used: prostate cancer, prostatic cancer, farmer, farming, agricultural, agriculture, pesticides, cadmium, chromium,

rubber, tire, shiftwork, shift work, nightwork, night work, polycyclic aromatic hydrocarbons, cutting oils, mineral oils, ionizing radiation, flight personnel, pilots, physical activity, and acrylonitrile. For each occupational factor the abstracts were reviewed to assess the relevance of the article. Additional relevant articles referred in each article were also considered and included if appropriate. Results of these searches are presented for each selected occupational exposure in flowcharts (Supplementary Fig. SF2, SF4, SF6, SF8, SF10, SF12, SF14, SF16, SF18, SF20, SF22, SF24, SF26, SF28, SF30, SF32). Selected articles were reviewed in the full text format.

Inclusion criteria for articles were as follows: Articles written in English; Clear objective of the study investigating the relationship between specific workplace exposures and prostate cancer; Longitudinal study design (case/control and cohort); Clear definition of study population; The study with the longest follow-up period if more than one article was published for the same cohort; Appropriate way of exposure assessment (measurements, job exposure matrix (JEM), expert assessment, self-reported); The highest exposure level was used if risk estimates were reported for different exposure categories so that risk in the group with the highest exposure level was compared with the lowest exposure level; The number of exposed cases equal to or greater than five; Diagnosis of prostate cancer based on biopsy and pathohistological results or solely on death certificates, but not on self-report; Participants in cohort studies free of prostate cancer at the start of study; Controls in case-control studies free of any cancers; Results reported as the relative risk estimates (standardized mortality ratio [SMR], standardized incidence ratio [SIR], incidence rate ratio [IRR], or hazard ratio [HR] for cohort studies and odds ratio [OR] for case-control studies) and 95% confidence intervals (CIs). In some cases, the CIs were not reported, but were calculated based on reported data with the Mid-P exact test [81]; Incidence rates were presented if article reported both mortality and incidence results; Minimum requirement for adjustment for confounding included age. If the publication reported both age-adjusted risk and risks adjusted for multiple variables, the age-adjusted risk was used. If only multivariable adjusted risk had been reported it was used.

Studies of polycyclic aromatic hydrocarbons and prostate cancer were considered and analyzed, but due to the low quality of exposure data were not presented.

For the meta-analysis calculations, the program Stata ver. 11 was used and random effect model. Heterogeneity was expressed as Q statistics and I^2 index. Interpretation of I^2 was as follows: very consistent (0%-24%); low heterogeneity (25%-49%), medium

heterogeneity (50%-74%), and high heterogeneity (75%-100%) [82].

RESULTS

A summary of results obtained for selected occupational risk factors related to prostate cancer are presented on Table 1. Significant results and tables are presented here while non-significant tables (Supplementary Table ST1-10) and all figures (Supplementary Figure SF1-33) are shown in the Supplement.

Among the huge number of "pesticides" in use, in this meta-analysis we decided to include the non-specified pesticide use, as well as exposure to four most frequently used and reported pesticides groups: organochlorine and organophosphate pesticides, carbamates, and triazines. The literature search for the whole group of pesticides (Table 2, Supplementary Fig. SF2) shows that a total of 18 studies were included in meta-analysis, 14 cohort studies and 5 case control studies [83-100]. Significantly increased risk for prostate cancer was found, however, the heterogeneity was large (Table 1, Supplementary Fig. SF3). Separate analysis for cohort and case control studies reported non-significantly increased risks. Heterogeneity was large for cohort studies and low for case-control studies.

On Table 3 and Supplementary Figure SF4, 17 selected studies of "organochlorine" pesticides are presented, 10 cohort and 7 case-control studies [92,101-116]. There is a significantly increased risk for prostate cancer among workers exposed to organochlorine pesticides, study results were homogenous (Table 1, Supplementary Fig. SF5), as was also observed for cohort studies.

Table 1. Meta-analysis summary of the examined risk factors for prostate cancer

Occupational risk factor	No. of studies	No. of cases	MetaRR	95% CI	Q	P-value	I^2 (%)
Pesticides	18	3,474	1.15	1.01-1.32	110	<0.001	84
Coh	13	3,067	1.13	0.97-1.32	96	<0.001	86
CC	5	407	1.26	0.86-1.83	15	0.006	33
Organochlorines	17	2,730	1.08	1.03-1.14	43	0.49	0
Coh	10	1,003	1.12	1.05-1.19	13	0.6	0
CC	7	1,727	0.99	0.89-1.10	26	0.53	0
Chromium	8	964	1.19	1.07-1.34	10	0.18	31
Shiftwork	6	1,355	1.25	1.05-1.49	36	<0.000	78
Coh	4	861	1.14	0.98-1.32	11	0.052	55
CC	2	494	1.50	0.91-2.48	21	<0.000	90
Flight personnel	3	180	1.26	0.90-1.76	8.9	0.031	66
Pilots	3	163	1.41	1.02-1.94	5.4	0.07	63
Occupational physical activity	18	3,417	0.90	0.80-1.02	55	<0.000	69
Coh	10	1,684	0.87	0.80-0.94	8.5	0.48	0
CC	8	1,733	0.91	0.68-1.20	44	<0.000	84
Whole body vibration	10	6,224	1.03	0.98-1.09	66	<0.000	77
Coh	5	4,768	1.01	0.98-1.05	19	0.004	69
CC	5	1,456	1.31	1.00-1.72	47	<0.000	83
Farming, farmers	26	66,749	0.99	0.95-1.02	118	<0.001	79
Coh	15	65,448	0.97	0.94-1.00	90	<0.001	58
CC	11	1,301	1.04	0.90-1.21	21	0.021	33
Organophosphates	7	1,350	0.98	0.87-1.11	8	0.44	0
Coh	4	901	0.97	0.82-1.14	1.1	0.77	0
CC	3	449	0.99	0.78-1.25	7	0.15	41
Carbamates	5	520	1.05	0.89-1.24	8	0.22	27
Triazines	4	471	1.02	0.92-1.14	7	0.13	45
Cadmium	7	71	1.12	0.82-1.53	6	0.42	0
Cutting fluids	8	446	1.03	0.92-1.16	9	0.42	0
Coh	5	285	1.03	0.88-1.21	7	0.29	18
CC	3	161	0.89	0.66-1.21	0.9	0.64	9
Acrylonitrile	4	54	0.93	0.71-1.21	0.41	0.94	0
Rubber manufacturing	15	923	0.98	0.87-1.09	0.33	0.005	55
Ionizing radiation	9	1,624	1.07	0.97-1.17	20	0.009	61

MetaRR, meta relative risk; CI, confidence interval; Coh, cohort study; CC, case control study.

Table 2. Description of studies examining the association between pesticides and prostate cancer

Reference (first author)	Design	Country	Exposure	No. of cases	Measure of risk	Risk	95% CI
Alberghini (1991) [83]	Coh	Italy	Pesticide users	19	SMR	0.59	0.28-1.24
Beard (2003) [84]	Coh	Australia	Laboratory staff	16	SIR	1.05	0.46-2.40
Boers (2005) [85]	Coh	The Netherlands	General population	32	RR	0.64	0.41-1.00
Cantor (1999) [86]	Coh	USA	Pesticide users	140	SMR	1.40	0.87-2.25
Dich (1998) [87]	Coh	Sweden	Pesticide users	401	SIR	1.13	1.02-1.25
Ewings (1996) [88]	CC	Great Britain	Pesticide users	97	OR	0.68	0.44-1.05
Figà-Talamanca (1993) [89]	Coh	Italy	Pesticide users	6	SMR	1.00	0.37-2.73
Fleming (1999) [90]	Coh	USA	Pesticide users	353	SIR	1.91	1.72-2.12
Fleming (2003) [91]	Coh	USA	Pesticide users	22	RR	1.30	0.80-2.11
Fritschi (2007) [92]	CC	Australia	Pesticide users	52	OR	1.02	0.69-1.51
Frost (2011) [93]	Coh	Great Britain	Pesticide users	205	SIR	1.07	0.93-1.23
Koutros (2010) [94]	Coh	USA	Private users,	1,719	SIR	1.19	1.14-1.24
			commercial users	73	SIR	1.28	1.00-1.64
Meyer (2007) [95]	CC	USA	Pesticide users	177	OR	1.60	1.20-2.13
Sperati (1999) [96]	Coh	Italy	Pesticide users	5	SMR	0.80	0.26-2.46
Subahir (2009) [97]	CC	Malaysia	Pesticide exposure	9	OR	2.40	1.11-5.19
Torchio (1994) [98]	Coh	Italy	Pesticide users	66	SMR	0.96	0.74-1.25
van der Gulden (1995) [99]	CC	The Netherlands	Pesticide users	72	OR	1.47	0.88-2.46
Zhong (1996) [100]	Coh	Island	Pesticide users	10	SIR	0.70	0.33-1.48

CI, confidence interval; Coh, cohort study; CC, case control study; SMR, standardized mortality ratio; SIR, standardized incidence ratio; RR, relative risk; OR, odds ratio.

A total of eight cohort studies were selected for studying association between "chromium" exposure and prostate cancer (Table 4, Supplementary Fig. SF6) [117-124]. A significant excess of meta-risk for prostate cancer was observed with a low heterogeneity (Table 1, Supplementary Fig. SF7).

Search for the association between "shift work" and prostate cancer revealed six studies, three cohort and three case-control studies (Table 5, Supplementary Fig. SF8) [125-130]. We observed significantly elevated risk associated with prostate cancer (Table 1, Supplementary Fig. SF9), heterogeneity was large. Separate analysis for cohort and case-control studies revealed positive non-significant associations. A separate literature search for "flight personnel" (pilots and cabin crew) revealed three cohort studies (Table 5, Supplementary Fig. SF10) [131-133]. Our meta-analysis among flight personnel revealed non-significantly increased risk estimate for prostate cancer. When only pilots were included in the analysis, the risk estimate was significantly elevated; however, the heterogeneity was still large (Table 1, Supplementary Fig. SF11).

A total of 18 studies were included in the meta-analysis of "occupational physical activity", 10 cohort and 8 case-control studies (Table 6, Supplementary Fig. SF12) [134-151]. Our meta-analysis revealed negative association with higher workplace physical strain, not statistically significant (Table 1, Supplementary Fig. SF13). Similar results were obtained for separate analysis of case-control studies; however, in cohort studies reduced risk was significant, and studies were homogeneous.

Non-significant results are presented in the Supplement (Supplementary Table ST1-ST10, Supplementary Fig. SF15, SF17, SF19, SF21, SF23, SF25, SF27, SF29, SF31, SF33) [85,88,92,95,101,108,111,147,152-227].

DISCUSSION

A total of 168 original studies that met the inclusion criteria were considered in this meta-analysis, with 90,688 prostate cancer cases. Meta-analyzes of selected work-related risk factors for prostate cancer revealed significant excess in risk for pesticides (without specification of the type of pesticides), and specifically organochlorine pesticides, chromium and shift work. In addition, increased risk for pilots was observed. Physical activity at work was associated with a reduced risk; it was statistically significant only in cohort studies.

1. Pesticides

Pesticides were already in use in the mid-1800s, most commonly Paris Green produced of copper and arsenic trioxide [228], replaced progressively in the late 1800s by lead arsenate. In the 1960s the use of lead arsenate was reduced since its adverse health effects were recognized, but it was not banned as late as in 1988, and large areas of agricultural land in the United States are

Table 3. Description of studies examining the association between organochlorine pesticides and prostate cancer

Reference (first author)	Design	Country	Exposure	No. of cases	Measure of risk	Risk	95% CI
Alavanja (2003) [101]	Coh	USA	Organochlorine pesticides	47	OR	1.39	0.99-1.95
Aronson (2010) [102]	CC	Canada	DDE	24	OR	0.73	0.38-1.40
			DDT	26	OR	1.05	0.55-2.00
			Trans-nonachlor	22	OR	0.83	0.42-1.64
			Oxychlordane	24	OR	0.95	0.49-1.84
			Hexachlorobenzene	29	OR	1.27	0.66-2.44
			Mirex	24	OR	0.58	0.32-1.05
			β-hexachlorocyclo-hexane	29	OR	1.08	0.57-2.05
Asp (1994) [103]	Coh	Finland	Chlorophenoxy	6	SIR	0.37	0.14-0.98
Burns (2001) [104]	Coh	USA	2.4-D	7	SMR	1.34	0.54-3.33
Coggon (2015) [105]	Coh	Great Britain	Fenoxy	129	SMR	1.14	0.92-1.41
Fritschi (2007) [92]	CC	Australia	Organochlorine pesticides	36	OR	0.76	0.33-1.75
Hardell (2006) [106]	CC	Sweden	Chlordane	15	OR	1.50	0.50-4.50
Kogevinas (1997) [107]	Coh	9 countries	Phenoxy, chlorophenol	68	SMR	1.10	0.85-1.42
Koutros (2013) [108]	Coh	USA	Aldrin	64	RR	1.25	0.97-1.61
			Chlordane	58	RR	1.02	0.78-1.33
			DDT	95	RR	1.18	0.95-1.47
			Dieldrin	18	RR	0.93	0.58-1.49
			Heptachlor	44	RR	1.05	0.78-1.41
			Lindane	39	RR	1.16	0.84-1.60
			Toxaphene	38	RR	0.97	0.70-1.34
Lee (2004) [109]	Coh	USA	Alachlor	325	SIR	1.16	1.04-1.29
Lynge (1998) [110]	Coh	Denmark	Phenoxy	15	SIR	1.00	0.60-1.67
Mills (2003) [111]	CC	USA	Chlorothalonil	135	OR	1.06	0.71-1.58
			Dichloropropene	131	OR	1.00	0.68-1.47
			Dicofol	131	OR	0.94	0.65-1.36
			Heptachlor	140	OR	1.35	0.91-2.00
			Lindane	129	OR	1.32	0.88-1.98
Mozzachio (2008) [112]	Coh	USA	Chlorothalonil	23	RR	0.79	0.52-1.20
Multigner (2010) [113]	CC	French West Indies	Chlordecone	161	OR	1.27	0.93-1.73
Ritchie (2003) [114]	CC	USA	Dialdrin	58	OR	0.28	0.09-0.87
			Heptachlor	58	OR	0.33	0.10-1.09
			Trans-nonachlor	58	OR	1.18	0.45-3.09
			Oxychlordane	58	OR	1.23	0.42-3.60
Samanic (2006) [115]	Coh	USA	Dicamba	67	RR	1.08	0.81-1.44
Sawada (2010) [116]	CC	Japan	o,p´-DDT	47	OR	1.07	0.59-1.94
			p,p´-DDT	46	OR	1.02	0.57-1.83
			DDE	53	OR	0.96	0.58-1.59
			Trans-nonachlor	52	OR	0.83	0.43-1.60
			Cis-nonachlor	51	OR	0.84	0.45-1.57
			Oxychlordane	49	OR	0.77	0.39-1.52
			HCB	42	OR	0.49	0.21-1.14
			Mirex	56	OR	0.95	0.54-1.67
			β-HCH	43	OR	0.78	0.46-1.32

CI, confidence interval; Coh, cohort study; CC, case control study; OR, odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; RR, relative risk.

still contaminated by lead arsenate [228]. As a proven carcinogen, exposure to arsenic may have contributed to cancers in workers' cohorts exposed before the 1980s. Since then, there have been many different pesticides on the market. This make a problem in the assessment of hazardous effects of pesticides as individuals were exposed to many various pesticides and different chemical substances have been used over time.

Pesticides are used to control pests, such as molds, insects and unwanted plants [21] and are commonly grouped based on the target of their effect, such as herbicides, fungicides and insecticides. Pesticides may also be grouped based on their chemical composition; most frequently used are organochlorine

Table 4. Description of studies examining the association between chromium and prostate cancer

Reference (first author)	Design	Country	Exposure	No. of cases	Measure of risk	Risk	95% CI
Axelsson (1980) [117]	Coh	Sweden	Ferrochromium workers	10	SMR	1.10	0.68-1.78
Gibb (2000) [118]	Coh	USA	Chromium chemical production	16	SMR	1.22	1.00-1.49
Huvinen (2013) [119]	Coh	Finland	Ferrochromium, stainless steel	89	SIR	1.31	1.05-1.63
Jakobsson (1997) [120]	Coh	Sweden	Grinding stainless steel	36	SIR	1.70	1.20-2.41
Knutsson (2000) [121]	Coh	Sweden	Concrete	769	SIR	1.08	1.01-1.15
Langård (1990) [122]	Coh	Norway	Ferrochromium	12	SMR	1.56	0.68-3.58
Rafnsson (1997) [123]	Coh	Island	Masons	25	SIR	1.04	0.67-1.61
Sorahan (2000) [124]	Coh	Great Britain	Chrome platers	7	SMR	1.06	0.43-2.61

CI, confidence interval; Coh, cohort study; SMR, standardized mortality ratio; SIR, standardized incidence ratio.

Table 5. Description of studies examining the association between shift work and flight personnel, and prostate cancer

References (first author)	Design	Country	Exposure	No. of cases	Measure of risk	Risk	95% CI
Shift work							
Conlon (2007) [125]	CC	Canada	Rotating shift	369	OR	1.19	1.00-1.42
Gapstur (2014) [126]	Coh	USA	Rotating shift	268	RR	1.13	1.00-1.28
			Permanent afternoon/evening	55	RR	1.35	1.04-1.75
			Permanent night	16	RR	0.78	0.47-1.29
Kubo (2006) [127]	Coh	Japan	Rotating shift	7	RR	3.0	1.20-7.30
Papantoniou (2015) [128]	CC	Spain	Permanent night	156	OR	1.10	0.86-1.41
			Rotating night shift	206	OR	1.17	0.93-1.47
Parent (2012) [129]	CC	Canada	Night shift	132	OR	2.77	1.96-3.91
Yong (2014) [130]	Coh	Germany	Rotating shift including night	146	RR	0.95	0.76-1.19
Flight personel							
Band (1996) [131]	Coh	Canada	Pilots	34	SIR	1.87	1.38-2.53
Irvine (1999) [132]	Coh	Great Britain	Pilots	15	SMR	1.11	0.62-1.99
Hammer (2014) [133]	Coh	9 countries in Europe and USA	Pilots	114	SMR	1.23	0.98-1.54
			Cabin crew	17	SMR	0.75	0.40-1.41

CI, confidence interval; CC, case control study; Coh, cohort study; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

pesticides, organophosphorus pesticides, carbamates and triazines.

There have been concerns that pesticide exposure can cause cancer, however, International Agency for Research on Cancer (IARC) [229] concluded in 1991 that there is only a limited evidence to support its carcinogenicity (Group 2B). Since then, numerous studies investigated carcinogenic potential of pesticides among farmers, other agricultural workers, persons who are occupationally spreading pesticides and workers in the industrial manufacturing of pesticides. The most valuable data came from the Agricultural Health Study (AHS) that still follows the pesticide cohort of almost 90,000 participants since 1993 [94].

Several mechanisms have been proposed to explain cancer development due to pesticides. Most pesticides are not mutagenic; however, they may contain endocrine disruptors that act by either blocking or stimulating hormonal receptors and lead to an increase of testosterone. Evidence from epidemiologic studies however, could not prove with certainty that exposure to endocrine disruptors or circulating levels of endogenous androgens are associated with increased risk of prostate cancers [230]. Furthermore, animal and tissue studies have shown that some pesticides, e.g., carbamates can induce chromosomal damage [231-233]. Pesticides can also cause oxidative stress in the cells that forms reactive oxidative radicals which can damage the cells [234].

Studies of the AHS cohort have reported that there is an interaction between exposure to the herbicide and the individual genes [235]. Exposure to fonofos only is not sufficient to increase the risk of prostate cancer, but the interaction with the base excision repair (BER) genes, a mechanism which helps to repair damaged DNA, can increase the risk of prostate cancer in exposed workers. It is also reported that heredity may interact with

Table 6. Description of studies that examined the relationship between physical activity and prostate cancer

Reference (first author)	Design	Country	No. of cases	Measure of risk	Risk	95% CI
Bairati (2000) [134]	CC	Canada	8	OR	0.20	0.10-0.40
Clarke (2000) [135]	Coh	USA	17	SMR	0.79	0.46-1.36
Doolan (2014) [136]	CC	Australia	494	OR	1.19	0.97-1.46
Friedenreich (2004) [137]	CC	Canada	255	OR	0.90	0.66-1.23
Grotta (2015) [138]	Coh	Sweden	107	HR	0.85	0.67-1.08
Hartman (1998) [139]	Coh	USA	28	RR	1.20	0.74-1.95
Hrafnkelsdóttir (2015) [140]	Coh	Island	450	HR	0.84	0.74-0.95
Lacey (2001) [141]	CC	China	39	OR	2.9	1.30-6.47
Le Marchand (1991) [142]	CC	USA	37	OR	0.80	0.50-1.28
Lund Håheim (2006) [143]	Coh	Norway	507	RR	0.86	0.53-1.40
Lund Nilsen (2000) [144]	Coh	Sweden	116	RR	1.04	0.82-1.32
Orsini (2009) [145]	Coh	Sweden	111	RR	0.72	0.58-0.89
Pierotti (2005) [146]	CC	Italy	386	OR	0.75	0.61-0.92
Sass-Kortsak (2007) [147]	CC	Canada	205	OR	1.33	1.02-1.73
Severson (1989) [148]	Coh	USA	169	RR	1.05	0.73-1.51
Thune (1994) [149]	Coh	Norway	25	RR	0.81	0.50-1.31
Wiklund (2008) [150]	CC	Sweden	309	OR	0.84	0.66-1.07
Zeegers (2005) [151]	Coh	The Netherlands	154	RR	0.91	0.70-1.18

CI, confidence interval; CC, case control study; Coh, cohort study; OR, odds ratio; SMR, standardized mortality ratio; HR, hazard ratio; RR, relative risk.

exposure to pesticide [101]. People who have both a family history of prostate cancer and exposure to pesticides have a significantly elevated risk of prostate cancer, which was proven for carbamates, fonofos, chlorpyrifos, and phorate.

There is also evidence that pesticide exposure can lead to an increased aggressiveness of the cancer. The study of Koutros et al. [108] demonstrated that some pesticides, such as fonofos, malathion, and terbufos may stimulate the development of aggressive forms of prostate cancer.

Our meta-analysis showed a statistically significant excess risk of prostate cancer of 1.15 (95% CI = 1.01-1.32), with a high degree of heterogeneity. Our risk estimate was lower than in the meta-analysis of Van Maele-Fabry and Willems [27], which included 22 cohort and case-control studies published between 1986 and 2003 (meta rate ratio = 1.24; 95% CI = 1.06-1.45). The update of the AHS by Koutros et al. [94] found that both private and commercial pesticide applicators had an increased risk of prostate cancer (SIR = 1.19; 95% CI = 1.14-1.25 and SIR = 1.28; 95% CI = 1.00-1.61, respectively). On the other hand, the meta-analysis by Ragin et al. [11] based on four case-control studies (one unpublished) reported statistically significant decreased risk for pesticide exposure (metaRR = 0.68; 95% CI = 0.49-0.96). A meta-analysis of 18 cohort studies among workers manufacturing pesticides by Van Maele-Fabry et al. [25] reported a significant increase in risk (metaRR = 1.28; 95% CI = 1.05-1.58). These inconsistent results can probably be explained by different exposure patterns both with respect to the type of pesticide and the quantities of pesticides to which an individual user is exposed.

2. Organochlorine pesticides

Separate analysis for exposure to organochlorine pesticides was associated with a significantly elevated risk of prostate cancer (metaRR = 1.08; 95% CI = 1.03-1.14), and study results were consistent. Separate analysis of cohort studies showed the similar results (metaRR = 1.12; 95% CI = 1.05-1.19). Two studies included in our meta-analysis had the opposite results: Alavanja et al. [101] also reported an increased risk (RR = 1.39; 95% CI = 0.99-1.95), while Fritschi et al. [92] reported decreased risk for organochlorine pesticides in a study from Australia (RR = 0.76; 95% CI = 0.33-1.75).

The highest risk estimates for specific organochlorine pesticides were estimated for chlordane (RR = 1.50) in a Swedish study [106], heptachlor (RR = 1.35), 2,4-dichlorophenoxyacetic acid (2,4-D) (RR = 1.34) and lindane (RR = 1.32) in the USA studies [104,111]. In a study of chlordecone [113] a dose-response relationship was found, as the risk of prostate cancer increased gradually from 1.0 to 1.33 with the increase in cumulative exposure index in quartiles and increase in plasma concentrations of chlordecone, strengthening the evidence for a causal relationship.

A problem in many studies examining specific pesticides is

commonly self-reported exposure, different exposures patterns and the quantities of used pesticides, and multiple exposures to different pesticides which can interfere with each other. A confounding problem may occur if these various types of pesticides are risk factors for prostate cancer.

In recent decades, the use of pesticides has decreased due to the ban of the pesticide use, such as in Sweden [236] where the most frequent use is in the industry, mostly for impregnation of wood [237]. However, the legislation is not uniform worldwide. For example, atrazine has been banned in Sweden since 1989 and in Europe since 2004, but it is still one of the most commonly used herbicides in the USA and Australia.

Our results and previous review articles provide some support that pesticides may increase the risk of prostate cancer although the increase in risk was small. It is however difficult to indicate which specific pesticide is responsible for the increased risk.

3. Chromium

Workers engaged in the manufacturing or handling stainless steel are exposed to chromium in varying degrees. As early as in the 1980s chromium was classified as carcinogen with respect to lung cancer [238], and this applies only to hexavalent chromium and not to trivalent or metallic chromium.

Our results revealed a small but significant increase in prostate cancer risk for chromium exposure (metaRR = 1.19; 95% CI = 1.07-1.34), and study results were consistent. This is similar with the results reported by Cole and Rodu [58] in its meta-analysis of 21 studies who also reported a slight but significant excess in risk among workers exposed to chromium (SMR = 114; 95% CI = 100-129).

We included eight, all incidence studies in our meta-analysis. The highest risk estimates were reported in a Swedish study [120] which included workers who cut and polished stainless steel and were exposed to high concentration of airborne chromium ranging 70-730 $\mu g/m^3$. Three studies examined workers in the ferrochrome production [117,119,122], and risk estimates varied between 1.10 and 1.56. In the study by Huvinen and Pukkala [119], the average airborne concentration of hexavalent chromium was 6.6 $\mu g/m^3$, and in the study by Langård et al. [122] it varied between 10 to 300 $\mu g/m^3$. One study examined workers in chrome production [118], where the measured airborne concentration of hexavalent chromium was on average 9 $\mu g/m^3$, reporting increased risk of 1.22, with a borderline significance.

Two studies investigated the cancers in masons and concrete workers dealing with cement that contained chromates [121,123]. These studies reported the lowest risk estimates of

1.04 and 1.08, respectively. In the Icelandic study [123] of masons, chromium concentration in the cement was in the range 5.8-9.4 mg/kg, while airborne concentrations of total chromium (both trivalent and hexavalent) were 3-8 $\mu g/m^3$. The personal exposure measurements in urine showed that on Monday levels of chromium were 0.0084 $\mu mol/L$ and on Thursday 0.0367 $\mu mol/L$, indicating a significant chromium uptake during the working days.

Exposure to chromium in all included studies was associated with other exposures. In the manufacture of ferrochromium workers were also exposed to nickel, zinc, molybdenum, and polycyclic aromatic hydrocarbons. None of these exposures, however, were linked to prostate cancer. Handling cement generates a dust which besides chromium contains quartz, a carcinogen with respect to lung cancer, but not to prostate cancer. The strength of included studies is that exposure assessment was based on the chromium measurements at workplaces. However, in some cases information on specific exposure to hexavalent chromium was missing.

Our results provide moderate evidence that chromium exposure increases the risk of prostate cancer.

4. Shift work

Shift work as a possible cause of prostate cancer has been reviewed thoroughly, but results were inconclusive [47-55]. Several mechanisms are proposed to explain the association of prostate cancer and shift workers. Sleep deprivation affects various endocrine mechanisms, including immune system which in turn can increase the risk of cancer development [239]; however, this was not documented in a cohort of 32,141 persons from the USA [240]. Second hypothesis states that a production of melatonin can be reduced due to a lower exposure to light at night and may stimulate cancer cell growth, which has been proved in animal experiments. An Icelandic study documented that a reduced amount of a melatonin metabolite in urine was associated with increased risk of advanced or lethal prostate cancer in older men [241], however, more studies are needed in younger men. There is also a hypothesis that circadian rhythm affects hormone secretion, including sex hormones, which in turn affects the appearance and growth of cancer cells of prostate. This was supported by a Spanish case-control study which found that night shift workers had higher levels of androgens than day workers [128]. Genetic studies have been also published searching for genetic polymorphism of the clock genes associate with prostate cancer [239,242]. However, the results are inconsistent.

Our meta-analysis demonstrated a significant association between exposure to shift work and prostate cancer (RR = 1.25; 95% CI = 1.05-1.49). The degree of heterogeneity was high, which might be caused by exposure assessments as there is no uniform definition of shift work. Shift work is usually considered as work other than day work that is defined as work between 6 a.m. to 6 p.m. (06:00-18:00). Therefore, permanent night work is defined as shift work. The study included in our meta-analysis that mainly contributed to heterogeneity was published by Parent et al. [129] (calculation not presented). Five studies defined shift work as a night shift that is a part of the shift schedule, while study by Gapstur et al. [126] reported a subgroup of permanent afternoon-evening shift. When this study was excluded, the results of meta-analysis differed only marginally.

Our results are in line with the results of a meta-analysis by Rao et al. [243], which included eight studies (RR = 1.24; 95% CI = 1.05-1.46), all six studies from our meta-analysis and in addition studies by Kubo et al. [244] and Schwartzbaum et al. [245]. The former study reported only 4 exposed cases and the later had inadequate exposure assessment, so they were excluded from our meta-analysis.

A review article by Sigurdardottir et al. [246] included 16 studies investigating the relationship between circadian rhythms sleep disorder and the risk of prostate cancer. Studies among flight personnel were considered as well. In 15 studies a positive association was reported and 10 were statistically significant. Three studies in this review examined the relationship between exposure duration (measured as the number of years of night shift work) and prostate cancer risk [125,128,129] and showed a U-shape with the highest risk estimates for short and long duration of exposure. The studies of Conlon et al. [125] and Papantoniou et al.128 had similar risk estimates and shapes, while the study of Parent et al. [129] had a much higher risk estimates for all three intervals of exposure. Categorization of exposure time, however, differs between the three studies; therefore, the results are not entirely comparable.

In summary, there is the evidence from our and previous meta-analyses that shift work including night work can increases the risk of prostate cancer. A weakness of studies is assessment of exposure, as various work schedules were used in the different studies. Moreover, there are only a few reports on the dose-response relationship, and their results are difficult to interpret. There are several biological mechanisms that could explain this relationship, but the evidence of the various stages in the causal chain is not clear enough and can be assessed as "possible" association.

5. Flight personnel

A relatively large number of studies have examined a cancer risk among flight personnel. A flight personnel is commonly considered as a proxy for circadian rhythm disorder, as they often fly over many time zones. However, they are also exposed to ionizing cosmic radiation, which is carcinogenic as well. Therefore, an increased risk of cancer can be caused by multiple exposures.

The European Study of Cancer Risks among the Airline Personnel (ESCAPE), a collaboration between researchers from different European countries studied prostate cancer risk among the air personnel. Initially, nine national cohorts from Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, Sweden, and Great Britain were included [247]. Later, a flight personnel from the USA was added [133]. The ESCAPE included studies of national populations [248-252], but also a study that pooled the Nordic countries' cohorts [253]. Results of the nine European countries revealed that SMR of prostate cancer was 0.94 (95% CI = 0.71-1.26). The latest report from ESCAPE by Hammer et al. [133] presenting results from 10 countries, showed the slight excess of overall risk of prostate cancer (SMR = 1.09; 95% CI = 0.35-2.68) which was more pronounced among pilots in separate analysis of pilots and cabin crew (SMR = 1.23; 95% CI = 0.98-1.53). The authors speculated that the differences in risks of prostate cancer between the pilots and cabin crew could be due to differences in sleeping patterns and light exposure, but this was not investigated in more details.

We obtained a non-significant increase in risk of prostate cancer for flight personnel (metaRR = 1.26; 95% CI = 0.90-1.76); excess of risk was statistically significant for pilots only (metaRR = 1.41; 95% CI = 1.02-1.94). This was similar as the results from ESCAPE. In our meta-analysis, we did not include any publication of individual country or region that was a part of the ESCAPE, but only the results from 10 countries as a part of ESCAPE [133].

The proposed mechanism for increased prostate cancer risk is that long distance flights over several time zones can induce circadian rhythm disorder. The ESCAPE study did not separately report excess risk among flight personnel that were crossing time zones. Therefore, some other risk factors could also play a role in an increased risk of specific cancers. In the Nordic study on prostate cancer risk among pilots, different duration of flights was considered [253]. Time spent on long-distance flights was measured as the "block hours", which was the sum of the time from the departure gate to the arrival gate. It was observed that the relative risk of prostate cancer in pilots older than 60 years of

age increased with the number of block hours. Relative risk of prostate cancer was 3.88 (95% CI = 1.26-11.90) for pilots with more than 10,000 block hours compared to the pilots with ≤4,999 block hours. This study, however, did not perform separate analysis for the flights that go across time zones.

In summary, our meta-analysis shows that pilots have a significantly increased risk of prostate cancer. The difference between the pilots and cabin crew is difficult to explain by circadian rhythm disorder or cosmic radiation and could be due to uncontrolled confounding. The evidence suggests that the association between the pilots and prostate cancer is possible.

6. Occupational physical activity

It has been shown that physical activity reduces the risk of several cancers, including prostate cancer [254]. Studies of physical activity at work, however, have produced conflicting results regarding the risk for prostate cancer [255]. In our meta-analysis we found that physical activity at work was associated with a non-significant reduced risk (RR = 0.90; 95% CI = 0.80-1.02). Meta-analysis showed a great heterogeneity, which could be due to the difficulty in recalling the physical strain at work in the past. However, in 10 included cohort studies, the risk was significantly reduced (RR = 0.87; 95% CI = 0.81-0.94), and studies were consistent. In the remaining eight case-control studies reduced risk was of the same magnitude, but not statistically significant (RR = 0.91; 95% CI = 0.69-1.20) with a high heterogeneity.

In the meta-analysis published by Liu et al. [66] a significantly reduced risk of prostate cancer was found for those who had a higher level of physical activity at work (27 trials; RR = 0.81, 95% CI = 0.73-0.91). Similar results were reported for separate meta-analysis of cohort and case-control studies (RR = 0.91; 95% CI = 0.80-0.95 and RR = 0.73; 95% CI = 0.68-0.87, respectively). Several studies included in this meta-analysis were excluded from our meta-analysis due to the weak definition of physical activity and because patients with other cancers were used as controls.

A frequent problem with studies of occupational physical activity is a poor definition of exposure. Four studies in our meta-analysis had a good quality of assessed occupational physical activity that included information on the exposure frequency, intensity and duration, which allowed the estimation of total exposure over time [137,138,145,150]. Several studies estimated exposure based on one or two questions [135,139,140,143,144,147,149]. Lund Nilsen et al. [144] based the exposure assessment on the single question of whether "worker

felt physically exhausted after a day's work". The study by Zeegers et al. [151] defined walking and cycling to and from work as a recreational physical activity. Four studies estimated exposure on only occupational title [134,136,142,151] which is an uncertain variable having in mind a great difference in exposure intensity within the same occupations as well as over time in the same occupation.

In most of studies, physical activity is estimated based on self-report, not objective enough measure of exposure. Specifically, case-control studies may contain a recall bias. Cohort studies usually report the exposure before or at the time of inclusion in the study with no data on exposure during follow-up.

We can summarize that there is weak evidence that physical activity at work is associated with a reduced risk of prostate cancer.

7. Farming

Total mortality rates in farmers and other agricultural workers are often lower compared to the general population and many other occupations, which has been attributed to a healthy lifestyle, and lower smoking prevalence [20,256]. However, farmer's occupation involves a wide range of tasks, including care of animals, handling of feed, seed and animal wastes, salvage of hay and various grains, driving tractors and other vehicles, handling different machines and tools, maintenance and repair. Therefore, they have multiple exposures, such as organic and inorganic dust, pesticides, fungi, microbes, viruses, oils, gasoline, diesel exhaust, welding fumes, and ultraviolet light [15].

Since the 1970s, more studies reported significant excess risk of prostate cancer among farmers compared to other occupations [20,257,258]. In the 1980s a series of studies were initiated to identify specific carcinogens associated with farm work.

Our meta-analysis provided no evidence that farm work was associated with increased risk of prostate cancer (metaRR = 0.99; 95% CI = 0.95-1.02), based on 26 included studies from 15 countries with a total of 66,749 cases, and with a moderate degree of heterogeneity in the results. This is consistent with the meta-analysis by Van Maele-Fabry and Willems [30] based on 11 studies (metaRR = 0.97; 95% CI = 0.92-1.03). However, some previous meta-analyses found excess risk for prostate cancer among farmers such as an early meta-analysis of 22 studies by Blair et al. [32] reporting risk of 1.08 (95% CI = 1.06-1.11), followed by meta-analysis of 24 studies by Keller-Byrne et al. [16] (metaRR = 1.12; 95% CI = 1.01-1.24), and the meta-analysis by Acquavella et al. [259], which included 30 studies (RR = 1.07; 95% CI = 1.02-1.13). Meta-analyses by Keller-Byrne et al. [16] and

Acquavella et al. [259] included proportional mortality studies (PMR) (three vs. one, respectively) and the later one included nine studies not published in international peer review journals. The recent meta-analysis of twelve case-control studies by Ragin et al. [11] showed significantly elevated risks for farmers and agricultural workers, irrespective of the way of control selection, i.e., when controls were people diagnosed with benign prostatic hyperplasia the risk estimate was 3.83 (1.96-7.48), while when controls were persons free of benign prostatic hyperplasia the risk was 1.38 (1.16-1.64). However, inclusion of unpublished studies in all three meta-analyses [11,16,259] can be a source of a methodological weakness due to the possible lower quality of selected studies not being ready for publication.

The inconsistent results may occur for many reasons such as different study designs as studies performed prior to 1990 were often PMR, generally regarded as having a lower quality than longitudinal studies and giving higher risk estimates. This was documented in the meta-analysis of Acquavella et al. [259], who performed a separate analysis for PMR and cohort studies and reported higher risk in the former (metaRR = 1.12; 95% CI = 1.08-1.18 vs. metaRR = 0.95; 95% CI = 0.93-0.98, respectively). Second, studies from different geographical areas might reflect different work practice, use of different pesticides, etc., as was shown in the study of Van Maele-Fabry and Willems [30] who concluded that studies derived from the USA and Canada reported a non-significantly elevated risk among farmers (RR = 1.26; 95% CI = 0.83-1.90; 5 studies), whereas farmers in Europe had non-significantly decreased risk (0.96; 95% CI = 0.92-1.01; 6 studies).

8. Organophosphate pesticides

Our analysis of organophosphate pesticides showed no increased risk of prostate cancer (metaRR = 0.98; 95% CI = 0.87-1.11), heterogeneity in results was low. The pesticide associated with the highest risk of prostate cancer was dichlorvos [111], an insecticide classified as a possible carcinogen by the IARC [229] based on animal studies. No more epidemiological studies supporting association between dichlorvos and prostate cancer were found.

9. Carbamates

Meta-analysis of carbamates showed a non-significant increase in risk for prostate cancer (metaRR = 1.05; 95% CI = 0.89-1.24) and the heterogeneity was low. The single study showed significantly increased risk of prostate cancer due to exposure to butylates (RR = 1.44; 95% CI = 1.04-1.99) [180]. This study, a part

of the AHS cohort, reported also a dose-response relationship.

10. Triazines

Meta-analysis of triazines showed a slightly elevated risk, not statistically significant (metaRR = 1.02; 95% CI = 0.92-1.14). The increase in risk of prostate cancer was reported among workers in production of atrazine [184], and farmers applying simazine [111], both belonging to the chlorotriazines. However, in both studies increased risk was insignificant. The later study reported a dose-response relationship. Data from the literature were insufficient to support carcinogenicity of chlorotriazine.

11. Cadmium

IARC [260] classified cadmium as a carcinogen. Some earlier studies reported causal relationship between cadmium exposure and prostate cancer, but this could not be confirmed in later epidemiologic studies [38]. Cadmium is used in a production of nickel-cadmium batteries, soldering alloys, pigments, stabilizer, coatings, etc.

We found an insignificant excess of risk for prostate cancer related to cadmium exposure (metaRR = 1.12; 95% CI = 0.92-1.14). Our results are consistent with the conclusions of the meta-analysis by Sahmoun et al. [34] of 21 studies published in 2005 that reported statistically non-significant excess of risk (summary SMR score = 126; 95% CI = 83-184). Several narrative reviews [2,33,35] concluded that existing studies in humans, particularly recent ones, could not confirm that cadmium exposure can result in excess risk of prostate cancer.

12. Cutting fluids

When talking about cutting fluids we consider fluids that are used in metalworking to lubricate and cool. They are usually classified as cutting oils based on mineral oil or synthetic oil, water soluble cutting fluids, mostly in the form of water-oil emulsion, and synthetic fluids which do not contain mineral oils. Cutting fluids contain several suspected carcinogens, such as aliphatic hydrocarbons, polycyclic aromatic hydrocarbons, nitrosamines, and certain metals [42] and are commonly used in metal manufacturing and in mechanical workshops.

Our meta-analysis showed no evidence that exposure to cutting fluids could be associated with the increased risk of prostate cancer (metaRR = 1.03; 95% CI = 0.91-1.16), heterogeneity did not exist. The review article of six studies by Tolbert [42] provided a limited evidence that metalworking fluids can be associated with prostate cancer. A major methodological problem in studies of cutting fluids is that the workers exposed to cutting

fluids are also exposed to other chemicals such as metals and solvents which may increase the risk of prostate cancer.

In this review, data from selected studies were too limited to analyze the various cutting fluids separately. There is no sufficient evidence that exposure to cutting fluids increases the risk of prostate cancer.

13. Acrylonitrile

Acrylonitrile has been used since the 1920s, mostly to produce acrylic fiber, necessary material in the apparel industry. Following the experiments on animals showing that acrylonitrile could be carcinogenic, a first epidemiological study was conducted among the workers exposed to acrylonitrile in a German plant, but no excess risk of cancers was reported [261]. In 1980s the epidemiologic studies were performed in USA [262] and Germany [263], however only study in the USA at a plant producing fibers reported three prostate cancer cases vs. 0.9 expected. Later series of epidemiological studies did not support an association of exposure to acrylonitrile in different plants and prostate cancer [196,198,264], with exception of a follow-up study by O'Berg et al. [265] that reported 6 prostate cancers against 1.8 expected. In 1999 IARC [266] classified acrylonitrile as possible human carcinogen.

Our meta-analysis showed no increased risk of prostate cancer (RR = 0.93; 95% CI = 0.71-1.21) and study results were consistent. This is in line with the meta-analysis by Rothman [267] who included eight studies, and Collins and Acquavella [71] who included 25 studies, but no increased risk estimates for prostate cancer were reported. The overview article by Cole et al. [70] did not support a causal relationship between acrylonitrile exposure and prostate cancer. There is no enough evidence that acrylonitrile increases the risk of prostate cancer.

14. Rubber manufacturing

Carcinogenic risk in rubber industry such as in cable and tire production and rubber goods manufacturing was evaluated by IARC in 1982 and 1987 and was classified as definitely carcinogenic (Group 1), mostly due to exposure to aromatic amines and solvents [268,269]. However, excess risk of prostate cancer was not demonstrated.

Our meta-analysis, which included 15 studies, showed no increased risk of prostate cancer in workers in the rubber and tire industry (metaRR = 0.98; 95% CI = 0.87-1.09). Heterogeneity was moderate. Previously published meta-analyzes showed similar results. Meta-analysis by Stewart et al. [45] included 12 studies and reported the risk estimate of 1.03 (95% CI = 0.96-1.11).

Similarly, the review article by Kogevinas et al. [46] found no evidence of increased risk of prostate cancer in the rubber industry. Mullins and Loeb [12] summarized the findings from six studies and reported that no specific occupational exposure in rubber industry had shown conclusive evidence of an association with prostate cancer.

According to our assessment, there is no evidence that exposures in the rubber and tire industry increase the risk of prostate cancer.

15. Whole body vibration

Occupational exposure to WBV is common in drivers of heavy vehicles, such as forest machines, tractors and other construction vehicles. However, the exposure can vary in a great extend depending on the conditions of surface they are driving on and the dampers provided in the vehicle during the working hours. Moreover, professional drivers can also have other carcinogenic exposures.

Our results found a slightly lower risk estimates (RR = 1.03; 95% CI = 0.98-1.09) than the meta-analysis by Young et al. [44], who reported a risk of 1.14 (95% CI = 0.99-1.30). In Young's analysis [44], however, two included studies used other cancers as controls. Heterogeneity in our meta-analysis was high, probably because the weak exposure assessment in all original studies based on job titles that included all types of vehicle drivers. Three included studies used questionnaires and interviews supplemented by expert judgment to assess exposure to WBV [147,215,218]. Even in these cases, there are shortcomings. The study by Nadalin et al. [218] assessed the exposure intensity referring to information from a German website, which however could not be obtained in a search. Moreover, authors created an index of the WBV by multiplying these data with their own measurements. Similar method of exposure assessment was done in the study by Jones et al. [215] while in the article by Sass-Kortsak et al. [147] WBV variable was not defined clear enough and was based on positive answer (yes) on the question: "Longest job in occupation with whole-body vibration".

Based on our assessment there is no evidence that WBV is a risk factor for prostate cancer.

16. Ionizing radiation

Ionizing radiation is one of the most extensively studied carcinogens. Case reports have been published starting the late 1800s. Since 1902 when the association between exposure to ionizing radiation among radiologists and skin cancer was

published, knowledge about the ionizing radiation has accumulated [270]. IARC evaluated ionizing radiation in 2000 and 2012 and concluded that X- and γ-radiation were carcinogens [271,272]. However, not a clear relationship is established for prostate cancer [273].

Our meta-analysis did not provide evidence that exposure to ionizing radiation increased the risk of prostate cancer (RR = 1.07; 95% CI = 0.97-1.17); heterogeneity was moderate. Studies examined workers occupationally exposed to ionizing radiation from nuclear plants, nuclear research centers, nuclear tests and radiologic technicians. Strength of the included studies is that personal dosimeters were used for exposure assessment; exception is the study of radiological technicians. A meta-analysis by Park et al. [274], which included 11 studies, showed a significantly reduced risk of prostate cancer (RR = 0.84; 95% CI = 0.75-0.96). Follow-up studies of populations that survived the atomic bombs dropped on Japan in 1945 did not show that the risk of prostate cancer was increased (RR = 0.29; 95% CI = 0.21-1.2) [275].

Epidemiologic studies demonstrated no association between ionizing radiation and prostate cancer.

SUMMARY

Prostate cancer is the most common cancer in men in the western developed world. Heredity and age play a major role in the development of prostate cancer. The significance of occupational exposures is uncertain. Our literature review supports a causal association for a few of the previously suggested factors, such as pesticides, chromium, and shift work are significantly associated with prostate cancer, as well as occupational physical activity. The highest risk estimates for prostate cancer of 25% was revealed for shift work, which included night shifts. The pilots, occupation sometimes used as a surrogate for the night shift exposure, had an increased risk of 41%, however, the exposure assessment was not uniform, and pilots do not always have shift work. We found increased risk for pesticide exposure in general, and separately for organochlorine pesticides. It was not possible to identify individual pesticides as carcinogenic. Exposure assessment in studies with occupational exposure to pesticide is also a concern as workers often use multiple pesticides simultaneously or over time, and possible uncontrolled confounding may also be present. Chromium exposure increased the risk for prostate cancer of 19%. All included studies on chromium were cohort studies and results were consistent. Weak association with occupational physical

activated was observed.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/ 10.15430/JCP.2019.24.2.100

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