

REVIEW

An Update on Occupation and Prostate Cancer

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Abstract

Background: Our aim was to identify gaps and limitations in the current literature and to make recommendations for future research required to address these. **Materials and Methods:** We reviewed occupational exposures and related factors associated with the risk of prostate cancer between 2000 and 2012. These included chemical, ergonomic, physical or environmental, and psychosocial factors which have been reported by epidemiological studies across a range of industries. **Results:** The results are inconsistent from study to study and generally this is due to the reliance upon the retrospectivity of case-control studies and prevalence (ecological) studies. Exposure assessment bias is a recurring limitation of many of the studies in this review. **Conclusions:** We consider there is insufficient evidence to implicate prostate cancer risk for ergonomic, physical, environmental or psychosocial factors, but there is sufficient evidence to implicate toxic metals, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs). More research is required to identify specific pesticides that may be associated with risk of prostate cancer.

Keywords: Occupational exposure - risk - risk factors - maximum allowable concentrations - threshold - prostate cancer

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Introduction

Epidemiological research on prostate cancer is difficult because of the large proportion of men who, with increasing age, will develop prostatic tumours of low malignant potential that will have no discernible effect on a man's health or longevity. This presents a problem because many ageing men will develop lower urinary tract symptoms (LUTS) related to benign prostatic hypertrophy (BPH) which when investigated and treated by transurethral resection of the prostate (TURP) foci of prostatic adenocarcinoma will be identified in the tissue removed by this procedure. Thus, increased medical surveillance, common for many occupational cohorts, is likely to result in increased prostate cancer diagnosis compared with the general male population. This problem has been exacerbated since the advent of prostate specific antigen (PSA) testing two decades ago which has led to gross over diagnosis of tumours that otherwise would have remained undetected. It follows that epidemiological studies of prostate cancer must take into account, where possible, some index of tumour aggressiveness and potential to progress to invasive disease. For an overview of references on the background to Prostate Cancer and occupational exposure, see Tables 1 for reviews and for research studies.

The topic of principal interest to public health practitioners is the question of the causes of clinically significant prostate cancer and the identification of potentially avoidable risk factors that men encounter in their everyday lives. It is necessary to answer the question:

what constitutes harmful exposure to certain substances or experiences in relation to men's occupations? Greater levels of prevention will then lead to a reduction in the incidence, morbidity and consequent mortality from prostate cancer. The importance of such research can be underscored by the fact that prostate cancer was the 4th ranking cause of cancer death and the 3rd highest for cancer incidence for men in Victoria in 2008 (Thursfield et al., 2010). The median age at diagnosis was 67 years (Thursfield et al., 2011b). The incidence rate in 2010 was 115.4 per 100,000 men and the mortality rate was 13.3 per 100,000 men (Thursfield et al., 2011a). Five year survival in Victoria is 91% (Thursfield et al., 2012). In comparison, the median overall survival in Canada for intermittent therapy is 8.8 years and continuous therapy 9.1 years (Crook et al., 2012).

It is not known what causes prostate cancer, the only established risk factors being age, race (African and Caribbean) and having a family history of prostate cancer. Over the last two decades, researchers have investigated a range of risk factors (Bostwick et al., 2004) that includes the intensity of exposures to a range of hazardous chemicals (Sharma-Wagner et al., 2000; Achanzar et al., 2001) including genetic factors (Cui, 2001), alcohol consumption (Lumey et al., 1998) (not in the time period but included as a starting point and for completeness), the impact of smoking over time (Giles et al., 2001), sexual activity (Dennis and Dawson, 2002), early growth, body size and body mass index (Giles et al., 2003), and to radiation (Gershkevitsh et al., 2002) (Table 1). Also,

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Table 1. Risk-factor Reviews and Risk-factor Studies

Risk-factor Reviews			Findings/ OR(95% CI)	Summary
Review Country	Method	Findings/ OR(95% CI)	Summary	
Dennis et al., (2002) USA	Meta Analysis 36 independent Studies	Overall RR=1.4; 95%CI=1.2-1.7 Syphilis RR=2.3; 95%CI=1.3- 3.9 Increasing no. of sexual partners RR=1.2; 95%CI=1.1-1.37	The data suggest an elevated relative risk of prostate cancer among men with a history of sexually transmitted infections. The risk is also associated with an increasing frequency of sexual activity, and an increased number of sexual partners. The data does not support associations with multiple marriages, age at first intercourse, or age at first marriage. It is suggested that infections may represent one mechanism through which prostate cancer develops.	
Bostwick et al., (2004) USA	In depth Review	1546 Reference citations	This review is a contemporary and comprehensive, literature-based analysis of the putative risk factors for human prostate cancer. Prostate cancer has the highest prevalence of any non-skin cancer in the human body, with similar likelihood of neoplastic foci found within the prostates of men around the world regardless of diet, occupation, lifestyle, or other factors. Essentially all men with circulating androgens will develop microscopic prostate cancer if they live long enough.	
Thursfield et al., (2010) Australia	Epidemiological Report on cancer incidence in Victoria in 2008	SR standard rate 13.5 Age Standard rate 128.7	A digest of facts and figures on cancer in Victoria, Australia in 2008. Age group by gender of cancer incidence is given as a summary table. Prostate cancer has the leading cancer incidence in males.	
Thursfield et al., (2011) Australia	Epidemiological Report on social context of cancer in Victoria for 2010	Median age at diagnosis=67years (a decrease in seven years in a decade). The median age at death=82 (78 in 1990). Diagnosed In 7 Victorian Men Aged 75years	Fact sheets of the social drivers and recent trends for the top five most common cancers and cervical cancer in 2008. These include the ageing population, early detection, and gender differences. Partner publication to previous publication.	
Thursfield & Farrugia, (2011) Australia	Epidemiological Report on cancer statistics and trends in Victoria for 2010	Incidence Rate=115.4/Survival Rate=13.3 Steady increase in survival over the last 20 years.	A digest of facts and figures on cancer in Victoria, Australia in 2010. Age group by gender of cancer incidence summary table and trends in survival.	
Thursfield et al., (2012) Australia	Epidemiological Report on estimates of survival in Victoria	5 year survival (%) PCA=91% Rate of death=13.3/Incidence Rate=115.4	Descriptive information regarding survival patterns for Victorians with cancer in 2006-2010. Prognostic information relating to staging for PCA is through the ascertainment of Gleason Scores.	
Risk-factor Studies			Findings/ OR (95% CI)	Summary
Study Country	Cases (N)	Controls (N)	Findings/OR (95% CI)	Summary
Lumey et al., (1998) USA	699	2,041	Any OR=1.2 (95%CI=0.9-1.5)	Alcohol use and prostate cancer in U.S. whites admitted between 1977 – 1991. No association was seen between prostate cancer and alcohol intake comparing ever, current and former to never drinkers, not even for the highest reported level of alcohol consumption.
Cui et al., (2001) Australia	1476	1409	Penetrance to 80yrs was the Dominant effect~70% (95% CI 57-85%) Recessive and X linked ~ 100%	Segregation analysis aiming to detect genetic factors of 1,476 population-based Australian families affected by prostate cancer at age less than 70years; accessed through population registries in Melbourne, Sydney and Perth. Approximately 1/30 (95% CI 1/80- 1/12) men would carry the dominant risk, and 1/140 (95% CI 1/220-1/90) would carry the recessive risk or 1/200 (95% CI 1/380-1/100) would carry risk, and 1/140 (95% CI 1/220-1/90) would carry the X-linked risk.
Giles et al., (2001) Australia	1498	1434	Former Smokers/Current Smokers: 1.02 (0.85-1.22)/0.82 (0.65-1.05) Moderate grade tumours: 0.95 (0.78-1.15)/0.76 (0.59-0.99) High-grade tumours: 1.28 (0.96-1.70)/1.00 (0.67-1.47)	An Australian case-control study that examines the risk of smoking and moderate and high grade prostate cancer. There was no evidence of a dose-response effect for duration of smoking, amount smoked, pack-years of smoking and years since quitting; and most OR's at the 95% confidence interval for these variables were close to unity. It was concluded that smoking was not associated with the incidence of prostate cancer.
Giles et al., (2003) Australia	1476	1409	Having a growth spurt later than friends reduced risk (odds ratio [OR] 0.79 [0.63-0.97]) and some measures of acne also gave odds ratios less than 1, for example, having facial acne scarring gave an OR of 0.67 (0.45-1.00).	Investigation of associations between prostate cancer risk and a number of markers of body growth, size and changes to size in a population-based, case-control study in Australia from 1994 to 1998. Analysis was performed on all cases and also by tumour grade. No associations were reported with measures of body size including body mass index and lean body mass at age 21 or later in adult life. Concluded that markers of delayed androgen action, such as delayed growth spurt in puberty, and markers of other androgen-dependent activity in puberty, such as facial acne scarring, are associated with prostate cancer risk but no associations with markers of adult body size and growth including lean body mass could be detected.
Dombi et al., (2010) USA	729	636	Greatest risk in USA: a Black, married man, older than 60years, with at best a high school diploma who made between \$25,000-\$65,000	Investigated the potential relationship between occupation history and prostate cancer risk in a population-based case-control study. The variables included: race, age group, smoking status, income, marital status, education and the first 15 years of employment history were examined by sequential odds ratio analysis then compared to a neural network consensus model. This work supported previous studies by finding well known demographic risk factors for prostate cancer including certain processing jobs and chemical related jobs.
White et al., (2011) USA	Cohort study 87,449		Black men: HR, 1.70 [95% CI, 1.58-1.83] Hispanic men: HR, 1.11 [95% CI, 1.02-1.20] both men were more likely to die of prostate cancer compared with white men.	An investigation to determine whether racial disparities in survival for men diagnosed with prostate cancer in Texas from 1995 through 2002. The SES measure was based on census tract data reflecting median household income, median home value, and percentages of men living below poverty, with a college education, and with a management or professional occupation. The pattern of survival disadvantage for black men held for those diagnosed with localized disease and advanced disease, and for those with an unknown stage of disease at diagnosis. Substantial racial disparities in prostate cancer survival were reported for men in Texas.
Crook et al., (2012) Canada	690 Intermittent	696 Continuous	Median Overall survival Intermittent Therapy=8.8 years/Continuous Therapy=9.1 years HR=1.02 at CI at 95%:0.86-1.21	Randomised control trial that investigated intermittent androgen deprivation for PSA elevation after radiotherapy would improve quality of life and delay hormone resistance. Concluded that intermittent androgen deprivation was non-inferior to continuous therapy with respect to overall survival.

several U.S. authors have identified racial disparities for Black men (Dombi et al., 2010) with a hazard Ratio of 1.70 (95%CI 1.58-1.83) (White et al., 2011).

Literature Review

In this update, we review in narrative form the literature between 2000 and 2012, dividing occupational risk factors into four groups: chemicals and heavy (and toxic) metals (Klaassen et al., 1996), ergonomic, physical, environmental and psychosocial factors. We reviewed a number of systematic reviews and believe they are of good strength and quality of evidence and have added subsequent articles not covered in the reviews.

The following key words and phrases were used in an online literature search of the PubMed Medline (NLM) and Medline 1996-present databases at OVID database links. Alcohol, aliphatic, alicyclic and aromatic hydrocarbon solvents, andrology, arsenic, cadmium, diet, environmental factors, ergonomic, fungicides herbicides and insecticides, heat, incidence, inconvenient & difficult work postures, ionizing radiation, lead, low frequency magnetic fields (EMF), manual handling of burdens, maximum allowable concentrations, mortality, nickel, occupational exposure, organic solvents and chlorinated hydrocarbon solvents, physical workloads, physical factors, prevalence, prevention, prostate cancer, prostate neoplasms, psychosocial factors, radiation exposure, radio frequency radiation (RFR), risk factors, risk, sedentary work, smoking, standing work, threshold, toxic metals, ultraviolet radiation and workload.

Articles published between 2000 and 2012 were reviewed and selected on the basis of their adherence to review methodology were included in this update. The reviews which have been evaluated on the strength of their methodology are listed separately to the new studies and both groups are presented in chronological order in the tables to illustrate the order and knowledge progression in which this research has been undertaken.

Heavy and toxic metals

The main chemical risk factors within this category include aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents, arsenic, cadmium, chromium, lead, nickel, fungicides, herbicides and insecticides. Past reviews have separately discussed individual elements within this category.

Table 2A lists important reviews (7 in-total) and Table 2B studies (14 in-total) related to heavy metals. An early review by Wong and Raabe (2000), which was confined to lead exposure related to petroleum workers, reported no association. Another investigation (Siddiqui et al., 2002) from India, concluded that environmental exposure of ageing males to lead might be a risk factor, but more recent studies by Lam et al. (2007) and Gwini et al. (2012) reported that lead was not associated with prostate cancer. Overall, the evidence pertaining to lead is inconsistent and it is unlikely occupational exposure to lead is associated with prostate cancer incidence.

A recent review of arsenic exposure by Benbrahim-

Tallae and Waalks (2008) suggested there was clear in vitro evidence of arsenic precipitating events leading to androgen independence during prostate cancer cell progression. However, the authors suggest there is essentially no available information on arsenic levels in the human prostatic tissue and urged that further work in this area was required.

Arsenic is a major risk factor for Blackfoot Disease (BFD), a unique peripheral vascular disease that was endemic to the south-western coast of Taiwan. A Taiwanese study (Yang et al., 2008) of BFD, arsenic exposure and prostate cancer investigated the tap-water supply system before and after replacing the use of an artesian well water source for drinking and cooking in the early 1960s. The objective of this study was to determine whether prostate cancer mortality decreased after the improvement of the drinking-water supply system by eliminating arsenic ingestion from the artesian well water. Standardized mortality ratios (SMRs) for prostate cancer were calculated for the BFD endemic area for the years 1971-2006. Results showed that mortality attributed to prostate cancer declined gradually after the improvement of the drinking-water supply system. The authors claimed a direct cause and effect relationship associated with arsenic exposure.

With respect to cadmium exposure Koyama et al. (2002) reported in a review that cadmium increases the occurrences of tumours in testis, lung, prostatic, haematopoietic tissues and injection sites. It was recently restated by the IARC that in view of positive associations observed between cadmium and cadmium compounds and cancer of the prostate, cadmium and cadmium compounds are carcinogenic to humans, and therefore are classed as Group 1 (IARC working group, 2012). Cadmium exposure is occupationally associated with nickel-cadmium battery manufacture and cadmium recovery plant smelting and is also associated with cigarette smoking; but has not been associated with prostate cancer in this instance. Verougstraete et al. (2003) in the latest available update of their systematic review did not confirm an association between cadmium exposure and prostate cancer and concluded that environmentally exposed populations were not at an increased relative risk of prostate cancer.

In 2001, Achanzar et al. (2001) investigated the intensity of exposure to a range of hazardous chemicals including cadmium and a year later Achanzar et al. (2002) investigated acquired apoptotic resistance in cadmium-transformed human prostate epithelial cells (CPTe). They hypothesized that acquired apoptotic resistance might be a key aspect of cadmium-induced malignant transformation of prostate epithelial cells and could contribute to both tumour initiation and the acquisition of aggressive characteristics subsequent to tumour formation. However, other researchers (Singh et al., 2012) have identified this self destructive cell (apoptotic) process as the key to finding a method of destroying prostate cancer cells.

In a later review of laboratory rodent studies, Waalkes (2003) described cadmium as a heavy metal of considerable environmental and occupational concern. Waalkes concluded that cadmium could cause a number of molecular lesions that would be relevant to oncogenesis

Table 2A. Toxic Metals Reviews

Review Country	Method	Findings OR(95%CI)	Summary
Wong & Raabe, (2000) Mainly USA.	Review and meta-analysis of 350,000 petroleum workers	Summary: SMR=0.98% (CI 0.94-1.03) Limitation: No length of employment	In addition to the qualitative review of individual studies, a meta-analysis was performed to combine data from individual cohort studies of petroleum workers. Elevated mortality from prostate cancer was noted in short-term workers at a U.S. refinery and in short-term workers employed in certain crafts at U.S. crude oil operations. However, the absence of an upward trend by length of employment in these workers argued against an association between exposure to petroleum products and prostate cancer. For all petroleum workers as a whole, mortality from prostate cancer was as expected.
Koyama et al., (2002) Japan	Laboratory Review	Carcinogenicity tests showed that exposure to Cd increased the occurrence of tumours in testis, lung, prostate, hematopoietic tissues, and injection sites.	Studies were reviewed on genotoxicity and carcinogenicity of cadmium (Cd), Salmonella typhimurium and Escherichia coli exposed to Cadmium (Cd) did not show mutagenicity, whereas cultured mammalian cells exposed to Cd showed mutation, DNA strand breaks, and chromosomal aberrations. All available data suggest that Cd should be reassigned to IARC Group 2A (probably carcinogenic to humans) from the current Group 1.
Verougstraete et al., (2003) Belgium	Systematic review	SMR <1.30 Cd OR=1.7 (95% CI: 1.0-3.1) SMR 99.75 Cd (1943 - 89)	The association between cadmium exposure and prostate cancer was not confirmed in the latest available updates. Studies in environmentally exposed populations do not indicate an increased relative risk of prostate cancer.
Walkes, (2003) USA and Holland	Laboratory Review	Cadmium could potentially affect all the various stages of the Carcinogenic Process, including initiation, promotion and progression.	Cadmium exposure has been linked to human prostate cancer. Most studies indicate cadmium is poorly mutagenic and probably acts through indirect or epigenetic mechanisms, potentially including aberrant activation of oncogenes and suppression of apoptosis.
Goyer et al., (2004) USA and Holland	Review 29 articles	Zinc deficiency depresses cadmium induced prostate cancer secondary to testicular toxicity. Reduction in secretion of testosterone.	Cadmium and cadmium compounds are known to be human carcinogens based on findings of increased risk to lung cancer among exposed workers, but a relationship between cancer of the prostate and/or testis in humans is unclear. The pathogenesis of prostatic cadmium carcinogenesis might include aberrant gene expression resulting in stimulation of cell proliferation or blockage of apoptosis. Activation of transcription factors such as the metallothionein gene and activation of some proto-oncogenes may enhance cell proliferation with damaged DNA. Suppression of DNA repair would add to the population of cells with damaged DNA. Chemically induced apoptosis can be blocked by cadmium, facilitating aberrant cell accumulation.
Sahmoun et al., (2005) USA	3 descriptive studies (75%) reported a positive association between cadmium and prostate cancer. 5 case-controls (50%) reported a positive association. 3 cohorts (33%) reported a positive association. 4 cohorts exposed in occupational nickel-cadmium batteries SMRs was weakly but not significantly positive: 1.26 (95% C.I.: 83-184).		This article reviews the epidemiological literature on cadmium and prostate cancer with a special focus on highly exposed occupational cohorts between 1966 and 2002. All published analytical and descriptive studies that included relevant data were reviewed in addition to the experience of cohorts highly exposed to cadmium in nickel-cadmium battery plants. In contrast to laboratory studies, epidemiological studies do not convincingly implicate cadmium as a cause of prostate cancer. Future epidemiological studies that attempt to resolve the discrepancy between laboratory and epidemiological studies of cadmium carcinogenesis may benefit from incorporating biological measures of cadmium exposure.
Huff et al., (2007) USA	Review	The basic metal cationic portion of cadmium is responsible for both toxic and carcinogenic activity, and the mechanism of carcinogenicity appears to be multi-factorial.	Available information about the carcinogenicity of cadmium and cadmium compounds is reviewed, evaluated, and discussed. Cadmium and cadmium compounds have been classified as known human carcinogens by the International Agency for Research on Cancer and the National Toxicology Program based on epidemiologic studies showing a causal association with prostate cancer, and studies in experimental animals, demonstrating that cadmium causes tumours at multiple tissue sites, by various routes of exposure, and in several species and strains.

in various cellular model systems. However, other investigations indicate cadmium to be poorly mutagenic and probably acting through indirect or epigenetic mechanisms, potentially including aberrant activation of oncogenes and suppression of apoptosis. A later review (Goyer et al., 2004) concluded that suppression of DNA repair added to the population of cells with damaged DNA and chemical-induced apoptosis could be blocked by cadmium, facilitating aberrant cell accumulation. These hypotheses gained further support (Achanzar et al., 2002; Nakamura et al., 2002; Platz et al., 2002; Vinceti et al., 2007) following investigations by Platz et al. (2002) and Nakamura et al. (2002). Further investigations have suggested that a combination of lead and cadmium may initiate the development of prostate cancer due to their combined effect on testosterone (Telisman et al., 2007).

In contrast to the earlier findings, Huff et al. (2007), Van Wijngaarden et al. (2008) and Li et al. (2011) failed to implicate cadmium in prostate carcinogenesis. Although Li et al. (2011) did suggest there was a dose response relationship with carcinogenesis at other organs. Other studies have examined the zinc: cadmium ratios (Drasch et al., 2005, Anetor et al., 2008) and the possibility that reduced selenium uptakes may have a more pronounced effect in the presence of high cadmium levels. Lee et al. (2009) proposed that a cysteine-rich protein called metallothionein (MT) binds heavy metals (such as cadmium) and would, thus, protect against prostate cancer.

Sahmoun et al. (2005) in a review of 15 studies concluded that in contrast to laboratory studies, epidemiological studies do not convincingly implicate cadmium as a cause of prostate cancer and suggested that incorporating biological measures of cadmium exposure in epidemiological studies might remove this discrepancy.

A further metal of interest that may be associated with prostate cancer is hexavalent chromium, which has been classified as an IARC group 1 carcinogen since the 1980s. Trivalent chromium compounds are not considered carcinogenic and are necessary for sugar and lipid metabolism. In the review update period we found no reviews or studies addressing chromium compounds and prostate cancer.

Chemical exposures

A number of other miscellaneous occupational chemical exposures have been investigated in regard to prostate cancer risk. See Table 3A and 3B for summaries on occupational chemical exposure. For example, Ruder et al. (2004) investigated mortality rates

Table 2B. Toxic Metals Studies

Study Country	Cases (N)	Controls (N)	Findings OR(95% CI)	Summary
Sharma Wagner et al., (2000) Sweden	36,269		Agriculture: SIR 1.05 95% CI 1.03-1.08 farmers: SIR 1.07 95% CI 1.04-1.10 soap and perfume manufacture, SIR 1.46 95% CI 1.10-1.89 leather processing: SIR 1.18 95% CI 1.00-1.48	Occupation and prostate cancer risk in Sweden. Linked prostate cancer cases reported to the Swedish National Cancer Registry during 1961 to 1979 with employment information from the 1960 National Census. Standardized incidence ratios for prostate cancer, within major (1-digit), general (2-4 digit), and specific (3-digit) industries and occupations, were calculated. Significant excess risks were seen for agriculture-related industries, soap and perfume manufacture, and leather processing industries. Significantly elevated standardized incidence ratios were also seen for the following occupations: farmers, leather workers, and white-collar occupations. The results suggested that farmers, certain occupations and industries with exposures to cadmium, herbicides, and fertilizers and men with low occupational physical activity levels have elevated prostate cancer risks.
Achanzar et al., (2001) USA	Laboratory Investigation		Malignant transformation of the non-tumorigenic human prostate epithelial cell line RWPE-1 by <i>in vitro</i> cadmium exposure.	The cadmium-transformed cells exhibited a loss of contact inhibition <i>in vitro</i> and rapidly formed highly invasive and occasionally metastatic adenocarcinomas upon inoculation into mice. The transformed cells also showed increased secretion of MMP-2 and MMP-9, a phenomenon observed in human prostate tumours and linked to aggressive behaviour. Cadmium-induced malignant transformation of human prostate epithelial cells strongly fortifies the evidence for a potential role of cadmium in prostate cancer.
Platz et al., (2002) USA	115	227	OR=459/54.5ppm OR=155/164ppm	Age matched controls. Toenail samples tested. Supports the hypothesis that cadmium exposure increases PCa, in the presence of a low zinc intake.
Nakamura et al., (2002) USA	Laboratory Investigation		Tumours characterized histologically as poorly-differentiated adenocarcinomas, expressing prostate-specific antigen (PSA), androgen receptor (AR), prostate stem cell antigen (PSCA), NKX3.1 and cytokeratin 8 (CK8).	Epidemiological and animal studies have suggested its carcinogenic potential on the prostate. Non-tumorigenic human prostate epithelial cells (pRNS-1-1) immortalized by simian papovavirus (SV40) were transformed after repeated exposures to cadmium. Such transformants showed morphological alterations, anchorage-independent growth <i>in soft agar</i> , and formed tumours when transplanted into SCID mice. These findings provide evidence of malignant transformation of human prostate epithelial cells exposed to this environmentally important chemical.
Siddique et al., (2002) India	x	x	Prostate (r = 0.77, P < 0.05) BPH (r = 0.32, P < 0.05) and normal (r = 0.30, P < 0.05).	Evaluating the possible role of environmental exposure to lead as a risk factor for prostate pathology in patients suffering from prostate cancer and benign prostatic hyperplasia. BpB was significantly higher in PCA and BPH cases than usual. Blood levels of zinc and copper were significantly lower in PCA and BPH cases when compared with controls. However, positive association between blood lead and TBARS was relatively higher in PCA patients than in BPH and normal. These results seem to suggest for the first time that environmental exposure of aging males to lead may be a risk factor for prostate cancer and/or benign prostatic hyperplasia possibly through generation of reactive oxygen species and/or reducing the level of zinc which acts as a cellular growth protector.
Achanzar et al., (2002) USA	Laboratory Investigation		CTPE cells exhibited increased resistance to apoptosis induced by cadmium, cisplatin, and etoposide. CTPE cells also exhibited lower caspase-3 activity vs. RWPE-1 after etoposide treatment.	Performed molecular comparisons between the cadmium-transformed prostate epithelial cell line CTPE and the nontumorigenic parental line RWPE-1. Ribonuclease protection assays confirmed global down-regulation of caspase gene expression in CTPE. CTPE cells exhibited altered expression of important apoptotic regulators as well as resistance to several apoptotic stimuli. It was hypothesized that acquired apoptotic resistance may be a key aspect of cadmium-induced malignant transformation of prostate epithelial cells and that this may contribute to both tumour initiation and the acquisition of aggressive characteristics subsequent to tumour formation.
Drasch et al., (2005) USA	129	Lab. Study	Normal Se: Cd 1:1 PCa Se: Cd < 1:1	A laboratory study of prostate glands from deceased men between 15-90 years indicated a lower risk with moderate to high zinc intake. The excessive accumulation of Cadmium in the prostates of smokers along with sub-optimal selenium intakes could explain why smokers develop more aggressive and lethal forms of prostate cancer than nonsmokers.
Vincenti et al., (2007) Italy	40	58	OR 3 rd quartile 1.3 OR 4 th quartile 4.7 p=0.004	A study supporting Platz et al. (2002) study on Cadmium toe nail clipping levels. Both support the hypothesis that cadmium exposure increases PCa.
Lam et al., (2007) USA	86	3072	Cancer SIR 0.51 (0.41-0.62) CaP SIR 0.35 (0.20-0.57)	USA study on occupational exposure to lead is not associated with Cancer. Limitations: healthy worker effect.
Telisman et al., (2007) Croatia	240		BpB Median 49 Micro g/L Range: 11-149 Micro g/L	Blood Lead (BpB) levels were ascertained. Results in line with general populations worldwide. The observed significant synergistic effect of BpB and BcD initiates the development of PCa because testosterone augments the progress of PCa in its early stages.
Benbrahim-Fallaa et al., (2008) USA	Clinical Report and review		Indicates more of an environmental problem than an occupational exposure problem.	The prostate is a target for inorganic arsenic carcinogenesis. Inter and Intra-racial differences promote prostate cancer incidence and mortality rates world-wide. Foundry Workers (Copper) had a higher PSA level.
Yang et al., (2008) Taiwan	79	Time Series	The estimated slope for the SMR (rate of decrease per year) in the linear time trend analysis was - 5.33 and significant.	Taiwan study (1971-2006) which examined the effects of the improvement in water supply. Mortality from PCa declined gradually after use of clean water. This is seen as a cause and effect result concerning Arsenic.
Anetor et al., (2008) Nigeria	55	41	Zn: Cd (p<0.001)	Study on tobacco smoke and cadmium. They hypothesize that increased Cadmium: Zinc ratio is a potential biomarker for PCa.
Van Wijngaarden et al., (2008) USA	422	1,320	An increase in 1 micro g/g creatinine cadmium exposure was associated with a 35% increase in PSA level.	2001-2002 National Health and Nutrition Examination Survey (NHANES). Little evidence for an association between cadmium and elevated PSA level was observed. Zinc is protective in cadmium exposure. When zinc levels decline PSA levels increased when cadmium levels remained high.
Lee et al., (2009) Taiwan	18	35	MT expression in patients with BPH was 3.4-fold higher than in those with CaP	Cysteine-rich protein called metallothionein (MT) which binds heavy metals and is protective for PCa. Additional studies are needed to reveal the factors that influence the expression of MT in prostate epithelial cells, and to analyze the free and compound forms of Cd at the same time.
Singh et al., (2012) India	Laboratory Investigation		Protection of N-acetyl cysteine (NAC) against ROS clearly suggested the implication of ROS in hyper-activation of apoptosis and cell death.	This study was designed to investigate the possible mechanisms of apoptosis induced by bisulfenylated stabilized CdS QDs (denoted as "bsCdS QDs") in human prostate cancer LNCaP cells. The authors conclude that biologically stabilized CdS QDs bear the potential of its applications in biomedicine, such as tumour therapy specifically by inducing caspase-dependent apoptotic cell death of human prostate cancer LNCaP cells.
Li Quian et al., (2011) China	1403 Men		Compared with urinary Cd < 3.0 µg/g Cr group, the HR of 5.0-9.9 µg/g Cr and ≥ 10.0 µg/g Cr groups were significantly increased after adjustment for age in both sexes: 1.24 (95% CI 1.01-1.51) and 1.48 (95% CI 1.17-1.90) for men; The most frequent cause of death was malignant neoplasm in men.	This study aimed to assess the influence of environmental exposure to Cd on long term outcome of inhabitants living in an area polluted by Cd. The subjects were divided into 4 groups according to the amount of urinary Cd level (<3.0 µg/g Cr, 3.0-4.9 µg/g Cr, 5.0-9.9 µg/g Cr, and ≥10.0 µg/g Cr). Mortality was calculated by the person-years method. Hazards ratios (HR) and 95% confidence intervals (CI) were assessed by the Cox's proportional hazard model. These results suggest a dose-response relationship between Cd body burden and mortality for cardiovascular diseases, cerebro-vascular diseases and nephritis. The sample size for Prostate cancer was n=3 and was not significant.
Gwini et al., (2012) Australia	406	4114	Overall death SMR= 111; 95% CI, =101-123 GI deaths SMR= 167; 95% CI= 110-250 deaths from SMR= 135; 95% CI= 105-174 external causes	This cohort study measures mortality and cancer incidence in a cohort of lead-exposed workers by using blood lead levels to assess exposure. Subjects were matched to cancer and death registries. Observed death and cancer incidence rates were compared with population rates to obtain standardized mortality ratios (SMR) and standardized incidence ratios (SIR). Overall mortality was elevated. Although incidence rates of overall cancer were low, further studies and analysis are required to investigate any biologically plausible associations between inorganic lead and liver or oesophageal cancer.

Table 3A. Chemical Reviews

Review Country	Method	Findings OR(95% CI)	Summary
Van Maele-Fabry et al., (2006) Belgium	Meta Analysis of 18 studies published between 1984 and 2004.	OR = 1.28 [95%CI (1.05-1.58)].	A review of cohort studies that examined the occurrence of prostate cancer in pesticide manufacturing workers in order to undertake a qualitative and quantitative evaluation of the risk as well as to assess the level of epidemiological evidence for each class of chemical compounds. After stratification by specific chemical class, consistent increases in the risk of prostate cancer were found in all groups but statistical significance was reported only for accidental or non-accidental exposure to phenoxy herbicides contaminated with dioxins and furans. There was no obvious indication of publication bias. The overall meta-analysis provides additional quantitative evidence consistent with prior reviews focusing on other groups exposed to pesticides (farmers, pesticide applicators). The results again point to occupational exposure to pesticides as a possible risk factor for prostate cancer but the question of causality remains unanswered.
Mink et al., (2008) USA	A Review of eight cohort studies and five case control studies.	No meta-analysis	A review of the epidemiologic literature to evaluate the hypothesis that agricultural exposure to pesticides is causally associated with prostate cancer risk. Despite sporadic positive findings, these studies did not show consistently increased risks to support a causal association between agricultural pesticide use and prostate cancer. It is clearly not possible to exonerate any particular pesticide as a putative cause of prostate cancer - to do so would require an inverse empirical association with an upper confidence limit below the null value. Existing evidence does not point to any pesticide as satisfying widely used guidelines for establishing causation: a strong, exposure-dependent and demonstrably unconfounded, unbiased association, documented in several studies.
Prins, (2008) USA	Commentary	No meta-analysis	This author suggests there is increasing evidence both from epidemiology studies and animal models that specific endocrine-disrupting compounds may influence the development or progression of prostate cancer. In large part, these effects appear to be linked to interference with oestrogen signalling, either through interacting with ERs or by influencing steroid metabolism and altering oestrogen levels within the body. In humans, epidemiologic evidence links specific pesticides, PCBs and inorganic arsenic exposures to elevated prostate cancer risk. There appears to be heightened sensitivity of the prostate during the critical developmental windows including in-utero and neonatal time points as well as during puberty. Thus infants and children may be considered a highly susceptible population for ED exposures and increased risk of prostate cancers with aging.
Ndong et al., (2009) France	Review	No meta-analysis	Diverse studies have consistently demonstrated a higher risk of prostate cancer in agricultural populations than in the general population. The hypothesis that this higher risk is linked to the use of pesticides has been tested in a number of studies, mostly in North America and Europe. However, to date, with a few possible exceptions, it has been impossible to demonstrate a significant association between exposure to pesticides or a chemical family of pesticides and prostate cancer.
Soto & Sonnenschien., (2010) USA	Review of over 70 studies as a result of the 1991 Wingspread Conference	No meta-analysis	Highlights the carcinogenic properties of Environmental endocrine disrupting chemicals (EDC's) . Exposures to EDC's generate prostate cancer. Looks at the dose effect response at different ages. Examines the usefulness of the adoption of mathematical modelling and computer simulation afforded by system biology approaches. Calls for public health policy on the reduction of the use of EDC's .
Park et al., (2010) South Korea	Meta-Analysis	Significant decreased deaths from all cancers (SMR = 0.75, 95% CI = 0.62 - 0.90)	Investigate the relationship between low external doses of ionizing radiation exposure and the risk of cancer mortality among nuclear power plant worker from 1990 to January 2009. A total of 11 epidemiologic studies were included. The findings of this meta-analysis were similar with those of the 15 Country Collaborative Study conducted by the International Agency for Research on Cancer. Further studies are needed to clarify the low SMR of cancers, for which there is no useful screening tool, in nuclear power plant workers.
Sathiakumar et al., (2011) USA	Review of 36 studies on mainly atrazine exposure.	No meta-analysis	This is an update of a previous review of epidemiological evidence pertaining to the human carcinogenic potential of triazine herbicides. In the 36 studies evaluated, atrazine was the most common triazine investigated. Non-Hodgkin lymphoma, prostate cancer, and breast cancer were most frequently investigated. Collectively, the available epidemiology studies do not provide consistent, scientifically convincing evidence of a causal relationship between exposure to atrazine or triazine herbicides and prostate cancer in men. Based upon the assessment studies, there is no scientific basis for inferring the existence of a causal relationship between triazine exposure and the occurrence of cancer in humans.
Budnik et al., (2012) Germany	Systematic review	Overall, exposure to methyl bromide is associated with an increased risk of prostate cancer.	Although ozone-depleting methyl bromide was destined for phase-out by 2005, it is still widely applied as a consequence of various critical-use-exemptions and mandatory international regulations aiming to restrict the spread of pests and alien species (e.g. in globalized transport and storage). Focus is on toxic (especially chronic) or carcinogenic effects from the use of methyl bromide, on bio-monitoring data and reference values. Only 91 referred to toxicity of methyl bromide and 29 used the term "carcinogenic", "neoplastic" or "mutagenic". Both the epidemiological evidence and toxicological data suggest a possible link between methyl bromide exposure and serious health problems, including prostate cancer risk from occupational and community exposure. The environmental risks of methyl bromide are not in doubt.
Mullins & Loeb, (2012) USA	Review	No Meta-Analysis Overall, no specific environmental or occupational exposure has been definitively shown to cause CaP.	This manuscript reviews the literature on environmental exposures and CaP. While no definitive causative evidence linking CaP and Agent Orange exists, the United States Department of Veteran Affairs considers CaP as related to Agent Orange exposure. While a causative relationship between pesticide exposure and CaP has not been established, the data do suggest that men with significant pesticide exposure may be at increased risk and should be carefully screened. Despite some data demonstrating a direct association between cadmium and CaP risk, the literature does not convincingly implicate cadmium as a cause of CaP. Limiting excessive exposure to cadmium and lead likely has a beneficial impact on overall health and possibly prostate health.

for workers in plastic boat building plants in Ohio and reported excess mortality for prostate cancer associated with styrene exposure. In 2004, Zeegers et al. (2004) reported an increased prostate cancer risk for rubber workers but it was not statistically significant. Manufacturers of rubber tyres use rubber, coal black, sulphur, phenolic resins, chlorine, sulphuric acid and cobalt compounds which would make it difficult to identify a causative agent. A further mortality study (Hauptmann et al., 2004) reported an elevated risk in formaldehyde industry workers for prostate cancer but a dose-response relationship was not reported. Rybicki (2006) reported that petroleum workers with high polycyclic aromatic hydrocarbons (PAH) exposure, and who carry the GSTP1 Val (105) variant allele, were at increased risk of prostate cancer, especially if aged under 60 years or had a family history of the disease. A small Australian case control study (Fritschi et al., 2007) reported non-significant excess risks of prostate cancer associated with occupational exposure to oils other than mineral oil. But a recent USA study (Koutros et al., 2011) reported significant associations between petroleum and prostate cancer. In mining, Girschik et al. (2010) reported Australian miners had a statistically significantly reduced risk of prostate cancer, which may be explained by the healthy worker effect.

More recently, exposure to PAHs was implicated in prostate carcinogenesis by a prospective study of 15 million Scandinavians that reported elevated SIRs (Pukkala, 2009) for chimney sweeps and hairdressers. Chimney sweeps are exposed to carcinogens such as PAHs from chimney soot and the work environment of hairdressers has also varied over time with respect to exposure to chemical agents.

In the vehicle manufacturing industry, mortality rates are reported to be higher than expected for workers in casting operations (Delzell et al., 2003) where exposure to oil-based fluid use is part of the production process. Exposure of auto industry workers to oil-based fluids was reported to be modestly associated with prostate cancer with a latency period of at least 25 years (Agalliu et al., 2005a; 2005b). Prince et al. (2006) reported that electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs) had increased prostate cancer mortality associated with cumulative PCB exposure.

We identified three recent reviews by Van Maele-Fabry et al. (2006) Mink et al. (2008) and Ndong et al. (2009) of exposure to pesticides, herbicides and insecticides. The first review by Van Maele-Fabry et al. (2006) included 18 cohort studies of prostate cancer risk in pesticide manufacturing workers. A qualitative

and quantitative evaluation of the risk was assessed together with the level of epidemiological evidence for each class of chemical compounds used between 1984 and 2004. Meta-analyses were performed for each chemical class separately, resulting in a meta-rate ratio estimate for all studies of 1.28 (95%CI= 1.05-1.58). Consistent increases in the risk of prostate cancer were observed for all chemical classes but statistically significant increases in risk were observed only for exposure to phenoxy herbicides contaminated with dioxins and furans, and a recent study (Burns et al., 2011) reported fewer cancer cases were observed than expected.

Mink et al. (2008) analyzed eight cohort studies and five case-control studies that quantified and/or evaluated agricultural exposure to particular pesticide classes or chemicals. Although there were some positive findings, these studies did not show sufficiently consistent increased risks to support a causal association between agricultural pesticide use and prostate cancer. Mink et al. (2008) argued strenuously those studies of prostate cancer that use an 'external' comparison group must be interpreted in the context of confounding by differences in prostate-specific antigen (PSA) screening intensity. They further identified that most studies failed to adjust for potential confounders other than age and time period and concluded that it was clearly not possible to exonerate any particular pesticide as a putative cause of prostate cancer.

Studies of agricultural workers have consistently demonstrated a higher risk of prostate cancer compared with the general population (Ndong et al., 2009). The hypothesis that risks to agricultural workers might be linked to the use of pesticides has been investigated in a number of studies, mostly in North America and Europe. With only a few limited exceptions such as Koutros et al. (2010a; 2011) it has not been demonstrated that a significant association between exposures to pesticides, or a chemical family of pesticides, and prostate cancer exists. The pesticides studies are summarised in Table 3 which includes limited evidence of elevated risk of prostate cancer in relation to exposure to organochlorines (Kumar et al., 2010; Sawada et al., 2010). Organochlorines, which have the capacity to move up the food chain and bioaccumulate in the fat of large animals and humans, affect the nervous system in particular and also have an association with prostate cancer. Other authors (Prins, 2008) have indicated that infants and children may be considered susceptible to Endocrine Disrupting Chemical (EDC's) exposure and increased risk of prostate cancer with aging. Soto and Sonnenschein (2010) have reported that exposure to EDC's generates prostate cancer as well as other cardiovascular and thyroid endocrinology.

Of recent interest is the finding of a novel study (St-Hilaire et al., 2010) of weather patterns in the USA that finds there is a higher rate of prostate cancer in the North, than in the South of the USA. The study relates this finding to organic pollutants and pesticides that are endocrine disrupting chemicals.

Insecticides (2003) also showed an increase in risk among farmers exposed to organochlorine insecticides and acaricides (OR=2.5, 95%CI=1.4-4.2) and DDT (OR=2.1, 95%CI=1.2-3.8) and dicofol, (OR=2.8, 95%CI= 1.5-5.0).

Recently a study (Cockburn et al., 2011) reported an association between prostate cancer and methyl bromide OR=1.62 (95%CI=1.02-2.59) and a review (Budnik et al., 2012) on methyl bromide, which was used as a soil fumigant against pests, reported it to be significantly associated with prostate cancer with an OR of 1.21 (95%CI 0.98-1.49) but the p value was >0.05.

A number of other studies have examined the more recently available and commonly used organophosphate insecticides which include the early biological warfare agents such as nerve gas or the more modern Sarin gas. Organophosphate insecticides used primarily in farming affect acetylcholine control in nerve stimulation, such as Phorate (sometimes in combination with family history, (Mahajan et al., 2006b) Fonfos (Mahajan et al., 2006a; Koutros et al., 2010b; Barry et al., 2011; 2012), Coumaphos (Christensen et al., 2010) and fumigants, such as triazine herbicides (Mills and Yang, 2003), all were reported to contribute to a small increased risk of prostate cancer. Atrazine was also investigated by Hessel et al. (2004) but no association was reported with prostate cancer. This was supported recently by Sathiakumar et al. (2011), who indicated that there was no scientific basis for inferring the existence of a causal relationship between triazine exposure and the occurrence of cancer in humans. Pesticides in general have been investigated by a number of researchers (Boers et al., 2005; Fritschi et al., 2007; Strom et al., 2008; Lynch et al., 2009; Subahir et al., 2009; Xu et al., 2010; Band et al., 2011) with some studies reporting weak associations with prostate cancer and another (Mullins et al., 2012) concluding overall there are no specific environmental or occupational exposure identified that causes prostate cancer.

A recent study from Martinique (Landau-Ossondo et al., 2009) considered that pesticides and especially organochlorine pesticides could be causally associated with prostate cancer due to their carcinogenic properties. This was also supported by Xu et al. (2010) and suggested a reduction in world-wide use of OC's. However, two other studies, Boers et al. (2005) and Fritschi et al. (2007) failed to find a significant association with pesticides. Furthermore, no association is reported with cyanazine exposure (Lynch et al., 2006) or metachlor exposure (also found in surface and ground water). Metachlor was reported to have a significantly decreased relative risk with prostate cancer (2006). Aronson et al. (2010) and Sawada et al. (2010) also suggest that long term low-level exposure to organochlorine pesticides and PCBs in the general population does not contribute to increased prostate cancer.

A recent Australian study by Macfarlane et al. (2009) examined the occupational classification of workers who were exposed to pesticides and concluded that only about 30% of farm workers actually came in contact with pesticides, herbicides or insecticides and, therefore, the level of pesticide exposure for this group of workers may be over estimated.

Ergonomic factors

Ergonomic factors include inconvenient and difficult work postures, manual handling of burdens, occupational

Table 3B. Chemical Studies

Study Country	Cases (N)	Controls (N)	Findings OR(95%CI)	Summary
Delzell et al., (2003) UK	40,131 obs. deaths	43,859 expected deaths	Prostate Cancer (SMR = 128, CI = 102-158)	198,245 motor vehicle industry workers during the period of 1973 to 1995. Mortality rates were higher than expected for prostate cancer in casting operators.
Mills et al., (2003) USA	222	1110	CaP in Mushroom Farmers OR=1.91, (95% CI = 0.87-4.18)	Farm workers with relatively high levels of exposure to organochlorine, organophosphate pesticides, fumigants, or triazine herbicides experienced elevated risk of prostate cancer compared to workers with lower levels of exposure.
Settimi et al., (2003) Italy	124	659	PCa & Tob. (OR=2.1, 95%CI=1.4-4.1) PCa & Chem. (OR=2.2, 95%CI=0.7-7.2) OCl & acaricide (OR=2.5, 95%CI=1.4-4.2) Dicofof (OR=2.8, 95%CI=1.5-5.0)	Prostate cancer is related positively to food and tobacco and chemical products industries. The association between different types of pesticides and prostate cancer showed increased risks among farm-ers exposed to organochlorine insecticides and acaricides, more specifically to the often contemporary used compounds DDT, and dicofol, whose effects could not be well separated.
Ruder et al., (2004) USA	860 deaths	5,204 workers	Deaths SMR 1.09, 95% CI 1.02-1.17 PCa SMR 1.71, 95% CI 1.09-2.54	A cohort study, in which 5,204 workers exposed to styrene between 1959 and 1978 at two reinforced plastic boatbuilding plants. Unanticipated excess urinary tract cancer and respiratory disease mortality, possibly associated with styrene exposure, were difficult to interpret and could be chance findings. Excess mortality for CaP.
Zegers et al., (2004) Holland	830	1525	RR = 4.18 (99% CI = 0.22-80.45) Rubber RR = 3.91 (99% CI = 1.14-3.42) Policemen RR = 4.00 (99% CI = 1.19-13.37) police last profession	Prospective cohort study (N=58,279) who reported to have ever worked in the rubber industry, it was reported that a substantially increased prostate cancer risk, but not statistically significant. For policemen, they reported a substantial and marginally statistically significant increased prostate cancer risk, especially for those who reported working as a policeman for most of their occupational life or as the last profession held at baseline.
Hauptmann et al., (2004) USA	1,921 deaths	25,619 workers	Pop. SMR = 0.91 Study SMR = 0.78	Cohort study of mortality from solid cancers among workers in formaldehyde industries. Although relative risks for prostate cancer (145 deaths) were elevated for some measures of formaldehyde exposure, the trend was inconsistent. Some evidence was reported of an exposure-response relation with mortality from other cancers but not for cancer of the prostate.
Hessel et al., (2004) USA	12	130	OR = 8.54; (95% CI 1.69-82.20) > ω = 1	A study of prostate cancer and atrazine exposure. Cases had more PSA tests than control subjects. There was no association between atrazine exposure and prostate cancer when those with > ω = 1 test were compared.
Agalliu et al., (2005) USA	872	4,360	RR = 2.4 per 10 mg/m ³ -years	Risk of prostate cancer linearly increased with exposure to straight Autoworkers exposed to Metal Working Fluid (MWF) and at a young age also had an increased risk associated with MWF exposure incurred later in life. For soluble MWF there was a slightly increased risk in the third window.
Agalliu et al., (2005) USA	872	4,360	RR= 1.12 per 10mg/m-years of exposure (95% CI 1.04-1.20)	Exposure to oil-based fluids, soluble and straight, is modestly associated with prostate cancer risk among autoworkers, with a latency period of at least 25 years.
Bovers, (2005) Holland	1386	2335	metal dust (RR 1.01; 95% CI 0.72 to 1.40) metal fumes (RR 1.11; 95% CI 0.80 to 1.54)	When comparing the highest tertile of exposure with no exposure there was a negative association for pesticides. No association was reported for occupational exposure to PAHs, diesel exhaust, metal dust, metal fumes and mineral oil.
Prince et al., (2006) USA	146	14458	PCa - 34 deaths, SMR 1.04; (95% CI, 0.72-1.45), increased with Cum. Exposure. (trend p-value=0.0001)	N=14,458 electrical capacitor manufacturing workers exposed PCBs. Cumulative PCB exposure was estimated using a new job exposure matrix. This was the first PCB cohort showing a strong exposure-response relationship for prostate cancer mortality.
Lynch et al., (2006) USA	20,824	57,311	PCa RR=1.23 (95% CI, 0.87-1.70)	Cancer incidence among pesticide applicators exposed to cyanazine in the Agricultural Health Study (AHS). No clear or consistent associations between cyanazine exposure and any cancer analyzed.
Rybicki et al., (2006) USA	637	244	<60 OR= 4.52 (95% CI=1.96-10.41)+FH, OR= 3.02 (95% CI=1.15-7.92).	Prostate cancer risk from occupational exposure to PAHs interacting with the GSTP1 Ile105Val polymorphism These results suggest men who carry the GSTP1 Val(105) variant and are exposed at high levels to occupational PAH have increased risk for prostate cancer.
Ruskeki et al., (2006) USA	50,193		PCa LTD RR=0.59 (95% CI=0.39-0.89)PCa IWL RR = 0.66 (95% CI=0.45-0.97)	No clear risk for any cancer subtype was reported for exposure to mesoalchlor. A significantly decreased RR was reported for prostate cancer in the highest category of lifetime days' exposure and in the second highest category of intensity-weighted lifetime days exposure; however, the test for trend was not significant for either exposure metric.
Mahajan et al., (2006) USA	45,372		PCa RR = 1.53 (95% CI = 0.99 - 2.37)	Although prostate cancer risk was not significantly related to phorate (a popular pesticide) use overall or among those without a family history, the risk tended to increase among applicators with a family history of prostate cancer. The observed statistical interaction suggests a gene-environment interaction between family history and phorate exposure in the incidence of prostate cancer, but other explanations are also possible.
Mahajan et al., (2006) USA	45,372		a significant dose-response trend for lifetime exposure-days (P trend=0.02), highest vs unexposed: RR=1.77 (95%CI=1.03-3.05)Interaction RR=1.28 (95%CI= 1.07-1.54)	Although prostate cancer risk was unrelated to fonfos use overall, among applicators with a family history of prostate cancer, we observed a significant dose-response trend for lifetime exposure-days. Intensity-weighted results were similar. Further study is warranted to confirm findings with respect to leukemia and determine whether genetic susceptibility modifies prostate cancer risk from pesticide exposure.
Fritsch et al., (2007) Australia	606 PCa, 400 BPH	471	BPH OR=1.39 (95%CI=1.1 to 1.84) PCa OR=1.25 (95%CI=0.96 to 1.61) Oils OR=1.54 (5%CI=0.95 to 2.51) PAHs OR=1.20 (95%CI=0.91 to 1.58) OPP'S OR=0.69 (95%CI=0.43 to 1.12).	Exposure to toxic metals at a non-substantial level increased the risk of BPH and led to a non-significant excess risk of prostate cancer. Non-significant excess risks were observed for prostate cancer after exposure to oils other than mineral oil and for BPH after exposure to PAHs. A non-statistically significant protective effect for prostate cancer was seen after exposure to organophosphate pesti-cides. No other associations were reported for either prostate cancer or BPH and no dose-response relationships were seen for the exposures investigated.
Strom et al., (2008) USA	176	174	obesity at time of diagnosis: OR = 2.50 (95% CI = 1.20 - 5.20 agricultural exposure: OR = 4.65 (95% CI = 1.97-10.97)	Increased risk of being diagnosed with advanced PCa was associated with obesity at time of diagnosis and high levels of agricultural exposure. This case-control study, the first conducted in a homogeneous Hispanic population, identified modifiable PCa risk factors, such as agricultural exposure, which may be useful in developing interventions for this understudied population. An inverse relationship between low and high activity levels.
MneFarlane et al., (2009) Australia	1172		Likely Pesticide Exposure=68%Farm Jobs & Unlikely pesticide exposure =78.3%	Most (68.8%) jobs with likely pesticide exposure were farm jobs, but 78.3% of farm jobs were assessed as having no likelihood of pesticide exposure. Classification of all farm jobs as pesticide exposed is likely to substantially over-estimate the number of individuals exposed.
Lynch et al., (2009) USA	5297	14,358	PC a RR (LD) = 2.09 (95% CI = 1.27 - 3.44) PCa +FHRR(LD) = 2.00 (95% CI=1.07-3.74)	Prostate cancer risk was significantly elevated among applicators in the highest LD category in both referent groups. A significantly elevated joint effect of prostate cancer family history and high butylate usage across both exposure metrics and both referent groups, and a non-significant, elevated interaction between butylate use and prostate cancer family history (FH).
Pukkala et al., (2009) Finland	2.8M	15 M	Domestic asst. SIR=0.79 (95%CI=0.66-0.95) Waiters SI=1.48 (95%CI=1.43-1.54) Chimney S/S SIR=1.03 (95%CI=1.03-1.17)	Chimney sweeps are exposed to carcinogens such as polycyclic aromatic hydrocarbons from the chimney soot, and hairdressers' work environment is also rich in chemical agents.
Subahir et al., (2009) Malaysia	112		Pesticide exposure OR = 5.57 (95% CI=1.75 - 17.78)	Some lifestyle and occupation factors are strong predictors of the occurrence of prostate cancer among patients in Malaysia. Whilst frequent ingestion of tomatoes and vegetables and sexual inter-course were protective.
Landau-Ossondo et al., (2009) Martinique	Epidemiological comparison of two populations demographic data		IR in France 152.7/100,000 IR in Martinique 75.3/100,000	Using a linear regression analysis, it was reported that the growth curves of incidence rates for Martinique and metropolitan France have been significantly diverging since 1983. Although a Caribbean genetic susceptibility factor may be involved in prostate carcinogenesis, this factor, because it could not have changed during the observation period, cannot per se account for the growing incidence of this cancer in the island. Pesticides and especially organochlorine pesticides may be causally implicated in the growing incidence of prostate cancer in Martinique due to their carcinogenic proper-ties.

Table 3B (continue). Chemical Studies

Study Country	Cases (N)	Controls (N)	Findings OR(95%CI)	Summary
Xu et al., (2010) USA	65	4,109	HCH (p for trend=0.02)/Trans-nonachlor (p for trend = 0.002) Dieldrin (p for trend = 0.04)	Associations between serum concentrations of OC pesticides and prostate cancer in US adults. Results were significantly associated with the risk of prevalent prostate cancer in this cohort study. These results suggest that OC pesticide exposures may have a significant effect on cancer risk. Efforts to reduce worldwide OC use are warranted.
Kumar et al., (2010) India	70	61	beta-HCH p = 0.04/gamma-HCH p = 0.008/p,p'-DDE p=0.01 advanced stages of PCA gamma-HCH (<or=T(2) vs. >or=T(3)), (p=0.04)	Higher levels of organochlorines, especially beta-HCH, gamma-HCH and p,p'-DDE might be associated with prostate cancer risk.
Ginschik et al., (2010) Australia	604	466	adjusted OR 0.35, (95% CI = 0.16 to 0.75)	In this population based case control study, miners had a statistically significantly reduced risk of prostate cancer. The systematic literature search of studies examining mining and prostate cancer reported a reasonably consistent trend of a decreased risk of prostate cancer among miners.
Aronson et al., (2010) Canada	79	329	PCB congeners+ total PCBs OR < 1.0 Most Pesticides close to null.	This case-control study suggests that long-term low-level exposure to organochlorine pesticides and PCBs in the general population does not contribute to increased prostate cancer risk.
Christensen et al., (2010) USA	1,196	44,133	PCa + (FH) RR = 2.07 (95% CI = 1.19-3.62) p-interaction = 0.005	Cumulative exposure to coumaphos (common pesticide) was not associated with cancer risk overall or with prostate cancer. In men with FH, of prostate cancer, a positive association between coumaphos and prostate cancer in both early and later periods of follow-up was observed. In men with a family history of disease, there was evidence of an association between coumaphos and prostate cancer.
Sawada et al., (2010) Japan	201	402	No statistically significant association with total prostate cancer was seen for any plasma organochlorine.	A nested case-control study using data from the Japan Public Health Center-based Prospective (JPHC) Study. A total of 14,203 men 40-69 years old who returned the baseline questionnaire and who provided blood samples were followed from 1990 to 2005 and the researchers identified 201 participants who were newly diagnosed with prostate cancer. Two matched controls for each case were selected from the cohort. The authors observed an insignificant inverse association for plasma HCB and [beta]-HCH. Total PCB in plasma was also inversely associated with advanced prostate cancer but without statistical significance.
Koutros et al., (2010) USA	776	1,444	Fonofos subjects with three or four risk alleles at rs783728 and rs4242382 had approximately three times the risk of prostate cancer (OR: 3.14; 95% CI: 1.41-7.00) compared with subjects who had zero risk alleles and never used fonofos.	Genome-wide association studies have identified 8q24 region variants as risk factors for prostate cancer. In the Agricultural Health Study, a prospective study of licensed pesticide applicators, it was observed that there was an increased Prostate cancer risk with specific pesticide use among those with a family history of prostate cancer. Also observed a significant interaction among variants on chromosome 8q24, pesticide use, and risk of prostate cancer. Insecticides, particularly organophosphates, were the strongest modifiers of risk, although the biological mechanism is unclear. This is the first report of effect modification between 8q24 and an environmental exposure on prostate cancer risk.
Koutros et al., (2010) USA	776	1,444	A significant excess of prostate cancer was seen for private applicators (SIR=1.19, 95% CI 1.14, 1.25 and commercial applicators SIR=1.28, 95% CI=1.00, 1.61).	A re-evaluation of cancer incidence among Agricultural Health Study participants. Standardized incidence ratios (SIRs) and relative standardized ratios were calculated. Although lower rates of smoking and increased physical activity probably contribute to the lower overall cancer incidence, agricultural exposures including pesticides, viruses, bacteria, sunlight, and other chemicals may increase risks for specific cancer sites.
Kumar et al., (2010) India	70	61	Higher levels of c-HCH were observed in advanced stages of prostate cancer cases (6T2 vs. 6T3), (p-value = 0.04). Dieldrin was reported significantly higher in cases with initial stages (p-value = 0.03).	Organochlorine pesticides (OCPs) and polymorphisms of xenobiotic metabolizing enzymes are reported to be associated with the possible risk of prostate cancer. OCPs are endocrine disruptors (EDs) which may act by disrupting the physiologic function of endogenous hormones and therefore possibly increase prostate cancer risk. CYP1A1 metabolizes several carcinogens and estrogens, etc. and hence polymorphism of this gene has been reported to be associated with prostate cancer risk. The researchers did not observe any correlation between prostate cancer and CYP1A1 polymorphisms. Hence, higher level of OCPs, especially b-HCH, c-HCH and p,p'-DDE might be associated with prostate cancer risk.
Sh-Hiarte et al.(2010) USA			Meteorological analysis	There exists a north-south pattern to the distribution of prostate cancer in the U.S., with the north having higher rates than the south. The current hypothesis for the spatial pattern of this disease is low vitamin D levels in individuals living at northerly latitudes; however, this explanation only partially explains the spatial distribution in the incidence of this cancer. The trends reported in this USA study suggest prostate cancer may be partially correlated with Meteorological factors. The patterns observed were consistent with what we would expect given the effects of climate on the deposition, absorption, and degradation of persistent organic pollutants including pesticides. Some of these pollutants are known endocrine disruptors and have been associated with prostate cancer.
Band et al., (2011) Canada	1,516	4,994	DDT OR = 1.68 (95% CI = 1.04- 2.70)/Simazine OR = 1.89 (95% CI = 1.08 - 3.33) Lindane OR = 2.02 (95% CI = 1.15- 3.55)	Exposure to specific active compounds in pesticide with prostate cancer patients and age-matched internal controls: The significant association between prostate cancer risk and high exposure to DDT, simazine, and lindane supports previous reports in the literature.
Barry et al., (2011) USA	776	1,444	Among men with C/T/T genotypes for rs198132, Fonofos exposure was associated with a monotonic increase in prostate cancer risk: low & high use OR=1.65 (0.91, 3.01) and no use OR= 3.25 (1.78, 5.92).	Because base excision repair (BER) is the predominant pathway involved in repairing oxidative damage, the researchers evaluated interactions between 39 pesticides and 394 tag single-nucleotide polymorphisms (SNPs) for 31 BER genes among 776 prostate cancer cases and 1,444 male controls in a nested case-control study of white Agricultural Health Study (AHS) pesticide applicators. The significant finding regarding fonofos is consistent with previous AHS findings of increased prostate cancer risk with fonofos exposure among those with a family history of prostate cancer.
Burns Et al., (2011) USA	Cohort	1256	(SIR = 0.74, 95% CI 0.57-0.94).	The researchers matched an existing cohort of herbicide 2,4-D manufacturing employees with cancer registries in three US states resulting in 244 cancers compared to 276 expected cases. Risk estimates were higher in the upper cumulative exposure and duration subgroups, yet not statistically significant. Overall, fewer prostate cancer cases were observed than expected.
Kouros et al., (2011) USA	776	1444	PCa risk (OR=3.7, 95% CI: 1.9-7.3), no petroleum (OR=1.9, 95% CI: 1.1-3.2, P interaction=0.01); petroleum oil (OR=2.1, 95% CI: 1.4-4.0, P interaction=0.01); petroleum distillate (OR=3.0, 95% CI: 1.5-6.0, P interaction=2.0x10 ⁻⁶)	The authors evaluated pesticide-SNP interactions between 45 pesticides and 1913 XME SNPs with respect to prostate cancer in the Agricultural Health Study. The investigators observed several pesticide-SNP interactions in oxidative stress and phase I/II enzyme genes and risk of prostate cancer. Additional work is needed to explain the joint contribution of genetic variation in XMEs, pesticide use, and prostate cancer risk.
Cockburn et al., (2011) USA	173	162	methyl bromide OR= 1.62, (95% CI = 1.02- 2.59) and a group of organochlorines OR=1.64 (95% CI = 1.02, 2.63)	In a population-based case-control study in California's intensely agricultural Central Valley (2005-2006), the authors investigated relations between environmental pesticide/fungicide exposure and prostate cancer. In comparison with unexposed persons, increased risks of prostate cancer were observed among persons exposed to compounds which may have prostate-specific biologic effects but not among those exposed to other compounds that were included as controls (simazine, maneb, and paraquat dichloride). This study provides evidence of an association between prostate cancer and ambient pesticide exposures in and around homes in intensely agricultural areas. The associations appear specific to compounds with a plausible biologic role in prostate carcinogenesis.
Barry, et al., (2012) USA	776	1444	Variant A allele OR=2.98; (95% CI 1.65-5.39) Pinteract 5.36 3.1024; FDR-adjusted P 5.011; Wild-type genotype (OR 2.01; 95% CI 1.31-3.10 for rs1744596; Pinteract 5.72 3.1024; FDR-adjusted P 5.009).	This article investigates interactions between pesticide exposure and 324 single-nucleotide polymorphisms (SNPs) tagging 27 NER genes among prostate cancer cases and male controls in a nested case-control study of white Agricultural Health Study pesticide applicators. Of the 17 interactions that met FDR <0.2, 3 displayed a monotonic increase in prostate cancer risk with increasing exposure in one genotype group and no significant association in the other group. Men carrying the variant A allele at ERCC1 rs2298881 exhibited increased prostate cancer risk with high versus no fonofos use. Men carrying the variant A allele at ERCC1 rs2298881 exhibited increased prostate cancer risk with high versus no fonofos use. Men carrying the homozygous wild-type TT genotype at two correlated CDK7 SNPs, rs1744596 and rs292778 (2.5 1.0), exhibited increased risk with high versus no carbofen use. While requiring replication, these findings suggest a role for NER genetic variation in pesticide-associated prostate cancer risk.

physical activity, perceived physical workloads, sedentary work and standing work. Table 4 summarizes reports that investigated ergonomic risk factors for prostate cancer. Past research has mainly focused on physical activity in the workplace. MacLennan et al. (2002) investigated the physical activity of company employees and Lagiou et al. (2008) examined the association of occupational physical activity with the risk of prostate cancer. The association with physical activity tended to be more pronounced for men aged 65 years or younger. Both research teams advised that preventive measures should focus on increasing physical activity. Strom et al. (2008) in analysis stratified by cancer stage, concluded that cases with organ-confined prostate cancer were 56% less likely to have moderate /high levels of occupational physical activity. In a cancer registry study, Flinton and Walters (2004) reported an elevated risk for working subjects with low levels of physical activity compared with a high activity group. They also reported the retired group to have a slightly elevated risk, although it was not statistically significant. This study suggested that physical activity might offer a small but significant reduction in prostate cancer risk for currently employed workers. A Canadian study, Friedenreich et al. (2004) investigated types of physical activity and reported that risks were decreased for occupational and recreational activity but were increased for household activity when comparing the highest and lowest quartiles. For physical activity performed throughout life, only that activity done during the first 18 years of life was associated with decreased risk. When the intensity of activity was examined (i.e., low, <3; moderate, 3-6; and vigorous, >6 metabolic equivalents) only vigorous activity was associated with decreased prostate cancer risk. This study provided inconsistent evidence for an inverse association between physical activity and prostate cancer. This is supported recently by Orsini et al. (2009) who concluded that not sitting for most of the time at work is associated with reduced incidence of prostate cancer.

However, Krishnadsan et al. (2007) reported that radiation workers were associated with a higher incidence of prostate cancer as opposed to aerospace workers who have higher activity levels at work which are also invariably associated with prostate cancer.

Young et al. (2009) in a systematic review on the risk of prostate cancer from whole body vibration (WBV) exposure related occupations and estimated a combined meta-rate ratio from a systematic review of five case-control and three cohort studies published between 1996 and 2004. A random effects model gave an overall pooled RR estimate of 1.14 (95%CI 0.99-1.30) based on 17 estimates of RR from the eight studies. Significant heterogeneity was found and it was concluded that the non-statistically significant increased pooled RR for prostate cancer obtained from this meta-analysis indicated that occupational exposure to WBV could not be ruled out as a possible risk factor for the disease. This conclusion is not supported by the data. All the studies included in the meta-analysis involved driving occupations that exposed participants to other risk factors such as PAHs, lack of exercise and obesity that could not be controlled

for in the analysis. The non-significant point estimate is, thus, likely to be due to residual confounding. Any future epidemiological studies on this topic need to take these issues seriously in the research design and conduct. A population-based case-control study of men in Northeastern Ontario, Canada, failed to provide evidence for significant occupational risk factors for prostate cancer (Sass-Kortsak et al., 2007) but the authors persisted in their view that whole body vibration exposures and physical activity were worth pursuing in future occupational studies.

Physical and environmental factors

Table 5A which summarises relevant reviews and Table 5B which summarises relevant studies, investigating physical and environmental factors that include heat, ionizing radiation, low frequency electromagnetic fields (hence-forth to be referred to as electromagnetic fields (EMF)), radio frequency, and ultraviolet radiation. Our literature search found no reports of studies that implicated either heat or radio frequency radiation with prostate cancer risk.

A recent meta-analysis of 11 epidemiological studies of nuclear power plant workers (Park et al., 2010) assessed the relationship between low doses of external ionizing radiation and the risk of cancer mortality. Significant decreased deaths from all cancers except prostate cancer were reported. The authors concluded that further studies were needed to clarify the low SMR of cancers, for which there is no useful screening tool for nuclear power plant workers.

A further investigation by Beal et al. (2005) reported that prostate cancer incidence was associated with working in the storage device facilities/within the facility's laboratories, but employee mortality was lower than expected. Krishnadasan et al. (2007) also suggested that radiation workers compared with aerospace workers were at increased risk of prostate cancer and this was possibly related to lower levels of physical activity. Atkinson et al. (2007) re-assessed early epidemiological studies of the UKAEA workforce that had followed up the mortality of those who worked to the end of 1979, and had reported a significant excess of prostate cancer deaths in some subsets of the cohort, particularly workers internally monitored for tritium contamination and those employed at the Winfrith laboratories. The excess seemed to have been associated with work involving heavy-water reactors. The finding of lower prostate cancer mortality levels during later observational periods led them to conclude that the early findings may have been related to chance.

Two recent reviews have investigated cosmic ionizing radiation and risk of prostate cancer (Buja et al., 2005; Ott and Huber, 2006). Ott and Huber, (2006) reviewed 20 studies in detail, 14 retrospective, 3 prospective cohort studies and 3 meta-analyses. Sixteen studies were set in the civil aviation environment, two in the military aviation environment and two in both environments. Three studies reported increased risks for pilots to develop prostate cancer but there was insufficient evidence to support the hypothesis that cosmic radiation might be the causative agent.

Table 4. Ergonomic Studies

Study Country	Cases (N)	Controls (N)	Findings OR(95%CI)	Summary
MacLennan et al., (2002) USA	46 obs. 40 exp.	1999	PCa 11/6.3 (SIR=175, CI = 87-312) A/Workers 5/1.3 (SIR=394, CI=128-920) C/Workers 6/8.0 3 (SIR=119, CI=44-260)	In a study on atrazine and other triazine herbicides, of the 11 prostate cancer cases, nine were diagnosed at an early clinical stage. Indicates no causal relationship between atrazine and PCa.
Flinton & Walters (2004) Ireland	3,008	15,737	High Activity level OR = 2.13, (95%CI = 1.29 - 3.52)	An investigation into physical activity and prostate cancer. Despite limitations in the data, an elevated risk was seen in working subjects with low levels of activity compared with the high activity group. In the retired group there was a slight elevation of risk, although it was not statistically significant. The study suggests that physical activity offers a small but significant reduction in prostate cancer risk for those people in work.
Friedenreich et al., (2004) Canada	988	1,063	OA OR=0.90 (95% CI = 0.66 - 1.22) FEYL OR = 0.78 (95% CI = 0.59 -1.04) VA OR=0.70 (95%CI=0.54-0.92)	No association for total lifetime physical activity and prostate cancer risk was reported. The risks were decreased for Occupational Activity (OA) but were increased for household activity when comparing the highest and lowest quartiles. For activity performed at different age periods throughout life, activity done during the First 18 years of Life (FEYL) decreased risk. Vigorous activity decreased prostate cancer risk.
Sass-Kortsak et al., (2007) Canada	760	1,632	LCOPA OR = 1.33 (95% CI = 1.02 - 1.74) WBV OR = 1.38 (95% CI = 1.07 - 1.78)	This study does not provide strong evidence for significant occupational risk factors for prostate cancer. Whole-body vibration (WBV) exposures, as well as physical activity (PA), may be worth pursuing in future occupational studies. Physical Activity (LCOPA) was reported to have a significant odds ratio.
Lagiou et al., (2008) Greece	PCa 320 BPH 184	246	High versus low activity for PCa OR=0.69 (95%CI=0.40-1.22) BPH OR=0.59 (95%CI =0.31-1.11)	There was a suggestive inverse association of physical activity with prostate cancer (P for trend 0.12) and a significant one with BPH (P for trend 0.04). The association of physical activity with both conditions tended to be more pronounced among men 65 years old or younger.
Strom et al., (2008) USA	176	174	OPA OR=0.44 (95%CI=0.26-0.76) Obesity OR=2.50 (95%CI=1.20-5.20)	Compared to controls, cases were three times more likely to work in jobs with high agricultural exposure, and 54% less likely to work in jobs with moderate/high occupational physical activity. Increased risk of being diagnosed with advanced PCa was associated with obesity at the time, but not with occupational physical activity.
Krishnadasan et al., (2008) USA	362	1,805	ASW OR=0.55 (95%CI=0.32-0.95) RW OR=0.95 (95%CI=0.43-2.1)	Investigating occupational physical activity and prostate-cancer incidence among workers at a nuclear and rocket engine-testing facility in Southern California. High activity levels at work were inversely associated with prostate-cancer incidence among aerospace workers (ASW), but not among radiation workers (RW). The results suggest that adult men who are more continually active at work may have a decreased risk of prostate cancer.
Orsini et al., (2009) Sweden	Fatal=190 Incidence=2,735	Total Cohort =45,887	Men who sit half of the time at work experienced a 20% lower risk (95% CI: 7-31%).	The possible benefit of lifetime physical activity (PA) in reducing prostate cancer incidence and mortality is unclear. This prospective cohort of 45 887 men aged 45-79 years was followed up from January 1998 to December 2007 for prostate cancer incidence (n: 2735) and to December 2006 for its subtypes and for fatal (n: 190) prostate cancer. Multivariate-adjusted incidence in the top quartile of lifetime total Physical Activity decreased by 16% (95% confidence interval (CI): 2-27%) compared with that in the bottom quartile. It was also observed that an inverse association between average lifetime work or occupational activity and walking or bicycling duration and prostate cancer risk for advanced prostate cancer for every 30 min per day increment of lifetime walking or bicycling in the range of 30 to 120 min per day. These results suggest that not sitting for most of the time during work or occupational activity and walking or bicycling more than 30 minutes per day during adult life is associated with reduced incidence of prostate cancer.

Buja et al. (2005) performed a meta-analysis of cosmic rays and prostate cancer risk using a random effect model for 9 cohort studies on pilots and male flight attendants. For civil pilots the meta-SIR was 1.47 (1.06-2.05) for prostate cancer. They suggested that non-occupational risk factors such as age (civil pilots are older than military pilots and cabin attendants) and disrupted sleep pattern (entailing hyposecretion of melatonin, which has been reported to suppress proliferative effects of androgen on prostate cancer cells) might be involved. Previously, an investigation of cosmic rays and risk of prostate cancer for airline pilots reported an association with the number of long distance flights (Pukkala et al., 2002), but the authors stressed that the finding needed to be confirmed and queried whether this association could be confounded by sexual activity or other factors, such as time spent in unusual locations.

When looking at the reported risk in relation to diagnostic radiation procedures and the risk of prostate cancer, Myles et al. (2008) reported a risk to patients undergoing barium enema and hip x-rays at the 5 year interval and with those with a family history, at the 20 year interval, the adjusted odds ratio for hip x-rays was 5.01 (95%CL=0.36-3.43) at the ten year interval and 14.23 (95%CL=0.53-4.02) at the 20 year interval. Unfortunately there was no reported adjustment for age. In relation to occupational exposure to radiation in treating physicians (Schiefer et al., 2009) in the seeding of the prostate,

the cumulative effect of treatment applications on the physician was such that experienced physicians could undertake 400 applications per year without exceeding the threshold value, but inexperienced physicians could only safely undertake 200 applications per year. This study had too small a sample to give more definitive associations regarding prostate cancer and occupational radiation exposure in the physicians themselves.

Electro-Magnetic Fields

A nested case-control study of US electricity utility workers investigated a possible association between exposure to electromagnetic fields or polychlorinated biphenyls (PCBs) and mortality from prostate cancer (Charles et al., 2003). It reported that workers categorized in the highest decile of EMF exposure were twice as likely to die from prostate cancer as those in lower deciles of exposure to EMFs, following adjustment for PCB exposure, race, and active work status within the past 2 years. Exposure to high levels of both EMFs and PCBs was not associated with prostate cancer mortality. They concluded that the possible association between EMF exposure and prostate cancer mortality warranted further investigation.

Ultraviolet Radiation

Evidence from various studies using different experimental approaches has been interpreted as showing

Table 5A. Physical and Environmental Reviews and Studies

Reviews Country	Cases (N)	Controls (N)	Findings OR(95%CI)	Summary
Buja et al., (2005) Italy	meta-analysis		Male cabin attendants & civil and military pilots, meta-SIRs were 3.42 (CI = 1.94-6.06). In civil pilots, meta-SIR was 1.47 (1.06-2.05) for prostate cancer.	Flight personnel are exposed to cosmic ionizing radiation, chemicals (fuel, jet engine exhausts, cabin air pollutants), electromagnetic fields from cockpit instruments, and disrupted sleep patterns.. These tumours share as risk factors, ionizing radiation, recreational sun exposure and socioeconomic status. The meta-SIRs are not adjusted for confounding; the magnitude of risk for melanoma decreased when we corrected for socioeconomic status. Age (civil pilots are older than military pilots and cabin attendants) and disrupted sleep pattern (entailing hyposecretion of melatonin, which has been reported to suppress proliferative effects of androgen on prostate cancer cells) might be involved.
Moon et al., (2005) UK	Review		No Meta-Analysis	Collectively, these data suggest the hypothesis that, UVR exposure has beneficial effects on susceptibility and outcome to a variety of complex diseases including PCa. We describe evidence from studies in various diseases, but mainly from prostate cancer patients, that supports this hypothesis, but we emphasize that, although supportive data are available, the concept is unproven. Indeed, other explanations are possible. However, given the potentially important public health implications of the hypothesis and the potential for the development of novel therapeutic modalities, we believe the concept is worthy of further investigation.
Ott & Huber, (2006) Switzer-land	Review of 20 studies 1990 - 2003, 1 retro-/prospective 13 retrospective 3 prospective cohort 3 meta-analysis studies		Seven out of nine studies reported an identical or decreased over-all risk for aviators to develop cancer of any kind compared to the general population. Three studies reported an increased risk for the development of prostate cancer.	Sixteen studies were set in the civil aviation environment, two studies in the military aviation environment and two studies were set in both environments.. Although this review reported some studies that identified higher risks for pilots to develop cancer of the skin, prostate cancer or leukaemia, there is not enough scientific evidence to support the hypothesis, that cosmic radiation is the cause for these findings. It shows to be important to include other factors in the interpretation of the results, since some of the findings may be well explained by life-style factors of the aviation community.
Young et al., (2009) Canada	systematic review and meta-analysis		The overall pooled RR estimate was 1.14 (95% CI 0.99-1.30) for the random effects model, based on 17 estimates of relative risk from the eight studies. Significant heterogeneity was reported.	The risk of prostate cancer in whole body vibration was estimated in related occupations and a combined meta-rate ratio. Five case-control and three cohort studies published between 1996 and 2004 were analysed. There was no indication of publication bias. The increased, though not statistically significant pooled RR for prostate cancer obtained in this meta-analysis indicates that occupational exposure to WBV cannot be ruled out as a possible risk factor for the disease. However, all included studies involved driving occupations with exposure to other risk factors for prostate cancer. Therefore, further epidemiologic studies are needed to better understand this association.

that, apart from harmful effects on the pathogenesis of the common skin cancers, ultraviolet radiation (UVR) might exert a beneficial effect on development of various internal cancers and other chronic diseases. Moon et al. (2005) describe evidence from studies investigating various diseases, including prostate cancer, that supports a beneficial effect of UVR, but they emphasize that the concept is yet to be convincingly established but worthy of further investigation. Other researchers such as Freedman et al. (2002) have supported this position and reported residential and occupational exposure to sunlight to be negatively and significantly associated with mortality from female breast, ovarian, prostate, and colon cancer. Bodiwala et al. (2003a) identified a combination of exposure parameters to UVR that distinguished prostate cancer patients from those with BPH. This study, however, did not investigate UVR exposure related to occupation, but a review of previously unpublished data (Bodiwala et al., 2003b) confirmed that high levels of cumulative UVR exposure, adult sunbathing, childhood sunburns and regular holidays in hot climates were each independently and significantly associated with a reduced risk of prostate cancer. Others (de Vries et al., 2007) also reported UVR exposure to significantly decrease the risk of advanced prostate cancer, indicating a possible anti-progression effect of UVR. Patients with a skin cancer on the chronically UVR exposed head and neck area and those diagnosed after the age of 60 years had decreased prostate cancer incidence rates. These results support

the hypothesis that UVR exposure might protect against prostate cancer.

Psychosocial factors

In occupational exposure research Workload refers to an individual’s workload as they perceive it. The question arises whether a worker who believes they have had a high or onerous workload over a number of years is likely to develop the disease under investigation. This includes workers who admit to continuously working more than fifty hours a week over more than twelve months at a time. The hypothesis is that associated stress over a number of years or decades could influence risk. No recent literature was identified on this exposure and prostate cancer.

Conclusions

IARC classifies the heavy or toxic metals including lead, cadmium, hexavalent chromium compounds and arsenic as carcinogenic. Blood levels of zinc and selenium and their ratio to cadmium levels seem to be intricately entwined and may point to aggressive prostate cancer diagnosis in the future, but these links require further clarification. Evidence concerning risks related to chemical exposures such as hydrocarbon solvents and pesticides remains unconvincing. Although the evidence for PAHs and PCBs is stronger, there are many specific pesticide agents that have not been significantly associated with prostate cancer. Further research to clarify the

Table 5B. Physical and Environmental Studies

Reviews Country	Cases (N)	Controls (N)	Findings OR(95%CI)	Summary
Freedman et al., (2002) USA			sunlight OR = 0.82 (95%CI=0.70-0.97)	An investigation into mortality from prostate cancer. Residential exposure to sunlight was negatively and significantly associated with mortality from prostate cancer.
Gershkevitch et al., (2002) Germany	6	3	Observational Human laboratory study	Studying the analysis of blood samples in relation to Chromosomal aberration in peripheral lymphocytes and doses to the active bone marrow in radiotherapy of prostate cancer.
Bodiwala et al., (2003) UK	PCa 453 BPH 312		78.7% increase in scores (<30) 40% increase in scores (>8)	Cohort study of two cohorts of PCa & BPH of self reported exposure. Low sunlight exposure confers increased prostate cancer risk. This study did not look at occupational exposure.
Bodiwala et al., (2003) UK	PCa 212 BPH 135		Decreased level sunbathing 5 times x PCa Risk	A confirmatory study. Exposure to ultraviolet (UV) radiation may be protective to prostate cancer. It was confirmed that higher levels of cumulative exposure such as adult sunbathing and childhood sunburns and regular holidays in hot climates were each independently and significantly associated with a reduced risk of this cancer.
Pukkala et al., (2002) Finland	466	10,051	There was an increase in the relative risk of prostate cancer with increasing number of flight hours in long-distance aircraft (p trend 0.01).	Based on a cohort of 138,405 air craft workers. Work-related factors affect cancer pattern of the pilots. A cohort of 10,051 male and 160 female airline pilots from Denmark, Finland, Iceland, Norway, and Sweden was followed for cancer incidence through the national cancer registries. It did not indicate a marked increase in cancer risk attributable to cosmic radiation.
Charles et al., (2003) USA	387	1935	EMFs OR=2.02, 95%CI=1.34-3.04 PCBs OR=1.47 (95%CI=0.97-2.24) Non-White OR = 3.67 (95%CI=2.66-5.06)	Investigated EMFs and PCBs and mortality from prostate cancer among US electric utility workers. Workers categorized in the highest 10 percent of EMF exposure were twice as likely to die from prostate cancer as those exposed to EMFs at lower levels. Exposure to high levels of both EMFs and PCBs showed no association with prostate cancer mortality. Non-White race was strongly associated with risk of prostate cancer mortality. The association between EMF exposure and prostate cancer mortality warrants further investigation.
Atkinson et al., (2007) England	475	39,546	Comparison of two data sets 1946-1979 and 1980 -1997.	Confirmed the 2004 results by the same authors in the workforce of the UK Atomic Energy Authority (UKAEA). The association of prostatic cancer with radiation dose was much less significant than in previous reports. Overall, radiation workers at UKAEA showed no excess mortality. The previously detected association of prostate cancer with high radiation dose may have been a statistical artifact or a risk associated with discontinued activities.
Beall et al., (2005) USA	6,579	120,257	Exp. deaths SMR=65 (95%CI=64-67) PCa SMR=198 (95%CI=117-313)	Cohort study of mortality with 6,579 observed deaths, for all cancers combined (2159 observed) and for other major diseases. Prostate cancer was associated with facilities/laboratories at the storage device facility.
de Vries et al., (2007) Holland		13,541	CPa SIR=0.89 (95%CI=0.78-0.99) ACPa SIR=0.73 (95%CI=0.56-0.94)	Cohort study in which skin cancer patients were at decreased risk of developing prostate cancer compared with the general population especially shortly after diagnosis. The risk of advanced prostate cancer (APCa) was significantly decreased indicating a possible anti-progression effect of UVR. UVR protects against PCa.
Myles., et al., (2008) UK	431	409	Hip x-rays 5yrs adj. OR=2.23 (95%CI=1.42-3.49) adjusted for family history of cancer, 10yrs adj. OR=5.01(95%CI=1.64-15.31) 20yrs adj. OR 14.23(95%CI=1.83-110.74)	A case-control study to investigate whether exposure to low dose ionisation radiation from diagnostic x-ray procedures could be established as a risk factor for prostate cancer. For those with a family history of cancer, exposures to hip x-rays dating 10 or 20 years before diagnosis were associated with a significantly increased risk of prostate cancer. Findings show that exposure of the prostate gland to diagnostic radiological procedures may be associated with increased cancer risk. This effect possibly modified by a positive family history of cancer which suggests that genetic factors may play a role.
Schiefer et al., (2009) Australia	4 Doctors plus 24 Patients			Radiation exposure of the treating physician during prostate seed implantation. If no other radiation exposure needs to be considered, an experienced physician can perform about 400 applications per year without exceeding the limit of 500mSv/year; for novices, the corresponding figure is about 200.

hypothesis of acquired apoptotic resistance in relation to cadmium exposure whereby the body's ability to kill off cancer cells is inhibited also needs to be clarified and tested on males.

Recent investigations of ergonomic risk factors showed high levels of occupational activity level to be beneficial and low levels to be modestly positively associated with prostate cancer risk. The association was stronger in the presence of a family history of prostate cancer which is known to be a significant risk factor and, thus, a possible confounding factor. Whole body vibration was also implicated in two articles related to physical activity, but further research on male workers will require cohort studies to provide firm evidence.

In relation to physical or environmental risk factors, for ionizing radiation all three reviews since 2002 (Buja et al., 2005; Ott and Huber 2006; Park et al., 2010) agree that there is insufficient evidence to support a relationship between ionizing radiation exposure and prostate cancer, but none could rule out the possibility of a very small risk. Several reports implicate UVR as being protective against PC. It was also concluded (Buja et al., 2005) that there were too many confounders such as age, disrupted

sleep patterns, long distance flights and unusual stopovers and the presence of such factors require to be further investigated. EMFs were reported to be related to high mortality rates for US utility workers at high exposure levels compared with lower exposure levels, but overall the mortality levels were not significantly different to unity.

Three recent reviews of pesticides and prostate cancer suggested that reported risk levels were too low to significantly implicate pesticides, although modest effects associated with pesticides could not be excluded. The major limitation of these reviews is they tend to target a single specific agent, not the full range of possible agents and few attempt to address mixtures and co-carcinogens. Unfortunately, no major reviews have been published regarding low occupational physical activity simply due to the lack of publications on this topic. Methodological difficulties in occupational and non occupational exposure to UVR have resulted in a limited number of studies investigating occupational UVR exposure and prostate cancer.

The major limitation of the occupational literature is the lack of prospective cohort studies in most areas

reviewed. The results are inconsistent from study to study and generally this is due to the reliance upon the lack of homogeneity of the case-control studies and prevalence (ecological) studies. Exposure assessment bias is a recurring limitation of many of the studies in this review, primarily due to the poor exposure assessment methodology. Many past studies have relied upon occupation or industry to describe exposure, with only a few studies using Job Exposure Matrices (JEMs) or expert assessment. Occasionally, marginally significant results are attributed to chance and significant results attributed to age or genetics. A limitation suggested by Macfarlane et al. (2009) is that the job title of "farm worker" is a poor surrogate exposure metric for pesticides, herbicides or insecticides, with serious misclassification potential for level and duration of exposure. Future studies must improve exposure assessment methodology for more meaningful results.

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