Review

Occupational Causes of Testicular Cancer in Adults

B Mester[1], T Behrens[1], S Dreger[1], S Hense[1], L Fritschi[2]

[1]Bremen Institute for Prevention Research and Social Medicine (BIPS), University of Bremen, Bremen, Germany
[2]Western Australian Institute for Medical Research, University of Western Australia, Perth, Australia

Abstract

Testicular cancer is one of the commonest cancers in men of working age, and is increasing in incidence in Europe and North America. One suggested mechanism of causation is that there is impaired differentiation of germ cells in the pre- or perinatal period, followed by malignant transformation in later life, possibly by a hormonal mechanism. Endocrine disrupting chemicals (EDCs) have been a major focus of interest for etiological research into testicular cancer because they interact with various hormonal pathways. Several EDCs including bisphenol A, phthalates, metals, polychlorinated biphenyls, and organochlorines have been investigated, but there are few studies and those that exist have not been able to assess exposure well. In addition, several studies, particularly those with better exposure assessment, have suggested that workers in electrical occupations have increased risks of testicular cancer. Electromagnetic radiation may have subthermal effects or may disrupt hormone release. Chronodisruption such as due to shift-work could potentially increase the risk of testicular cancer via disruption of hormonal cycles, but only one study has so far investigated this possibility. Lastly, solvent exposure, particularly to dimethylformamide, has been suggested to be associated with testicular cancer, but almost all these studies are based on job title only, with no specific assessment of solvent exposure. In conclusion, there is little evidence available on which to base definitive statements about occupational causes of testicular cancer. Future studies need to improve exposure assessment and develop ways to adjust for possible prenatal factors.

Keywords: Testicular neoplasm; Urogenital neoplasm; Environmental exposure; Occupational exposure; Testis

Introduction

Testicular cancer is a relatively rare cancer which is unusual in having a peak of incidence between the ages of 20 and 40 years. The incidence of testicular cancer is highest among European populations, particularly in the northern regions including the Scandinavian countries and Germany.[1] Rates in these countries have been increasing for the past few decades and are now around 8 to 9 per 100 000. Rates in other northern European countries, Australia, and the US are around 5 to 6 cases per 100 000 and are also increasing. Rates are much lower in Asian and African populations and there is little evidence of any change in these rates.[1] The changes in rates in Northern Europe may be related to perinatal exposures or to environmental exposures later in life.[2]

Many patients with cancer worry about whether their cancer was caused by their work. In particular, cancers which occur at a young age such as testicular cancer, are often linked in people's minds with their occupation at the time of diagnosis. Several studies of different designs described elevated testicular cancer risks for various occupational groups such as food preparation workers, draughtsmen, managers,

Correspondence to Lin Fritschi, PhD, Western Australian Institute for Medical Research, University of Western Australia, B block, Hospital Ave, Nedlands, Perth, Australia
Phone: +61-8-9346-1061
Fax: +61-8-9346-1818
E-mail: fritschi@waimr.uwa.edu.au

salesmen, clerical workers, electricians, policemen, fire-fighters, farmers, leather industry employees, aircraft repairmen, metal workers, and pulp and paper workers.[3-15] Some of these results were used to detect shared causative exposures, but overall little is known about the environmental and occupational causes of testicular cancer. However, the evidence we do have is continuing to grow and occupational physicians should be aware of the new and emerging possible causes of testicular cancer when a patient presents to them.

About 95% of testicular cancers are male germ-cell tumors; only 5% arise from interstitial cells. The germ-cell tumors are broadly categorized into two main groups—seminomatous germ cell tumors and non-seminomatous germ cell tumors—both presumably developing from primordial germ cells or gonocytes via carcinoma *in situ*.[16] One model for an underlying pathomechanism focuses on an impaired differentiation of primordial germ cells initiated in the pre- or perinatal period, followed by malignant transformation in later life.[17] As cryptorchidism and subfertility are associated with testicular cancer, they were—together with hypospadias— grouped (not uncontradicted) as the "testicular dysgenesis syndrome."[18-20] The responsible prenatal factors are still unknown, but endocrine disrupting chemicals (EDCs) seem to be a key.[21] Also, possible initiators for a malignant transformation from carcinoma *in situ* cells to germ-cell tumors in later life are unknown. Therefore, different possible occupational exposures with biological plausibility should be considered.

In this paper, which complements and updates a previous German review by our group on the **etiology of testicular cancer**,[22] we will summarize the literature for a selection of occupational exposures which may be linked to testicular cancer: endocrine-disrupting compounds; electromagnetic radiation; chronodisruption (disruption of sleep/wake cycles); and solvents. These exposures were chosen as they are the ones which have had the most interest and which have a potential biological basis. For each exposure, we will outline the proposed biological basis for the association and the mechanism by which each substance might cause cancer, and briefly review the existing evidence for and against each hypothesis.

Occupational Exposures

Endocrine disrupting chemicals

EDCs are substances able to interact with the human endocrine systems such as the system of the sexual hormones testosterone and estrogen. The effects can be direct by acting like the hormones themselves or indirect[23] for example by blocking the hormone-receptors or by alteration of the degradation of hormones. Pentachlorophenol, bisphenol A, and phthalates are examples of known EDCs humans are exposed to via the environment, but little is known about occupational exposure of many EDCs.

Bisphenol A: Bisphenol A is a widely used chemical in polycarbonate plastics and epoxy resins. Humans are exposed to bisphenol A by various products in daily life such as food cans. Occupational exposures occur by the production and processing of polycarbonate plastics and epoxy resins. Bisphenol A has estrogenic actions via binding to nuclear and plasma membrane-bound estrogen receptors. Bouskine[24] demonstrated that bisphenol A stimulates seminoma cell proliferation triggered through a membrane receptor belonging to the G-protein-coupled non-classical membrane estrogen receptor family. Various *in vivo* studies showed that fetal exposure to bisphenol A has several effects on the male reproductive

TAKE-HOME MESSAGE

- Testicular cancer is one of the most common cancers in men of working age, and is increasing in incidence in Europe and North America.
- A number of occupational factors have been suggested as causes of testicular cancer, including endocrine disrupting chemicals, electromagnetic radiation, chronodisruption such as shift-work, and solvents.
- Most existing studies are based on job title only, with no specific assessment of actual chemical or physical exposure, meaning that the current evidence on causation is fairly weak.
- Exposures in occupational settings are high enough to produce biological effects which may eventually lead to an increased risk for testicular cancer.

organs like a shortened anogenital distance and decreased sperm counts in test-animals.[25] Up to now, there are no results of epidemiological studies on bisphenol A and male germ cell tumors. One study on testicular cancer from Sweden first showed an excess risk for occupational exposure to polyvinyl chloride,[26] which tended to vanish in the later update.[27] Exposure to polyvinyl chloride, bisphenol A, and phthalates were discussed as possible causes for this elevated risk.[26]

Phthalates: Phthalates are esters of o-phthalic acid used as plasticizers, lubricants, solvents, and with other functions in polyvinyl chloride products and other materials in many fields of application. Exposures to humans can for example occur via gloves, personal care products, medical devices, surfactants, and paints. Information on occupational exposures is rare. A pilot biomonitoring study on urinary phthalate metabolite concentrations among workers from different industries identified workplaces with exceeding metabolite concentration for different phthalates.[28] Phthalates are anti-androgenic, but the exact mechanism is unclear. Phthalates have been shown to be associated with anomalies of the male reproductive tract after *in utero* exposure in animals[29] and in humans[30]. Two hypotheses for the underlying pathomechanism focus on the effect on fetal or adult Leydig cells leading also to testicular cancer via reduced testosterone production and decreased germ cell differentiation.[31] Studies on effects of phthalate exposure to male adults focus on decreased sperm quality and testosterone levels, but the results are inconsistent.[30] There are no epidemiological study results on phthalate exposure to adults and testicular cancer.

Metals: There are also some metals with endocrine disrupting properties such as cadmium and tributyl tin, which could be relevant occupational exposures. Parental doses of cadmium lead to testicular necrosis in rats followed by the occurrence of testicular interstitial cell tumors and loss of androgen production with potential later tumor formation.[32] There are no results on epidemiological studies on cadmium exposure and testicular cancer in humans. One epidemiological study on 88 workers exposed to wood preservatives beneath others containing tributyl tin and pentachlorophenol showed no excess risk of cancer.[33]

Organochlorines: Some organochlorines such as polychlorinated biphenyls (PCBs) and chlordane insecticides act like EDCs. Until a worldwide ban in 2001, PCBs were used in transformer oils, in hydraulic systems, and as softener in lacquers and plastics. They were also often found as

contamination in pesticides. The group of PCBs consists out of 209 congeners with different properties. Their ways of action are various, estrogenic, anti-estrogenic, androgenic and anti-androgenic.[34] Single ways of pathomechanism are unclear.

Since 1984 there have been reports of an association between work on a farm and testicular cancer.[12,35-38] However, there are also studies which have not found such an association[8,39-41] and meta-analyses[42,43] in 1992 and 1997 did not find an increased risk of testicular cancer in farmers.

Farmers are exposed to a range of potential carcinogens, including pesticides, chemical fertilizers, solvents, engine fuels and exhausts, organic and inorganic dusts, welding fumes, mycotoxins, and zoonotic viruses.[44] The most commonly-studied exposure in relation to testicular cancer is to pesticides. However, there are still only a few studies which have specifically examined pesticide exposure and the risk of testicular cancer and none have information on use of specific types of pesticides in individuals. A US study of registered pesticides applicators found a standardized incidence ratio (SIR) of 2.48 (95% CI: 1.57–3.72) which was higher in those who used pesticides in earlier years.[45] A similar register-based study in Sweden found an SIR of 1.55 (95% CI: 0.92–2.45) in agricultural workers using pesticides which again increased with time since use.[37] However, a follow-up study which included 10 more years of data found this risk had decreased to 1.09 (95% CI: 0.68–1.67).[46] A Finnish study using census data and a job exposure matrix to assign exposure to pesticides found an exposure-response relationship between pesticide exposure and seminoma.[5] No association between pesticide purchase and testicular cancer was found in a Norwegian study but there was an association with orchard and greenhouse work (SIR = 1.63; 95% CI: 1.01–2.62).[47]

Some of the interest in pesticides is due to the fact that some have endocrine-disrupting properties. This group of chemicals includes the insecticides chlordane and hexachlorobenzene, and pesticide contaminants such as poly-chlorinated biphenyls (PCBs). Case-control studies (in Sweden, Norway and the US) have examined serum organochlorines in cases as opposed to controls in post-diagnostic[48,49] and pre-diagnostic[50,51] samples. Although chlordanes have been found to be associated with seminoma in some of these studies,[48,50,51] the specific type of chlordane varies and the picture is not yet clear.

Electromagnetic fields

Epidemiological studies that have investigated the association between occupational exposure to extremely low frequency electromagnetic fields (EMF) or radio frequency (RF) and cancer are sparse. Most evidence for a positive association comes from studies of occupational exposures to EMF, but the majority of these studies focused on crude job descriptions or on putative exposure among workers in electrical trades.

Several older studies point towards higher risks of workers in electrical occupations[12,14,35] although these findings were not consistent[36,52-54]. However, more detailed estimations, *e.g.*, by using a job exposure matrix yielded increased risks, particularly for non-seminoma germ cell cancers among men under 40 years of age.[55] However, working close to overhead power lines as assessed by a detailed questionnaire did not yield an increased risk for testicular cancer in a subsequent German case-control study.[56]

The picture is also not clear for potential RF and radar exposure and germ cell tumor risk. Employees who are potentially exposed to radar-emitting sources (*e.g.*, in the military,[7,14,52,57] seamen and fishermen,[12] and policemen who used radar devices[3,58]) have shown increased incidence

rates of testicular cancer, although a direct link to RF- or EMF-exposure was not observed in these studies. Direct, albeit mostly non-significant risk increases were observed for amateur radio operators[35] and workers exposed to microwave/radio waves[40].

In contrast to radiation of higher frequency, the energy transfer resulting from EMF (frequency of 0.1 Hz to 30 kHz) and RF (frequency 300 kHz to 300 GHz) is not sufficient to break covalent bonds.[59,60] However, some authors suggested that even weak electromagnetic radiation at appropriate frequencies may trigger significant subthermal effects in biological systems resulting in a cancer-promoting effect by EMF.[60] Some experimental studies showed that EMF may have an inhibitory effect on melatonin-production in the pineal gland. Suppression of melatonin exerts an antigonadotropic effect which leads to an enhanced prolactin production in the pituitary gland.[61,62] In rats, high doses of RF radiation increased the level of plasma luteinizing hormone, although this effect was not observed among humans who use mobile phones.[63] Prolactin and luteinizing hormone are able to stimulate testosterone secretion from testicular Leydig cells, which may overstimulate testicular cells in early carcinogenesis and reduce DNA-repair, leading to a cancer-promoting effect.

In summary, most of the published evidence on the association between EMF and testicular cancer comes from older cohort and case-control studies. These studies mainly relied on rather crude exposure estimations and their findings were not consistent. Studies with more detailed exposure scenarios in which EMF-exposure was quantified in more detail tended to demonstrate increased associations with testicular cancer. However, the ubiquitous presence of EMF/RF in modern societies impedes quantification of exposure to a single source. However, it still cannot be ruled out that exposures in occupational settings are high enough to produce biological effects which may eventually lead to an increased risk for testicular cancer.

Chronodisruption

Persons who engage in night shift work tend to show altered levels of melatonin and reproductive hormone profiles due to chronodisruption, which may be associated with an enhanced risk for hormone-related cancers. In fact, an association between night shift work and endocrine cancers has been discussed for several years.[64] The biological mechanisms involved in this process may be due to reduced melatonin production caused by light at night with the subsequent steps as described previously in this paper (see EMF). The research has mainly focused on breast and prostate cancer. As for the association between shift work and testicular cancer, the only study published to date is a case-control study from the Czech Republic.[65] This showed an odds ratio of 1.48 (95% CI: 1.07–2.06) for persons who reported to have regularly worked on night shift for at least three years before diagnosis.

Solvents

The suggestion that solvents might increase the risk of testicular cancer comes from various reports examining job titles and testicular cancer. For example, a study which linked 7519 cases of testicular cancer reported to the Scandinavian cancer registries with census data on occupation found a raised risk of testicular cancer in printers (SIR = 1.25; 95% CI: 1.01–1.54).[66] A study in the Swedish pulp and paper industry found an increased risk in maintenance men but not production workers,[67] and there have been several reports of increases in testicular cancer in the leather industry[68,69]. None of these studies have

had good assessment of solvent exposure and all the subjects may well have been exposed to other agents.

A specific solvent that is discussed as a possible risk factor for testicular cancer is dimethylformamide (DMF). DMF is an organic solvent, which is primarily used during the production of acrylic fibres and plastics. Occupational exposure to DMF occurs through skin contact and inhalation of vapors.[70] Epidemiological studies that examine the association between DMF and testicular cancer are scarce, and the ones that exist are of older age. The evidence for the potential of DMF to induce testicular cancer is inconsistent.[71] Several authors have theorized that DMF induces testicular cancer,[4,10,68,72,73] however, these results have not been confirmed in epidemiological studies[74,75].

Ducatman and colleagues[4] investigated a cluster of testicular cancer cases in workers engaged in repairing electronic equipment of tactical aircrafts or conducting surface work on those aircrafts. Another case-control study was conducted within the Royal Navy, in which 110 cases of testicular cancer and 440 controls were examined. An increased risk was found for members of the fleet air arm (OR = 1.90; 95% CI: 1.04–3.48), air engineers (OR = 2.32; 95% CI: 1.20–4.48), and the aircraft handling sub-specialty (OR = 7.31; 95% CI: 1.81–29.53).[10] Similar results were found in a historical cohort study, examining the mortality of employees of an aircraft construction company. It was found that the mortality of testicular cancers in workers who were exposed to a mixture of solvents, was increased when compared with the general population.[72] In all these studies, it is speculated that the causative factor for testicular cancer might be DMF exposure in the occupational environment. However, no occupational exposure assessment was conducted, so no causative conclusions can be drawn.

Different results were found in a case-control study, which examined four different types of cancers (including testicular cancer) in relation to DMF exposure in four plants of a chemical company. No significant association between ever having been exposed to DMF and subsequent development of cancer of the testis was found.[75]

In all these studies, except for the last-mentioned,[75] there has been no specific assessment of exposure to solvents or to other occupational hazards. In addition, no biological mechanism has been suggested for this association.

Difficulties and Gaps

The literature on occupational causes of testicular cancer is sparse, and much of it is several decades old. There have been few comprehensive studies which have included detailed data on occupational factors. Two of the major problems with the existing literature are poor exposure assessment and an inability to take into account prenatal factors. These will be discussed in more detail here.

Poor exposure assessment

The biggest limitation of the existing literature on occupational causes of testicular cancer is the poor quality of the exposure assessment. In many of the studies published up until now, job title or industry has been used as a surrogate measure of exposure to specific chemical agents. On one hand, repeated findings of testicular cancer clusters in a particular industry may point towards a possible common denominator in exposure that may give rise to studies with more detailed exposure assessment. On the other hand, the obvious problem with this approach is that exposure to specific chemicals will vary within each job title or industry. Not all workers in a particular job will be exposed to each

specific chemical, and levels of exposure will also vary. This means that misclassification of exposure will occur, with "unexposed" workers classified as "exposed" which will result in a weakening of the observed effect measures.

A more subtle problem, and one which is potentially more dangerous, is the tendency to seize upon one specific exposure and assume that that is the relevant one for causation of testicular cancer. An example of this is the assumption that any increase in risk in aircraft maintenance workers is due to exposure to DMF.[4] While some workers in this job are exposed to DMF, there are also other exposures including other solvents, lubricants, and paints, which may be the actual causative agents. Another example is the focus on pesticides as the agent responsible for the possible increased risk of testicular cancer in farmers. In fact, one study in Norway which was designed to investigate the relationship between pesticide exposure in the mothers of sons with testicular cancer, found no association with pesticide exposure but an association with fertilizer exposure in the mother.[47] And a later study found that testicular cancer was more common in men who lived in areas of Denmark with high nitrate levels in the soil due to fertilizer use.[76]

Studies of job titles and industries are useful for generating hypotheses but the process should not stop there. Findings from these studies should lead to a comprehensive examination of possible exposures within the job title or industry. Focussing on one agent at an early stage of an investigation may mean that other more relevant agents are not investigated, and much time and energy is wasted on non-productive studies. For some of the exposures identified, there will be plausible biological mechanisms. The next important step is to examine these possible exposures in well-designed studies which involve high level assessment of the specific exposures. Only with such studies we can ensure that we are making correct assumptions about the causes of testicular cancer.

A further problem with the exposure assessment in existing data is one which plagues occupational epidemiology generally and that is exposure to mixtures of agents.[77] This is particularly important in the case of EDCs as multiple chemicals may have endocrine-disrupting activities and perhaps some overall measure of the effect might be a useful area of investigation.

Adjustment for prenatal factors

The dominant theory of the causation of testicular cancer is that it is part of the spectrum of "testicular dysgenesis syndrome"[19] as discussed above, although this has been criticized[18]. If so, then only those men who have already developed carcinoma *in situ* are likely to be susceptible to occupational influences in adulthood.

The important prenatal factors for testicular dysgenesis, however, are not clear. For some factors, such as cryptorchidism, the link with testicular cancer is well-established. However, the evidence is not yet definitive for many of the other factors investigated. In addition, measurement of prenatal factors is difficult. Many of the prenatal factors investigated are thought to be proxies for the fetal hormone milieu. These include the presence of morning sickness and use of hormonally-active agents during pregnancy. This will most probably not be known by the case subjects themselves. If the mother of the case is still alive, it may be possible to obtain some information from her, but the difficulties in remembering those details from many decades ago are well known. While some of the studies we have discussed above were able to adjust for some known factors such as cryptorchidism, the more

difficult prenatal factors are rarely adjusted for in the studies. In addition, in order to confound on the association with occupational exposures, an association between prenatal factors and later occupation should be present, which will unlikely be the case in the majority of the studied risk factors.

We have confined this review to direct occupational influences on the subject who developed cancer. For conditions such as testicular cancer, in which perinatal conditions may play such a large role, there is some interest in studying occupational exposures in the mother, especially around the time of pregnancy. We have not discussed this literature, as it mainly refers to testicular cancer which occurs in children not adults.

Conclusions

The knowledge regarding occupational risk factors for initiating testicular cancer in adults is limited. Most of the studies on occupational risk factors for testicular cancer focus on industries or job titles associated with increased risks. A detailed exposure assessment on single agents or chemical groups is often lacking. Further studies on occupational risks for initiating testicular cancer in adulthood should concentrate on agents with a biologic plausibility in pathomechanism and be based on refined exposure assessment methods.

Acknowledgements

This work was funded by a grant from the Group of Eight—Deutscher Akademischer Austausch Dienst Australia—Germany Joint Research Cooperation Scheme. LF is supported by a National Health and Medical Research Council (NHMRC) Fellowship.

We would like to thank Wolfgang Ahrens and Nils Schmeisser for their contributions to an earlier study on testicular cancer which helped frame this paper.

Conflicts of Interest: None declared.

References

1. Chia VM, Quraishi SM, Devesa SS, *et al*. International trends in the incidence of testicular cancer, 1973-2002. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1151-9.
2. Beiki O, Granath F, Allebeck P, *et al*. Subtype-specific risk of testicular tumors among immigrants and their descendants in Sweden, 1960 to 2007. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1053-65.
3. Davis RL, Mostofi FK. Cluster of testicular cancer in police officers exposed to hand-held radar. *Am J Ind Med* 1993;**24**:231-3.
4. Ducatman AM, Conwill DE, Crawl J. Germ cell tumors of the testicle among aircraft repairmen. *J Urol* 1986;**136**:834-6.
5. Guo J, Pukkala E, Kyyronen P, *et al*. Testicular cancer, occupation and exposure to chemical agents among Finnish men in 1971-1995. *Cancer Causes Control* 2005;**16**:97-103.
6. Knight JA, Marrett LD, Weir HK. Occupation and risk of germ cell testicular cancer by histologic type in Ontario. *J Occup Environ Med* 1996;**38**:884-90.
7. McDowall ME, Balarajan R. Testicular cancer mortality in England and Wales 1971-80: variations by occupation. *J Epidemiol Community Health* 1986;**40**:26-9.
8. Pollan M, Gustavsson P, Cano MI. Incidence of testicular cancer and occupation among Swedish men gainfully employed in 1970. *Ann Epidemiol* 2001;**11**:554-62.
9. Rhomberg W, Schmoll HJ, Schneider B. High frequency of metalworkers among patients with seminomatous tumors of the testis: a case-control study. *Am J Ind Med* 1995;**28**:79-87.
10. Ryder SJ, Crawford PI, Pethybridge RJ. Is testicular cancer an occupational disease? A case-control study of Royal Naval personnel. *J R Nav Med Serv* 1997;**83**:130-46.
11. Stang A, Jockel KH, Baumgardt-Elms C, Ahrens W. Firefighting and risk of testicular cancer: results from a German population-based case-control study. *Am J Ind Med* 2003;**43**:291-4.

12. Van Den Eeden SK, Weiss NS, Strader CH, Daling JR. Occupation and the occurrence of testicular cancer. *Am J Ind Med* 1991;**19**:327-37.

13. Walschaerts M, Muller A, Auger J, *et al*. Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. *Int J Androl* 2007;**30**:222-9.

14. Knoke JD, Gray GC, Garland FC. Testicular cancer and Persian Gulf War service. *Epidemiology* 1998;**9**:648-53.

15. Langner I, Schmeisser N, Mester B, *et al*. Case-control study of male germ cell tumours nested in a cohort of car manufacturing workers: findings from the occupational history. *Am J Ind Med* 2010 (in press).

16. Rajpert-de Meyts E, Hoei-Hansen CE. From gonocytes to testicular cancer: the role of impaired gonadal development. *Ann N Y Acad Sci* 2007;**1120**:168-80.

17. Sonne SB, Kristensen DM, Novotny GW, *et al*. Testicular dysgenesis syndrome and the origin of carcinoma in situ testis. *Int J Androl* 2008;**31**:275-87.

18. Akre O, Richiardi L. Does a testicular dysgenesis syndrome exist? *Hum Reprod* 2009;**24**:2053-60.

19. Skakkebaek NE, Rajpert-De ME, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;**16**:972-8.

20. Wohlfahrt-Veje C, Main KM, Skakkebaek NE. Testicular dysgenesis syndrome: foetal origin of adult reproductive problems. *Clin Endocrinol (Oxf)* 2009;**71**:459-65.

21. Hardell L, Bavel B, Lindstrom G, *et al*. *In utero* exposure to persistent organic pollutants in relation to testicular cancer risk. *Int J Androl* 2006;**29**:228-34.

22. Behrens T, Pesch B, Peplies J, *et al.* [Epidemiology of testicular germ cell tumors]. *Umweltmed Forsch Prax* 2006;**11**:142-56.

23. Wuttke W, Jarry H, Seidlova-Wuttke D. Definition, classification and mechanism of action of endocrine disrupting chemicals. *Hormones (Athens)* 2010;**9**:9-15.

24. Bouskine A, Nebout M, Brucker-Davis F, *et al*. Low doses of bisphenol A promote human seminoma cell proliferation by activating PKA and PKG via a membrane G-protein-coupled estrogen receptor. *Environ Health Perspect* 2009;**117**:1053-8.

25. Maffini MV, Rubin BS, Sonnenschein C, Soto AM. Endocrine disruptors and reproductive health: the case of bisphenol-A. *Mol Cell Endocrinol* 2006;**254-255**:179-86.

26. Ohlson CG, Hardell L. Testicular cancer and occupational exposures with a focus on xenoestrogens in polyvinyl chloride plastics. *Chemosphere* 2000;**40**:1277-82.

27. Hardell L, Malmqvist N, Ohlson CG, *et al.* Testicular cancer and occupational exposure to polyvinyl chloride plastics: a case-control study. *Int J Cancer* 2004;**109**:425-9.

28. Hines CJ, Nilsen Hopf NB, Deddens JA, *et al.* Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. *Ann Occup Hyg* 2009;**53**:1-17.

29. Foster PM. Disruption of reproductive development in male rat offspring following in utero exposure to phthalate esters. *Int J Androl* 2006;**29**:140-7.

30. Meeker JD, Sathyanarayana S, Swan SH. Phthalates and other additives in plastics: human exposure and associated health outcomes. *Philos Trans R Soc Lond B Biol Sci* 2009;**364**:2097-113.

31. Hu GX, Lian QQ, Ge RS, *et al.* Phthalate-induced testicular dysgenesis syndrome: Leydig cell influence. *Trends Endocrinol Metab* 2009;**20**:139-45.

32. Goyer RA, Liu J, Waalkes MP. Cadmium and cancer of prostate and testis. *Biometals* 2004;**17**:555-8.

33. Gilbert FI Jr, Minn CE, Duncan RC, Wilkinson J. Effects of pentachlorophenol and other chemical preservatives on the health of wood-treating workers in Hawaii. *Arch Environ Contam Toxicol* 1990;**19**:603-9.

34. Ulbrich B, Stahlmann R. Developmental toxicity of polychlorinated biphenyls (PCBs): a systematic review of experimental data. *Arch Toxicol* 2004;**78**:252-68.

35. Hardell L, Nasman A, Ohlson CG, Fredrikson M. Case-control study on risk factors for testicular cancer. *Int J Oncol* 1998;**13**:1299-303.

36. Swerdlow AJ, Douglas AJ, Huttly SR, Smith PG. Cancer of the testis, socioeconomic status, and occupation. *Br J Ind Med* 1991;**48**:670-4.

37. Wiklund K, Dich J, Holm LE, Eklund G. Risk of cancer in pesticide applicators in Swedish agriculture. *Br J Ind Med* 1989;**46**:809-14.

38. Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. *Lancet* 1984;**1**:207-10.

39. Brown LM, Pottern LM. Testicular cancer and farm-

ing. *Lancet* 1984;**1**:1356.

40. Hayes RB, Brown LM, Pottern LM, *et al.* Occupation and risk for testicular cancer: a case-control study. *Int J Epidemiol* 1990;**19**:825-31.
41. Jensen OM, Olsen JH, Osterlind A. Testis cancer risk among farmers in Denmark. *Lancet* 1984;**1**:794.
42. Acquavella J, Olsen G, Cole P, *et al.* Cancer among farmers: a meta-analysis. *Ann Epidemiol* 1998;**8**:64-74.
43. Blair A, Zahm SH, Pearce NE, *et al.* Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 1992;**18**:209-15.
44. Blair A, Freeman LB. Epidemiologic studies in agricultural populations: observations and future directions. *J Agromedicine* 2009;**14**:125-31.
45. Fleming LE, Bean JA, Rudolph M, *et al.* Cancer incidence in a cohort of licensed pesticide applicators in Florida. *J Occup Environ Med* 1999;**41**:279-88.
46. Dich J, Wiklund K, Holm LE. Testicular cancer in pesticide applicators in Swedish agriculture. *Scand J Work Environ Health* 1996;**22**:66.
47. Kristensen P, Andersen A, Irgens LM, *et al.* Incidence and risk factors of cancer among men and women in Norwegian agriculture. *Scand J Work Environ Health* 1996;**22**:14-26.
48. Hardell L, Van BB, Lindstrom G, *et al.* Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. *Environ Health Perspect* 2003;**111**:930-4.
49. Biggs ML, Davis MD, Eaton DL, *et al.* Serum organochlorine pesticide residues and risk of testicular germ cell carcinoma: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:2012-8.
50. McGlynn KA, Quraishi SM, Graubard BI, *et al.* Persistent organochlorine pesticides and risk of testicular germ cell tumors. *J Natl Cancer Inst* 2008;**100**:663-71.
51. Purdue MP, Engel LS, Langseth H, *et al.* Prediagnostic serum concentrations of organochlorine compounds and risk of testicular germ cell tumors. *Environ Health Perspect* 2009;**117**:1514-9.
52. Pearce N, Sheppard RA, Howard JK, *et al.* Time trends and occupational differences in cancer of the testis in New Zealand. *Cancer* 1987;**59**:1677-82.
53. Tornqvist S, Norell S, Ahlbom A, Knave B. Cancer in the electric power industry. *Br J Ind Med* 1986;**43**:212-3.
54. Tynes T, Andersen A, Langmark F. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. *Am J Epidemiol* 1992;**136**:81-8.
55. Floderus B, Stenlund C, Persson T. Occupational magnetic field exposure and site-specific cancer incidence: a Swedish cohort study. *Cancer Causes Control* 1999;**10**:323-32.
56. Baumgardt-Elms C, Ahrens W, Bromen K, *et al.* Testicular cancer and electromagnetic fields (EMF) in the workplace: results of a population-based case-control study in Germany. *Cancer Causes Control* 2002;**13**:895-902.
57. Garland FC, Gorham ED, Garland CF, Ducatman AM. Testicular cancer in US Navy personnel. *Am J Epidemiol* 1988;**127**:411-4.
58. Finkelstein MM. Cancer incidence among Ontario police officers. *Am J Ind Med* 1998;**34**:157-62.
59. Repacholi MH. Radiofrequency field exposure and cancer: what do the laboratory studies suggest? *Environ Health Perspect* 1997;**105 Suppl 6**:1565-8.
60. Sagan LA. Epidemiological and laboratory studies of power frequency electric and magnetic fields. *JAMA* 1992;**268**:625-9.
61. Shah PN, Mhatre MC, Kothari LS. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 1984;**44**:3403-7.
62. Stevens RG, Davis S. The melatonin hypothesis: electric power and breast cancer. *Environ Health Perspect* 1996;**104 Suppl 1**:135-40.
63. Black DR, Heynick LN. Radiofrequency (RF) effects on blood cells, cardiac, endocrine, and immunological functions. *Bioelectromagnetics* 2003;**Suppl 6**:S187-S195.
64. Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of the epidemiologic evidence. *Scand J Work Environ Health* 2008;**34**:5-22.
65. Dusek L, Abrahamova J, Lakomy R, *et al.* Multivariate analysis of risk factors for testicular cancer: a hospital-based case-control study in the Czech Republic. *Neoplasma* 2008;**55**:356-68.
66. Pukkala E, Martinsen JI, Lynge E, *et al.* Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;**48**:646-790.
67. Andersson E, Nilsson R, Toren K. Testicular cancer among Swedish pulp and paper workers. *Am J Ind Med* 2003;**43**:642-6.

68. Levin SM, Baker DB, Landrigan PJ, *et al.* Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* 1987;**2**:1153.

69. Marshall EG, Melius JM, London MA, *et al.* Investigation of a testicular cancer cluster using a case-control approach. *Int J Epidemiol* 1990;**19**:269-73.

70. Lauwerys RR, Kivits A, Lhoir M, *et al.* Biological surveillance of workers exposed to dimethylformamide and the influence of skin protection on its percutaneous absorption. *Int Arch Occup Environ Health* 1980;**45**:189-203.

71. Cai SX, Huang MY, Xi LQ, *et al.* Occupational dimethylformamide exposure. 3. Health effects of dimethylformamide after occupational exposure at low concentrations. *Int Arch Occup Environ Health* 1992;**63**:461-8.

72. Boice JD, Jr., Marano DE, Fryzek JP, *et al.* Mortality among aircraft manufacturing workers. *Occup Environ Med* 1999;**56**:581-97.

73. Ducatman AM. Dimethylformamide, metal dyes, and testicular cancer. *Lancet* 1989;**1**:911.

74. Chen JL, Fayerweather WE, Pell S. Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. *J Occup Med* 1988;**30**:813-8.

75. Walrath J, Fayerweather WE, Gilby PG, Pell S. A case-control study of cancer among du pont employees with potential for exposure to dimethylformamide. *J Occup Med* 1989;**31**:432-8.

76. Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. *Cancer Causes Control* 1997;**8**:904-12.

77. Kortenkamp A. Low dose mixture effects of endocrine disrupters: implications for risk assessment and epidemiology. *Int J Androl* 2008;**31**:233-40.