UC Irvine

UC Irvine Previously Published Works

Title

Thinking about the role (largely ignored) of heavy metals in cancer prevention: hexavalent chromium and melanoma as a case in point.

Permalink

<https://escholarship.org/uc/item/6kx8m432>

Journal

Recent results in cancer research. Fortschritte der Krebsforschung.
Progrès dans les recherches sur le cancer, 188

ISSN

0080-0015

Authors

Meyskens, Frank L
Yang, Sun

Publication Date

2011

Peer reviewed

Thinking About the Role (Largely Ignored) of Heavy Metals in Cancer Prevention: Hexavalent Chromium and Melanoma as a Case in Point

5

Frank L. Meyskens and Sun Yang

Abstract Ultraviolet (UV) light exposure accounts for only 40–50% of the attributable risk for cutaneous melanoma (CM); also classical UV-induced lesions are rare in melanomas (especially among CM with NRAS or BRAF mutations). It is therefore likely that an additional environmental factor exists as familial and genetic factors play a role in less than 5%. A large amount of (largely forgotten) epidemiologic data indicates that heavy metal exposure is strongly associated with the development of CM. Also, epidemiologic studies of patients with joint replacement indicate a marked subsequent time-related increase in melanoma in patients with metal-on-metal hip arthroplasties. In these patients chromium and cobalt levels rise to 10x normal and stay elevated at levels two- to threefold normal for at least 10 years. Chromium is widely used in industry for its anticorrosive and steel-strengthening properties and is widespread in everyday materials. Our

hypothesis is therefore that chromium, alone or in conjunction with UV, plays a major role in the pathogenesis of CM. We have incubated human neonatal melanocytes for more than 10 weeks in the presence of a wide range and concentrations of metals without effect except by hexavalent chromium Cr(VI) and to a lesser degree Co^{2+} . After prolonged culture, chromium-incubated cells produced foci and when replated secondary colonies formed. We have just begun to study this phenomenon in more detail and studies without and with different wavelengths of UV will be explored. Of interest is that aneuploidy (a universal chromosomal change in cutaneous melanoma) in lymphocytes in patients with hip-on-hip metal prostheses has been demonstrated by others.

5.1 Background

5.1.1 The Evolution of the Idea

University of California, Irvine was one of the clinical sites for the conduct of the β -carotene and retinol trial (CARET) to prevent lung cancer in smokers. The results were shocking: patients supplemented with high doses of β -carotene

F.L. Meyskens (✉) and S. Yang
Departments of Medicine,
University of California, Irvine
Biological Chemistry, University of California,
Irvine, and
Chao Family Comprehensive Cancer Center,
University of California, Irvine, CA, USA
e-mail: flmeyske@uci.edu

developed more rather than fewer lung cancers (Omenn et al. 1996). The overall conclusion had to be: an antioxidant could act as a pro-oxidant in the clinical setting. This observation led me to take a sabbatical with a world-class oxidant chemist (Helmut Sies, Düsseldorf, Germany). Subsequently, my basic laboratory work on CM has been driven by two vexing clinical observations:

1. *Why is nonmelanoma skin cancer common and melanoma rare in black or white albinos?* After nearly 10 years worth of work, mainly with organic chemist Pat Farmer, these studies led to the recognition that melanomagenesis is a redox-driven process (Meyskens et al. 2001a, b; Gidanian et al. 2008) and that this process could be co-opted to develop new therapies for melanoma, observations translated by us and others (Fruehauf and Meyskens 2007).
2. *Why are melanomas more common in patients with metal-on-metal hip replacements?* Although this finding was initially made over 15 years ago (Nyren et al. 1995), recognition of its potential broader importance was missed by us and others until a large meta-analysis (Onega et al. 2006) demonstrated that melanoma was increased in patients with metal-on-metal hip replacements. This observation plus our growing interest in redox-changes in melanin during melanomagenesis inevitably led to the question: *could metals contribute to the pathogenesis of cutaneous melanoma?*

5.1.2

Substances That Bind Melanin

5.1.2.1

Metals

It has been known for some time that metals bind melanin (Sarna et al. 1976; Crippa et al. 1989; Hong et al. 2004; Hong and Simon 2007), the

Table 5.1 Possible metals as pro-carcinogens in melanomagenesis

Metals that have been identified in natural melanins
<i>Biometals</i> Cu, Zn, Fe
<i>Trace biometals</i> Ni, Mo, Mn, Co
<i>Nonbiological</i> Cr, Au, Ag, Pb
Promotion of OH predicted for
• <i>Redox active metals</i>
Cu, Fe, Cr, Mn, Co, Pb
• <i>Increase in semiquinone radical</i>
Sc ³⁺ , La ³⁺ , In ³⁺ , Al ³⁺ , Zn ²⁺ , Cd ²⁺

major differentiation product of melanocytes. A summary of metals known to bind melanin is provided in Table 5.1. Although the biochemistry and chemistry of melanin, with two major forms, eumelanin and pheomelanin, is very complex (Simon et al. 2009) the simple concept is that when reduced melanin (usual state) is partially oxidized, the metal bound to melanin serves as a low-grade superoxide generator with downstream effects on signaling pathways (Meyskens et al. 2001a, b). We have discussed elsewhere the importance of free Cu²⁺ and Fe²⁺ contributing, respectively, to oxidative stress during melanosomal disruption that accompanies the process of melanomagenesis (Gidanian et al. 2008) and during sub-burn-induced angiogenesis and the release of free hemoglobin-Fe (Meyskens and Berwick 2008). Of related interest is that we have known for some time that the imaging compound ⁶⁷Ga^{III} (an Fe^{III} analog) binds avidly to the melanin in melanoma patients. However, we will not delve further into the issue of the importance of free iron and copper during melanomagenesis as Cr(VI) is the focus of this essay.

5.1.2.2

Nonmetals

A wide variety of other nonmetal substances bind melanin including most notably a variety

of insecticides and polychlorinated biphenyls (generated in electrical situations). Other non-metal-binding substances include thioureas (food preservatives) and various other organic compounds including β -blockers, alpha-agonists, antibiotics, antimaterials, organic amines, and polycyclic aromatic hydrocarbons. Interestingly, melanin was also found to be bound with different chemotherapeutic agents such as Doxorubicin (900 nmol/mg) and daunorubicin (760 nmol/mg), which was associated with the development of drug resistance (Svensson et al. 2003; Chen et al. 2006).

5.2

Major Risk Factors for Cutaneous Melanoma

5.2.1

Epidemiology

5.2.1.1

Sunlight

Numerous studies from several countries have implicated exposure to sunlight (ultraviolet light radiation or UV) as a causative agent in the development of nonmelanoma (NMSC) and CM skin cancer (Berwick and Wiggins 2006; Maddodi and Setaluri 2008; review Abdel-Malek et al. 2010). However, the details are quite different. NMSC is associated with cumulative lifetime UV exposure. In contrast, melanoma is associated with prepubertal and intermittent adult sunburns, especially in individuals who have type I and type II skin and hence burn easily. *How could that work? How biologically would a sunburn at age 12 translate to a melanoma 20, 30, 40 years later?*

Another unique feature is that NMSC consistently exhibits evidence of UV damage, i.e., classical pyrimidine dimers. In contrast such damage is rarely detected in primary horizontal growth phase melanomas although a distinct set

of genetic alterations are found (Curtin et al. 2005) in which genomic instability is already evident (Hussein et al. 2005). During vertical growth phase, and subsequently, metastatic disease shows extensive aneuploidy, a chromosomal abnormality somewhat unique to CM. Of related interest is the recent complete genomic sequencing of a metastatic melanoma and the cataloging of mutations with an imprint of past UV-induced DNA damage and evidence of independent mechanisms of damage, including most notably selective application of DNA repair to transcribed genomic regions and evidence of G→T changes as being common (Pleasant et al. 2010). These genomic results strongly suggest that UV is only one player in the pathogenesis of CM and that other cocarcinogens are at work either in conjunction with UV-induced damage or as a parallel operator in producing DNA damage.

5.2.1.2

Occupational Epidemiology

The first review of this topic appeared over 20 years ago (Austin and Reynolds 1986) and suggested a general role for metals in melanoma pathogenesis. Many studies have appeared since. Major studies that demonstrate an increased risk of melanoma for printers/lithographers, electrical workers, and insecticides are briefly summarized in Table 5.2. What is remarkable about these occupational epidemiology studies is that only an increase in CM was found and that no increase for any other cancer was detected.

5.2.1.3

Melanoma After Total Joint Arthroplasty

The field of joint replacement has been concerned for quite some time about the effect of shed metals from arthroplastic devices, with

Table 5.2 Occupational epidemiology of cutaneous melanoma

Reference	Cohort	Risk for melanoma
<i>Printers/Lithographers (metals)</i>		
Dubrow 1986	(1968–78) 577	PMR460($p=0.01$)
(RI) ^a Nielson 1996	(b 1933–42) 837	RR 3.4
(Danish) Bouchardy 2002	(d 1968–78) 262	OR 1.6
(Swiss) Perez 2004	(1971–89) 1.8M (6,187 melanoma)	RR 2.8
<i>Electrical Workers (polychlorinated biphenyls)</i>		
Loomis 1997	Retrospective 138, 905	RR 1.23–1.71 dose response 1.29–4.8 (10 year)
Sinks 1992	Retrospective 3,588	8 years 2 expected (SMR 4.1)
Clapp 206 (US)	31,941 decedents	PCMR 179 (131–244)
Nichols 1999 (GB)	>1,000 workers	SMR 221
Ruder 2006	3,569 workers	SMR2.43 (1.1–4.6)
<i>Pest control (insecticides)</i>		
Macfarlane 2009	Pest control workers, Mortality and CA (1980–2000)	SIR 1.56 (1.03–2.37)
Mahajan 2007	Commercial pesticide Carbamate 21,126 workers, 1,291 cases	RR 4.11 (1.33–12.75)UV adjusted
Fortes 2007	Residential pesticide 287 cases, 299 controls	OR 2.18 (1.07–4.43)UV adjusted dose response

^aRI, Rhode Island

the major initial concern being local sarcomas (review, Learmonth and Case 2007; IARC 1999; Keegan et al. 2008). However, two large studies (Nyren et al. 1995; Visuri et al. 2006) and a very extensive meta-analysis (Onega et al. 2006) have demonstrated an unexpected result. CM was increased post metal-on-metal hip replacements, an increase that parallels levels of chromium in the bloodstream and urine (Heisel et al. 2005). Confirming the importance of these observations was no increase in hip metal-on-plastic or knee (no direct metal contact) arthroplasties. Not unexpectedly, since Cr(VI) is excreted via the kidney, there was an increase in renal cancer, but no evidence of dose–response effect (which is consistent with many studies of chromium pharmacokinetics

and urinary damage (Onega et al. 2006)). Several studies have shown that Cr(VI) and cobalt increases to ten and fivefold normal, respectively in the first 2 years after implantation and remain elevated (two- to threefold) for over 10 years (Skipor et al. 2002; Dunstan et al. 2005; Ladon et al. 2004).

A logical question then: *Is there evidence of DNA damage from this release of these insoluble and soluble materials (ions and particles) into the blood stream?*

Papageorgious et al. (2007) has demonstrated the genotoxic effects of particles of the alloy on human cells in vitro. No one has looked at the skin (see below) yet, but Ladon et al. (2004) have demonstrated chromosomal aberrations in peripheral blood leukocytes after metal-on-metal hip arthroplasty.

5.3 Metals

5.3.1 Chemistry and Genetic Damage

The biochemistry and chemistry of metal-induced oxidative stress, downstream effects, and carcinogenesis are extremely complex (Leonard et al. 2004; O'Brien et al. 2003; Beyersmann and Hartwig 2008). Although both Cu^{2+} and $\text{Fe}^{2+}/\text{Fe}^{3+}$ probably play a role in the ongoing pathogenesis of melanoma, the emphasis in this chapter is on the externally introduced metal hexavalent chromium, which as an anticorrosive and a steel strengthener is literally everywhere including the groundwater. The Department of Defense has actually been concerned about this issue for quite some time (Young 2009). Some of the sources of Cr(VI) and materials which contain it are shown in Table 5.3.

Chromium-6 is currently regulated under the 50-micrograms per liter ($\mu\text{g}/\text{L}$) maximum contaminant level (MCL) for total chromium, which equals to 0.05 parts per million (ppm) (<http://www.cdph.ca.gov/CERTLIC/DRINKINGWATER/Pages/Chromium6.aspx>). In August 2009, the Office of Environmental Health Hazard Assessment (OEHHA) of the

Table 5.3 Sources and human exposure of chromium Cr(VI), an anticorrosive and a steel strengthener

Chromate manufacture	Joint replacements
Catalytic convertors	Orthodontics
Chrome plating	Razor blades
Stainless steel welding	Blownup steel structures—e.g., 9–11, Iraq

California Environmental Protection Agency announced a draft technical support document for hexavalent chromium in drinking water, indicating a new risk assessment and stressing arising concerns of ingested Cr(VI). A PHG of 0.06 $\mu\text{g}/\text{L}$ or 0.06 parts per billion (ppb) is proposed for hexavalent chromium in drinking water, based on tumor incidence data from rodent cancer bioassays.

5.3.2 Chromium Chemistry

The chemistry of chromium is certainly the most complex of all metals and affects cells in a manner, for the most part, *not* driven by the production of oxo-8-dG lesions, but by a diversity of other effects including interruption of topoisomerase DNA binding which leads to infidelity in replication (Snow 1991).

A unique feature of chromium chemistry is that during the reduction of Cr(VI) to Cr(III), highly mutagenic ternary complexes are formed within cells, and in the attempt to repair this damage, aneuploidy results.

Most recently, Arakawa et al. (2006) demonstrated that Cr(III)-DNA adducts induce mainly G → T mutations, which is evident in Pleasance's report with melanoma genomic study.

The remarkable aspect of this process is that 8-oxo-dG damage does not occur, p53 is not inactivated, and G/C pairs are the major target. The overall consequence is that aneuploidy and an ever-evolving mutator phenotype result. We propose that the carcinogenesis of melanocyte transformation may follow the path below (also see Meyskens and Berwick 2008).

- (a) *Sunlight*: (UV) → classical pyrimidine dimers → 8-oxo-dG lesions
- (b) *Sunburn* (angiogenesis): free $\text{Fe}^{2+}/\text{Fe}^{+3}$ recycling, $\text{OH}^\bullet$, OH^- → more 8-oxo-dG lesions
- (c) *External exposure* (melanin binding): Cr(VI) → Cr(III) aneuploidy
- (d) *Progression, melanosomal damage*: free Co^{2+} → $\text{OH}^\bullet$, OH^-

The first comprehensive study detailing the mutational spectrum of chromium (VI) in human cells was done by Chen and Thilly (1994) on the exon 3 of hypoxanthine guanine phosphoribosyl transferase (hprt) gene. They found four Cr(VI)-induced hotspots within the target sequence: C:G → A:T (4.5% of mutants); A:T → T:A (2.0%); G:C → A:T (2.5%); and C:G → T:A (4.0%). Notably, these differed markedly from that observed with H_2O_2 , molecular oxygen, iron (II), or Copper (I)/(II), which are all thought to be dependent on and proceeded via oxygen-free radicals intermediates.

5.3.3

Upregulation of Metallothioneins (MTs)

A key question is: *how do metals get into cells*. In the past decade it has been apparent that a whole family of metal-handling proteins exist to protect cells from free metals (Ekschlager et al. 2009). Weinlich et al. (2006) demonstrated that

- MTS were overexpressed in melanoma cells.
- The percent of cells (and amount) with MTs increase with depth of the primary lesion.
- Presence of MTs predicted progression (RR 2.9, $p < 0.02$ and survival (RR 4.1, $p < 0.001$).
- Presence of MTs predicted aggressive disease for thin melanomas.

To date no studies have been reported on the levels of MTs or SNPs of MTs and melanoma risk, but such results would be of great interest.

5.3.4

Some Preliminary Experimental Data

5.3.4.1

Effects of Metals on Human Melanocytes

What is the effect of metals on melanocytes? To date we have done several preliminary experiments, the results of one which are shown in Fig. 5.1.

Fig. 5.1 Effects of different metals on human primary melanocytes growth. **(a):** Primary normal melanocytes were cultured in MCDB medium with different metals (CrCl_6 , CuCl_2 , and FeSO_4) for more than 10 weeks. Cells were passaged once a week and fresh media containing different metals were replaced three times a week. Foci were found in Cr^{6+} (0.05 ppm)-

treated cells. After separation and re-passage, cells still form foci in culture dish even at low density. After 10 weeks, photos were taken with control, Cu^{2+} (20 μM) and Fe^{2+} (20 μM) treatments. **(b):** Melanocytes exposed to Cr^{6+} (0.5 ppm) exhibited more dendritic-shaped morphologic changes. *Left*, $\times 40$; *Right*, $\times 100$ magnification

Utilizing primary normal melanocytes cultured from human foreskin, we measured the effects of different metals on cell growth including Cr(VI) (0.05 and 0.5 ppm), Cu^{2+} (20 μM), or

Fe^{2+} (20 μM) for at least 10 weeks. As shown, all tested metals and dosages exhibited no notable toxicities in melanocytes even after a long-term exposure except Cr(VI) at a concentration of 0.5

ppm, which is tenfold of the upper limit standardized for drinking water (0.05 ppm) (California Department of Public Health). Cells exposed to Cr(VI) (0.5 ppm) showed a much slower growth rate compared to control and were associated with significant morphologic changes (Fig. 5.1a) – more dendritic-shaped with a flatter cell body. Significant slowdown of cell proliferation was noticed within 4 weeks of treatment and even switching back to regular growth medium could not rescue the cells from toxicity. No significant proliferation rate or morphologic changes were observed with Cu²⁺ or Fe²⁺ treatments.

In distinct contrast from the toxic effects of Cr(VI) at 0.5 ppm, a ten times lower dosage of Cr(VI) (0.05 ppm, drinking water standard), produced a strong stimulating effect on melanocyte growth. Notably, after 3–5 weeks, small foci started to occur in culture dishes (Fig. 5.1b). On collecting these foci and replating them separately, we found that even at a very low cell density, cells still formed foci in vitro exhibiting a gain of extra vertical growth potential (Fig. 5.1b). Further detailed analyses of tumorigenicity and malignant transformation are underway now.

Measurement of Chromium in Primary Melanomas

The use of x-ray synchronization radiation (Bohic et al. 2008) should allow measurement of metals in single cells. Chromium has been detected in metastatic melanoma cells (L. Peterson, personal communications 2009) as has iron, but the hard job of measuring metals in primary melanomas remains to be done.

5.4 Future Prospects

Large cohorts of patients are available who have had hip arthroplasty who are being closely fol-

lowed, particularly in Scandinavian countries and the United Kingdom. The availability of both tumor registries and arthroplasty registries will provide a source of patients to study. We have already established relationships with investigators there and look forward to detailed studies of chromium in patients who have had arthroplasties and subsequently developed melanomas.

The intriguing results from our preliminary experimental data also suggest that detailed biologic and mechanistic studies of chromium and human melanocytes should be highly informative. Perhaps UV-activated chelators can be developed that will remove this toxic metal (Yiakouvaki et al. 2006).

References

- Abdel-Malek ZA, Kadarko AL, Swope VB et al (2010) Stepping up melanocytes to the challenge of UV exposure. *Pig Cell Mel Res* 23:171–186
- Arakawa H, Wu F, Costa M et al (2006) Sequence specificity of Cr(III)-DNA adduct formation in the p53 gene: NGG sequences are preferential adduct-forming sites. *Carcinogenesis* 27:639–645
- Austin DF, Reynolds (1986) Occupation and malignant melanoma of the skin. *Recent Results Cancer Res* 102:98–107
- Berwick M, Wiggins C (2006) The current epidemiology of cutaneous malignant melanoma. *Front Biosci* 11:1244–1254
- Beyersmann D, Hartwig A (2008) Carcinogenic metal compounds: recent insights into molecular and cellular mechanisms. *Arch Tox* 82:493–512
- Bohic S, Murphy K, Paulus W (2008) Intracellular chemical imaging of the developmental phases of human neuromelanin using synchrotron x-ray microspectroscopy. *Anal Chem* 80:9557–66
- Bouchardy C, Schuler G, Minder C (2002) Cancer risk by occupation and socioeconomic group among men – a study by the Association of Swiss Cancer Registries. *Scand J Work Environ Health* 28:1–88
- Clapp RW (2006) Mortality among US employees of a large computer manufacturing company: 1969–2001. *Environ Health* 5:30–44

- Chen J, Thilly WG (1994) Mutational spectrum of chromium Cr(VI) in human cells. *Mut Res* 323:21–27
- Chen KG, Valencia JC, Lai B et al (2006) Melanosomal sequestration of cytotoxic drugs contributes to the intractability of malignant melanomas. *Proc Natl Acad Sci USA* 103:9903–9907
- Crippa R, Horak V, Prota P (1989) Chemistry of melanins in Alkaloids. Academic, New York
- Curtin JA, Fridlyand J, Kageshita T et al (2005) Distinct sets of genetic alterations in melanoma. *N Engl J Med* 353:2135–47
- Dubrow R (1986) Malignant melanoma in the printing industry. *Am J Ind Med* 10:119–26
- Dunstan E, Sanghrajka AP, Tilley S et al (2005) Metal ion levels after metal-on-metal proximal femoral replacements. *Jour Bone Joint Surg* 5:628–631
- Ekschlager T, Adam V, Hrabeta J et al (2009) Metallothioneins and cancer. *Curr Protein Pep Sci* 10:360–375
- Fortes C, Mastroeni S, Melchi F et al (2007) The association between residential pesticide use and cutaneous melanoma. *Eur J Cancer* 43:1066–1075
- Fruehauf JP, Meyskens FL (2007) Reactive oxygen species: a breath of life or death? *Clin Cancer Res* 13:789–94
- Gidanian S, Mentelle M, Meyskens F et al (2008) Melanosomal damage in normal human melanocytes induced by UVB and metal uptake - a basis for the pro-oxidant state of melanoma. *Photochem Photobio* 84:556–564
- Heisel C, Silva M, Skipor AK (2005) The relationship between activity and ions in patients with metal-on-metal bearing hip Prostheses. *J Bone Joint Sur An* 87:781–787
- Hong L, Liu Y, Simon JD (2004) Binding of metal ions to melanin and their effects on the aerobic reactivity. *Photochem Photobio* 80:477–481
- Hong L, Simon JD (2007) Current understanding of the binding sites, capacity, affinity, and biological significance of metals in melanin. *J Phys Chem B* 111:7938–47
- Hussein MR, Haemel Ak, Sudilovsky O (2005) Genomic instability in radial growth phase melanoma cell lines after ultraviolet irradiation. *Journal of Clinical Pathology* 58:389–396
- International Agency for Research on Cancer (IARC) (1999) Surgical implants and other foreign bodies. IARC Monograph 74:303–311
- Keegan G, Learmonth I, Case P (2008) A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. *Critic Rev Toxicol* 38:645–674
- Ladon D, Doherty A, Newson R et al (2004) Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplast* 19:78–83
- Learmonth ID, Case CP (2007) Metallic debris from orthopaedic implants. *Lancet* 369:542–4
- Leonard S, Harris G, Shi X (2004) Metal-induced oxidative stress and signal transduction. *Free Rad Biol Med* 37:1921–1942
- Loomis D, Browning SR, Schenck AP (1997) Mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med* 54:720–8
- MacFarlane E, Benke G, Del Monaco A et al (2009) Cancer incidence and mortality in a historical cohort of Australian pest control workers. *Occup Environ Med* 66:818–823
- Maddodi N, Setaluri V (2008) Role of UV in cutaneous melanoma. *Photochem Photobiol* 84(2): 528–36
- Mahajan R, Blair A, Cable J et al (2007) Carbaryl exposure and incident cancer in the Agricultural Health Study. *Int J Cancer* 121:1799–1805
- Meyskens FL, Farmer P, Fruehauf JP (2001a) Invited Review: redox regulation in human melanocytes and melanoma. *Pigment Cell Res* 14:148–154
- Meyskens FL, McNulty SE, Buckmeier JA (2001b) Aberrant redox regulation in human metastatic melanoma cells compared to normal melanocytes. *Free Radical Biol Med* 31:799–808
- Meyskens FL, Farmer P, Anton-Culver H (2004) Etiologic pathogenesis of melanoma: a unifying hypothesis for the missing attributable risk. *Clin Cancer Res* 10:2581–2583
- Meyskens FL, Berwick M (2008) UV or not UV: metals are the answer. *Cancer Epidem Biomarkers Prev* 7:268–270
- Nichols L, Sorahan T (2005) Cancer incidence and cancer morbidity in a cohort of UK semiconductor workers (1970–2002). *Occup Med* 55:625–630
- Nielsen H, Henriksen L, Olsen JH et al (1996) Malignant melanoma among lithographers. *Scand J Work Environ Health* 22:108–11
- Nyren O, McLaughlin JK, Gridley G et al (1995) Cancer risk after hip-replacement with metal implants: a population based cohort study in Sweden. *J Natl Cancer Inst* 87:28–33

- O'Brien TJ, Ceryak S, Patierno SR (2003) Complexities of chromium carcinogenesis: role of cellular response, repair and recovery mechanisms. *Mutation Res* 533:3–36
- Omenn GS, Goodman GE, Thornquist MD et al (1996) Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New Eng J Med* 334:1150–1155
- Omega T, Baron J, Mackenzie T (2006) Cancer after total joint arthroplasty: a meta-analysis. *Cancer Epidem Biomarkers Prev* 15:1532–1537
- Papageorgious I, Yin Z, Ladon D et al (2007) Genotoxic effects of particles of surgical cobalt chrome alloy on human cells of different age in vitro. *Mutation Res* 619:45–58
- Perez-Gomez B, Pollan M, Gustavsson P et al (2004) Cutaneous melanoma: hints from occupational risks by anatomic site in Swedish men. *Occup Environ Med* 61:117–26
- Pleasance ED, Cheetham K, Stephens PJ et al (2010) A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* 463:191–197
- Rhodes AR, Seki Y, Fitzpatrick TB et al (1988) Melanosomal alterations in dysplastic melanocytic nevi: a quantitative, ultrastructural investigation. *Cancer* 61:358–69
- Ruder AM, Hein MJ, Nilsen N et al (2006) Mortality among workers exposed to PCBs in an electrical capacitor manufacturing plant in Indiana: an update. *Environ Health Perspect* 114:18–23
- Salnikow K, Zhitkovich A (2008) Genetic and epigenetic mechanisms in metal carcinogenesis: nickel, arsenic and chromium. *Chem Res Toxicol* 21:28–44
- Sarna T, Hyde JS, Swartz HM et al (1976) Ion-exchange in melanin: an electron spin resonance study with lanthanide probes. *Science* 192: 1132–4
- Simon JD, Peles D, Wakamatsu K et al (2009) Current challenges in understanding melanogenesis: bridging chemistry, biological control, morphology, and function. *Pigment Cell Melanoma Res* 22:563–79
- Sinks T, Steele G, Smith AB et al (1992) Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol* 136:389–98
- Skipor A, Campbell P, Patterson C et al (2002) Serum and urine metal levels in patients with metal-on-metal surface arthroplasty. *Mater Sci Mat Med* 13:1227–1234
- Snow ET (1991) A possible role for chromium (III) in genotoxicity. *Environ Health Perspect* 92: 75–81
- Sotomatsu A, Tanaka M, Hirai S et al (1994) Synthetic melanin and ferric ions promote superoxide anion-mediated lipid peroxidation. *FEBS Lett* 342:105–108
- Svensson SP, Lindgren S, Powell W et al (2003) Melanin inhibits cytotoxic effects of doxorubicin and daunorubicin in MOLT 4 cells. *Pigment Cell Res* 16:351–354
- Visuri TI, Pukkala F, Pulkkinen P et al (2006) Cancer incidence and causes of death among total hip replacement patients: a review based on Nordic cohorts with a special emphasis on metal-on-metal bearings. *Proc Inst Mech Eng H* 220: 399–407
- Weinlich G, Eisendle K, Hassler E (2006) Metallothionein-overexpression as highly significant prognostic factor in melanoma: a prospective study on 1270 patients. *Br J Cancer* 94: 835–41
- Wondrak GT (2007) Let the sun shine in: mechanisms and potential for therapeutics in skin photodamage. *Curr Opin Investig Drugs* 8: 390–400
- World Health Organization (1996) Biological monitoring of chemical exposure in the workplace, vol 1, p 102 WHO/HPR/OCH96.1. WHO, Geneva
- Yiakouvaki A, Al SJ, Qengei A et al (2006) Caged-iron chelators a novel approach towards protecting skin cells against UVA-induced necrotic cell death. *J Invest Dermatol* 126:2287–95
- Young JL (2009) Memorandum for secretaries of the military departments: minimizing the use of hexavalent chromium (Cr6+). Acquisition technology and logistics, Department of Defense, USA