Basic Research

1-1

Role of DNA repair in skin cancer

Annemieke de Vries[1], Henk van Kranen[1], Bert van der Horst[2], Tyler Jacks[3], Leon Mullenders[4], Frank de Gruijl[4], Harry van Steeg[1]
[1]Natl Inst of Public Health & Environment, Toxicology, Pathology & Genetics, Bilthoven, The Netherlands; [2]Erasmus University, MGC-Dept. of Cell Biology & Genetics, Rotterdam, The Netherlands; [3]Massachusetts Institute of Technology, Center for Cancer Research, Cambridge, United States; [4]Leiden University, MGC-Dept. of Toxicogenetics, Leiden, The Netherlands

Upon UV exposure, Xeroderma pigmentosum (XP) patients are highly skin cancer prone, due to defects in their nucleotide excision repair system (NER) normally required to remove DNA photoproducts. NER functions with different kinetics depending on the damaged DNA, resulting in two sub-pathways known as transcription coupled repair (TCR) and global genome repair (GGR). Several mouse models with defects in genes involved in NER have been generated up to now, and tumor development after exposure to UV and a number of chemical compounds has been studied.
Xpa-deficient mice, completely defective in both TCR and GGR, closely resemble the human phenotype with respect to UV-induced epidermal hyperplasia and squamous cell carcinomas (SCC). To study the process of skin carcinogenesis more thoroughly, we crossed Xpa-deficient mice with hairless mice (HRA:SKH), and exposed them to UVB. Hairless Xpa-deficient mice appeared extremely sensitive in that all animals developed tumors with short latency times (<20 wks). Surprisingly, hairless Xpa-deficient mice developed papillomas with high frequency at the lowest daily UVB dose (32 J/m2), whereas at higher daily UVB doses mainly SCCs were found. To analyze the relative contributions of both NER sub-pathways to skin cancer development, Csb-deficient mice (only defective in TCR) and Xpc-deficient mice (only defective in GGR) were also crossed with hairless mice. Single exposure and repeated longterm exposure experiments with UVB radiation were carried out. Both Csb-/- and Xpc-/- mice developed epidermal hyperplasia, but only in Csb-/- mice marked parakeratosis was found. After chronic UVB exposure, both Xpc-/- and Csb-/- mice develop SSCs with much shorter latency time compared to wild type mice. Interestingly, only Csb-/- mice developed a fairly high number of papillomas, a phenomenon also observed in hairless Xpa-deficient mice. A possible explanation for this shift in skin tumor type, based on mutation spectra of ras and p53, will be presented. To further explore the correlation between primary DNA damage, DNA repair defects, mutagenesis and tumorigenesis, we are currently exposing different NER-deficient mice crossed with lacZ reporter mice to UVB, enabling the analysis of mutation induction in the skin. In addition, we have initiated studies to explore the role of p53 in preventing cancer caused by NER compounds using so-called 'knockin' mutant mice, and newly obtained results and insights will be presented.

1-2

Role of epidermal stem cells in skin cancer

David Mitchell[1], Rudiger Greinert[2], Beate Volkmer[2]
[1]UT MD Anderson Cancer Center, Carcinogenesis, Smithville, United States; [2]Centre for Dermatology, Dermatology, Buxtehude, Germany

Chronic exposure to ultraviolet radiation can cause profound and persistent changes in the epidermis that lead to premature aging and skin cancer. Over the course of our studies in mice we learned that DNA damage is induced and persists for long periods of time in a small number of epidermal cells located at the dermal-epidermal boundary and that these cells are no longer evident 24 h after exposure to a tumor promoter. We hypothesize that the distribution of damage in the epidermis is not random but is preferentially targeted to label-retaining stem cells and that division of these cells in response to a hyper-proliferative stimulus (tumor promoter) produces clusters of p53-positive cells that may ultimately lead to actinic keratoses and skin cancer. We observe a similar distribution of DNA damage in human skin chronically exposed to sunlight, suggesting that mechanisms underlying this phenomenon in the mouse model may be relevant to the human condition. Should these cells prove important in skin carcinogenesis they would provide a novel and perhaps more relevant focus for assessing risk and evaluating preventive strategies in the human population.

1-3

Molecular genetics of Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

Rune Toftgård
Karolinska Institutet, Department of Biosciences, Stockholm, Sweden

Basal cell carcinomas (BCC) are the most common malignancy in fair skinned people and show an increase in incidence. The vast majority of BCCs are sporadic, presumably with UV-radiation as the most important etiologic factor, but a minor fraction is associated with dominant cancer predisposition syndromes such as Xeroderma Pigmentosum and Nevoid Basal Cell Carcinoma Syndrome (NBCCS). The PTCH1 gene is mutated in patients suffering from NBCCS and is inactivated by mutation/LOH in a major fraction of sporadic BCCs consistent with a funtion as a tumor suppressor of general importance for BCC development. PTCH1 serves as a receptor for ligands belonging to the hedgehog family (SHH, IHH, DHH) and mutations in PTCH1 result in constitutive activation of hedgehog signalling.
One important transcriptional effector of hedgehog signaling in vertebrates is GLI1 and increased expression of this factor is often seen in BCC and medulloblastomas. Transgenic mice expressing GLI1 in the skin under the control of the keratin 5 promoter developed high numbers of tumors resembling BCC, trichoepitheliomas, cylindromas and trichoblastomas strongly supporting the hypothesis that GLI1 overexpression is sufficient for tumor development. Confirming a role of deregulated hedgehog signalling in additional hair follicle associated skin tumors PTCH1 mutations have been detected in a fraction of human trichoepitheliomas and increased expression of PTCH1 and GLI1 is observed in human cylindromas. These findings suggest a possible link between the cylindromatosis gene (CYLD), in which mutations predispose to cylindromas and trichoepitheliomas, and components of the hedgehog signalling pathway.
Second generation mouse models harboring an inducible GLI1 gene show the key role of this transcription factor not only for the induction of basaloid skin tumors but also for the maintenance of the tumors. Furthermore, mice heterozygous for a mutation in the suppressor of fused (SUFU) gene, an intracellular negative regulator of hedgehog signalling, develop basaloid skin tumors supporting a tumor suppressor function. Hedgehog signalling is of key importance in hair follicle morphogenesis, specification of hair follicle cell fate, induction of hair follicle anagen phase and hair follicle associated skin tumors such as BCC, trichoepithelioma and cylindroma are hypothesized to develop from skin appendage progenitor cells.

1-4

Skin cancer models – from mice to men

Arne Van Schanke, Frank De Gruijl
Leiden University Medical Centre, Dermatology Dept., Leiden, The Netherlands

The most common forms of skin cancer, squamous cell carcinoma, basal cell carcinoma and malignant melanoma, are related to sun exposure. Experiments with mice play a pivotal role in the understanding of the underlying processes. Extrapolation from mice to men is complicated by species differences (e.g. differences in skin morpholgy and DNA repair proficiency).Several approaches have been taken to develop proper mouse models for specific tumors. Such adaptations include the use of hairless mice, introduction of transgenes and point mutations or ablation of genes. This has resulted in mice strains that are specifically prone to either squamous cell carcinoma, basal cell carcinoma or malignant melanoma. Thus, important information has been obtained on time-, dose- and wavelength-dependent induction of DNA damage and skin cancer by ultraviolet light. Especially short-wave ultraviolet-B light was found to be a potent carcinogen, causing mutations in genes that regulate cell cycling, differentiation and apoptosis such as p53 and H-Ras.
Knowledge on crucial gene mutations can help to identify sensitive subsets of the population or to discriminate between patients with a good or bad prognosis. Mouse models can also help refine risk assessments for humans that are based on epidemiological data. Finally, mouse models may help to identify targets for new therapies and testing the effectiveness of these therapies.

1-5

Malignant melanoma: tumor progression – molecular events

Meenhard Herlyn, Carola Berking, Gang Li
The Wistar Institute, Molecular and Cellular Oncogenesis, Philadelphia, United States

Experimental investigations on melanoma development have been hampered by two major difficulties: i) the mouse is not an ideal experimental animal for melanoma-related studies because normal melanocytes are differently located in mouse versus human skin; ii) biologically early lesions cannot be obtained from pathologists because of their small size and the necessity for histological scanning of the entire lesion. Our laboratory has developed a model of human melanoma in which human skin from healthy donors is grafted to immunodeficient mice, followed by intradermal adenovirus vector-mediated expression of three growth factors, bFGF (FGF 2), SCF (c-kit ligand) and ET-3 (endothelin-3) and concomitant irradiation with UVB (ultraviolet light in the B range). After a treatment period of only three to four weeks, highly invasive lesions developed in the human skin grafts that histologically resembled primary melanomas in patients. However, the lesions regressed in the absence of growth factors and cells cultured from the lesions showed limited life span suggesting that genetic alterations are required in cells to initiate the switch towards malignancy.
Recent investigations have identified a novel mutation in the B-RAF gene in the majority of human melanomas. Melanoma cells show activation of central signaling pathways but we only begin to understand the mechanisms of activation. All members of the MAPK kinase pathway, including ras, raf, MEK, and ERK are activated. The AKT pathway is similarly activated and β-catenin is stabilized by endogenous or exogenous growth factors or through cadherin/WNT signaling. These pathways appear critical in melanoma growth and survival and make them sensitive to therapy with specific inhibitors. Due to the frequent mutations in melanomas of the B-RAF gene, new opportunities for therapeutic inhibition arise and several groups are actively investigating the clinical utility of B-RAF inhibitors. The next few years should see a multitude of novel strategies for therapy of melanoma.

1-6

Molecular genetics and human malignant melanoma

Johan Hansson
Karolinska Hospital and Institute, Radiumhemmet, Cancer Centre Karolinska, Department of Oncology-Pathology, Stockholm, Sweden

In the last decade considerable advances have been made in the molecular genetics of human cutaneous melanoma. One of the most important findings is the presence of melanoma predisposing germline CDKN2A mutations in a proportion of kindreds with familial cutaneous melanoma. In several populations specific founder CDKN2A mutations have been identified. Germline CDKN2A mutations may be considered as high-risk melanoma predisposing mutations, since such mutations are most commonly seen in kindreds with several affected melanoma cases. It has recently been demonstrated there is a geographical variation in the penetrance of CDKN2A mutations, indicating that environmental UV-exposure influences the risk of melanoma development in mutation carriers. The interaction between CDKN2A and polymorphic variants in risk-modifying genes such as MC1R remains an important issue. Likewise, since the genetic background in the majority of kindreds with familial melanoma is unknown, identification of novel melanoma predisposing genes is an important field of research.
It has recently been established that somatic activating mutations in the ras-raf-MEK-ERK signaling pathway are very frequent in melanoma tumors. Thus, it has previously been known that activating NRAS mutations occur in melanoma tumors, particularly at sun-exposed sites. Recently, it has been demonstrated that activating mutations in the BRAF gene, downstream of NRAS in the signal transduction pathway, are even more common. For instance, in a Swedish population of melanoma patients 47 of the 53 patients (89%) had tumors that were mutated in either BRAF (55%) or NRAS (34%). These BRAF and NRAS mutations seem to occur early during melanoma development and persist during tumor progression. This indicates that the ras-raf-MEK-ERK signaling pathway is an interesting target for future developments in melanoma therapy and prevention. Of interest, in a separate study of Swedish patients with familial melanoma who all had germline CDKN2A mutations, the frequency of UV-inducible NRAS mutations was much higher (95%) than that seen among patients with sporadic melanoma. This may indicate that the CDKN2A germline mutations are associated with a UV-hypermutability phenotype, which results in a high risk of developing melanomas with NRAS mutations.

POSTERS

1-7

Xeroderma Pigmentosum

Camillo Di Cicco
DNA Repair Interest Group NIH, Clinical Professor of Dermatology, Rome, Italy

Hereditary disease,transmitted with recessive autosomical modality, the XP is characterized from extreme photosensitivity that causes strict and premature damages to level of the cutis and of the eyes.Its incidence is of 1:250000 in Europe and USA, while in Japan the relationship is of 1:40000. In the child affected by XP also short exposure to the sun's ultraviolet rays determines severe cutaneous sunburn with slow resolution.The cutaneous displays that characterize the disease,

which pigmented specks, dry skin, atrophic lesion, keratoses, bubbles, carry to the apparence, also before the ten years of age, skin cancers.These manifestations are due to the defect of the mechanism of DNA Repair, often develop on the face and other sun-exposed parts of the body, including the eyes, lips and tip of the tongue.To level of the eyes, from the initial phases of the disease, in approximately 80% of the patients they are photophobia, conjunctivitis, ectropion, symblepharon with ulceration, blindness, BCC, SCC and MM. To find that the skin it introduces the first alterations after the six months of life, being moreover normal to the birth. Less of the 40% of the patients it survives after the twenty years of age, developing they prematurely numerous skin cancers.Beyond the manifestations described to level of the skin and the eyes,20% of the patients with XP introduce problems of neurological type:deafness,microcephaly,spasticity,ataxia,chorea,opthalmoplegia and mental delay.The determining causes the XP are from searching in the altered mechanism of DNA repair. In normality conditions,the fragment of the altered DNA comes eliminated and replaced from a new fragment synthesized,according to the called mechanism “excision-repair”.The basic defect of the XP is from searching in the excision-repair of nucleotide, the NER (GLOBAL GENOME GG NER-Trascription Coupled TC NER), that it determines altered repair of the DNA damaged from ultraviolet rays.The diagnosis,beyond that clinical, can be carried out in laboratory measuring the defect of repair of DNA. Therapy for XP does not exist,moreover can be put into effect of the procedures that attenuate the manifestations:protection from the ultraviolet beams,frequent controls of the skin and the eyes,timely removal of the cancerous tissue,neurological controls and last but not least ,psychosocial care,remembering that the children with XP are forced living during the nocturnal hours in order to avoid the sunlight.

1-8

Induction of delayed mutations and chromosomal instability by ultraviolet-A and -B radiation

Jostein Dahle, Egil Kvam
The Norwegian Radium Hospital, Biophysics, Oslo, Norway

Mutations in critical genes are believed to be a necessary part of cancer induction. The conventional view of radiation mutagenesis is that radiation induces most mutations in cells shortly after irradiation. In contrast, we here show that delayed mutations in the HPRT locus of Chinese hamster fibroblasts (V79) occur many cell generations after three types of carcinogenic irradiation: ultraviolet A, ultraviolet B or X-radiation. The frequency of mutations at the HPRT locus was measured in clones 14 days after irradiation with doses killing 80 % of the cells. The proportion of unstable clones, as indicated by mutant fractions 10-7500 fold above background, was slightly higher for the cells treated with ultraviolet A (13.2 %) than for cells treated with ultraviolet B (9.2 %) and X-radiation (9.6 %). In contrast, ultraviolet A produces few immediate mutations compared with ultraviolet B and X-radiation. Thus, ultraviolet A radiation, which is suspected to cause melanomas, produces few immediate mutations but more delayed mutations than ultraviolet B or X-radiation. Clones of cells that developed delayed mutations were examined for markers of chromosome instability, such as increased numbers of centrosomes, DNA content and variability in number of chromosomes. All radiation types increased the variability in number of chromosomes in unstable clones. Whereas ultraviolet B and X-radiation, which damages DNA by direct interaction, resulted in an increased number of centrosomes in cell clones, the oxidative ultraviolet A radiation did not. Thus, the mechanism of ultraviolet A induced chromosomal instability is apparently different from that of ultraviolet B and X-radiation.

1-9

Real time PCR indicates frequent p14ARF inactivation in melanoma metastases with INK4 deletions

Eva Grafström, Suzanne Egyhazi, Ulrik Ringborg, Johan Hansson, Anton Platz
Oncology-Pathology, Cancer Center Karolinska, Karolinska Hospital , Stockholm, Sweden

Both the retinoblastoma and p53 pathways are often mutationally altered in human cancers and part of their complex regulation is mediated via the three known gene products p16, p14ARF and p15 of the INK4 locus on chromosome 9p21. Bi -allelic deletions of the INK4 locus, partial or complete, have frequently been recognized in a variety of malignant tumors including malignant melanoma. Approximately one third of human melanomas harbor activating mutations in the NRAS oncogene and an additional 60% have mutations in the BRAF gene. Both genes are centrally involved in signal transduction. Activation and/or over expression of RAS genes have been recognized to cooperate with CDKN2A deficiency resulting in accelerated melanomagenesis in a mouse model. We have, against this background, developed and evaluated a quantitative real time PCR assay in order to perform measurements of the relative allelic concentrations of both the INK4 gene regions and the NRAS oncogene in archival human tumor samples which were also previously genotyped for NRAS and BRAF. Interestingly 13/18 metastases indicated homozygous exon 1b loss, out of which 10 also indicated loss of the CDKN2A specific target sequence and 6 also indicated loss of the targeted CDKN2B sequence. p14ARF deficiency may lead to deregulated proliferation both via the p53 pathway and via upregulation of E2F dependent transcription. The measurements of relative allelic concentrations of the INK4 genes and N-RAS in sections of 18 formalin fixed melanoma metastases described here demonstrate the successful application of this assay to clinical samples not accessible to analysis by less sensitive methodologies such as Southern blotting.

1-10

Frequent activation of the Ras-Raf-MEK-ERK signaling pathway in malignant melanoma

Katarina Omholt, Anton Platz, Ulrik Ringborg, Johan Hansson
Karolinska Institute, Oncology-Pathology, Stockholm, Sweden

It has long been known that activating NRAS codon 61 mutations occur in up to 30% of all melanoma cases. Recently, Davies et al reported that BRAF mutations also occur at a high frequency in melanoma. We have screened a series of paired primary and metastatic cutaneous melanomas for both NRAS codon 61 and BRAF exons 11 and 15 mutations, using single-strand conformation polymorphism and nucleotide sequence analyses. Primary tumors (n=73) and corresponding metastases (n=88) from in total 71 patients were analyzed. Twenty-one patients (30%) had NRAS codon 61 mutations and 42 patients (59%) had BRAF mutations, of which Val599Glu was the most frequent mutation. The NRAS and BRAF mutations were mutually exclusive and thus no tumor had mutations in both genes. Paired primary and metastatic tumors generally had the same genotype. That is, mutations present in the primary lesions were preserved in the corresponding metastatic lesion(s) and mutations did not arise at the metastatic stage if they had not been present in the primary lesions. Using the laser capture microdissection technique, the mutations were detected already in the radial growth phase of the primary lesions. Taken together, these results demonstrate that the Ras-Raf-MEK-ERK signaling pathway is frequently activated during melanoma tumor development and that activation occurs through either NRAS or BRAF mutations. Furthermore, these results show that the NRAS and BRAF mutations arise early during melanoma development and are preserved throughout tumor progression.

1-11

Gene silencing of activated nras in a human melanoma cell line by sirna

Malihe Eskandarpour, Johan Hansson, Ulrik Ringborg
Karolinska Institute, Oncology-Pathology, Stockholm, Sweden

Our previous studies demonstrated a very high frequency of activating codon 61 NRAS mutations in tumor cells in hereditary melanomas carrying CDKN2A germline mutations and also suggested that activated NRAS may be an important target for specific anticancer therapy in melanoma patients who carry codon 61 mutations. In order to better define the role of such mutations for melanoma development, we started using small double stranded RNAs (siRNA) to suppress mutated NRAS. It has been recently shown that siRNA appear to be very efficient agents to inhibit gene expression in mammalian cells. A 21 bp siRNA with TT overhangs and also pSilencer vector were designed to target NRAS with the codon 61 Arg (CGA) substitutions. The 224 and 397 human melanoma cell lines carry Arg mutation in codon 61 of the NRAS gene, and wild type NRAS, respectively, were used. Cell lines were targted in optimized transfection conditions using transfection reagents; oligofectamine, lipofectamine and PEI (polyethyleneimine). One day after plating, cells were transfected and the silencing was analyzed by immunofluorescence staining with polyclonal N-ras antibodies during 1–5 days.
This silencing was highly sequence specific since while there was no significant silencing of N-ras expression in the 397 cell line and 80% reduction of N-ras expression in transfected 224 cells after 2 days. We could detect apoptosis by TUNEL assay and Annexin V detection on transfected cells and arrest in cell proliferation by incorporation of 3H thymidine.
We conclude that silencing of the mutant NRAS gene by siRNA leads to apoptosis in a human melanoma cell line and that this support the concept of utilizing mutant NRAS as a therapeutic target.

1-12

Screening for a founder Val59Gly CDKN2A mutation in non-Ashkenazi Jewish melanoma patients living in Israel: preliminary results

Hava Peretz[1], Micha Barchana[2], Tovi Morad[1], Elisheva Grynberg[1], Sali Usher[1], Nadir Arber[3], Raphael Shafir[4]
[1]Tel Aviv Sourasky Medical Center, Clinical Biochemistry Laboratory, Tel Aviv, Israel; [2]Ministry of Health, National Cancer Registry, Jerusalem, Israel; [3]Tel Aviv Sourasky Medical Center, Cancer Prevention Unit, Tel Aviv, Israel; [4]Tel Aviv Sourasky Medical Center, Plastic Surgery, Tel Aviv, Israel

The incidence (cases/100000) of melanoma in Israel is among the highest in the world, being much higher among Ashkenazi Jews born in Europe/America (M: 17.1; F:15.5) or in Israel (M:23.6; F:19.4) than in non-Ashkenazi Jews born in Africa (M:8.4; F:5.0) or Asia (M: 3.9; F:4.2) and in Arabs (M:1.4; F:2.6). Around 5–10% of melanoma cases world wide are familial, some harboring germline mutations in the CDKN2A tumor suppressor gene. In a screen of 40 Ashkenazi Jewish and 9 non-Ashkenazi Jewish familial cases of melanoma we have identified none and three different CDKN2A mutations, respectively. One of these mutations, Val59Gly, occurred in a large Moroccan-Jewish pedigree and was also detected in two kindreds from France and one from Spain. Haplotype analysis indicated a founder effect. The aim of the present study was to assess the frequency of the Val59Gly mutation among non-Ashkenazi Jewish melanoma patients living in Israel. Following approval of the Helsinki Committee of Ministry of Health, cases of melanoma patients born in Asia or Africa diagnosed between 1995 to 1999 were listed from the Israel National Cancer Registry (INCR). Parents and siblings of patients were searched in the Population Registry by using patient's Unique Identity Number. A linkage was made to the INCR to trace the affected relatives. Israel confidentiality law allows the INCR to send identified data on patients only to the Medical Center that provided the data. By now, a list of 62 such individuals was received at our Medical Center. Out of the 62 letters sent to these individuals, 14 returned. Five patients responded within the first week. Twenty patients were contacted by phone of which 9 responded positively. A fast and sensitive real-time PCR assay has been developed and validated for identification of the Val59Gly mutation. One out of the 14 (7%) individuals tested was found carrier of the mutation. These preliminary results suggest that the Val59Gly mutation may be relatively frequent among the non-Ashkenazi Jewish melanoma patients living in Israel. Work is in progress to enroll more patients from our and other Medical Centers in Israel in order to evaluate the frequency of the Val59Gly mutation more precisely. In addition, further screening for the mutation in families in which an index case will be found positive, will allow assessment of the penetrance of the mutation. This in turn will allow risk stratification and genetic counseling in the affected families.

1-13

Study of serotonin in the development of melanoma

Clara Naimi-Akbar[1], Mari-Anne Hedblad[1], Efrain Azmitia[2], Klas Nordlind[1]
[1]Karolinska Institutet, Unit of Dermatology and Venerology, Dept. of Medicine, Stockholm, Sweden; [2]New York University, Dept of Biology and Psychiatry, New York, United States

Malignant melanoma may be influenced by stress. Thus, different neuromediators might be involved in the development of melanoma. One important neuromediator for different body functions, including stress, is serotonin(5-HT). It is also of importance for cellular functions such as proliferation, differentiation, migration and apoptosis.
In the present study we investigated the expression of 5-HT and its well-characterized receptors, the 5-HT1A and 5-HT2A receptors(R), and of serotonin transporter protein(SERT), in deparaffinized sections from eight biopsies of compound nevi, dysplastic nevi and superficial malignant melanoma, respectively, in humans. Immunohistochemistry and a biotinylated streptavidine technique were used.
There was a cytoplasmic expression of 5-HT1AR and 5-HT2AR, but not 5-HT nor SERT, in normal melanocytes (in perilesional areas). In the nevi/melanoma areas, expression of the receptors as well as SERT and 5-HT was found in tumour cells mainly in the basal epidermis and dermis, the highest activity being found in the junctional area. There was a more homogenous dermal cellular staining for these markers in the normal nevi, compared to melanocyte atypias. The 5-HT1A staining showed a more reticular pattern, with long tumour cell dendrites, in the basal epidermis.
A major difference between normal nevi and atypias was the migration of round tumour cells into the suprabasal part of the epidermis in the latter conditions. Double staining for 5-HT1AR and 5-HT2AR in malignant melanoma showed that there were tumour cells in the suprabasal part of the epidermis, which were only 5-HT2AR positive. These cells also had a round appearance.
Blood vessels in the dermis expressed 5-HT2A receptors more evidently in the dysplastic nevi and superficial melanomas. SERT was highly expressed by mononuclear cells in the perilesional area, sometimes of a dendritic appearance, invading the epidermis. In the central part of the compound and dysplastic nevi, and the melanoma, the number of these cells was decreased.
The results may indicate a role of serotonin in melanoma development and may create new therapeutic possibilities, both pharmacological and non-pharmacological, in the treatment of melanoma.

1-14

Antioxidants can prevent ultraviolet and visible radiation-induced DNA damage exacerbated by arsenate

Nick Morley[1], Alison Curnow[1], Leo Salter[2], Sandra Campbell[1], David Gould[1]
[1]Cornwall Dermatology Research Project, Royal Cornwall Hospital, Truro, United Kingdom; [2]Environmental Sciences, Cornwall College, Camborne, United Kingdom

Cornwall has the highest rates of skin cancer and the highest environmental concentrations of arsenic in the United Kingdom. Although arsenic exposure is associated with an increased risk of certain cancers including those of the skin, the carcinogenic mechanism of arsenic is uncertain. Using the comet assay to assess DNA damage in single cells, an investigation was conducted to determine the genotoxicity of arsenic (as arsenate) and its effects on ultraviolet and visible radiation (280–700 nm)-exposed cultured human lung fibroblasts, skin fibroblasts and epidermal keratinocytes. Two light sources (150 W xenon-arc and a 200 W xenon-mercury lamp) with or without a 320 nm cut-on filter were used in this study.
It was found that arsenate could induce detectable DNA damage in human lung fibroblasts and exacerbate the effects of ultraviolet A (UVA) and visible (VIS) radiation (320–700 nm)-induced DNA damage in all three cell types. The data obtained confirm observations by previous workers that arsenic induces DNA damage by an oxidative stress mechanism. This hypothesis is further supported by the observation that after incubating the cells in medium supplemented with low molecular weight antioxidants less DNA damage was recorded following exposure to UVA/VIS radiation in all three cell types. Four antioxidants were examined, two thiols: N-acetylcysteine and ergothioneine; and two polyphenols: epigallocatechin gallate and quercetin. The thiols were more effective when used at millimolar concentrations whereas the polyphenols were more effective at micromolar concentrations. The results of this study warrant further investigation into the use of antioxidants to reduce the exacerbation of UV/VIS radiation-induced DNA damage by arsenic.

1-15

Establishment and cytogenetic characterization of a new melanoma cell line by CGH and FISH

Andrea Treszl[1], Andrea Ladányi[2], Zsuzsa Rákosy[1], Zsuzsa Buczkó[3], Róza Ádány[1], Margit Balázs[1]
[1]Medical and Health Science Center, University of Debrecen, Department of Preventive Medicine, Debrecen, Hungary; [2]National Institute of Oncology, Department of Tumour Progression, Budapest, Hungary; [3]Medical and Health Science Center, University of Debrecen, Department of Obstetrics and Gynaecology, Debrecen, Hungary

Malignant melanoma is the most lethal form of skin cancers with an overall 5 year survival rate of less than 50 %. Late stage primary tumours usually become very aggressive, as they have already obtained metastatic potential. Although our knowledge about the molecular mechanisms underlying the development and progression of the disease is increasing rapidly, little is known about the specific genetic changes that occur during metastasis formation. Investigation of the biological behaviour and the chromosomal alterations of melanoma cell lines that metastasize to known organs can help to develop better therapies and improve patients' survival. Even though a large number of human cell lines derived from malignant melanoma have been reported, most of them from metastatic lesions, their molecular cytogenetic characterisation has been limited. Here we report the cytogenetic analysis of a new primary melanoma cell line (SSM-35/01) established from a vertical growth phase superficial spreading melanoma of a 69 year old man. One year after the surgery of the primary tumour, a liver metastasis was discovered. When the SSM-35/01 melanoma cell line was inoculated subcutaneously into SCID mice, the tumour cells didn't metastasised. However, after intrasplenic transplantation of cells into SCID mice, liver metastases were observed. Using flow cytometric analysis, the expression level of the following receptors were determined: HLA-A2, HLA II, HMB45, MART-1, S100B. The cells showed positive expression for the HLA-A2, HMB45 and intermediate expression for MART-1. No positive expression of the S100B antigen was detected. Cytogenetic characterization of the cell line was carried out using G-banding, FISH and CGH. By G-banding a nearly triploid karyotype was observed. CGH analysis revealed gains on chromosomes 6, 7q, 13q, 19, 20q, 21 and Y, and losses on 9, 10, 12, 16, 17 and 18. FISH analysis was performed on 21 chromosomes including chromosomes X and Y. Except chromosome 18, none of the chromosomes showed normal copy number distribution for centromeric probes. Chromosome painting probes specific for chromosome 13 and 21 showed the most remarkable abnormality: translocation of chromosome 21 was noticed at the telomeric part of chromosome 13. Using different painting probe combinations we couldn't identify other translocations, therefore we've decided to perform SKY-FISH analysis, which is in progress.

1-16

Mutagenic and cytotoxic DNA lesions induced by wavelengts longer than 300 nm

Anna Biverståhl, Klaus Erixon, Dag Jenssen
Stockholm University, Genetic and Cellular Toxicology, Stockholm, Sweden

The type of mutagenic lesion(s) responsible for induction of malignant melanoma is still a matter of speculation. In this study we have challenged this issue by asking the question whether wavelengths longer than 300 nm might be considered as a risk for induction of mutations in mammalian cells. We applied an in vitro model for induction of gene mutations in the hprt locus of Chinese hamster cells. Treatments with different wavelengths were created by using a UVA and UVB source in combination with different filters.
The results so far indicate that at wavelengths between 254 and 302 nm, cytotoxicity and mutagenicity in V79 Chinese hamster cells parallels the formation of pyrimidine dimers. Mutation frequencies in nucleotide excision repair (NER) deficient hamster cells indicate that the (6-4) photoproduct is at least 25 times more mutagenic than the cyclobutyl pyrimidine dimer. At wavelengths above 302 nm, however, cell death and mutations were found to be produced not only by pyrimidine dimers, but by other lesions as well. At 313 nm, only about 40% of the mutations could be accounted for by pyrimidine dimers. Other lesions, not yet identified, should be responsible for the remaining number of induced mutations.
UVA exposure was also mutagenic. Both NER and BER were triggered by this exposure and the level of oxidated lesion, 8-OH-dG, was measured by an enzymatic assay. It is still a matter of speculation whether oxidative lesions from UVA may contribute to mutagenicity and whether these may be a potential risk factor in developing malignant melanoma.

Epidemiology

2-1

The epidemiology of non-melanocytic skin cancer

Richard Gallagher, Tim Lee
B C Cancer Agency, Cancer Control Research, Vancouver, Canada

Non-melanocytic skin cancer (NMSC) is the most common tumor type in the world, and although usually not life-threatening, its treatment is potentially disfiguring and a major financial burden in Western countries.
Light skin colour, freckling, and sun-sensitivity phenotypically identify the most susceptible population for both major NMSC types, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).
The major environmental factor responsible for NMSC is sunlight exposure, and this is thought to account for about 90% of these cancers. Investigations of the relationship between solar ultraviolet radiation exposure and NMSC have found different patterns of sun exposure for BCC and SCC. Intermittent sunlight exposure, usually reported as recreational activities in adolescence and early adult life appears to be most strongly related to subsequent BCC, while chronic solar exposure, usually reported as occupational or cumulative exposure, appears most stongly associated with SCC.
Studies of transplant and HIV patients have shown increased risk of NMSC associated with immune compromise, and careful examination of these results may suggest avenues of investigation for the etiology of sporadic skin cancers in healthy individuals. In addition, the study of polymorphisms in the melanocortin receptor (MC1R) and other genes suggest that more specific information on individual susceptibility than that provided by simple phenotype characterization may become available in the near future.
These developments should help elucidate the interactions between susceptibility and exposure which lead to the development of skin malignancy, and may eventually result in the generation of individually tailored skin cancer prevention regimens.

2-2

Risk factors for cutaneous malignant melanoma

Margaret A. Tucker
Genetic Epidemiology Branch, DCEG, NCI, Bethesda, United States

Cutaneous melanoma is rapidly increasing in most western countries, particularly in young women and older men. Epidemiologic studies in the past two decades have identified sun or other ultraviolet radiation exposure as a major environmental risk factor, and a number of host factors that confer risk including family history of melanoma, dysplastic nevi, common nevi, freckles, skin type, and history of sunburns. In a hospital-based case-control study, we have assessed both sun exposure and host risk factors. We developed a residence-based assessment of UVB exposure using life-time residence information and average annual UVB flux at the surface of the earth. For every 10% increase in average annual UVB flux, we found a 19% increase in risk of melanoma in men and 16% increase in women. Exposure as an adult was as important as exposure as a child. People who tanned well spent much more time outdoors; among women who tanned well, for every 10% increase in hours outdoors, there was a 5.8% increase in melanoma risk. This implies that our messages about melanoma prevention must include adult exposure and exposure among those who tan well.
We have also evaluated a number of host risk factors. Family history of melanoma in a first-degree relative was associated with an approximately 2-fold increased risk. We could not detect an increase of pancreatic, breast, neural, or gastrointestinal cancer among relatives of melanoma cases. Multiple dysplastic nevi conferred approximately a 10-fold increased risk; multiple large and small nevi in the absence of dysplastic nevi conferred a 2 to 4-fold increased risk. Extensive freckling was associated with a 3-fold increased risk. We evaluated the attributable risk for easily obtained host factors for primary care providers to use for possible screening. Using a few factors which are easily captured by a quick examination of the back, we found very stable relative risk estimates that were robust for different age groups and geographic locations, yielding attributable risks of approximately 86% for men and 94% for women. These could be used to develop screening and intervention trials if validated in other populations.

2-3

Mortality and skin cancer in Europe

Peter Boyle
Italy

No abstract submitted.

2-4

EUROSUN. A public health project for the quantification of sun exposure in Europe and its effects on health

Jean-Francois Doré[1], Lucien Wald[2], Ulrik Ringborg[3], Peter Boyle[4]
[1]EpiMel, EORTC Melanoma Group, INSERM U 590, Lyon, France; [2]ARMINES, Ecole Nationale des Mines de Paris, Sophia Antipolis, France; [3]EuroSkin, Karolinska Institute, Stockholm, Sweden; [4]European Institute of Oncology, Department of Epidemiology and Biostatistics, Milan, Italy

The project aims to quantify the spectrum of ultraviolet exposure in the various regions of the European Union and its effects on the incidence of skin cancers. By monitoring European and regional changes it will be possible to predict changes in health impact. A new tool measuring daily ultraviolet exposure in Europe will be developed in co-operation with the SoDa project, from satellite data. Exposure to the various UV wavelengths will be calculated for every geographical site within Europe. A database will be created from which exposures in regions and individuals can be assessed and monitored. An atlas of UV exposure in Europe, based on UV irradiation values over 5 year periods, will be produced. Levels of UV exposure (total and maximal) in individuals will be calculated, by reconstructing individual exposure over the last 10 years in random samples of the population in each Member State and applicant countries. The level, distribution and trends of sun exposure in the various European populations will be derived from these calculations. The effects of the levels of sun exposure in the different European populations on the incidence of skin cancers will be estimated by comparing trends in sun exposure obtained from the project with trends in the geographical incidence of melanoma and non-melanoma skin cancers. Eurosun will provide the first quantification of individual UV exposure of different age and gender population categories, and identify time trends. Eurosun will provide indicators of exposure to the various fractions of the UV radiation, and use past UV exposure experience to predict the likely global EU burden in future years (non-melanoma skin cancers, melanoma). By developing a sustainable monitoring of changes in UV exposure dose throughout Europe, likely changes in disease occurrence should be able to be predicted. Specific deliverables of the

project will be: – Eurosun database; – levels of UV solar exposure throughout EU, temporal trends within particular areas; – quantitative estimation of past UV solar exposure among populations of the EU; – comparison of the geographical occurrence of skin cancers with sun exposure in the different EU countries;– early indicators of changing risk of skin cancers. Outputs of the project will be disseminated through technical reports, scientific publications, and through an open access Eurosun web site (platform for epidemiological studies, Public Health officers, general public).

POSTERS

2-5

A new computerised method to analyse tumour site and biological and epidemiological characteristics of cutaneous malignant melanoma – results and visions

Peter Gillgren[1], Ulrik Ringborg[2], Jan Frisell[3], Jan-Olov Persson[4], Johan Hansson[2]
[1]Institutionen Södersjukhuset, Department of Surgery, Stockholm Söder Hospital, Stockholm, Sweden; [2]Oncology and Pathology, Department of Oncology, Karolinska Hospital, Stockholm, Sweden; [3]Karolinska Institute at Huddinge University Hospital, Department of Surgery, Stockholm, Sweden; [4]Mathematics and Statistics, Depatment of Mathematics, Stockholm University, Stockholm, Sweden

Background: It is clear that several characteristics of Cutaneous Malignant Melanoma (CMM) vary with the site where the tumour originated. The different types of sun exposure (chronic/occupational and/or intermittent/recreational) may be one reason for this. A new computer software, EssDoll©, has been developed for detailed studies of site of CMM.
Material and Methods: Data on 2517 patients with 2608 CMMs from a population based regional cancer registry was used and analyses of primary tumour site were performed with EssDoll©. The software enables us to analyse any chosen body area(s) with reference to the tumours arising there. In a sub-analysis, patients with sporadic multiple CMM (MCMM – 69 patients) and hereditary CMM (HCMM – 104 patients) were used. In analyses of tumour site and prognosis the body surface was divided into 24 areas.
Results: The tumour site distribution in relation to histogenetic type and patient gender were consistent with previous data. When the sites of the first and second tumours in patients with sporadic MCMM were analysed in a skin "field division", there was a significant concordance with respect to site ($p<0.0001$). When patients with HCMM were compared to patients with a single sporadic CMM, HCMM patients had significantly fewer tumours in the head-neck area and more on the trunk ($p<0.05$). In a multivariate analysis, using Cox's proportional hazard regression model, we found a significantly elevated risk for CMM death in patients with primary tumour site in the middle and lower back ($p=0.05$).
Conclusions: Our findings verify several site specific properties of CMM. These findings could be due to different types of sun exposure. A possible explanation could be the relationship between mutations in genes such as N-RAS and B-RAF and the type of UV exposure. Furthermore, work on site-specific prognosis, using the whole data base of >6000 patients is in progress.

2-6

Oncoepidemiological aspects of skin cancer in Azerbaijan Republic

Djamil Aliyev[1], Fuad Mardanly[2], Isa Isayev[3], Elchin Mansurov[2]
[1]National Center of Oncology, Director, Baku, Azerbaijan; [2]National Center of Oncology, Epydemiology, Baku, Azerbaijan; [3]National Center of Oncology, Radiation Therapy, Baku, Azerbaijan

We analyzed skin cancer distribution features in different regions of Azerbaijan Republic with revealing criteria significant risk factors for development measurements on theirs primary prevention. At investigation of population sickness we analyzed data of state oncological clinics and Republic Ministry of Health for the period 1989–1998. Sick rate was investigated in connection with such factors as patients residence, sex, age, profession, results of clinical-laboratory and instrumental investigations. Besides, for specification of climate-geographical indexes influence on skin cancer sick rate in connection with size of summary solar and photosynthetic active radiation, we conditionally divided republic territory on 5 region (see fig).

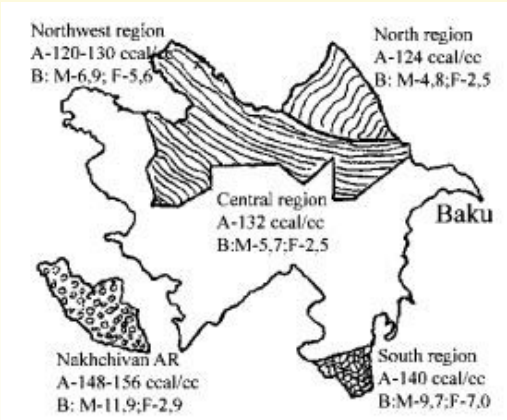


Figure. Analysis of skin cancer connection with some indexes (A-summary solar and photosynthetic active radiation; B-morbidity, M-male; F-female)

In the structure of oncological diseases sickness skin cancer in Azerbaijan Republic take 6 places, which intensive index is 3,1–3,5 on 100.000 of population. It was revealed that around persons, who engaged in agricultural works and having long contact with solar radiation the sick rate is considerably high. Thus, males are in 1,5 times frequently subject of skin cancer, that females (standardized index for male - 3,6, female-2,1). It is necessary to note, that sickness "peak" note at age group – for male 65–69, for female 55–69. Thus, at males after 40 year note sharp rise of sickness. So, if before 40 year intensive index is 5,1 on 100.000 of population, in age group 50–59 this index size is 14,5, that is fluctuation amplitude is 2,8 time. Frequently tumor localized on body open surfaces (72,4%), and more seldom on closed surfaces (27,6%). As was established, persons with blood group A(II) more frequently are exposed by skin cancer (43,9%), and more seldom peoples with blood group AB(IV) (2,0%).
Moreover, considerably frequent cancer developed on damaged skin and seldom on intact (69% and 31% accordingly). As shows analyzed material approximately at 14–20% of patients skin cancer developed on intact, and at other cases on earlier damaged skin. The major factors that promoting skin cancer development in that case were occurrence of scar after received burns (app.70%) and more seldom after trauma (app.33,3%).
One of the major factors that promoting risk of skin cancer development are climate conditions (summary solar, photosynthetic active radiation). In regions, where summary solar and photosynthetic active radiation indexes are high, the skin cancer sick rate is considerably high that in others regions. As it is visible from the figure, in south region and in Nakhchivan AR it is marked more sunny day per year and increased level of summary solar activity, that influence on skin cancer sick rate.

2-7

Epidemiology of skin cancer in Haut-Rhin (France): a population based study, with trends from 1991 to 1999

Jean-Michel Halna
ARER 68, Haut-Rhin, Mulhouse, France

The "departement" of Haut-Rhin, an area of 3522 km^2, is situated in the north-east of France, at the southern part of Alsace, close to the Swiss and the German borders. It has a total population of 706 790 inhabitants (census 1999). The Haut-Rhin Cancer Registry is a general population based registry. Created in 1989, it collects cases from 1988. Basal Cell Carcinoma (BCC) is recorded since 1991. WHO/IARC rules are applied. Cases of all new skin invasive cancers from 1991 to 1999 have been selected for more accurate comparisons. Three years periods are used to calculate Crude Incidence Rates (CR) and World Age Standardized Rates (WASR); these rates are calculated per 100 000 per annum.
Including BCC, skin is the main anatomical site of cancer for both sexes.
In 1997–1999, among men, 26% of all cancers occur on skin, before prostate (14%), lung (11%) and colon-rectum (10%). With 1721 cases during these 3 years, the annual WASR is 112.3. 70% of the skin cancers are BCC: 1218 cases, WASR: 81.8. Squamous Cell Carcinoma (SCC) takes the second place (20%) with 340 cases, WASR: 20. Melanoma takes the third place (9%) with 150 cases, WASR: 10.2. The other morphologies are more scarce (13 cases): Dermatofibrosarcoma protuberans (DFS), Merkel cell carcinoma, adnexal carcinoma and Kaposi sarcoma.
During the same time, among women, 28% of all cancers occur on skin, before breast (25%), colon-rectum (10%) and uterus (7%). With 1768 cases during the years 1997–1999, the annual WASR is 545.7. 73% of the skin cancers are BCC: 1291 cases, WASR: 67.6. SCC takes also the second place (17%), with 266 cases, WASR: 23. Melanoma follows with 180 cases, WASR: 11.8. The other morphologies are scarce (30 cases): adnexal carcinoma , Paget disease, Merkel cell carcinoma and DFS.
Trends between 1991–1993 and 1997–1999 are different among morphologies. Melanoma is the 2nd increasing incidence after women's breast, and non Melanoma skin cancer is the 2nd increasing incidence after prostate. Melanoma WASR increases by 79% among women, and by 44% among men. BCC WASR increases by 9% and 13% respectively. SCC WASR remains stable, although cases number increases by +25%, cases occurring mostly among old people. Incidence of Kaposi sarcoma decreases by 92%, following highly active antiretroviral treatments. DFS decreases by 80% among women.
In France, only Doubs and Haut-Rhin Cancer Registries are registering BCC. International comparisons are done.

2-8

Individual sensitivity to ultraviolet-B: a new independent risk factor for cutaneous melanoma

Rémi Pedeux[1], Francois Salès[2], Julie Pourchet[1], Mireille Kallassy[1], Mathieu Boniol[1], Gianluca Severi[3], Ghanem Ghanem[4], Hisayoshi Nakazawa[5], Philippe Autier[6], Jean-Francois Doré[1]
[1]INSERM, U 590, Lyon, France; [2]Institut Jules Bordet, Department of Surgery, Brussels, Belgium; [3]Europan Institute of Oncology, Department of Epidemiology and Biostatistics, Milan, Italy; [4]Institut Jules Bordet, LOCE, Brussels, France; [5]IARC, WHO, Lyon, France; [6]CRP Santé, CRESIS, Luxembourg, Luxembourg

The individual risk of cutaneous melanoma depends on two series of factors: individual pigmentary traits and sun exposure. However, the relationship between inherited susceptibility to ultraviolet light and risk of melanoma is poorly understood. We explored this relationship by measuring the apoptosis triggered in peripheral blood lymphocytes by a low dose of ultraviolet B irradiation in patients with cutaneous melanoma of the SSM type and in healthy controls. Inherited susceptibility to UV being likely to favor the occurrence of melanoma at an earlier age, we considered three age groups: 18–29 years old, 30–39 years old and 60–69 years old. We observed that: 1) UVB induces a similar apoptosis in all classes of age in controls; 2) by contrast, UVB induces more apoptosis in lymphocytes of melanoma patients younger than 40 years than in older patients; 3) there is a significant difference in apoptosis induced by UVB in lymphocytes of melanoma patients and of controls, this difference is highly significant ($P<0.001$) in the two younger classes of age but there is no difference in the older class of age. UVB-induced apoptosis is independent of phototype and hence appears as a new independent risk factor for melanoma. The genetic background of this individual sensitivity to ultraviolet light is not currently known and remains to be explored. Although melanocytes are generally considered as resistant to apoptosis, the increase in UVB-induced apoptosis in peripheral blood lymphocytes of melanoma patients could result from a reduced ability to properly repair UVB-induced DNA damage. Which mechanisms are involved in the susceptibility to melanoma is not yet clear. However, to the best of our knowledge, our study is the first indication that patients developing a melanoma may demonstrate an anomaly in their functional response to UV radiation, and that such an anomaly is only observed in younger melanoma patients. Apoptosis induction following a low UVB irradiation brings a new functional insight, enabling the identification of populations at risk and target subgroups for cancer prevention strategies.

2-9

Incidence, mortality, and survival trends of cutaneous malignant melanoma in Umbria (Italy), 1978–98

Fabrizio Stracci, Liliana Minelli, Ilaria Vescarelli, Francesco La Rosa
University of Perugia, Hygiene and Public Health, Perugia, Italy

Introduction: Both incidence and mortality from cutaneous malignant melanoma (CM) were reported to be increasing for decades among fair-skinned population including the Italian one. In Italy, the CM incidence rate in the areas covered by cancer registration was 8.5 and 9.6/100.000 in 1994–98 for men and women respectively; male mortality rate was 2.2 and female mortality was 1.9/100.000. The average five-years survival rate was 0.71 for males and 0.82 for females.
The aim of this study is to compare the CM incidence, mortality and survival rates in Umbria, a hilly rural region in central Italy, over the span 1978 to 1998.
Cases and Methods: Incident CM (ICD-9 172) cases derived from an ad hoc survey carried out in the Umbria region in the period 1978–1982 (n.131) and from the Population Based-Cancer Registry for the years 1994–99 (n. 360). Mortality data for the 1978–1999 period

were derived from official publications of the Italian Central Institute for Statistics. Rates were age-adjusted by direct method. Relative survival rates by sex and age were calculated by the Estève's method and age-standardised using the EUROCARE study standard population.
Results: In our study the CM incidence rate increased from 4.9 in 1978–82 to 7.2 per 100.000 in 1994–98 among males, and from 3.8 to 7.9 among females. The mortality rates increased from 1.2 to 2.6 per 100.000 in men 1994–98 and from 0.9 to 1.6 in women. Overall five-year relative survival changed from 0.60 (95%CI 0.45–0.73) in 1978–82 to 0.65 (95%CI 0.55–0.73) in 1994–98 among men, and from 0.61 (95%CI 0.47–0.73) to 0.81(95%CI 0.76–0.90) among women. The age class 55–64 showed the best prognosis both in males and females.
Conclusion: Higher than Italian average survival rates were reported for many cancer sites in Umbria but not for CM. Both mortality and survival were less than Italian average for Umbria males and average for females. Moreover, little improvement in survival was seen over the study period. Increasing survival difference by gender and best prognosis for the 55–64 are in contrast with results reported from the large EUROCARE study. Incidence in Umbria was lower than in Northern Italian areas covered by cancer registration. Overall our data indicate that interventions to improve awareness of CM and early diagnosis could be effective in our region, particlarly among males.

2-10

Cutaneous malignant melanoma-trends in incidence, survival and mortality in a Swedish population

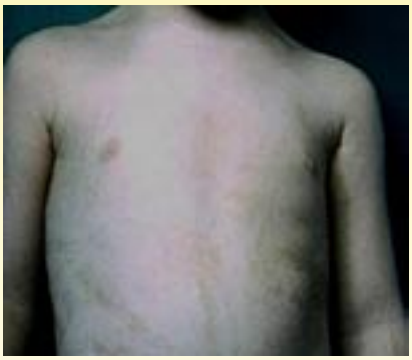
Eva Mansson-Brahme[1], Hemming Johansson[2], Olle Larsson[3], Lars E. Rutqvist[2], Ulrik Ringborg[1]
[1]Department of Oncology, Radiumhemmet, Karolinska Hospital, Stockholm, Sweden; [2]Department of Oncology, Huddinge University Hospital, Stockholm, Sweden; [3]Department of Pathology, Karolinska Hospital, Stockholm, Sweden

The aim of the study was to assess the possible impact of primary and secondary preventive activities in the population of Stockholm-Gotland, Sweden, with the objective to reduce the incidence and mortality from cutaneous melanoma.
The study base was cases with cutaneous melanoma reported to the Swedish Cancer Registry 1976–1994, patients registered in the Stockholm-Gotland Regional Melanoma Registry 1976–1994 and individuals reported with malignant melanoma as an underlying cause of death to the Swedish Cause-of-Death Registry 1970–1996.
The average annual increase of the age-standardised incidence was about 5 % in both genders. The increase mainly concerned thin tumours and melanoma in situ. During the 1990s the incidence in males levelled off. This apparent change in trend was not observed outside the Stockholm-Gotland region. The estimated five-year melanoma-specific survival rate in patients diagnosed with localised cutaneous melanoma increased from 84 % to 92 % during 1976–1994. No time-trend for melanoma-specific-survival was observed among patients with regional or distant metastases. The increased survival during 1976–1989 could be fully explained by a trend towards more favourable tumour characteristics. During 1990–1994, screening activities may have contributed to the observed survival improvement. An upward trend in melanoma mortality appeared to level off in the mid 1980s. In females a slight decrease was observed during 1987–1996. The change in trend was most pronounced in the Stockholm-Gotland region. The results indicate that the interventional activities in Stockholm-Gotland may have influenced both melanoma incidence and mortality.

2-11

Incontinentia Pigmenti

Camillo Di Cicco
DNA Repair Interest Group N.I.H., Clinical Professor of Dermatology, Rome, Italy



Incontinentia Pigmenti is a rare genodermatosis also called Bloch-Sulzberger or Bloch-Siemens syndrome, that shows early at birth or in the neonatal period. In its classical form, the cutaneous symptomatology develops through three steps.
1st step, with evidence of injuries, of erythematic-vescicular-blistered kind and one wave after another, linearly positioned and involving upper body and limbs; haematic hypereosinophilia is also present.
2nd step, that pops up between the second and the sixty life-week with papulo-lichenoid injuries, hyperkeratosic and warty, looking as elongatad striae in the distal limbs section (knee, foot-and- hand back).
3rd step, when at third-sixty month of life dark pigmented spots appear at the upper body level, positioned like a vortex, a whirl or spurts. Such chronology may be different form form from the above and furthmore the relationship among the injuries sequence has not been already explained. In its achromating form, incontinentia pigmenti is known as "Ito disease".
Incontinentia pigmenti is linked, in 80% of occurrencies to other anomalies: Neurological anomalies in 30% of occurrencies, with motor-spastic involvment, convulsions, intellective impairment.
Ocular anomalies in 35% of cases, with 7,5 of inducted blindness (cataract, retinitis, uveitis, optic nerve atrophy).
Dental anomalies in 65% occurrencies.
Alopecia 38% of cases.
Onychodystrophya 7%of occurrencies.
Late studies in molecular genetics identified the origin of incontinentia pigmenti in the failure of a gene named NEMO, placed on X-chromosome. Therefore, while the genetic mutation – in its very evident form – turns out to be fatal to the male foetuses (that do not reach full-term), on the other hand the presence of two X-chromosomes in the females seems to drive to survival and to the disease emergence.

2-12

Number and size of nevi are influenced by different sun exposure components : implications for the aetiology of cutaneous melanoma

Philippe Autier[1], Gianluca Severi[2], Remy Pedeux[3], Mathieu Boniol[3], Jean-François Doré[3], Maria-Sofia Cattaruzza[4], André-Robert Grivegnée[5]
[1]CRP-Sante, Epidemiology, Luxembourg, Luxembourg; [2]European Institute of Oncology, Epidemiology and Biostatistics, Milan, Italy; [3]INSERM , U453, Lyon, France; [4]University La Sapienza, Dept. of Public Health, Rome, Italy; [5]Jules Bordet Institute, Unit of Epidemiology and Prevention, Brussels, Belgium

Objective: The solar wavelength involved in melanoma occurrence remains unknown. Sunburns and latitude gradient are indicators of greater exposure to the ultraviolet B radiation. We examined the associations between the components of holiday sun exposure with numbers of small (2–4.9 mm) and large nevi (5+ mm) in young children.
Methods: Information about each holiday period from birth to interview was recorded from parents of 628 6-to-7-year-old children in four European countries. Sun exposure was characterized using 4 different components: cumulative duration of holidays, number of holiday periods, sunburn episodes and latitude gradient between habitual living place and holiday places.
Results: Individual susceptibility to sunlight, cumulative duration and number of holiday periods were moderately associated with increasing number of small but not of large nevi. The number of small nevi together with sunburn history and latitude gradient were strong predictors of large nevi number. In contrast, sunburn history and latitude gradient were not associated with small nevi.
Conclusions: Exposure to high doses of ultraviolet B radiation would be implicated in the formation of large nevi, while solar radiation other than the ultraviolet B could be implicated in the development of small nevi in children. Given that numbers of large nevi are strong predictors of melanoma in children and adolescents, these results agree with the hypothesis that high UVB doses are needed for melanoma occurrence, but probably not for nevi formation.

2-13

A multicentric epidemiological study on sunbed use and cutaneous melanoma in Europe

Philippe Autier[1], Mathieu Boniol[2], Marie-Christine Chignol[2], Ester De Vries[3], Gianluca Severi[4], Veronique Bataille[5], Alexander Eggermont[6], Jan Willem Coebergh[7], Yvonne Brandberg[8], Ulrik Ringborh[8], André-Robert Grivegnée[9], Jean-François Doré[2]
[1]CRP-Santé, Epidemiology, Luxembourg, Luxembourg; [2]INSERM, U590, Lyon, France; [3]Erasmus Medical Center, Dpt of Public Health, Rotterdam, The Netherlands; [4]European Institute of Oncology, Dpt Epidemiology and Biostatistics, Milan, Italy; [5]Cancer Research UK, Maths Stat and Epidemiology, London, United Kingdom; [6]Erasmus Medical Center, Dpt of Surgical Oncology, Rotterdam, The Netherlands; [7]Comprehansive Cancer Center South (IKZ), Epidemiology, Eindhoven, The Netherlands; [8]Karolinska Hospital, Dpt of Oncology-Pathology, Stockholm, Sweden; [9]Jules Bordet Institute, Unit of Epidemiology and Prevention, Brussels, Belgium

Background: Sunbed use has become considerably popular in European countries, mainly in the Nordic Countries, Germany and the Netherlands.
Objectives: To assess the association between sunbed use and cutaneous melanoma.
Methods: From April 1999 until July 2001, a case-control design compared sunbed use in 622 melanoma cases and 649 controls in Belgium, France, The Netherlands, Sweden, and the UK. All cases and controls were aged 18 to 49 years. Questions related to sunbed use and sunbathing activities were not pursued if subject reported that he/she never used a sunbed or never had sunbathing activities.
Results: Fifty-six % of subjects ever used sunbed, 15% subjects used sunbeds for more than 35 hours, and 15% started sunbed use at least 19 years before the interview. No evidence was found for an association between sunbed use and melanoma, even for subjects who reported highest levels of sunbed use, or for subjects who started sunbed use at least 19 years before interview, or for subjects who accumulated more than twelve hours of exposure to powerful two-panel tanning machines. Highest use of powerful two-panel tanning machines was found in Sweden. Although the melanoma risk increased with the mean number of holiday weeks spent in sunny areas, the adjusted melanoma risks associated with ever sunbed use and ever sunbathing were 0.86 (95% CI: 0.67–1.09), and 0.81 (95% CI: 0.63–1.04), respectively.
Conclusions: Former studies in similar populations showed that sunbathing activities are risk factor for melanoma. Therefore, our findings seem to be largely attributable to the underreporting of sunbed and sunbathing activities by the melanoma cases. Although sample size and amounts of sunbed use were higher than in any former study on the same topic, this study cannot formulate any conclusion on the existence or absence of an association between sunbed use and melanoma occurrence. Future epidemiological studies on skin cancer may no longer rely upon questionnaires for assessing environmental exposures to the ultraviolet radiation. If sunbed use is a risk factor for melanoma occurrence, then Sweden is most probably the first country where this risk should become apparent.

2-14

Sex differences in numbers and size of nevi on body sites of young European children: implications for the aetiology of cutaneous melanoma

Philippe Autier[1], Mathieu Boniol[2], Gianluca Severi[3], Remy Pedeux[2], Jean-François Doré[2]
[1]CRP-Santé, Epidemiology, Luxembourg, Luxembourg; [2]INSERM, U 590, Lyon, France; [3]European Institute of Oncology, Epidemiology and Biostatistics, Milan, Italy

Background: In males, the greatest increase in cutaneous melanoma incidence over time took place on the trunk and the head and neck, while in females, the greatest increase in incidence over time took place on the limbs, mainly the lower limbs. We examined the influence of sex on numbers and size of nevi on different body-sites in white European 6-to-7-year-old children.
Methods: Information about each holiday period since birth to interview was recorded from parents of 628 6-to-7-year-old children in four European cities (Brussels (BE), Bochum (GR), Lyons (FR), and Rome (IT)). Number and anatomic location of small (2–4.9 mm) and large (5+ mm) nevi and individual susceptibility to sunlight were independently assessed.
Results: After adjustment for skin phototype, eye colour, past sun exposure, sunburn history, clothing habits in the sun, past sunscreen use, and place of study, males had 7% (95%CI: -7%;19%) more small nevi than females. However, compared to females, the numbers of small nevi were increased by 17% (95% CI: 1%; 31%) on the head and neck, and by 16% (95%CI: 2%; 27%) on the trunk and shoulders. In contrast, in males, the number of small nevi on upper limbs was decreased by -5% (95% CI: -26%; 13%), and on lower limbs by -8% (95% CI: -34%; 13%). The number of large nevi was 6% higher in males than in females (95% CI: -26%; 30%).
Conclusions: The sex differences in small nevi distribution in children reflects the sex differences in the anatomic distribution of melanoma in adults. Sex differences in sun exposure behaviours, dressing and clothing would just come in addition to the inherited proneness to develop nevi on a given body site. These results reinforce the hypothesis by which childhood would be a critical period for the occurrence of sun-induced biological events implicated in the genesis of cutaneous melanoma. Since the number of small nevi and of large nevi are independent predictors of melanoma occurrence, these results also suggest that small nevi and large nevi are related to different biological events involved in the genesis of melanoma.

Primary and Secondary Prevention & Communication Strategies

3-1

Australian experiences of primary prevention of skin cancer

Robert Burton
National Cancer Control Initiative, Senior Adviser, Carlton, Australia

Australia has the highest incidence of skin cancer in the world, with age-standardized rates per 100,000 of melanoma 35.5 (1999), basal cell carcinoma (BCC) 876.6 (2002) and squamous cell carcinoma (SCC) 384.7 (2002). Melanoma incidence rates have been increasing since national registration began in 1982, when incidence in the two genders was the same. The most recent (1999) rates are 41.2 for men and 30.8 for women. BCC and SCC incidence rates are measured by national surveys of Australians treated for skin cancer, and four of these have been completed since 1985. The most recent (2002) survey shows that BCC incidence has increased by 33% and SCC incidence by 132% in this period, with interesting differences between incidence rates dependant upon gender, age, body site, sun tanning ability and latitude. Validated death certificate data on melanoma mortality in Australia has been available for more than half a century with world age standardised mortality per 100,000 rising from around 1 in 1950 in both genders to peak at 2.5 in 1985 for women and 5.0 in 1990 for men, following which mortality has declined.

Secondary prevention campaigns against melanoma began in Australia in the 1960s, and primary prevention about a decade later. The best developed of these campaigns has been SunSmart Victoria, which began in 1980. Knowledge, attitudes and behaviours relevant to sun exposure have been systematically monitored and have tracked its success. Sensible sun behavours, such as avoiding outdoor exposure around midday, and sun protective clothing and hat and sunscreen use have increased, and sunburn rates have halved since 1985. There has been a major focus on children, since Australian migrant studies revealed that most melanomas were initiated in childhood. For secondary prevention, these programs have resulted in a progressive decrease in the proportion of melanomas which are more than 1mm in thickness, with an improvement both in survival rates after treatment, and now a declining mortality rate.

It is harder to see such a clear impact of the primary prevention campaigns on skin cancer incidence, however age standardised incidence rates for BCC and melanoma in those aged under 50 have not increased over the last two decades, whereas they have for SCC. This is consistent with these campaigns which have targeted sunburn in childhood, since this appears to be a major factor in the causation of melanoma and BCC.

3-2

Association of Dermatological Prevention: 14 years of skin cancer prevention in Germany 1989–2003

Eckhard Breibart[1], Rüdiger Greinert[1], Beate Volkmer[1], Sabine Voss[2], Eva Kalbheim[3]
[1]Center of Dermatology, Association of Dermatological Prevention, Buxtehude, Germany; [2]Association of Dermatological Prevention, Hamburg, Germany; [3]German Cancer Aid, Köln, Germany

For a large extend, skin cancer is a preventable disease. Prevention can be done by reduction of risk exposure (primary prevention) and by early detection of skin cancers (secondary prevention). Therefore, in 1989, nation wide education campaigns concerning prevention of skin cancer were started in Germany by the Association of Dermatological Prevention (ADP), financially supported by the "Deutsche Krebshilfe e.V-". The short-term aims of the campaigns were:

Primary Prevention
- Information of the public and medical professionals about benefits and hazards of ultraviolet (UV) radiation.
- Change in "social style of life", i.e. to deal more critically and consciously with UV radiation.

Secondary Prevention
- Improvement of knowledge of the public and medical professionals about means of early detection of skin cancer
- Self-screening or screening of relatives
- screening of risk groups
- mass screening

The long-term aim is to decrease morbidity and mortality of skin cancer.

We'll introduce selected ADP-campaigns in the time period of 1989–2003, together with the information material and media used, both, for activities in primary prevention and secondary prevention. Furthermore, we'll show first evaluations of the effectiveness of these activities in achieving the short- and long-term aims of ADPs work in Germany.

3-3

Secondary Melanoma Prevention. Are we seeing melanoma patients earlier and saving lives?

Rona M MacKie
University of Glasgow, Department of Public Health, Glasgow, United Kingdom

Secondary prevention of malignant melanoma is prevention of death from melanoma. In the absence of advances in treatment, this requires to be targeted to earlier treatment of thinner tumours.

In Scotland in the years 1979–1980 we saw 270 new cases of cutaneous melanoma. 38% were under 1.5mm thick, 28%1.5–1.5mm thick, and 33% over 3.5mm thick. In the years 2000–2001 we saw 599 cases . 58% were under 1.5mm thick, 19% were 1.5–3.5mm thick, and 235 over 3.5mm thick. These changes in proportion of thin intermediate and thick tumours were statistically significant. ($p<0.001$).

However, over this 20 year period the absolute number of thick primary melanomas >3.5mm rose from 90 to 136, an increase of 51%. During this time the increase in total numbers of invasive melanomas rose by 220%.

Melanoma attributable mortality over this period was static in males, and showed a slight non significant fall in females.

These data suggest that while the epidemic of new cases of melanoma continues, earlier treatment is helping control melanoma attributable mortality.

3-4

Prevention programme for individuals with a high risk to develop malignant melanoma

Inger Rosdahl
Department of Biomedicine and Surgery, Division of Dermatology, Linköping, Sweden

Approximately 10% of all cutaneous malignant melanoma (CMM) occurs in kindreds with a hereditary predisposition for this disease. The life time risk to develop CMM in individuals with at least two family members with CMM and two or more with dysplastic nevi (DN) – the dysplastic nevus syndrome (DNS) – has been estimated to be approximately 100%, corresponding to a 150-fold increased risk over the general population.
The Swedish Melanoma Study Group initiated 1987 a national program with the aim to reduce the risk of developing CMM in kindreds with hereditary predisposition for CMM and DNS by performing a regular skin examinations and excision of suspicious lesions before developing into CMM. Further goals were to inform about self examination and sun-protective behavior. This ongoing program has been carried out in 12 specialized regional clinics and all family data have for scientific purposes been collected in a central data base. The collection of data from 14 year follow-up include 2080 individuals belonging to 280 melanoma families. Of these family members 614 were diagnosed with CMM, 600 were unaffected individuals with DN and 866 were unaffected without DN. Of these three groups, the CMM cases had more sun-sensitive skin and more red and blond hair. Further, they had a significantly elevated number of DN compared to the unaffected individuals with such nevi.
During follow-up 1,912 skin lesions were excised. At histopathological examination 53% were common nevi and 40% DN. During follow-up 45 CMM were excised, 42% were classified as CMM in situ and 58% as invasive. The median tumour thickness of the invasive melanomas was 0.45 mm and only one tumour had a thickness above 1 mm. 75% of the CMM (including in situ tumours) lacked vertical growth phase and ulceration was absent in all. When compared to CMM in the general Swedish population, the CMM identified in these kindreds during follow-up had considerably better prognostic characteristics. Thus, the present study shows that a coordinated program aimed at early detection of CMM and its precursors and concomitantly offering preventive activities in kindreds with hereditary predisposition for CMM and DNS results in a low incidence of CMM during follow-up. The tumours that developed had favourable prognostic characteristics, which indicates that careful follow-up can lead to removal of precursor lesions before development of CMM as well as early diagnosis and treatment of those CMM that arise.

3-5

Skin cancer screening in Germany

A Wende, EW Breitbart
Association of Dermatological Prevention, Dermatologisches Zentrum, Buxtehude, Germany

Background: In Germany since 1971 a national cost-free examination is offered by phy-sicians of different disciplines focussing on early detection of a variety of cancers including those of the skin. According to skin cancer screening some deficits are seen within this program, e.g.: the examination method is not standardized apart from the documentation of change in color or bleeding respectively itching of a mole or node, anamnestic criteria, which are often correlated with later stages of malignant melanoma and neglecting nonme-lanocytic skin cancers. A whole body-examination is not explicitly demanded, maybe leading to undetected lesions. The target population is restricted to women from the age of 30 and men from the age of 45. With 48% of women and 18% of men participating in this program, the attendancy is low. For these reasons the population based detection rate as well as the declining of mortality and morbidity of skin cancer according to screening are estimated as insufficient, demanding an improvement of the screening protocol.
Methods: To improve the effectiveness of skin cancer screening a standardized examination and documentation procedure was performed demanding a whole body examination of persons from the age of 20 targeting melanoma and nonmelanoma skin cancers in a 2 step screening protocol combining mass-screening with risk-group-screening: in a first step, examination of the whole target-population can be performed by physicians of different disciplines who then refer, in a second step, persons diagnosed to be likely to have skin cancer or to be at higher risk to develop skin cancer to a dermatologist. A first trial of this screening protocol was conducted in 200 medical practices with a total of 6.000 examinations of personal recruited patients. Routine data was analyzed and, in order to allow record linkage, the compliance to give person-identifying data was measured.
Results: High attendance and compliance shows feasibility and high acceptance of the program in the population and in the examiners. 10 early melanoma and 31 nonmelanoma skin cancers have been detected.
Implications: The improved screening protocol is feasible. Further studies and record linkage with cancer registries should provide more data on effectiveness, quality and validity of the screening methods as well as data related to cost-effectiveness before an implementation in the health system is to be recommended.

3-6

Behavioural aspects of primary prevention

Yvonne Brandberg
Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

UV-exposure is the only major causative factor for skin cancer for which prevention is feasable. The target is to minimize sun seeking, increase sun-protective behavious, and to decrease the use of artificial UV devices. Theese are three different behaviours, and subsequently interventions should be directed to each one of them. An important distinction is between intentional UV-exposure (sunbathing, sunbed use) and unintentional UV-exposure (leisure activities, out-door work etc). The willingness to take precautionary measures are different under these two circumstances.
Comprehensive social-psychological models have been developed trying to explain UV-related behaviours. Elements in these models are: ”demographic and cultural setting, outcome expectations (the expected effect in terms of pros and cons), normative beliefs (What are others thinking?), control beliefs (Is it possible to perform the behaviour?), intention to behave (the summarized evaluation of the elements above) and the behaviour itself.
Demographic and cultural settings varies through Europe, e.g. number of sunny days per year. This has an effect on UV-related behaviour. If you want to get tanned in the northern countries you have to take every opportunity, which conflicts with instructions to ”sunbathe slowly”. Sunprotection, on the other hand, is of great importance in southern Europe, where people get unintentionally exposed to the sun.
The following factors have been found to be associated with extensive sunbathing: gender, females sunbathe more; age, sunbathing increases from early adoclesence and peaks between 20 and 30 years of age; skin-type, knowledge, higher knowledge about the risks associated with sunbathing among people who sunbathe more.
The primary reason for sunbathing (sun-seeking) is to get tanned. Several European studies have shown a tan to be associated with attractiveness and healthiness. The warmth of the sun is also reported

as an important reason for sunbathing in the northern countries. Studies have shown that women, people with fairer skin, higher education, more knowledge, greater fear of skin cancer, and those who know someone with skin cancer practice more preventive habits. Understanding the complexity of theese behaviours and knowledge about the interaction between the individual and the environgment provide a basis for changing the behaviour through preventive interventions. Theoretical models also highlights the barriers to behaviour change.

3-7

Current approaches of skin caner education in the United States

Allan C. Halpern
Memorial Sloan Kettering Cancer Center, Dermatology Service, New York, United States

Several factors impact skin cancer education in the United States. Among these is the very limited funding for skin cancer education which derives from multiple uncoordinated funding sources. Another challenge is the lack of a centralized school system or school health curriculum. The extremely robust mass media in the United States presents unique opportunities and challenges for public education as well.
As of the late 1970s there were no formal programs for skin cancer educations in the United States. In the 1980s programs initiated by the Skin Cancer Foundation (SCF) set the stage for U.S. public education efforts. Over the next decade, the formal programs of the SCF were complemented by new programs of the American Academy of Dermatology, Environmental Protection Agency, and American Cancer Society. Over the course of the 1990s there was also a proliferation of skin cancer related private foundations in the U.S.. As a result of a conference held in 1995, the National Council on Skin Cancer Prevention and a sister organization, the Federal Council on Skin Cancer Prevention, were established with funding from the Centers for Disease Control (CDC) in 1998. The National Council was restructured in 2002 as an independent council supported by three core members: The American Academy of Dermatology, The American Cancer Society, and the Skin Cancer Foundation. There are over 25 participating member organizations. The goals of the council are to facilitate communication and cooperation among members, coordinate core messages, and advocate for skin cancer prevention legislative policies and research funding on the national level.
Over the past two decades there has been a significant increase in skin cancer knowledge and awareness among the US population. A source of frustration to this effort has been a limited impact of improvements in public knowledge on personal behavior. While there were initial encouraging trends in change of sun protective behaviors in the early 1990's, recent data suggest that improved knowledge has had little positive impact on the sun protective behaviors of the most important target population; children and adolescents. This has led to a growing awareness within the field of the need to coordinate public education efforts with advocacy for skin cancer prevention legislative policies and efforts to impact the social environment.

3-8

UICC communication strategies for skin cancer prevention

Helene Sancho-Garnier
UICC, Prevention and Early Diagnosis, Montpellier, France

The most recent prevention programmes carried out to reduce sun exposure indicate that:
– There is an increase in awareness of Ultraviolet radiation. risk in targeted populations, in particular the youngest age group (6–12 years old).
– Majority of studies highlight a moderate change in attitude with regard to sun protection but no study assesses objective behavioural change.
– In Australia, where the most significant campaigns were conducted, a decrease in the gradient of the incidence curve was observed only after 15 years of interventions.
Early clinical diagnosis, and campaigns have enabled the increase of public awareness and diagnostic performance of health professionals. This had lead to a decline in the seriousness of melanoma with an important increase in the median survival time of melanoma patients. But no one study really demonstrated the efficiency of mass screening programmes.
The evidence from these campaigns show that the most rapid and efficient impact could be obtained by improving early clinical diagnosis. Such a goal could be reached by: – Training of health professionals on the detection of early symptoms,
– Educating individuals in self-examination of the skin (identification of skin phenotypes and of suspicious lesions).
Alternatively, comprehensive preventive interventions could be developed which involves: – Collecting and spreading validated information adapted to age groups, skin phenotypes, geographical areas, occupation...,
– Providing educative material to schools,
– Lobbying for collective protection, legislation on artificial ultraviolet radiation, protective devices, change in population behaviours (tanning advertisement...),
– Promoting well designed studies with an evaluation plan to measure behavioural changes, and a decrease in incidence.

3-9

WHO: strategy for skin cancer prevention

Michael H. Repacholi
Switzerland

No abstract submitted.

3-10

ICNIRP: strategy for skin cancer prevention

Rüdiger Matthes
Germany

No abstract submitted.

3-11

EADO: strategy for skin cancer prevention

Herbert Pehamberger
Austria

No abstract submitted.

3-12

European Cancer Leagues: strategy for skin cancer prevention

Catharina af Ugglas Sandström
Sweden

No abstract submitted.

3-13

Swedish Radiation Protection Authority: national UV-protection in Sweden

Henrik Ullen[1], Ulrik Ringborg[1], Lars-Erik Paulsson[2]
[1]Radiumhemmet, Dept of Oncology, Stockholm, Sweden; [2]Swedish Radiation Protection Authority, Radiation Physics, Stockholm, Sweden

The development of a national programme for UV-protection in Sweden was initiated one year ago by the Swedish Radiation Protection Authority as a result of a political decision within the Ministry of Environment. Monitoring of ambient UVR has a fairly long history in Sweden and is included in the radiation protection responsibility. The Authority collaborates with the Swedish Hydrological and Meteorological Institute in this task, e.g. in following the ozone layer and calculating UV-index forecasts.
In 2002 the director general of the Swedish Radiation Protection Authority appointed a scientific board to give the Authority guidance in its planning of a prevention programme for UVR-protection. The board has ten members representing dermatology, oncology, ophthalmology, behavioural science, radiation biology and radiation physics and can call upon other expertise when needed. Once a year the board has to present a written report to the Authority covering the present evidence-based knowledge on the relation between UVR and its biological effects on humans. The board are further to support the Authority with advice in questions of official policy, where a scientific discussion of opinions and strategies is needed. The board are not supposed to communicate with the public or to put together health messages concerning UV-risks. The first report of the board was included in the strategic action plan on UV-prevention the Authority delivered to the government earlier this year. Among topics the board is focusing during 2003 are the epidemiology of basal cell carcinoma and malignant lymphoma. Further surrogate markers of early UV-exposure. Strategies for attitudinal change in a sun-seeking population have been considered a crucial topic. The role of chronic and intermittent UV-exposure, monitoring of ambient UVR and ozone layer as well as control of public solaria are dealt with by the scientific community and official authorities respectively. The Swedish Radiation Protection Authority has a high degree of public credibility and could thus influence the UV-exposure on a population level through a national prevention programme. It can give support and guide action in local municipalities, the health care system and media as well as act through regulations and legislation.

POSTERS

3-14

Willows for shade

Alexandra Gordon
Ulster Cancer Foundation, Cancer Prevention Services, Belfast, United Kingdom

This programme is being developed in response to the increasing incidence of Skin Cancer including Malignant Melanoma in Northern Ireland. Skin cancer is the most common type of cancer diagnosed in this country. Northern Ireland currently has the third highest level of skin cancer worldwide. Research has shown that children and babies who are sunburned may be twice as likely to develop malignant melanoma in later life (DHSSPS 1997).
Overall aim: To work in partnership with primary/nursery schools to highlight the issue of care in the sun and involve the school in an environment improvement project, creating living willow structures, to provide areas of shade for play or outside class work in the school grounds.
Aims:
- Provide more shaded areas within the school surroundings
- Provide an innovative way to educate primary and nursery school children on taking care in the sun
- Stimulate and facilitate schools/nurseries development of Sun Care Policies
- Lend schools the opportunity to become involved in an ecological project.

Methodology:
- Identify schools/nurseries who wish to participate in the project
- Develop an information pack
- Develop and run training sessions on the development and maintenance of willow structures and sun safety, for teachers/carers from participating schools/nurseries
- Use existing communication channels and develop new channels for dissemination of information
- Use the www.careinthesun.org web site to host project information and resource materials
- Develop support materials to facilitate further discussion and class-work
- Develop partnerships between relevant statutory, voluntary and community agencies
- Build on existing good practice and sun safety resources adding to the awareness programme

Evaluation:
(a) Teacher's opinions of the Living Willows for Shade Project including – training courses, support materials, willow structure construction, effectiveness as part of a care in the sun education programme and development of a school policy for Care in the Sun.
(b) Children's and parent's awareness and attitudes:
- Children's experience of working with willow and learning environmental skills
- Children's awareness and knowledge of the dangers of over-exposure to the sun
- Evidence of adherence to Care in the Sun code and school policy.

3-15

A measurement evaluation of a dosimeter study of preschool children's UV-exposure

Ulf Wester[1], Cecilia Boldemann[2], Henrik Dal[2], Weine Josefsson[3], Tomas Landelius[3], Lars-Erik Paulsson[1], Katarina Yuen[1]
[1]Swedish Radiation Protection Authority, SSI, Stockholm, Sweden; [2]Stockholm County, Community Medicine, Stockholm, Sweden; [3]Swedish Meteorological and Hydrological Institute, SMHI, Norrköping, Sweden

Solar UV monitoring instruments at SSI in Stockholm have been used to validate commercially available biotechnical dosimeters and a spatially resolved solar UV model system used in a research project to study sixty-two preschool children's UV-exposure with twice as many dosimeters. The study was a joint effort of the Swedish Radiation Protection Authority (SSI), the Swedish Meteorological and Hydrological Institute (SMHI), and Community Medicine (CM), Stockholm County.
The study of the children, reported in detail elsewhere, measured personal UV-exposure at two preschool daycare centres south of Stockholm for a total of eleven workdays during the last week of May and the first two weeks of June 2002. It also assessed the effect of shaded playground structures on childrens UV-exposure. One of the two centres had several more of its outdoor play structures placed in a shady environment than the other centre where play structures mainly were exposed to the sun.
We verified reliability of dosimeters of the same type as those used by the children by comparison to model data calculated for the near-real time by SMHI, and by comparison to measurements on the roof of the SSI. Fifteen dosimeters (BioSense Viospore blue-line type III, 0.8-33 MED) were tested on a roof platform with free horizon. Eleven dosimeters, one at a time, were given one-day exposures from sunrise to sunset on the same days as the ongoing study at the two day care centres. Weather conditions were dominated by clear skies and sun or variable cloudiness. The results of the dosimeters and of SMHI's model calculations for each day were compared to an average of four of SSI's different solar UV-monitoring instruments which are installed on the roof platform. Accuracy and variation of the biotechnical dosimeters was evaluated.
Shade structures at the preschools have been documented by helicopter photos from above and by "fisheye-photography" of sky-views from the ground for analysis of expected differences of ambient UV as compared to the actual differences of the dosimeter measurements of children at the two day care centres.

3-16

A comparison of the distribution of solar UV over the human body at high and low latitudes

Michael Kimlin
University of Georgia, National UV Monitoring Center, Dept of Physics and Astronomy, Athens, United States

Many studies linking skin cancer to exposure to solar ultraviolet radiation (UV) have focused on the change in ambient UV irradiances with respect to latitude. Indeed, populations close to equatorial regions are exposed to high UV irradiances whilst at high latitudes, ambient UV irradiances are reduced. Human exposure to solar UV is a complex issue. Not only does human exposure depend on the ambient UV irradiances, but also the solar zenith angle of the sun (angle of the sun with respect to zenith sky), the activity undertaken outdoors, the use of protection devices (such as hats and sunscreens) and the time spent outdoors. As a basis for this work, fully calibrated and characterized ambient solar UV data collected from the United States EPA Brewer Spectrophotometer network will be utilized. By using this solar UV data and knowledge of the fraction of UV incident of the human body, data is presented that indicates the distribution of solar UV over the human body and how it varies from high to low latitudes. This change in distribution of UV occurs along with a decreasing solar UV irradiance with latitude, which impacts the exposure to certain areas of the human body, such as the facial region. This paper will provide quantitative insights into how UV exposure to the human body corresponds or changes with latitude, and I further explore how the effectiveness of protective devices, such as hats, change at certain locals, particularly those located at high latitudes.

3-17

The project of the Italian Ministry of Health for the prevention of risks from UV radiation

Gianni F. Mariutti, Emanuela Bortolin, Alessandro Polichetti
Istituto Superiore di Sanità, Laboratorio di Fisica, Roma, Italy

The Italian Institute of Health (ISS), scientific and technical body of the Ministry of Health and the Italian Health System (SSN), since 1975 is actively involved in the risk assessment from exposure to solar and/or artificial ultraviolet radiation.
In 1999 the ISS has submitted to the Italian Minister of Health a proposal for a National Project of Prevention of risks from UVR based on the following data and considerations: – the scientific evidence for adverse health effects due to excessive exposure to UVR – the scarce or inadequate governmental programs of protection against UVR – the relevance of human and social costs associated to UVR induced health damage – most of these social costs are paid by the SSN and they are increasing also because of the ageing of Italian population.
The project has been approved in September 2000 and it has been funded by the Ministry of Health in June 2002. The ISS has been given the scientific responsibility for the project and for its implementation. The project is now in progress and will be fully operating by the end of this year.
This Project represents the first comprehensive institutional program of protection in Italy devoted to all people exposed to UVR in living environment, workplaces and during cosmetic and medical treatments.
The programme is aimed at achieving a more homogeneous and effective level of protection against UVR throughout our country, optimising the use of human and financial resources and promoting international co-operation in this field. The core of prevention programmes consists of education and information activities on health effects from excessive exposure to UVR and on suggested measures and changes of personal behaviour for reducing the risk. The effectiveness of education programmes, protection measures and suggested procedures for reducing the exposure and the associated risk will be periodically evaluated and reasons for their success and failure identified.

3-18

A proposal for a simulation tool for population UV-exposure and it's dependence of behavior and climate

Weine Josefsson, Tomas Landelius
Swedish Meteorological and Hydrological Institute, Research Department, Norrkoping, Sweden

The tanning habits vary a lot as do the potential solar UV radiation. Here we propose a method for estimating the contribution to the individual as well as the population UV-dose from various realistic habits and erythemal solar UV-radiation.
This is a very preliminary study to present the potential of the method. Therefore, some of the assumptions are rough. In the simulation we use hourly values of the CIE erythemally-weighted UV-irradiance as calculated by the STRÅNG model system. The STRÅNG

system primarily gives the UV-radiation (direct and total) on a horizontal surface. These values have been recalculated to represent the exposure on a human (either standing up or laying down) as approximated by a parallelepiped. By applying different factors we take into account that the sky may be obscured, e.g. by building in a city or by trees in a forest. The same procedure applies for how to account for the exposed skin area. For example a person in a sunbed is assumed to expose 100% of the skin area. This number is reduced according to the clothing.
In the preliminary study we have used three types of tanning behavior for people living at four different latitudes in Sweden. We know that there is a strong latitudinal gradient in solar UV on a horizontal surface as well as in skin cancer incidence in Sweden. How much of the yearly population average UV dose is due to the ambient solar UV and how much can attributed to the habits?

3-19

Improved UV index forecasting

Jussi Kaurola[1], Tapani Koskela[1], Antti Arola[1], Aapo Tanskanen[1], Lasse Ylianttila[2]
[1]FMI, Finnish Meteorological Institute, Ozone and UV Research, Helsinki, Finland; [2]STUK, Radiation and Nuclear Safety Authority of Finland, Non-ionizing Radiation Surveillance, Helsinki, Finland

Daily UV forecasts are one useful tool to increase the level of public understanding on UV exposure. In order to provide information relevant to the people's level of knowledge, such forecasts should be able to describe the dependence of UV irradiance on
- solar zenith angle (variation within a day and geographical distribution)
- cloudiness
- ozone column variation in time and geographically
- altitude above sea level
- surface reflectance
- tilt angle of the surface
- atmospheric aerosol contents

The new UV forecasting system of the Finnish Meteorological Institute (FMI) launched in May 2003 is already able to fulfil most of the above requirements. Its main features are as follows:
- UV index is forecasted for the whole Europe (27°W-45°E, 33°N-73.5°N)
- the spatial resolution is one degree in longitude and in latitude
- the time span is 72 hours with a resolution of three hours
- column ozone is obtained from the forecast of the European Centre (ECMWF)
- climatological distribution of aerosols is used
- surface reflectance is 0.03, or 0.4 for areas with more than 5 cm of snow
- surface topography from a fine resolution model (HIRLAM)
- a state-of-the-art radiative transfer model is utilised

The products of the forecast system are communicated to the public by a web site (http://www.fmi.fi/uvi) and by a national radio channel. The web site also shows near-real time observations from the national monitoring network. The future challenges of the system include the introduction of the cloudiness and the calculation for tilted surfaces.

3-20

Abstract withdrawn.

3-21

Swedish pre-school children's UVR exposure – a comparison between two outdoor environments

Cecilia Boldeman[1], Henrik Dal[1], Ulf Wester[2]
[1]Centre of Public Health, Stockholm County Council/Karolinska Institute, Stockholm, Sweden; [2]Radiation Protection Authority, Natural and Non-Ionizing Radiation, Stockholm, Sweden

Background: Overexposure to ultraviolet radiation (UVR) in childhood is a major risk factor for skin cancer. Shady environments are recommended as one method of protection, particularly low-reflectant vegetation.
Methods: Environmental exposure to UVR, and environmental protection were assessed by dosimeter measurements on 64 children aged 1–6 years at two geographically close and topographically similar preschools outside Stockholm. Outdoor play constructions of site 1(34 children) were mainly exposed to the sun, those of site 2 (30 children) mainly shaded by trees. Dosimetry was carried out during 11 workdays May–June 2002 under clear weather conditions. Reliability of dosimeters was tested with meteorological (SMHI) data, and stationary dosimeters exposed to free sky, and compared to other UV instruments. Differences between children's outdoor stays were adjusted for.
Results: The children's average absolute exposures were approximately 200 JCIE/m2 erythemally effective UVR. Average relative UVR exposures (% total available UVR 08:30 - 18:30) was 6.4% (7.0% at site 1, 5.7% at site 2). Fractions of available UVR during outdoor stay were 14.4 %, 15.3 % in site 1, and 13.3 % in site 2. In terms of relative differences, 5–6 year-old children at site 2 were exposed to 41% less UVR than 5–6 year-old children at site 1, and 1–4 year-old children at site were 2 exposed to 6% less UVR than 1–4 year-old children at site 1. In total, the children at site two were exposed to 13% less UVR than those at site 1.
Conclusion: The difference is explained by the children's outdoor preschool environments, and the behaviors linked to these environments. It is recommended to consider the attractiveness of shady environments in the design of children's preschool playgrounds, particularly if these are extremely exposed to the sun.

3-22

Protection against UV exposure during welding by new types of face-shields

Maila Hietanen[1], Gianni Mariutti[2], Patrick von Nandelstadh[1]
[1]Finnish Institute of Occupational Health, Dept of Physics, Helsinki, Finland; [2]Istituto Superiore di Sanita, Dept of Physics, Rome, Italy

Electric welding arcs are the most intense sources of ultraviolet (UV) and visible radiation, which workers normally can be exposed to. Traditionally welders wear opaque face-shields with a dark filter in front of the eyes and knock down the face-shield by the neck at the ignition of arc. These types of masks may not be effective enough for ensuring protection against UV radiation, because the face remain unprotected repeatedly during a working day. Recently, new types of welding masks have been developed. These contain a dual shade face-shield with a dark filter to protect the eyes and a light filter to protect the face. The dark filter is needed to attenuate bright visible light. For eliminating UV-radiation, a highly attenuative filter is also necessary, but it need not be dark.
The European Norm EN 169 restricts, however, use of dual filter masks by the requirement that the difference in scale numbers between the light and dark zones must not exceed 5. The scale numbers to be used for typical arc welding processes are 11–13. For dual shade filters, it means that the scale number of the light zone cannot be less than 6, with the consequence that the luminous transmittance will be less than 1 %. Hence, the basic idea of good visibility will be lost. Because the standard gives no justification for the

maximum difference of 5, the aim of this study was to evaluate whether a higher scale number difference would be arguable on the basis of biophysical assessments. The spectral transmittance of 49 dual filter combinations was measured and safe daily exposure times were determined. In addition, to evaluate subjectively the properties of various filter combinations, welders from four European countries were asked to give their assessments of different types of welding face-shields. Seven welding masks, representing different dual face-shield types with 38 filter combinations, were selected to be tested. Test persons' opinion the shielding capability of the light and dark filters, and the comfort of use were requested.
On the basis of the subjective evaluations, the preferred scale numbers for the light filter were 2 to 5. The scale number 1.7 was also acceptable, except for aluminium welding. These findings comply with the objective assessments by the spectral measurements. Hence, the results indicate that the requirements of the present standard seem to be too restrictive.

3-23

Effects of solaria inspections on the UV-dose

Lill T. N. Nilsen, Tommy N. Aalerud, Eva G. Friberg, Bjorn Johnsen, Merete Hannevik
Norwegian Radiation Protectino Authority, Radiation Protection and Nuclear Safety, Osteras, Norway

There are over 500 tanning saloons with more than 5000 sunbeds available in Norway. In addition, an unknown number of sunbeds exists in private homes, fitness centers, hotels, hair dressers and at workplaces. With a population of 4.5 million, the total ultraviolet (UV) dose to the public from solaria is considered substantial. With a high incidence of skin cancers, Norway implemented national sunbed regulations already in 1983. The purpose of this presentation is to evaluate the effect of inspections with respect to compliance with these regulations and thereby limiting the UV dose.
The Norwegian regulations are based on the European Standard EN 60335-2-27, which classifies the appliances into UV-type 1 to 4 according to the UVR output and set requirements for marking and user instruction. The Norwegian regulations set requirements for the use of sunbeds, particularly that only sunbeds classified as UV-type 3 are allowed for cosmetic use.
A previous inspection campaign of 130 tanning facilities revealed that nine out of 10 studios used none-approved and too strong UV-lamps, resulting in UV-intensities higher than tropical sun. As much as 57% did not provide the mandatory exposure schedule. The latter is severe since most studios were either partially (40%) or entirely unattended (37%), and the users could only receive information from any posters available. Only one studio complied with all the requirements. A second inspection campaign was, however, carried out in 56 of the 130 studios. Improvements were observed in as much as 93% of the studios. More than one third had accomplished all requirements, whereas 7% had not done any improvements.
To see if media publicity following the previous inspection campaign had any effect on the general tanning market, another campaign of 34 studios was recently carried out in a district with few previous inspections. Some improvements were observed, in which 2 studios complied with all regulations, 7 out of 10 studios used none-approved UV-lamps, and 24% did not provide any exposure schedule. The attendance level was lower than in the first district, in which 85% were partially or entirely unattended.
In conclusion, inspections seem to result in better compliance with the regulations and lower UV-doses. The Norwegian Radiation Protection Authority must, however, evaluate if the best way to improve compliance is by educating solarium owners or by more routine inspections followed by possible economical consequences.

3-24

Percutaneous absorption of benzophenone-3

Helena Gonzalez[1], Anne Farbrot[2], Olle Larkö[1], Ann-Marie Wennberg[1]
[1]Sahlgrenska University Hospital, Department of Dermatology, Göteborg, Sweden; [2]SCA, SCA, Göteborg, Sweden

Introduction: Skin cancer is a growing threat to our population. The most common types, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM) have an increased incidence in recent years. One of the most important etiological factors is the ultraviolet radiation (UVR). Actinic keratosis (AK), a precancerous lesion, is also caused by UVR. Sunscreens are widely recommended to people sensitive to the sun, to prevent sunburning, photo ageing, but also to prevent skin cancer. Sunscreens do have a protective effect against AK and SCC but when it comes to BCC and MM the results are not conclusive.
Sunscreens should be applied in a thick layer repetitively, thus percutanous absorption is an important factor to investigate. Previous studies have shown that 0.5–2% of the active ingredients are excreted in the urine. The aim of this study was to see how much of the UV-absorbing substance bensophenone-3 (BZ-3) that was excreted in urine.
Method: 24 human volunteers where randomly divided into two groups. All of them applied a commercially available sunscreen SPF 14, containing BZ-3 morning and night during five days. All urine was collected during these five days and the following five days, all together 10 days. A urine sample from before application was collected as a reference. One group received UVA and UVB radiation.
Results:

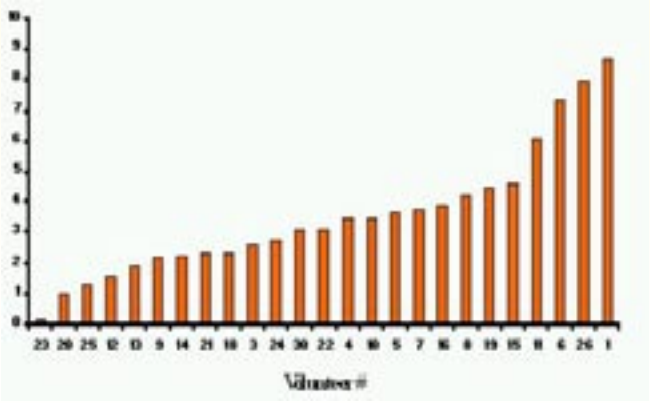


Fig 1. Excreted amount BZ-3 (%). The mean value BZ-3 was 3.5%.

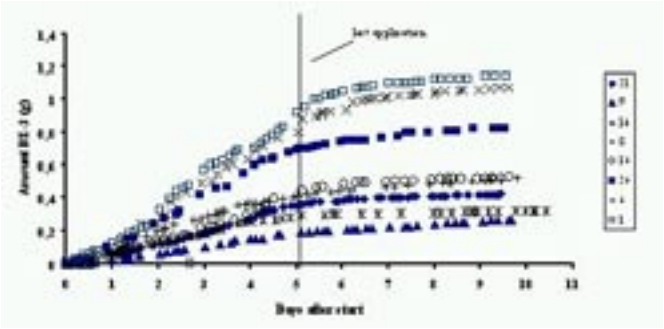


Fig 2. Accumulated amount BZ-3 in urine.

Conclusions: The mean value excreted amount BZ-3 was 3.5%. Percutaneous absorption is a factor to be considered. For sun protection clothes are recommended and sunscreens can be used as a complement. Small children should use sunscreens with precaution. The results are undergoing further evaluation.

3-25

Nurse screening of pigmented skin lesions in a primary health care setting

Sven Tornberg, Eva Mansson-Brahme, Henrik Ullen
Radiumhemmet, Dept of Oncology, Stockholm, Sweden

Individuals with a high risk for malignant melanoma of the skin are offered regular check-ups in Sweden. Whether screening of the general population to reduce mortality of melanoma is motivated is not known. In a feasibility study we used the primary health care setting in one randomly selected area in Stockholm county to study the optimal way of reaching the local population and to test the flow capacity of one specially trained nurse to perform whole body skin examinations. In a previous project of ours it was shown that nurses could be used as the primary screening professionals. The rational to use the primary health care setting was that during a 4 years period 80% of the population of the area will have contact with their health care centre. The screening project was run for 12 months (May 1999 through April 2000) by a nurse employed by the project. 7200 inhabitants were listed at the health centre, i.e. 60% of the local population. Apart from general practice (6 physicians and 7 nurses), the centre encompassed a physiotherapy unit, a maternity clinic and a blood chemistry laboratory.

Every patient over 18 years of age visiting the centre were offered to participate. The skin examination took 20 minutes and was supplemented with tanning advice. The screening capacity per day of the nurse was not possible to study, due to extraordinary disorganisation at the health centre during the period out of control of the study leaders. Skin abnormalities were referred to one of the GPs and if not settled at that level, the patient were seen by a consultant dermatologist or referred to hospital. In total, 5,380 individuals generated 33,298 visits at the centre during the study period. Of these, 1,916 individuals were asked if they wished to be examined. 1,066 (56%) accepted to participate and 119 (12%) of those were selected by the nurse for further assessment by the GP, who in turn consulted the dermatologist in 56%, referred to dermatological clinic in 13%, took a biopsy in 13% and found no signs of disease in another 18%. Dysplastic nevi was found in 8% and 7% had a family history of melanoma. Four cases of malignant melanoma and eight cases of basal cell carcinoma were detected through the project.

The primary aim of the study was to find the optimal way of reaching the population. In contrast to what was assumed, it was not through an invitation by the doctor, but via oral and written information about the test available at the reception.

3-26

EDUCE – European database for ultraviolet radiation climatology and evaluation

G. Seckmeyer[1], B. Kjeldstad[2], E. Putz[3], P. Taalas[4], B. Gardiner[5], A. Bais[6], H. Slaper[7], A. Kylling[8], A. Webb[9], P. Weihs[10], O. Engelsen[8], M. Blumthaler[11], J. Lenoble[12], M. Janouch[13], J. Krzyscin[14], K. Eerme[15], Z. Litynska[16], D. Gillotay[17], A.G. di Sarra[18], U. Feister[19], M. Steinmetz[20], J. Gröbner[21], A-M Siani[22], D. Henriques[23], M. van Weele[24], C. Brogniez[25], T. Koskela[4]
[1]University of Hannover, Hannover, Germany; [2]Norwegian University of Science and Technology, Trondheim, Norway; [3]University of Graz, Graz, Austria; [4]Finnish Meteorological Institute, Helsinki, Finland; [5]British Antarctic Survey, Cambridge, United Kingdom; [6]Aristotle University of Thessaloniki, Thessaloniki, Greece; [7]National Institute of Public Health and the Environment, Bilthoven, The Netherlands; [8]Norwegian Institute for Air Research, Kjeller, Norway; [9]University of Manchester, Manchester, United Kingdom; [10]Universität für Bodenkultur, Vienna, Austria; [11]University of Innsbruck, Innsbruck, Austria; [12]Université Joseph Fourier, Grenoble, France; [13]Czech Hydrometeorological Institute, Hradec Králové, Czech Republic; [14]Polish Academy of Sciences, Warsaw, Poland; [15]Tartu Observatory, Tartu, Estonia; [16]Institute of Meteorology and Water Management , Warsaw, Poland; [17]Institut d'Aronomie Spatiale de Belgique, Brussels, Belgium; [18]National Agency for New Technologies and Environment, S. Maria di Galeria, Italy; [19]German Weather Service, Potsdam, Germany; [20]Federal Office for Radiation Protection, Oberschleissheim, Germany; [21]Joint Research Centre, Ispra, Italy; [22]University of Rome, Rome, Italy; [23]Institute of Meteorology, Lisbon, Portugal; [24]The Royal Netherlands Meteorological Institute, De Bilt, The Netherlands; [25]Université des Sciences et Technologies de Lille, Lille, France

A European UV climatology is being developed based on measurements of spectral UV irradiance at 32 different locations, from 15 European countries. One major goal is to analyse long-term data sets for evidence of changes in UV radiation. The UV climatology and its analysis is achieved by a combination of radiation measurements, ancillary data, an appropriate quality assurance/quality control programme and radiative transfer modelling.

The EDUCE UV data base will be a helpful tool in designing a European network of excellence for solar UV radiation measurements. It also provides key data for the analyses of the spatial representativeness of solar UV measurements and for the validation of e.g. satellite algorithms for estimating UV at the ground.

By the close of this project, some stations will have spectral UV measurements spanning more than ten years. Nearly 140 publications and tens of reports have been printed within Educe and its predecessor Suvdama. The European UV Database currently holds more than 1,300,000 spectra from over 30 European stations. In addition broadband data are stored as well.

The latest reports include, among other things, developments in data analysis, quality control, radiative modelling and in data base management. These reports are also available at http://www.muk.uni-hannover.de/EDUCE.

User-friendly access to the European UV database is available for all registered users.

3-27

Provision of melanoma screening clinics and participation in melanoma screening within a randomised community based melanoma screening trial

Monika Janda[1], Mark Elwood[2], Ian Ring[3], David Firman[4], John Lowe[5], Pip Youl[6], Joanne Aitken[6]
[1]Queensland University of Technology and Queensland Cancer Fund, School of Public Health, Brisbane, Australia; [2]National Cancer Control Initiative, Medical Epidemiology, Carlton, Australia; [3]Queensland Health, Health Information Centre, Brisbane, Australia; [4]Queensland Treasury, Office of Economic and Statistical Research, Brisbane, Australia; [5]University of Iowa, Community and Behavioral Health, Iowa City, United States; [6]Queensland Cancer Fund, Epidemiology, Brisbane, Australia

Residents of Queensland, Australia are at highest risk for melanoma worldwide, carrying a lifetime estimated risk of 1 in 16 for men and 1 in 24 for women. Screening for melanoma may lead to early detection and increased survival from this disease. A randomised controlled trial of a community-based screening program for melanoma (SkinWatch) was developed and implemented in eighteen regional communities in Queensland. During the first year of the trial, three communities in the intervention group received a community education program only, three received the community education program and "ad hoc" skin screening clinics organised by local doctors within their own practices and three received the education program and SkinWatch clinics organised at hospitals and community locations as part of the SkinWatch program. The prevalence of whole-body skin examinations by a primary care physician was assessed by telephone and postal surveys prior to the introduction of the intervention, and again at 12 months follow-up. At baseline, the prevalence of a whole-body skin examination by a primary care physician during the past 12 months was similar within the 9 intervention (13.3%) and 9 control (11.7%) communities (P=0.25). At 12 months follow-up 19.5% of participants within intervention communities reported a whole-body skin examination compared to 11.1% of participants within control communities (p<0.001). Within intervention communities, 12.7% of participants in communities which received the education program only, 16.4% of participants in communities which received the education program and "ad hoc" skin screening clinics and 30.8% of participants in communities which received the education program and SkinWatch clinics reported a whole-body skin examination within the past 12 months (p<0.001). The SkinWatch intervention was successful in increasing participation in skin screening in intervention communities. However, a significant increase in the number of whole-body skin examinations compared to the control group was observed only in communities with skin clinics, with largest increases in those communities with clinics organised within the SkinWatch program.

3-28

The effects of a clinical-practice guideline for malignant melanoma in the Stockholm-Gotland health care region

The Clinical-Practice Guideline Group in the Stockholm Gotland Region[1], Eva Månsson-Brahme[2]
[1]Sweden; [2]The Clinical-Practice Guideline Group in the Stockholm Gotland Region, Sweden

Introduction: In 1999 415 new cases of malignant melanoma were recorded in the Stockholm-Gotland region (population approx. 1.9 million) in Sweden. The Clinical-Practice Guideline (CPG) Group was formed at the regional Oncologic Centre 1976 and the first guideline was issued the same year. The guideline has since then been updated regularly with the most recent issue 2003. A continuous registration of a number of variables meant to follow-up the care of malignant melanomas in the region is connected to the guideline.

Material and Methods: A continuously updated consensus CPG with a population-based registration in a regional quality registry for malignant melanoma.
Results: From 1976 to 1999 7,156 cases of malignant melanoma have been registered in the regional quality registry for malignant melanoma. When compared with the mandated regional cancer registry the yearly coverage in the quality registry for malignant melanoma ranges from 92 to 100% with an average of 97%. The age adjusted incidence in the region has increased from 10 to 23/100,000 during the period. The rates of closure with suture for primary and secondary excisions have increased from 75% to 90% and from 10% to 75%, respectively. In the first CPG 1976 a resection margin of at least 1 cm was recommended for invasive melanomas with a thickness of 0.1 to 0.8 mm. From being 75% 1976, the rate of resections with margins 2 cm or larger for these melanomas decreased to 35% within two years and 1999 this rate was 5%. The rate of resections with margins between 1 and 2 cm was approximately 90% 1999. For invasive melanomas with a thickness of 0.81 to 2.0 mm, 75% of the resections were done with a 4 cm or more margin 1975. Between 1982 and 1991 a randomised study of a 2 cm versus a 5 cm resection margin were conducted in this patient group in the region and 1990 the rates of resections with a 2 cm and 4 cm or more margin were approximately 35% each. After the study a 2 cm margin was recommended and within two years the rate of resections with a 4 cm or more margin fell to 10% and 1999 it was almost 0. During the period from 1975 to 1999 the relative survivals for all types of melanomas have increased gradually in the Stockholm-Gotland region while the age adjusted mortality from malignant melanoma rose until 1980 and was from then constant.
Conclusion: CPG:s can be effective in inducing changes in pattern of care. The changes must be monitored over time, preferably in dedicated registries, and compared with outcomes such as mortality etc. In the case of malignant melanoma in the Stockholm-Gotland region rapid changes towards smaller resection margins can be seen after the recommendations being given in the CPG. The rates of closure with sutures have increased. Thus, less plastic surgery and in-patient procedures are required sparing health care resources and most probably resulting in less distress to the patients.

3-29

Abstract withdrawn.

3-30

Sunbathe slowly

Catharina af Ugglas Sandström, Britta Hedefalk
the Swedish Cancer Society, Communication, Stockholm, Sweden

The Swedish Cancer Society has carried out skin cancer prevention work for a number of years under the slogan "Sunbathe Slowly". In 1995 and 1998, activities were oriented towards secondary prevention, with the offer of a free skin examination by doctors at several holiday resorts around Sweden.
In the summer of 2000, and even more in 2001, the Cancer Society focused its prevention work on young people aged 13–22, with a youth event with information combined with entertainment. We also carried out secondary prevention work by offering skin checks by experienced doctors.
After the second Euroskin conference in Orvieto in 2001, where it was shown so clearly that early influence is the only way to change sun habits, the Cancer Society changed strategy and we are now focusing all our sun prevention work on the parents of small children.

In the summer of 2002 we carried out a countrywide Sunbathe Slowly tour with an information tent and a high-quality children's theatre performance with a clear link to the sun issue. The main message was to sunbathe slowly and avoid the sun between the hours of 11 a.m. and 3 p.m.
In the summer of 2003 our efforts have been directed towards informing children and their parents via various types of mass media about how and why we should protect ourselves from the sun, and helping them to activate themselves in other ways than sunbathing in the middle of the day when the sun's rays are at their most dangerous. One of the information channels is the back of milk cartons. Over 2 million milk cartons have cartoon characters from various sunny countries, who demonstrate how they protect themselves from the sun. There is also text to inspire creative activity, games and recipes on the theme Sunbathe Slowly Around the World. At the same time, we are working on a special website that contains more information and ideas for creative activity, games and recipes from all over the world. Another information channel is Sweden's Well Baby clinics, which have been provided with an information folder. A well-known clothing chain sells printed T-shirts with our motto Sunbathe Slowly on them. We also use McDonald's tray covers, text TV and a special Sunbathe Slowly insert in one of our bigger evening papers.

3-31

New sun-advice program on the web at the SSI homepage (www.ssi.se)

Ulf Wester[1], Katarina Yuen[1], Christer Hult[2], Fredrik Lidén[2]
[1]Swedish Radiation Protection Authority, SSI, Stockholm, Sweden; [2]Digital Context AB, (Adelhart Publishing), Södra Sandby, Sweden

The Swedish Radiation Protection Authority (SSI) under the Ministry of Environment works to improve prospects of changing attitudes to UV-exposure (tanning).
A recent information initiative is a dynamic and interactive sun advice programme on the SSI website which was developed from the educational multimedia CD-Rom "Malignant Melanoma", originally funded by the EC and published in English, Swedish and German. It provides extensive sun protection information for the general public and worldwide travel advice based on the UV-index.
The program "The Sun – Facts & Information" on the SSI web site (www.ssi.se) has been newly revised and is presently available also in the English language (e.g. via the direct link: http://www.ssi.se/Solinformation/sol.asp?page=main_0100.htm&lan=en).
Apart from its "Travel Guide" and "Advice for safe sunbathing", the programme contains sections with informaton on "UV-radiation", "Malignant melanoma" and on the "History" of sunbathing and sunworship.

3-32

Ultraviolet Radiation and the Risks of Cutaneous Malignant melanoma and non-melanoma skin cancer: Perceptions of Danish and American adolescents

Michael R Savona[1], Michael D Jacobsen[2], Robert James[1], Medge D Owen[1]
[1]Internal Medicine, Wake Forest University School of Medicine, Fairfield, California, United States; [2]Department of Medicine, Hilleroed Hospital, Hilleroed, Denmark

Background: The incidence of skin malignancy has increased more than 600% worldwide since the 1940's, the greatest prevalence of which occurs in Australia and New Zealand. In the northern hemisphere, skin cancer is most common in Scandinavia and the United States. Most Danes and Americans, for example, receive 75% of the total lifetime ultraviolet (UV) radiation before age 21, representing a disproportionate amount of intermittent sun exposure and possible sunburn. It is crucial, therefore, to properly address the dangers of sun exposure and skin cancer with children and adolescents. Though there have been attempts to gauge public knowledge of skin malignancy risks, there are no published studies of the perceptions of Scandinavian adolescents or comparisons of perceptions between adolescents of different cultures. The project was undertaken to determine differences between Danish and American adolescents in: knowledge of sun exposure and risks of skin malignancy, activities accounting for sun exposure, and means used for sun protection.
Methods: Four hundred eighty-three surveys were disseminated to high school sophomores in Winston-Salem, North Carolina. The materials were translated into Danish (MDJ) and 674 surveys were disseminated in secondary schools in Hilleroed, Denmark. Differences in survey responses between the groups were tested using exact chi square analysis. In addition, subgroup analysis was also computed for gender, race, and chronological age.
Results: Danish and American respondents shared similar knowledge of the dangers of UV radiation, but American respondents were more familiar with the defining characteristics and malignant potential of melanoma. With regard to habits in which the respondents received UV exposure, the groups differed significantly, especially with regard to sunbathing or tanning bed use.
Comments: The frequency of use of sunbathing and tanning beds by adolescents in Denmark is alarming. Given the correlation between these modalities of UV exposure and skin malignancies, Danish adolescents may benefit from public education explaining these risks.

Histopathology Standards

4-1

Precursor lesions & risk markers for melanoma

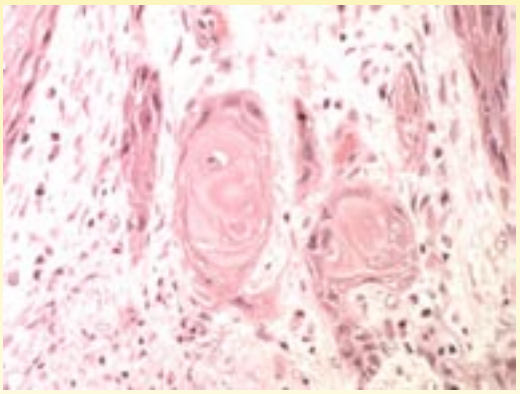
David E. Elder
University of Pennsylvania, Philadelphia, PA, United States

In the absence of effective therapy for metastatic disease, prevention of mortality from melanoma can be considered in two major categories (adapted from the WHO National Cancer Control Programmes, Executive Summary, 2002): 1) Reducing melanoma incidence by eliminating or minimizing exposure to its causes. 2) Reducing melanoma mortality by early diagnosis, and appropriate management of precursors. This presentation will focus on precursors of melanoma. Precursor lesions in general should be considered in two categories: 1) A potential precursor lesion is a neoplasm that may progress to a cancer, with a greater potential than chance. Such lesions (e.g. nevi including congenital and dysplastic nevi, adenomatous polyps of the colon, etc) are often multiple, and most lesions do not progress in the lifetime of the host. 2) An actual precursor lesion is a neoplasm that actually has progressed to a cancer. Examples include melanoma arising in a nevus, or adenocarcinoma arising in an adenoma. Melanocytic nevi are potential precursors of some (approximately 30%) but not all melanomas, however most nevi are stable, and do not progress. The risk of melanoma is sufficiently low in nevi that it is not practical to prevent melanoma by excising potential precursors. Nevi are also important as simulants of melanoma – nevi with clinical and histologic atypia must be distinguished from melanomas, and this is often difficult. Perhaps the greatest significance of nevi is as risk markers of individual risk for melanoma. Risk for melanoma may be increased because of an increased number of potential precursor cells at risk of transformation, and also because of shared epidemiological risk factors, both genetic and environmental. The total number of nevi is a strong risk factor for development of melanoma, but in many studies the strongest factor is the presence and number of dysplastic nevi. Dysplastic nevi are morphologically intermediate between nevi and melanoma, and are characterized by architectural and cytologic atypia. They are benign neoplasms of melanocytes that were first described in hereditary melanoma kindreds. Their incidence is 5–20% in random population members, depending on criteria, which have varied among published studies. Clinical and histologic diagnoses are reproducible when criteria have been agreed on. The risk of progression of an individual dysplastic nevus is of the order of one in about one thousand lesions per year, and the risk for nondysplastic nevi is even less. Therefore, nevi should be managed as risk markers (by education and surveillance, which have been shown to result in earlier diagnosis of melanoma) rather than as high-risk precursors (by excision). Melanoma in situ is another lesion that may be regarded as a precursor of invasive cancer. The risk of progression of an individual MIS lesion is unknown, but probably much higher than for a dysplastic nevus. Therefore, the aim of surveillance should be to recognize melanomas in their in situ or nontumorigenic phases, and excise them to prevent progression to the later life threatening invasive and tumorigenic stages of melanoma progression.

4-2

Histopathology standards – non-melanoma skin cancer

Nigel Kirkham
Royal Sussex County Hospital, Histopathology, Brighton, United Kingdom



Non-melanoma skin cancer is amongst the commonest of cancers in sun-exposed Caucasian populations. In the United Kingdom basal cell carcinomas are considered to be so common and trivial as to not merit inclusion in cancer registries.
In the United Kingdom the Royal College of Pathologists has addressed many of the issues involved in standard setting in histopathology in a series of 'Minimum Data Set' documents, one of which is devoted to melanoma and non-melanoma skin cancer. The document is available on the College website –
http://www.rcpath.org/resources/pdf/skincancers2802.pdf
The principles underpinning the process are:
1 – The minimum datasets for reporting tumours are used in the system of standard-setting, data collection, audit and feedback for those involved in caring for these patients.
2 – Histopathology laboratories nominate a lead pathologist for each of the main cancers with responsibility for liaising with relevant local committees and clinicians, and ensuring the relevant cancers are examined, sampled and reported appropriately and in a consistent fashion.
3 – Histopathologists should be members of multidisciplinary teams, dedicated to the diagnosis and management of patients with specific cancers (and be involved in auditing the service).
4 – The SNOMED coding system is used to achieve as much uniformity as possible from centre to center and to facilitate reliable cancer registration. Either the 1979 or 1993 version of SNOMED can be used, as there is currently no clear consensus for using one or the other.
5 – Histopathologists reporting cancers should participate in appropriate External Quality Assurance schemes.
6 – Cancer Centres and Units should be supported only by laboratories accredited with Clinical Pathology Accreditation (UK) and staffed in accordance with the recommendations of the College.
These principles must be applied within the context of the problems encountered in everyday diagnostic practice, especially in making diagnostic distinctions between in situ and invasive squamous tumours and in recognising different manifestations of basal cell carcinoma associated with different degrees of invasive growth and different degrees of risk for disease recurrence.
Areas of continuing difficulty and uncertainty will be reviewed together with consideration of lesions associated with immunosuppressive therapies and other tumourigenic factors.

4-3

Actinic keratosis versus squamous cell carcinoma. Where is the edge?

Jean-Pierre Cesarini
INSERM, Dermatology, Paris, France

According to the International statistical Classification of Disease, actinic keratosis (AK) (pre-malignant lesion of the epidermis) and squamous cell carcinoma (SCC) = epidermoid carcinoma (second commonest skin cancer...) are different entities. Dubreuilh (1898) suggested continuity between pre-cancerous AK and invasive SCC. Recently, a conference held by the American Academy of Dermatology stated : "AKs are cutaneous neoplasms... and are precursors of invasive SCC... AK is the first step in a continuum that may end in fatal SCC". This statement is challenged by some histo-pathologists "solar keratosis is a cancer, not a pre-cancer. It is from onset a SCC of one specific type". Clinically, several subtypes must be considered: exceptionally single but frequently multiple, at different stages of evolution, the lesion may remain stable, regress or progress. Most of the lesions are microscopic, not detectable clinically. They become obvious when they have dyskeratotic elements. Histologically, the epidermis, acanthotic, normal or atrophic, shows varying degrees of dysplasia: nuclear abnormalities, dyskeratosis, rare mitotic figures. Prominent infiltration by mononuclear cells is present in the dermis, which shows evidence of solar elastosis and telangiectasia. These features are found in AK and SCC. There are many more AK than SCC, per year, 0.1% to 10.% of AKs progress to SCCs. Multiple AKs increase the risk arithmetically. Patients with more than 10 AKs have 14% probability of developing SCC within 5 years. The occurrence of AKs depends on a combination of risk factors: cumulative sun exposure, persons sun sensitivity, age, place of birth, latitude of reference, weekend activities, occupation and social economic status. Mutation in the repressor gene, p53, has been identified as permanently expressed in the AK cells as well as in the SCC cells. Mutations exhibit the causal (UV) signature. The immune reaction is the major factor able to restrain the extension of abnormal cells. Further UV-exposures will favor the extension of the lesions. The histo-pathological report is an important document since constituting the base for epidemiological investigations and a tool for education and surveillance of the patients.
We believe that it should be clearly stated in the conclusion of the histo-pathology report: keratinocytic intra-epidermal neoplasia, i.e. in situ squamous cell carcinoma - invasive keratocytic neoplasia, i.e. invasive squamous cell carcinoma.

4-4

Dificits for histopathological diagnoses in skin cancer – proposals for standardization

Bernadette Schubert
Center of Dermatology , Association of Dermatological Prevention, Buxtehude, Germany

In Germany an optimum diagnosis of neoplastic skin diseases is handicapped by several circumstances. As there is no board graduation for dermatopathologists the training programme is disparate and the preconditions are ill defined. The majority of diagnoses are signed out by dermatologists, most of whom were never consequently trained in pathology. On the other hand, general pathologists are comparatively seldom confronted with cutaneous neoplasms and, therefore, are much less experienced in this field. This explains the high degree of variation in the content of reports, the quality of which depends on the formation the dermatopathologist has received. For instance, parameters that are indispensable for a reliable classification of tumours are often indistinctly or incompletely specified. In many instances, text prefabs insufficiently characterize the histological features of individual tumours, impeding a retrospective appraisal of the condition. In this way, statistical analyses on skin cancer are hardly feasible on a larger scale. Hence, the establishment of standard criteria for the diagnosis of skin tumours in daily routine is imperative. This chiefly concerns malignant neoplasms, as there are MM, BCC, and SCC. The fundamental histological criteria for the diagnosis of these entities and the informational details the clinician needs for adequate therapy and prognosis will be proposed herein for discussion. Moreover, certain entities may need revisiting with regard to their biological potential, such as keratoacanthoma and trichoepithelioma. Others would benifit from a more precise denomination, such as actinic keratosis, which is in fact carcinoma in situ. Ancillary techniques that may be helpful in cases of uncertain histogenesis or uncertain malignant potential (immunhistochemistry, molecular analyses) will be briefly outlined. Last but not least, we plead for the instauration of reference centres in dermatopathology.
The goal of this proposal is a unified concept for the training and graduation of dermatopathologists in all european countries.

Author Index

EUROPEAN SOCIETY OF SKIN CANCER PREVENTION
EUROSKIN

Conference Organiser

European Society of Skin
Cancer Prevention e.V.
EURO*SKIN*
c/o Centre of Dermatology
Am Krankenhaus 1
21614 Buxtehude
Germany

Telephone: +49 4161 703 69 91
Telephone: +49 4161 703 69 05
(Mrs. Sylvia Hinz)

Fax: +49 4161 703 67 45

Email: euroskin@t-online.de

Web Site: www.euroskin.org

Registration and Hotel

Congrex Sweden AB
Attn: EURO*SKIN*
P.O. Box 5619
SE-114 86 STOCKHOLM
Sweden

Telephone: +46 8 459 66 00

Fax: +46 8 661 91 25

Web Site: www.congrex.com

Photo: Photo Alto, Northern Pictures and SIS. Production: Congrex Sweden AB / Informationsbolaget Nyberg & Co