Clinical characteristics and management of melanoma families

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General introduction

General introduction and outline of the thesis

Cutaneous malignant melanoma (CMM) is a malignant skin tumor that develops from melanocytes, the pigment producing cells, in the skin. In the last decades melanoma incidence rates have been increasing considerably worldwide. In the Netherlands the age-standardized incidence per 100.000 person-years increased from 11.3 in 1989 to 21.7 in 2008, with an estimated annual percentage increase of 4.1%.[1] By 2008 melanoma ranked the 8th most diagnosed cancer in man and 5th most diagnosed cancer in women.[2] Age-standardized mortality increased (albeit to a lesser extent), from 2.2 per 100.000 person-years in 1989 to 3.9 per 100.000 person-years in 2009, with an estimated annual percentage increase of 2.3%.[1]

One of the strongest risk factors for CMM is a familial predisposition. The characteristics and management of melanoma families are the subject of this thesis. This chapter will provide a background to the subject by discussing the epidemiology, clinical characteristics, and genetics of melanoma families, as well as the Dutch management guidelines that constituted the starting point for this thesis. In the final section, dermoscopy, which has been established as an integrated part of the everyday practice of skin surveillance, will be introduced. We will start however by providing a short overview of the different melanoma risk factors.

Melanoma risk factors

Several melanoma risk factors have been identified. Solar UV is the main environmental cause of melanoma.[3] At present it is known that the risk of melanoma is significantly increased by intermittent exposure: particularly irregular and intense exposure (with sunburn), while more regular (chronic) exposure is to some degree inversely associated with melanoma.[4] Recent studies suggest that chronic UV, intermittent UV and UV independent melanomas may represent (clinical, histological, epidemiological and molecular) different melanoma subtypes.[5]

Much of an individuals' risk of developing a CMM can be learned by inspection of the patients external characteristics. Hair colour (red vs. dark, relative risk of melanoma (RR) = 1.74 (1.41 – 2.14)), skin colour (fair vs. dark: RR = 2.06 (1.68 – 2.52)), and eye colour (blue vs. dark: RR = 1.47 (1.28 – 1.69)), are all associated with melanoma risk, most likely due to their correlation with sensitivity to ultraviolet light.[6] More strongly correlated with melanoma risk are the number of common nevi (RR = 6.89 (4.63 – 10.25) for 101-120 nevi vs. < 15) and number of atypical nevi (AN) (RR = 6.36 (3.80 – 10.33) for 5 vs. 0).[7] The risk of melanoma for patients with large congenital nevi is estimated to be about 2.5% to 5%, and highest in the first 5 to 10 years of life.[8]

The relative risk of melanoma for individuals with a positive family history of melanoma has been estimated to be 1.74 (1.41 – 2.14).[6] This risk increases considerably in families with many melanoma patients. An early study in 23 families with at least two family members

with CMM and two relatives with AN, reported a relative risk of CMM of 89 for relatives with AN and a relative risk of 229 for relatives with a previous CMM.[9] These high relative risks are illustrative of the fact that familial susceptibility is likely the strongest risk factor (in terms of effect size) for melanoma.

Familial melanoma

In 1820 Norris was the first to describe familial clustering of melanoma.[10] It took almost one and a half century before others published similar observations.[11] A positive family history of melanoma has been reported in 6% to 14% of melanoma patients.[12] Familial melanoma is defined as the occurrence of at least two first degree relatives with melanoma or three melanomas in second-degree relatives.[13] Because of the co-occurrence of AN in many of the first described melanoma families, the term Familial Atypical Multiple Mole-Melanoma (FAMMM) syndrome was adapted.[14] The correlation between AN and familial melanoma was later shown to be more complex however. AN regularly occur in the general population, with an estimated prevalence of 2% to 8% in whites.[15-17] In addition AN and CMM do not fully co-segregate within FAMMM families.[18] This has been well illustrated in families with a mutation in the high-penetrance melanoma susceptibility gene CDKN2A; relatives with AN have a higher probability of being CDKN2A mutation carrier, but mutation carriers may be devoid of AN and mutation negative relatives may have many AN.[19,20]

The genetics of melanoma susceptibility

So far, two high-penetrance melanoma susceptibility genes associated with an autosomal dominant inheritance have been identified. In 1994, CDKN2A(MIM# 600160), located in the 9p21 region, was the first melanoma susceptibility gene to be identified.[21] By using different first exons (1α and 1ß) respectively, it encodes two distinct proteins: p16INK4 and p14ARF. Both proteins are tumour suppressors involved in cell cycle regulation.

Pathogenic germline mutations in the tumor suppressor gene CDKN2A are detected in approximately 39% of families with ≥3 melanoma cases.[22] CDKN2A mutations have an estimated penetrance for CMM of 67% by the age of 80 years.[23] In the Netherlands the most prevalent CDKN2A germline mutation is a founder mutation (c.225-243del19) that is frequently found in the Leiden region, and has therefore been denominated the p16-Leiden mutation.[24] In addition to an increased melanoma risk, the p16-Leiden mutation is associated with a cumulative risk of pancreatic cancer of 17% by age 75.[25]
Mutations in the second high penetrance melanoma susceptibility gene, the oncogene CDK4 (MIM# 123829) have been detected only in few families (estimated 2%).[26] CDK4 germline mutations have a similar impact on melanoma risk as CDKN2A mutations.[27]
For the majority of families the genetic risk factor has not been fully clarified, but appears

to be the result of a combination of low (e.g. MC1R) and moderate (e.g. MITF) risk modifier genes and (possibly) some rare high penetrance genes.[28,29] Environmental and lifestyle factors (as described above) likely attribute to clustering of melanoma in (some) families, and modify expression of genetic risk factors.

In clinical genetics a distinction is made between families with a proven germline mutation (CDKN2A/CDK4): 'hereditary melanoma' and families without a (proven) germline mutation: 'familial melanoma'. In families without a proven pathogenic germline mutation, melanoma susceptibility is suggested by familial clustering of melanoma patients, but cannot be confirmed by genetic testing and therefore remains a clinical diagnosis based on pedigree studies alone.

Clinical characteristics of melanoma patients from melanoma families

Several studies indicate that melanoma patients from melanoma families have an earlier age of onset and an increased risk of multiple primary melanomas (MPM). There are also reports on a different distribution of histological tumour types in melanoma families; i.e. an increased proportion of superficial spreading melanomas, decreased proportion of nodular melanomas and a possible absence of acral lentiginous melanomas.[30-32] Data on the characteristic of melanoma patients specifically from families with a CDKN2A mutation are more scarce however. Reports on the age of diagnosis of the first melanoma in these families range from 36.3 to 43.3 years.[27,33,34] The proportion of mutation carriers who develop MPM in the literature ranges from 18.6% to 25.6%, but duration of follow-up was not reported in the referred studies.[33,35]

In **chapter 2** we report a study in which we investigated the clinical and histological characteristics of melanoma(patients) from CDKN2A mutated families in comparison with sporadic melanoma patients. In **chapter 4** some of the characteristics reported in chapter 2 were compared between CDKN2A mutated families and CDKN2A wild-type melanoma families.

Management

Melanoma patient survival is highly dependend on the stage at diagnosis. Early melanomas can be cured by a wide local excision with proper resection margins, but, even though promising new therapeutic options are emerging, prognosis is still poor for advanced disease.[36-38]

Survival outcomes are to a considerable extent predictable based on the histological characteristics of the primary tumor, and the presence of lymph node involvement (including sentinel node procedure) and (distant) metastases. One of the main histological predictive characteristics, first described by Alexander Breslow in 1970 is the tumor

(Breslow) thickness, which is the depth of the tumor from the surface of the lesion (stratum granulosum) to the deepest point of invasion, expressed in millimeters.[39] Breslow thickness strongly correlates with survival, which is illustrated by the fact that 10-year survival is 92% in case of melanomas ≤ 1.00 mm, and 50% if > 4.00 mm. The presence of ulceration and the mitotic rate are additional tumor characteristics correlated with outcome.[40]

Early detection is considered the most effective way to prevent melanoma mortality. For this reason, regular surveillance of individuals at high risk of melanoma, such as members of melanoma families, is widely advocated.[41,42]

Effectiveness of melanoma surveillance

In a 2009 review, the U.S. Preventive Services Task Force (USPSTF) reinforced their 2001 statement that, quote: "evidence is lacking that skin examinations by physicians is effective in reducing mortality or morbidity from skin cancer.".[43,44] This statement was predicated on the lack of evidence from randomized controlled studies. Although this statement addressed skin cancer (including squamous- and basal cell carcinoma) screening of the general population, the same argument is brought forward for specific melanoma screening or surveillance. Given the fact that an adequately powered, population-based randomized controlled trial of screening demonstrating mortality outcomes would require approximately 800.000 participants (based on US melanoma-related mortality rate), it is unlikely however that a randomized controlled study will ever be conducted.[42,43]

Several studies have reported that melanomas detected by physicians have a thinner Breslow thickness than those detected by patients themselves.[45-50] A few studies have reported the detection of thinner melanomas in the context of surveillance of melanoma families.[51-54] Recently convincing arguments for a beneficial effect of screening on melanoma survival came from an observational study concerning a population-based skin cancer screening project in Schleswig-Holstein, Germany, reporting a significantly different and more favourable trend in mortality rates compared to adjacent regions in the years following the screening period.[55]

In a recent article the Melanoma Prevention Working Group commented on the USPSTF statement that, quote: "…the evidence is compelling enough to support the efficacy of targeted screening programs for detecting thinner melanomas, as a proxy measure for reduced mortality.", and, quote: "…absolute proof is not necessary in the public health domain to implement a targeted screening program that has the immediate potential to save lives.".[42]

As noted above the effectiveness of surveillance in melanoma families has been investigated only in a few studies, mostly with limited numbers of surveillance detected melanomas and confined to specialized pigmented lesion clinics.[51-54] In **chapter 3** we investigated the effectiveness of surveillance in CDKN2A mutated families and also

address some issues related to the effectiveness of surveillance that have gained little attention so far in the literature. In **chapter 4** effectiveness of surveillance was assessed in families registered at the NFDHT, that were under surveillance throughout the Netherlands.

Management of melanoma families in the Netherlands

In the Netherlands, the first surveillance program for familial melanoma was initiated at the Leiden University Medical Center (LUMC) in 1981. Individuals that were invited to the program encompassed melanoma patients, their first degree relatives (parents, siblings and children) as well as their second degree relatives (grandparents, uncles, aunts, nieces, nephews and grandchildren). Starting from the age 12, these relatives are offered (a minimum of) annual total skin examinations.

In 1989 a national registry for familial melanoma was established at the Netherlands Foundation for the Detection of Hereditary Tumors (NFDHT) in order to promote the detection and surveillance of members of melanoma families throughout the Netherlands. Clinicians refer families suspected for familial melanoma to the registry. Genealogical studies are performed and all reported malignancies are verified by medical records. If criteria for familial melanoma are met, the registry monitors the continuity of the surveillance program for all family members with a history of melanoma and their unaffected first degree relatives by annually sending letters to the responsible clinician (mostly dermatologists). In return these clinicians report the results of surveillance and histo-pathologic examination.[54,56]

Starting from 2000 (predictive) DNA testing for CDKN2A (later complemented by CDK4) became available for members of melanoma families.

The segments of the 2005 Dutch melanoma guidelines that cover the management of melanoma families, and that were in effect when this thesis was initiated, are presented in Box 1.

As can be seen in box 1, the surveillance recommendations for FAMMM families in the 2005 guidelines were similar for all families that fulfilled the criteria of at least two first-degree relatives or three melanomas in second-degree relatives. Surveillance recommendations were independent of the presence or absence of a germline mutation in CDKN4/CDK4 in the family and family characteristics (e.g. the number of affected relatives). Given the fact that the chance of CDKN2A mutation detection was proven to be positively correlated with the number of melanoma patients in a family, it is anticipated that melanoma risk is higher in families with a high penetrance melanoma susceptibility gene-mutation (CDKN2A/CDK4) compared to CDKN2A/CDK4 wild-type families.[22] In addition, it is expected that melanoma risk in families is positively correlated with the number of melanoma patients. There is a lack of prospective studies however that confirm these notions, and it is therewith unclear whether all melanoma families need to be surveillanced with the same scrutiny.

Box 1 Guidelines with respect to the management of melanoma families from the Dutch Melanoma guidelines 2005 (appendix 3)[13]

Paragraph 3.1: Familial Dysplastic Nevus Syndrome (DNS)
(= FAMMM syndrome = Familial Atypical Multiple Mole / Melanoma Syndrome)

Melanoma with/without dysplastic melanocytic nevi nevocellulares in at least two first-degree relatives or three melanomas in second-degree relatives.

Note: Presence of dysplastic melanocytic nevi increases the probability of being a mutation carrier, but absence does not exclude being a carrier of the predisposition to melanoma.

Paragraph 5.2:
Risk level 2 (greatly increased):

Being a members of a family (up to the second degree) with familial DNS / FAMMM syndrome (see section 3.1).

management:
- Information (oral and written)
- Once a year or more frequent skin examinations (absolute indication)
- Check children from the age of twelve years

Another point of discussion has been the necessity for second degree relatives to be under surveillance, as the yield of surveillance may be relatively small. Surveillance of second degree relatives has not been explicitly recommended in melanoma guidelines from other countries.[57-59] In this thesis we present two studies that investigated melanoma detection rates in families with different CDKN2A mutation status and family characteristics (**chapter 4**) and in second degree relatives from CDKN2A mutated families (**chapter 5**).

'Overdiagnosis'

A recurrent point of discussion related to melanoma surveillance is the issue of 'misclassification' of benign or indolent melanocytic proliferations as CMM. This point gained attention upon the observation that the incidence of melanoma has increased dramatically, while the mortality from melanoma has not increased proportionately. In addition, the increased melanoma incidence is disproportionally attributable to thin lesions.[1,60] It has been argued that the 'melanoma epidemic' could (at least partially) be explained by increased public and physicians' melanoma awareness and screening/surveillance, which resulted in three (overlapping) phenomena; 1. overdiagnosis, i.e. detection of indolent melanocytic tumors, that would either never progress or progress slowly enough that the patient dies of other

causes, and 2. diagnostic drift, i.e. classification of melanocytic lesions as CMM, that years ago would have been diagnosed as benign melanocytic lesions, and 3. increase in false positives as a result of submission of increasing numbers of equivocal melanocytic proliferations to the pathologist.[60-62] Adversaries of this line of argumentation claim that, in stead, the epidemiological trends are mainly attributable to a real and steep increase in melanoma incidence due to behavioural changes regarding sun exposure. At the same time, mortality is believed to have been successfully constrained by strategies to advance melanoma diagnosis. The debate is ongoing.[63] In **chapter 6** we report an observation concerning the misclassification of melanocytic lesions as melanoma in the context of surveillance of CDKN2A mutated families.

Dermoscopy

Dermoscopy is a non-invasive technique in which oil immersion or polarised light are used to make the epidermis translucent and a lens is used for magnification to allow the visualization of structures not visible to the naked eye. Although the basic technique was already described in the late 19th century, it was not until the last two decades of the 20th century, after the introduction of handheld dermatoscopes, that dermoscopy gradually became integrated in the dermatological armamentarium.[64], Dermoscopy is primarily used to supplement the clinical (naked eye) evaluation of (pigmented) skin lesions, that are suspicious of malignancy. The basic approach to these lesions consists of two steps: 1. to distinguish melanocytic from non-melanocytic lesions, and 2. distinguish benign from malignant lesions. Several algorithms have been developed to facilitate a standardized assessment of (pigmented) lesions, including the pattern analysis, and more accessible simplified algorithms like the ABCD-method, Menzies method and seven point checklist.[65-68]

The impact of dermoscopy on clinical practice

Numerous studies have confirmed that dermoscopy improves the diagnostic accuracy for pigmented lesions.[80-92] In 2008 a meta-analysis of dermoscopy studies performed in a clinical setting, reported a statistically significant better sensitivity for the diagnosis of melanoma for dermoscopy (0.90) compared to naked eye examination alone (0.71), without a significant difference in specificity (dermoscopy: 0.90, naked eye examination: 0.81).[69] Strikingly, the findings of the only randomized controlled study on dermoscopy in a dermatologist setting, presented a rather opposite view; a 42% reduction in patients referred to excision, without a change in sensitivity.[70]

These contradictory findings may be related to the fact that the design of many dermoscopy studies possibly limited their applicability to clinical practice: clinicians judged (macro- and dermoscopic) images rather than life patients, study sets included only lesions that had been excised, and contained a disproportionate high number of

melanomas, dermoscopic images were not preceded by their accompanying macroscopic images, studies focussed on the impact of dermoscopy on the clinical (preferential) diagnosis, rather than management of lesions and many studies were performed in the setting of dermoscopy expert dermatologists. Performance of dermoscopy is likely to be highly dependent on the clinical context in which it is performed. As a consequence the actual impact of dermoscopy on the clinical dermatological practice is not fully clarified.
In **chapter 7** and **chapter 8** we describe two studies in which we investigated the impact of dermoscopy on clinical practice both in general dermatology clinics as well as in the context of surveillance of melanoma families in an expert pigmented lesion clinic. These two clinic settings are expected to differ both in respect to the characteristics of the presented lesions (symptomatic lesions versus early asymptomatic lesions against the background of atypical nevi) as to the degree of dermoscopy expertise.

Aims and outline of the thesis

The general aims of this thesis are threefold. Firstly, we aimed to verify and substantiate the clinical and histological characteristic of melanoma (patients) from melanoma families with a pathogenic germline mutation in CDKN2A. Secondly, we aimed to investigate the effectiveness and yield of surveillance of melanoma families with different CDKN2A mutation status and family characteristics, and to identify possible causes for failure of surveillance. Thirdly, we aimed to investigate the impact of dermoscopy on the management of suspicious lesions in relatives from melanoma families under surveillance in a tertiary pigmented lesion clinic.

Chapter 2 investigates the clinical and histological characteristics of melanoma (patients) from families with a germline mutation in CDKN2A in comparison to sporadic melanoma (patients)
Chapter 3 investigates the effectiveness of surveillance by comparison of tumour thickness of surveillance detected cases with pre-surveillance detected cases in CDKN2A mutated families. Mode of detection and length of the surveillance interval are analyzed to identify possible causes for failure of surveillance.
Chapter 4 investigates the effectiveness of surveillance in families registered at the NFDHT. The yield of surveillance in families with different family characteristics- and CDKN2A mutation status was investigated by estimation of the melanoma detection rates.
Chapter 5 investigates the yield of surveillance of second degree relatives from families with a founder mutation in CDKN2A by estimating the melanoma detection rate and studying the family dynamics of two- to first-degree relative transitions.
Chapter 6 reports an observation related to the issue of 'overdiagnosis' in the context of surveillance of CDKN2A mutated families.

Chapter 7 investigates the impact of dermoscopy on the preferential diagnosis and management decisions towards suspicious pigmented lesions in every day clinical practice of general dermatologists. This chapter is intended as a background for the findings reported in chapter 8.

Chapter 8 investigates the impact of dermoscopy on the preferential diagnosis and management decisions of suspicious pigmented lesions in high-risk patients from melanoma families.

Chapter 9 summarizes and discusses the findings described in the preceding chapters.

Reference List

1. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de VE. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann.Oncol. 2012;23:524-30.
2. Integraal Kanker Centrum. Meest voorkomende kankersoorten in Nederland. http://www.cijfersoverkanker.nl/selecties/dataset_1/img507fdb687c352 (access date oktober 18 2012).
3. International Agency on the Research of Cancer. LARC Monographs on the evalutation of carcinogenic risks to humans: Solar and ultraviolet radiation. 55. 1992. Lyon, France.
4. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur.J.Cancer 2005;41:45-60.
5. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res. 2011;24:879-97.
6. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur.J.Cancer 2005;41:2040-59.
7. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur.J.Cancer 2005;41:28-44.
8. Shah KN. The risk of melanoma and neurocutaneous melanosis associated with congenital melanocytic nevi. Semin.Cutan.Med Surg 2010;29:159-64.
9. Tucker MA, Fraser MC, Goldstein AM, Elder DE, Guerry D, Organic SM. Risk of melanoma and other cancers in melanoma-prone families. J Invest Dermatol. 1993;100:350S-5S.
10. Norris, W. A case of fungoid disease. Edinb Med Surg J 16, 562-565. 1820.
11. CAWLEY EP, KRUSE WT, PINKUS HK. Genetic aspects of malignant melanoma. AMA.Arch.Derm.Syphilol. 1952;65:440-50.
12. Ang CG, Kelly JW, Fritschi L, Dowling JP. Characteristics of familial and non-familial melanoma in Australia. Melanoma Res. 1998;8:459-64.
13. Dutch Melanoma Society. *Guidelines Melanoma of the skin.* Alphen aan den Rijn: van Zuiden, 2005.
14. Lynch HT, Frichot BC, III, Lynch JF. Familial atypical multiple mole-melanoma syndrome. J.Med.Genet. 1978;15:352-6.
15. Crutcher WA, Sagebiel RW. Prevalence of dysplastic naevi in a community practice. Lancet 1984;1:729.
16. Lee G, Massa MC, Welykyj S, Choo J, Greaney V. Yield from total skin examination and effectiveness of skin cancer awareness program. Findings in 874 new dermatology patients. Cancer 1991;67:202-5.
17. Nordlund JJ, Kirkwood J, Forget BM, Scheibner A, Albert DM, Lerner E et al. Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. Cancer Res. 1985;45:1855-61.
18. Clark WH, Jr., Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. Arch.Dermatol. 1978;114:732-8.
19. Bishop JA, Wachsmuth RC, Harland M, Bataille V, Pinney E, MacK P et al. Genotype/phenotype and penetrance studies in melanoma families with germline CDKN2A mutations. J.Invest Dermatol. 2000;114:28-33.
20. Goldstein AM, Martinez M, Tucker MA, Demenais F. Gene-covariate interaction between dysplastic nevi and the CDKN2A gene in American melanoma-prone families. Cancer Epidemiol.Biomarkers Prev. 2000;9:889-94.
21. Kamb A, Gruis NA, Weaver-Feldhaus J, Liu Q, Harshman K, Tavtigian SV et al. A cell cycle regulator potentially involved in genesis of many tumor types. Science 1994;264:436-40.
22. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J.Med.Genet. 2007;44:99-106.
23. Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. J.Natl.Cancer Inst. 2002;94:894-903.
24. Gruis NA, van der Velden PA, Sandkuijl LA, Prins DE, Weaver-Feldhaus J, Kamb A et al. Homozygotes for CDKN2 (p16) germline mutation in Dutch familial melanoma kindreds. Nat.Genet. 1995;10:351-3.

25. de Snoo FA, Bishop DT, Bergman W, van L, I, van der DC, van Nieuwpoort FA et al. Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin.Cancer Res. 2008;14:7151-7.
26. Goldstein AM, Chan M, Harland M, Gillanders EM, Hayward NK, Avril MF et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res. 2006;66:9818-28.
27. Goldstein AM, Struewing JP, Chidambaram A, Fraser MC, Tucker MA. Genotype-phenotype relationships in U.S. melanoma-prone families with CDKN2A and CDK4 mutations. J.Natl.Cancer Inst. 2000;92:1006-10.
28. Udayakumar D, Mahato B, Gabree M, Tsao H. Genetic determinants of cutaneous melanoma predisposition. Semin.Cutan.Med.Surg. 2010;29:190-5.
29. Yokoyama S, Woods SL, Boyle GM, Aoude LG, MacGregor S, Zismann V et al. A novel recurrent mutation in MITF predisposes to familial and sporadic melanoma. Nature 2011;480:99-103.
30. Greene MH, Clark WH, Jr., Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann.Intern.Med. 1985;102:458-65.
31. Kopf AW, Hellman LJ, Rogers GS, Gross DF, Rigel DS, Friedman RJ et al. Familial malignant melanoma. JAMA 1986;256:1915-9.
32. Nagore E, Botella-Estrada R, Garcia-Casado Z, Requena C, Serra-Guillen C, Llombart B et al. Comparison between familial and sporadic cutaneous melanoma in Valencia, Spain. J.Eur.Acad.Dermatol.Venereol. 2008.
33. Mantelli M, Barile M, Ciotti P, Ghiorzo P, Lantieri F, Pastorino L et al. High prevalence of the G101W germline mutation in the CDKN2A (P16(ink4a)) gene in 62 Italian malignant melanoma families. Am.J.Med.Genet. 2002;107:214-21.
34. Masback A, Olsson H, Westerdahl J, Sandberg T, Borg A, Jonsson N et al. Clinical and histopathological features of malignant melanoma in germline CDKN2A mutation families. Melanoma Res. 2002;12:549-57.
35. Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A et al. High frequency of multiple melanomas and breast and pancreas carcinomas in CDKN2A mutation-positive melanoma families. J.Natl. Cancer Inst. 2000;92:1260-6.
36. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N.Engl.J Med 2011;364:2507-16.
37. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. N.Engl.J Med 2010;363:711-23.
38. Livingstone E, Zimmer L, Vaubel J, Schadendorf D. Current advances and perspectives in the treatment of advanced melanoma. J Dtsch.Dermatol.Ges. 2012;10:319-25.
39. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann.Surg 1970;172:902-8.
40. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR et al. Final version of 2009 AJCC melanoma staging and classification. J.Clin.Oncol. 2009;27:6199-206.
41. Katalinic A, Waldmann A, Weinstock MA, Geller AC, Eisemann N, Greinert R et al. Does skin cancer screening save lives?: An observational study comparing trends in melanoma mortality in regions with and without screening. Cancer 2012.
42. Curiel-Lewandrowski C, Chen SC, Swetter SM. Screening and Prevention Measures for Melanoma: Is There a Survival Advantage? Curr.Oncol.Rep. 2012;14:458-67.
43. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U.S. Preventive Services Task Force. Ann.Intern.Med. 2009;150:194-8.
44. Screening for skin cancer: recommendations and rationale. Am.J Prev.Med 2001;20:44-6.
45. Koh HK, Miller DR, Geller AC, Clapp RW, Mercer MB, Lew RA. Who discovers melanoma? Patterns from a population-based survey. J Am.Acad.Dermatol. 1992;26:914-9.
46. Epstein DS, Lange JR, Gruber SB, Mofid M, Koch SE. Is physician detection associated with thinner melanomas? JAMA 1999;281:640-3.
47. Brady MS, Oliveria SA, Christos PJ, Berwick M, Coit DG, Katz J et al. Patterns of detection in patients with cutaneous melanoma. Cancer 2000;89:342-7.
48. McPherson M, Elwood M, English DR, Baade PD, Youl PH, Aitken JF. Presentation and detection of invasive melanoma in a high-risk population. J Am.Acad.Dermatol. 2006;54:783-92.

49. Geller AC, Elwood M, Swetter SM, Brooks DR, Aitken J, Youl PH et al. Factors related to the presentation of thin and thick nodular melanoma from a population-based cancer registry in Queensland Australia. Cancer 2009;115:1318-27.
50. Kovalyshyn I, Dusza SW, Siamas K, Halpern AC, Argenziano G, Marghoob AA. The impact of physician screening on melanoma detection. Arch.Dermatol. 2011;147:1269-75.
51. Carey WP, Jr., Thompson CJ, Synnestvedt M, Guerry D, Halpern A, Schultz D et al. Dysplastic nevi as a melanoma risk factor in patients with familial melanoma. Cancer 1994;74:3118-25.
52. Hansson J, Bergenmar M, Hofer PA, Lundell G, Mansson-Brahme E, Ringborg U et al. Monitoring of kindreds with hereditary predisposition for cutaneous melanoma and dysplastic nevus syndrome: results of a Swedish preventive program. J.Clin.Oncol. 2007;25:2819-24.
53. Masri GD, Clark WH, Jr., Guerry D, Halpern A, Thompson CJ, Elder DE. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. J.Am.Acad.Dermatol. 1990;22:1042-8.
54. Vasen HF, Bergman W, van Haeringen A, Scheffer E, van Slooten EA. The familial dysplastic nevus syndrome. Natural history and the impact of screening on prognosis. A study of nine families in the Netherlands. Eur.J.Cancer Clin.Oncol. 1989;25:337-41.
55. Katalinic A, Waldmann A, Weinstock MA, Geller AC, Eisemann N, Greinert R et al. Does skin cancer screening save lives?: An observational study comparing trends in melanoma mortality in regions with and without screening. Cancer 2012.
56. Vasen HF, Gruis NA, Frants RR, Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int.J.Cancer 2000;87:809-11.
57. Bichakjian CK, Halpern AC, Johnson TM, Foote HA, Grichnik JM, Swetter SM et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. J.Am.Acad.Dermatol. 2011;65:1032-47.
58. Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH et al. Revised U.K. guidelines for the management of cutaneous melanoma 2010; Br.J.Dermatol. 2010;163:238-56.
59. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (2008) http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp111.pdf (access date oktober 18 2012)
60. Swerlick RA, Chen S. The melanoma epidemic. Is increased surveillance the solution or the problem? Arch. Dermatol. 1996;132:881-4.
61. Levell NJ, Beattie CC, Shuster S, Greenberg DC. Melanoma epidemic: a midsummer night's dream? Br.J Dermatol. 2009;161:630-4.
62. Welch HG, Black WC. Overdiagnosis in cancer. J Natl.Cancer Inst. 2010;102:605-13.
63. Erickson C, Driscoll MS. Melanoma epidemic: Facts and controversies. Clin.Dermatol. 2010;28:281-6.
64. Stolz W, Braun-Falco O, Bilen N *et al. Color Atlas of Dermoscopy*, 2nd edn. Berlin: Blackwell Wissenschafts, 2002.
65. Argenziano G, Fabbrocini G, Carli P, de G, V, Sammarco E, Delfino M. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions. Comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. Arch.Dermatol. 1998;134:1563-70.
66. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Arch.Dermatol. 1996;132:1178-82.
67. Pehamberger H, Steiner A, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. I. Pattern analysis of pigmented skin lesions. J.Am.Acad.Dermatol. 1987;17:571-83.
68. Stolz W, Riemann A, Cognetta A, Pillet L, Abmayr W, Hölzel D et al. ABCD rule of dermatoscopy: a new practical method for early recognition of malignant melanoma. Eur.J.Dermatol. 1994;4:521-7.
69. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br.J.Dermatol. 2008.
70. Carli P, de G, V, Chiarugi A, Nardini P, Weinstock MA, Crocetti E et al. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. J.Am.Acad.Dermatol. 2004;50:683-9.