General introduction and aims of this thesis

Burden of skin cancer

Skin cancer is the most common cancer worldwide, known for its increasing incidence rates and increasing burden.[1, 2] The aging of the population and increased sun-seeking behaviour contribute largely to this observed phenomenon.[1, 3] Skin cancer is usually divided in non-melanoma skin cancer or keratinocyte cancer (KC), and melanoma skin cancer. KC comprise the largest part of all skin cancers and can be subdivided into basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs).[4] BCCs account for approximately 80-85% of skin cancers and SCCs for 10-15%; malignant melanomas account for a smaller part (5-10%). Furthermore, some skin cancers may arise from pre-cancerous growth such as actinic keratosis (AK).

Epidemiology

One of the most common premalignant skin lesion is *AK*, affecting 24% of the Dutch population aged 50 years or older.[5] AKs are erythematous keratotic lesions which are caused by long-term UV exposure.[6] Although progression rates to KCs are reported to be low, and spontaneous regression may be as high as 63%, definable clinical characteristics to distinguish which AK lesion may progress and which may regress are lacking.[7] Furthermore, after initial regression, subsequent recurrence rates of 15% have been reported, suggesting AK being a rather chronic skin condition.[8]

BCC is the most common subtype of skin cancer, belonging to the subgroup of KC, with approximately 40,000 primary BCCs registered in the Dutch population of 17 million in 2014 (*Source: IKNL, personal communication*). It affects 1 in 5 men and 1 in 6 women before the age of 85 in the Netherlands.[9] The highest incidence rates are seen in Australia, with more than 1 in 2 persons affected before the age of 70.[1] Several studies have shown onward trends of increasing incidence of BCCs, without signs of a plateauing.[3, 9] This rising incidence may largely be influenced by increased sun-seeking behaviour (e.g. beach holidays, tanning-beds), as intense intermittent UV radiation is the major environmental risk factor for BCC.[3] Patients with a BCC are at increased risk for a subsequent cutaneous malignancy: 17-fold for subsequent BCC, three-fold for SCC and two-fold for melanoma.[10]

SCC, belonging to the subgroup of KC, is the second most common subtype of skin cancer with steeply increasing incidence rates.[1] While predictions from 2012 expected incidence to increase up to 11,827 primary SCC patients per year in 2020, these number are already exceeded in 2018 with 14,000 primary cases registered.[11, 12] The most important etiologic factor is cumulative UV exposure, which is illustrated by the average age of diagnosis being 74 years and most affected body sites being sun-exposed areas such as the face.[11] SCCs are thought to arise from precursor lesions such as AKs, although they may also arise de novo, and are characterized as a tender erythematous papule or nodule.[13] Similar to BCCs, patients with a SCC are at increased risk for a subsequent cutaneous malignancy: 15-fold for a subsequent SCC, 4-fold for BCC and three-fold for melanoma.[10] Whereas BCCs rarely metastasize, this is more common in SCCs[11, 14-16]; SCCs have a reported metastasis rate

of 1.9-2.6% (during the median follow-up of 70 months), of which 87% metastasizes to regional lymph nodes.[16]

The third most common subtype of skin cancer concerns *malignant melanoma*. In the Netherlands, incidence rates of cutaneous melanomas have doubled over the last 20 years with 7,000 incident cases registered in 2018. [17, 18] Melanomas are the most lethal skin cancer, with reported age-standardized mortality rates of 3.7 per 100,000 persons in 2013. The prognosis of patients with a cutaneous malignant melanoma depends on the tumour stage, which is determined by the tumour thickness (Breslow), tumour mitotic rate, and the presence of ulceration and metastases.[19] Since melanomas may metastasize with relative low tumour load, early diagnosis and treatment are of pivotal importance in the prognosis of patients with melanomas.

Overall burden of skin cancer compared to other cancers

Given the rising incidence of different types of skin cancer, it is not surprising the overall incidence of skin cancer is increasing worldwide.[1, 2] Furthermore, the incidence of skin cancer is increasing at a greater rate compared to other cancers (Figure 1).[12] This may be explained by several factors, including ageing population, increased sun-seeking behaviours, and improved awareness and registration.[1, 3] Although registration efforts have been improving lately, a registration gap still exists, for example for BCCs due to the high volume and associated low mortality.[1, 3, 20] This results in underestimation of the overall burden. In addition, this underestimation is further increased in two ways: (1) 30-60% of patients with a cutaneous malignancy develop (at least) a second cutaneous malignancy but these are not registered[10, 21-23], and (2) in patients with KCs (particularly when multiple) other manifestations of photodamage due to UV exposure such as AK, may also be present.[22, 24] Several terms have been appointed to this concept including 'field cancerization', 'cutane-

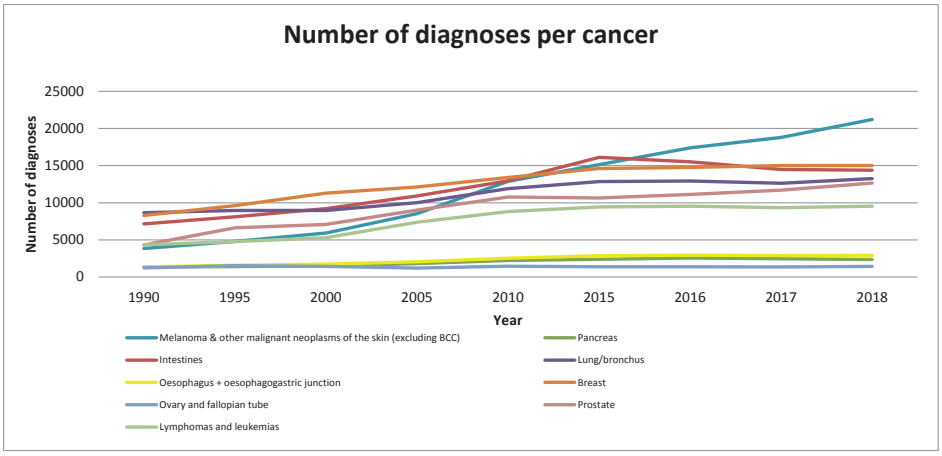

Figure 1. Number of diagnoses per cancer. *Source: Cijfersoverkanker.nl*

ous field dysplasia', and 'actinic neoplasia syndrome'. [24-26] However, divergent clinical views on this concept seem to result in its underappreciation, and therefore, its contribution to the overall burden may be undervalued.[4, 6]

The already heavy burden of skin cancer in terms of incidence rates is considerably increasing. It is assumable this translates into high and increasing associated costs of skin cancer. Although estimations of costs related to UV exposure are available, a comprehensive overview of the overall direct costs of skin cancer is currently lacking.

SKIN CANCER CARE IN VARYING HEALTHCARE SETTINGS

Each country has its own healthcare system with a varying role of general practitioners (GPs) and varying definition of general practice.[27] The Primary Care Health Activity Monitor for Europe defines general practice as 'the first level of professional care in Europe where people present their health problems and where the majority of the population's curative and preventive health needs are satisfied'.[28] In the current Dutch setting GP consultations are mainly patient driven[29], and GPs perform the role of gatekeepers for secondary and specialist care access.[30] This implies that without a referral note from the GP, specialist care is inaccessible. Although in theory this may be highly effective in optimizing and lowering use of health services in secondary care and cost containment, in practice GPs may sub-optimally fulfil this role; a survey study among Dutch GPs showed that a demand-satisfying attitude contributes to the delivery of too much care.[31]

In an international perspective, the level of gatekeeping varies widely between countries.[32] Whereas in some countries such as Germany and Austria free access to specialists applies, in other countries such as Australia and Canada a referral from a GP to access specialist care is required. Some countries may have adopted a system which is more or less in between; for example, in the US access to specialist care varies depending on the insurance coverage schemes.

In the Netherlands, the share of dermatological oriented consultations in primary care is 14%, of which 13% concerns skin cancer, benign skin tumours and neavi.[33] However, these numbers may be much higher when taking into consideration that often more than one problem is presented in each encounter, and skin problems may not be the main reason for a GP consultation.[34-37] Furthermore, Koelink et al. found an annual increase of 7.3% for skin cancer related encounters in primary care between 2001-2010, and a benign versus malignant ratio of 10:1.[38] This inherently means GPs play a critical role in skin cancer care as they are the ones to decide (1) if a cutaneous lesion is suspicious for malignancy, and (2) if patient referral to secondary care is needed. In secondary care almost half of the care provided by dermatologists concerns cutaneous malignancies, cutaneous premalignancies, benign tumours and naevi (Figure 2).[39]

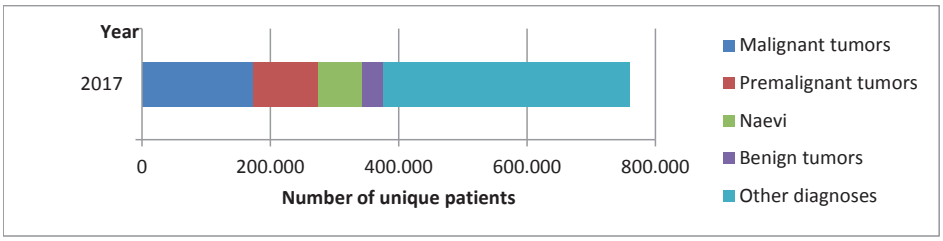

Figure 2. Number of unique patients per diagnostic group in secondary dermatological care, 2017. *Source: Opendisdata.nl*

CLINICAL GUIDELINES AND CURRENT SKIN CANCER MANAGEMENT

Clinical skin cancer guidelines

Whereas medical specialists have been equipped with guidelines on skin cancer management since 1985 (melanoma), 2002 (BCC), 2010 (AK) and 2012 (SCC)[40-43], only recently a Dutch primary care guideline on 'suspicious cutaneous lesions' was issued (June 2017), before which GPs had no guideline to rely on. In the section below, the key recommendations of current clinical guidelines on different skin cancer subtypes are outlined.

Premalignant skin lesions (actinic keratosis)

Resulting from the existing uncertainty regarding the disease course and its invasive potential, most international guidelines recommend treatment of AK (Figure 3A).[43-47] These recommendations are even stronger in patients with multiple AKs in one continuous area (i.e. cutaneous field dysplasia), as this is related to an increased risk of developing invasive disease.[5, 7, 48]

(A) (B) (C) (D)

Figure 3. Clinical presentation of actinic keratosis (A), basal cell carcinoma (B), squamous cell carcinoma (C), and malignant melanoma (D). Pictures obtained from the Dutch primary care guideline.[44]

In both primary and secondary care guidelines, management of AKs is divided into lesion-directed and field-directed treatment. Lesion-directed treatment, which predominantly consists of cryotherapy, can be used for solitary lesions. For field-directed treatment there a broader arsenal of therapies available, including fluorouracil cream, imiquimod cream, ingenol mebutate gel and photodynamic therapy (PDT). The results from a recently

published randomized clinical trial showed fluorouracil cream to be significantly more effective compared to imiquimod cream, ingenol mebutate gel and PDT.[49]

The Dutch primary care guideline advises to discuss the need and preference for treatment with the patient, and to include the extensiveness of AK in determining the choice of treatment.[50] Although all previously mentioned therapies excluding PDT can be used in the primary care setting, only cryotherapy and fluorouracil cream are included in the primary care guideline. A treatment evaluation follow-up visit is recommended after 3 months. Referral to secondary care is advised only in case of the skin lesion being unresponsive to treatment.

Whereas for solitary lesions the choice of treatment in secondary care is restricted to cryotherapy, recommendations on treatment choice for multiple AKs are not very stringent according to the secondary care guideline; choice of treatment mainly depends on patient and/or physician preferences.[43, 46] Follow-up is only advised for patients with high-risk: presence of extensive AK, cutaneous field dysplasia, history of skin cancer, presence of high-risk lesions (i.e. inflammation, diameter >1 cm, fast grow, bleeding, erythema or ulceration), and immune-comprised patients.

Basal cell carcinomas

Although BCCs rarely metastasize, tumour growth, local invasion and destruction of surrounding normal tissue can cause considerable morbidity (Figure 3B). This especially applies in case of failure to diagnose early or inadequate treatment.[51] As histopathological growth patterns guide treatment decisions, such as surgical margin, a biopsy is recommended by both international and national, and both primary care and secondary care guidelines in the diagnostic workup. Histological variants include superficial, nodular, micronodular, and morpheic/infiltrative BCCs.[50]

Nodular BCCs are the most frequent occurring subtype, and the recommended treatment concerns surgical excision with a 3-4mm surgical margin, which, according to the primary care guideline, can be performed in primary care.[44, 50, 52] Referral to secondary care is advised for high-risk BCCs (diameter >2 cm, located in the facial H-zone, recurrent tumours, micronodular or infiltrative subtypes) or incomplete excised BCCs of any type.

The secondary care guideline advises infiltrative BCCs to be excised with a clinical margin of 5 mm.[40] In addition to conventional excisions, the Dutch guidelines suggest Mohs-micrographic surgery for high-risk BCCs located in the face or BCCs in aesthetic subunits to completely remove these tumours, while sparing healthy tissue. Alternative treatments for BCCs that can be considered in selected cases, include radiation therapy, cryosurgery, PDT, curettage and coagulation. In case of inoperable or metastasized BCC, systemic treatment with vismodegib is recommended as a last resort. Annual follow-up visits in secondary care are advised for patients with high-risk BCCs.

Squamous cell carcinoma

As SCCs (Figure 3C) are considered high-risk tumours, referral to secondary care is recommended by the Dutch primary care guideline.[50] The prognosis of patients with SCC is dependent on several factors including the diameter, the degree of differentiation, and depth of tumour invasion. The presence of a metastasis is associated with decreased survival. In secondary care guidelines, surgical excision is the preferred treatment and radiation therapy is reserved for specific cases.[42] Strict follow-up schedules for 5 years onward are recommended.

Malignant melanoma

The Dutch primary care guideline clearly states that any skin lesion that could potentially be a melanoma (Figure 3D) should be referred to secondary care within 2 days.[50] Diagnosis in secondary care involves a diagnostic excision, and after histopathological confirmation of a melanoma a therapeutic re-excision, with a sentinel node procedure when indicated, is recommended by clinical guidelines.[41] Radiation and systemic therapy have a role in extended and metastatic disease.

Current skin cancer management

The Dutch primary care guideline recommendations are in line with the European recommendations on the approach of skin cancer in general practice, which state that patients with skin cancer may be curatively treated by the GP.[28, 50] With the issuing of the primary care guideline, care and treatment of relative low-risk tumours such as AKs and BCCs can be shifted from secondary care to primary care.[50] However, these recommendations are not very stringent and previous studies indicated guideline adherence among GPs is not optimal, for example due to lack of agreement with the recommendations and organizational constraints.[53-55] Furthermore, in addition to the former absence of a primary care guideline in the Netherlands, and presumably suboptimal guideline adherence, undergraduate and postgraduate dermatology training for GPs has been deemed insufficient, both national and international.[56-61] Altogether, there are indications that current management of skin cancer may lack efficiency.

URGENCY FOR CHANGE

Despite the known low mortality rates associated with cutaneous malignancies, the overall burden of skin cancer has increased significantly over the past decades.[1, 2, 4, 38, 62-65] This ultimately also translates into the associated costs. Furthermore, indications of inefficiencies in skin cancer management may further contribute to high expenditures. As a result, this causes an increasing pressure on health care systems and thereby the need

for change.[56, 63, 66, 67] Health policy makers are incentivized to look for alternative ways of qualitative good care at lower costs.[68] Two potentially effective innovations include substitution of care and e-health.

Substitution of care involves shifting tasks from secondary to primary care, and preventing unnecessary referrals to secondary care.[66] Several areas have been defined as potential targets for substitution of care, among which is low-risk skin cancer care. It can be argued that low-risk cutaneous premalignancies and malignancies such as AKs and BCCs can be managed in primary care, considering their low risk of progression. To strengthen and enlarge the role of the GP, the Dutch government stimulates more active and adequate gatekeeping at primary care level, as also reflected by the recommendations in the primary care guideline.[50, 69, 70] This shift can already be noticed for example looking at follow-up schemes for low-risk BCC; whereas previously dermatologists provided follow-up care, this responsibility is now increasingly shifted towards the GP or the patient.[71, 72] Although dermatologists have advocated low-risk skin cancer to be treated in primary care rather than secondary care resulting from the high burden in secondary care[56, 73], and most GPs have reported to be willing to expand their role in skin cancer management[74], a clear understanding of and insight in their views regarding substitution of care and the perceived barriers is currently lacking. Furthermore, the question remains if shifting treatment of these tumours to primary care is feasible in practice.

A second potential innovation to lower the burden and associated costs of skin cancer care involves innovative technologies. Several technologies are readily embedded in skin cancer care, for example teledermatology and teledermoscopy. These telecommunication technologies provide GPs with the possibility to forward digital images linked with medical information to a medical specialist, in order to receive advice on how to treat the skin condition. With the implementation of these innovative tools the number of referrals, and thus healthcare costs, have been shown to decrease.[70, 75, 76] Another example, on which we will focus in this thesis, is mHealth. mHealth differs from telemedicine in that it is centred around the patient rather than the health professional, thereby engaging in prevention and self-management of patients.[77] Furthermore, as such technologies can provide tools to support physicians in optimizing efficiency of care (for example by more accurately diagnosing diseases), it is recognized it has the potential to alleviate the pressure on physicians and the overall healthcare system. With the rising interest in e-health, and the need to optimize skin cancer care, it is essential to first explore the potential role of e-health and its added value in skin cancer care.

AIMS OF THIS THESIS

Before implementing a change in clinical practice, several steps need to be undertaken (Figure 4).[78] It starts with identifying existing issues or problems, followed by an analysis of current practice and performance. This is followed by an analysis of the target group and selection of strategies. The final step in the implementation of innovations is to develop and test implementation of innovations and to evaluate the results found.

The ultimate goal of this thesis is to explore and evaluate potentially effective innovations in skin cancer management, which in this case include substitution of care and e-health innovations in skin cancer care.

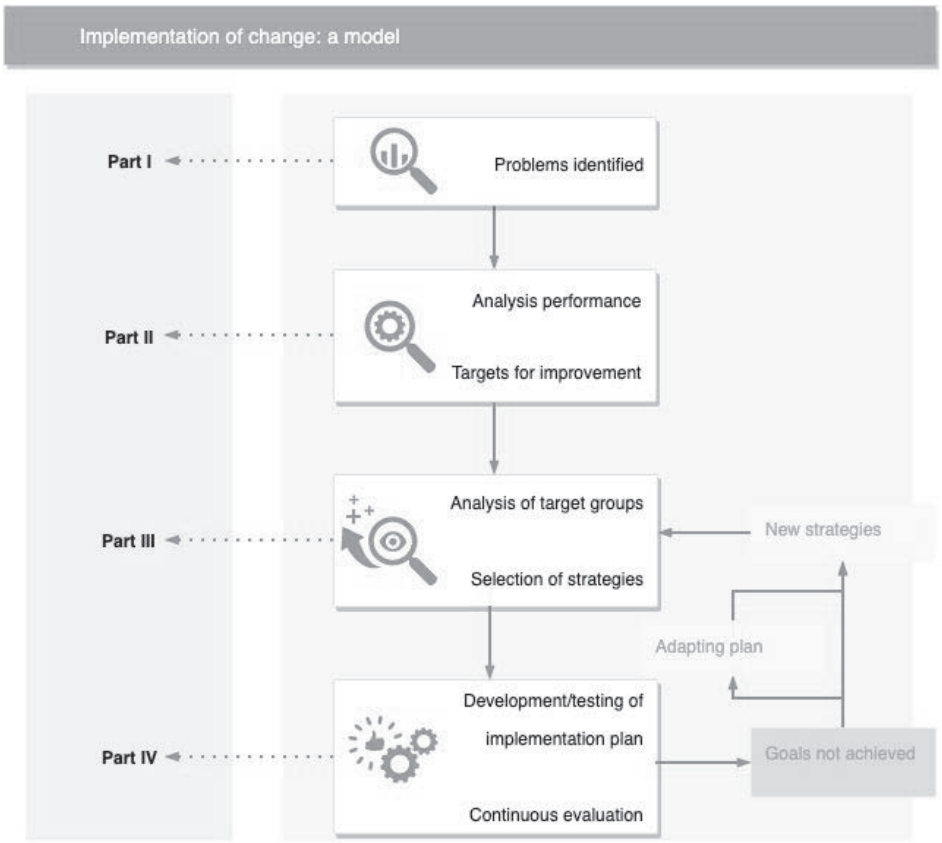

Figure 4. Implementation of change: a model. Model adapted from Grol & Wensing.[78]

Outline of this thesis

First, to gain insight into the current situation in terms of costs related to skin cancer **Part I** is focused on exploring the economic burden of skin cancer by assessing the reimbursed

costs of benign, premalignant and malignant skin tumour management (**Chapter 1.1**). In addition, projections for future costs up to 2030 are analysed.

To further assess the current performance, **Part II** is focused on *exploring* current practices regarding AK management and identifying areas of improvement. Both quantitative (**Chapter 2.1**) and qualitative (**Chapter 2.2**) analyses were used for this purpose. Whereas quantitative studies can identify inefficiencies, they do not provide insight into the underlying views and motives of stakeholders, which is essential to implement changes in practice. This can ultimately be used as input to tailor interventions or strategies to defined subgroups of stakeholders.

With the current situation in terms of costs and management being explored, and areas for improvement identified, **Part III** is focused on *exploring* potential innovations in skin cancer care. The perceived feasibility to *restructure* the organization of skin cancer management by substitution of care was assessed in **Chapter 3.1**. Therefore, we studied the views, perceived barriers and potential strategies among different subgroups of stakeholders. In **Chapter 3.2**, innovating skin cancer care through the concept of e-health is discussed.

Finally, in **Part IV** we aimed to *evaluate* the feasibility of these potential innovations. Restructuring the current provision of skin cancer care is evaluated in a multicentre cluster randomized controlled trial, the SKINCATCH Trial, of which the results are being discussed in **Chapter 4.1** and **4.2**. In **Chapter 4.3** the concept of e-health was studied in terms of validation of a smartphone application for skin lesions risk assessment.

REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069-80.
2. Global Burden of Disease Cancer C. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease StudyGlobal Burden of Cancer 2015Global Burden of Cancer 2015. JAMA Oncology. 2017;3(4):524-48.
3. Verkouteren JAC, Ramdas KHR, Wakkee M, Nijsten T. Epidemiology of basal cell carcinoma: scholarly review. Br J Dermatol. 2017;177(2):359-72.
4. Greinert R, de Vries E, Erdmann F, Espina C, Auvinen A, Kesminiene A, et al. European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. Cancer Epidemiol. 2015;39 Suppl 1:S75-83.
5. Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. J Invest Dermatol. 2013;133(8):1971-8.
6. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. Br J Dermatol. 2016.
7. Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of actinic keratosis: a systematic review. Br J Dermatol. 2013;169(3):502-18.
8. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a queensland community. J Invest Dermatol. 2000;115(2):273-7.
9. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011;91(1):24-30.
10. Flohil SC, van der Leest RJ, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. Eur J Cancer. 2013;49(10):2365-75.
11. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer. 2012;48(13):2046-53.
12. IKNL. Cases of cancer doubled in 30 years' time: Netherlands Comprehensive Cancer Organization (IKNL); 2019 [updated 03-02-2019]. Available from: https://i-.iknl.nl/over-iknl/nieuws/nieuws-detail/2019/02/03/aantal-gevallen-van-kanker-in-dertig-jaar-verdubbeld.
13. Point K. Cite as: Basal cell carcinoma, squamous cell carcinoma (and related lesions)–a guide to clinical management in Australia. Cancer Council Australia and Australian Cancer Network, Sydney. 2008. 2008.
14. Haisma MS, Plaat BEC, Bijl HP, Roodenburg JLN, Diercks GFH, Romeijn TR, et al. Multivariate analysis of potential risk factors for lymph node metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. J Am Acad Dermatol. 2016;75(4):722-30.
15. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713-20.
16. Brougham NDLS, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. Journal of Surgical Oncology. 2012;106(7):811-5.
17. Zoutendijk J, van der Leest RJT, Nijsten T, Mooi WJ, van der Rhee JI, de Vries E, et al. [Increasing incidence of thin melanomas in the Netherlands]

Stijgende incidentie van dunne melanomen in Nederland. Ned Tijdschr Geneeskd. 2017;161:D1030.

18. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. 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(2):524-30.
19. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: A Cancer Journal for Clinicians. 2017;67(6):472-92.
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394-424.
21. van der Leest RJ, Flohil SC, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior melanoma: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2015;29(6):1053-62.
22. Verkouteren JAC, van der Leest RJT, Nijsten T. Cohort studies (and skin cancer) never come alone. J Invest Dermatol. 2015;135(3):649-51.
23. Wehner MR, Linos E, Parvataneni R, Stuart SE, Boscardin WJ, Chren M-M. Timing of Subsequent New Tumors in Patients Who Present With Basal Cell Carcinoma or Cutaneous Squamous Cell CarcinomaTiming of New Tumors in BCC or SCCTiming of New Tumors in BCC or SCC. JAMA Dermatology. 2015;151(4):382-8.
24. Weinstock MA, Lee KC, Chren MM, Marcolivio K, Group VT. Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. J Am Acad Dermatol. 2009;61(2):207-15.
25. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. An Bras Dermatol. 2013;88(5):775-86.
26. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.
27. BMA. International models of general practice [updated 06-12-2018]. Available from: https://www.bma.org.uk/collective-voice/policy-and-research/nhs-structure-and-delivery/primary-and-community-care/international-models-of-general-practice.
28. Kringos DS, Boerma WGW, Bourgueil Y, Cartier T, Hasvold T, Hutchinson A, et al. The european primary care monitor: structure, process and outcome indicators. BMC Family Practice. 2010;11(1):81.
29. Ahmadi K, Prickaerts E, Smeets JGE, Joosten V, Kelleners-Smeets NWJ, Dinant GJ. Current approach of skin lesions suspected of malignancy in general practice in the Netherlands: a quantitative overview. J Eur Acad Dermatol Venereol. 2018;32(2):236-41.
30. Mossialos E, Wenzl M, Osborn R, Sarnak D. 2015 international profiles of health care systems: Canadian Agency for Drugs and Technologies in Health; 2016.
31. Wammes JJ, Jeurissen PP, Verhoef LM, Assendelft WJ, Westert GP, Faber MJ. Is the role as gatekeeper still feasible? A survey among Dutch general practitioners. Fam Pract. 2014;31(5):538-44.
32. Greenfield G, Foley K, Majeed A. Rethinking primary care's gatekeeper role. BMJ. 2016;354:i4803.
33. De Vries E. Huidaandoeningen bij huisarts en dermatoloog.2013 15-10-2018. Available from: https://www.ntvg.nl/academie/infographics/huidaandoeningen-bij-huisarts-en-dermatoloog.
34. Lowell BA, Froelich CW, Federman DG, Kirsner RS. Dermatology in primary care: Prevalence and patient disposition. J Am Acad Dermatol. 2001;45(2):250-5.
35. Flocke SA, Frank SH, Wenger DA. Addressing multiple problems in the family practice office visit. J Fam Pract. 2001;50(3):211-6.

36. Bjorland E, Brekke M. What do patients bring up in consultations? An observational study in general practice. Scand J Prim Health Care. 2015;33(3):206-11.
37. Beasley JW, Hankey TH, Erickson R, Stange KC, Mundt M, Elliott M, et al. How many problems do family physicians manage at each encounter? A WReN study. Ann Fam Med. 2004;2(5):405-10.
38. Koelink CJ, Kollen BJ, Groenhof F, van der Meer K, van der Heide WK. Skin lesions suspected of malignancy: an increasing burden on general practice. BMC Fam Pract. 2014;15:29.
39. The Dutch Healthcare Authority (Nederlandse Zorgautoriteit); DIS Open data: [updated 01-02-2019]. Available from: http://www.opendisdata.nl/.
40. NVDV. Guideline basal cell carcinoma: NVDV; 2015 [updated 25-07-2016]. Available from: http://www.nvdv.nl/wp-content/uploads/2014/08/20160725-eindversie-richtlijn-BCC-2015.pdf.
41. Werkgroep NM. Landelijke richtlijn Melanoom, versie 2.1: IKNL; 2012 [updated 01-03-2016]. Available from: https://www.oncoline.nl/melanoom.
42. NVDV. Guideline squamous cell carcinoma: NVDV; 2018 [updated 12-02-2019]. Available from: http://www.nvdv.nl/wp-content/uploads/2014/08/Herziening-richtlijn-Plaveiselcelcarcinoom-van-de-huid-2018_Definitieve-versie-4.pdf.
43. NVDV. Richtlijn Actinische keratose (Versie 15-10-2010) 2010. Available from: http://www.nvdv.nl/wp-content/uploads/2014/07/Richtlijn-Actinische-Keratose-2010-15-10.pdf.
44. Damen-van Beek Z, Opstelten W. [The Dutch College of General Practitioners practice guideline 'Suspicious skin lesions'] De NHG-standaard 'Verdachte huidafwijkingen'. Ned Tijdschr Geneeskd. 2017;161:D1897.
45. de Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. Br J Dermatol. 2017;176(1):20-43.
46. Beljaards RC, van der Sande A. Update richtlijn actinische keratosen 2017. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2017;27(04):190-2.
47. Primary Care Dermatology Society (PCDS); Actinic keratosis (syn. solar keratosis): 2017 [updated 17-11-2017]. Available from: www.pcds.org.uk/clinical-guidance/actinic-keratosis-syn.-solar-keratosis
48. Rosen T, Lebwohl MG. Prevalence and awareness of actinic keratosis: barriers and opportunities. J Am Acad Dermatol. 2013;68(1 Suppl 1):S2-9.
49. Jansen MHE, Kessels JPHM, Nelemans PJ, Kouloubis N, Arits AHMM, van Pelt HPA, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. New England Journal of Medicine. 2019;380(10):935-46.
50. Baaten GGG, Buis PAJ, Damen Z, De Haas ERM, Van der Heide WK, Opstelten W, et al. NHG-Standaard Verdachte Huidafwijkingen 2017 [Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-verdachte-huidafwijkingen.
51. National Institute for Health and Clinical Excellence; The management of low-risk basal cell carcinomas in the community: 2010 [updated May 2010]. Available from: https://www.nice.org.uk/guidance/csg8/resources/improving-outcomes-for-people-with-skin-tumours-including-melanoma-2010-partial-update-pdf-773380189.
52. Arits A, Schlangen MHJ, Nelemans PJ, Kelleners-Smeets NWJ. Trends in the incidence of basal cell carcinoma by histopathological subtype. Journal of the European Academy of Dermatology and Venereology. 2011;25(5):565-9.
53. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: a survey among general practitioners. BMC Fam Pract. 2011;12:98.
54. Lugtenberg M, Burgers JS, Han D, Westert GP. General practitioners' preferences for interventions to improve guideline adherence. J Eval Clin Pract. 2014;20(6):820-6.

55. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. Implement Sci. 2009;4:54.
56. Hollestein L, Weinstock M, Le Roux E, Olsen C. More Than Many: How to Manage the Most Frequent Cancer? J Invest Dermatol. 2017;137(9):1823-6.
57. Yaakub A, Cohen SN, Singh M, Goulding JMR. Dermatological content of U.K. undergraduate curricula: where are we now? British Journal of Dermatology. 2017;176(3):836-.
58. van Dijk CE, Verheij RA, Spreeuwenberg P, Groenewegen PP, de Bakker DH. Minor surgery in general practice and effects on referrals to hospital care: Observational study. BMC Health Services Research. 2011;11(1):2.
59. Schofield JK, Fleming D, Grindlay D, Williams H. Skin conditions are the commonest new reason people present to general practitioners in England and Wales. British Journal of Dermatology. 2011;165(5):1044-50.
60. Murase JE. Understanding the importance of dermatology training in undergraduate medical education. Dermatology practical & conceptual. 2015;5(2):95-6.
61. Lam TP, Yeung CK, Lam KF. What are the learning outcomes of a short postgraduate training course in dermatology for primary care doctors? BMC Medical Education. 2011;11(1):20.
62. Hollestein LM, Nijsten T. An insight into the global burden of skin diseases. J Invest Dermatol. 2014;134(6):1499-501.
63. Hollestein LM, de Vries E, Aarts MJ, Schroten C, Nijsten TE. Burden of disease caused by keratinocyte cancer has increased in The Netherlands since 1989. J Am Acad Dermatol. 2014;71(5):896-903.
64. De Vries E, Van De Poll-Franse LV, Louwman WJ, De Gruijl FR, Coebergh JWW. Predictions of skin cancer incidence in the Netherlands up to 2015. British Journal of Dermatology. 2005;152(3):481-8.
65. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev. 2015;24(2):141-9.
66. Van Dijk C, Korevaar J, De Jong J, Koopmans B, van Dijk M, De Bakker D. Room for substitution? Shift from secondary to primary care. . NIVEL: NIVEL, 2013.
67. de Jong J, Korevaar J, M. K, van Dijk C, Bouwhuis S, de Bakker D. Substitution potential between primary and secondary health care. www.nivel.nl: NIVEL, 2016.
68. OECD. Health at a Glance 20172017.
69. Westra D, Kroese ME, Ruwaard D. Substitutie van zorg: Wat weten we, wat moeten we weten en wat moeten we doen? Ned Tijdschr Geneeskd. 2017;161(D1354).
70. Heida J-P HJ. Next level gezondheidszorg: Hoe de zorg efficiënter en beter kan. SiRM, 2016.
71. de Vries E, Misirli Y, Nijsten T, Hollestein LM. Treatment and frequency of follow-up of BCC patients in the Netherlands. J Eur Acad Dermatol Venereol. 2018;32(9):e351-e4.
72. Van Egmond S, Wakkee M, Nijsten T, Van Rengen A, Bastiaens MT, Lugtenberg M. Factors influencing current low-value follow-up care after basal cell carcinoma and suggested strategies for de-adoption: a qualitative study.
73. Leiter U, Keim U, Eigentler T, Katalinic A, Holleczek B, Martus P, et al. Incidence, Mortality, and Trends of Nonmelanoma Skin Cancer in Germany. J Invest Dermatol. 2017;137(9):1860-7.
74. van Rijsingen MC, van Bon B, van der Wilt GJ, Lagro-Janssen AL, Gerritsen MJ. The current and future role of general practitioners in skin cancer care: an assessment of 268 general practitioners. Br J Dermatol. 2014;170(6):1366-8.
75. van der Heijden JP, de Keizer NF, Bos JD, Spuls PI, Witkamp L. Teledermatology applied following patient selection by general practitioners in daily practice improves efficiency and quality of care at lower cost. Br J Dermatol. 2011;165(5):1058-65.

76. Snoswell CL, Caffery LJ, Whitty JA, Soyer HP, Gordon LG. Cost-effectiveness of Skin Cancer Referral and Consultation Using Teledermoscopy in Australia. JAMA Dermatol. 2018;154(6):694-700.
77. Maheu M, Whitten P, Allen A. E-Health, Telehealth, and Telemedicine: a guide to startup and success: John Wiley & Sons; 2002.
78. Grol R, Wensing M, Eccles M. Improving patient care: the implementation of change in clinical practice: Elsevier Butterworth Heinemann; 2005. 290 p.