1.

Smoking and disease-specific mortality in women diagnosed with breast cancer – a systematic review with meta-analysis based on 400.944 breast cancer cases.

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Background: Knowledge of the modifiable risk factors increasing mortality is essential when advising cancer patients on their lifestyle. Smoking is causing disease and increased mortality in general, and on this basis, we strongly advise our breast cancer patients to seize smoking. Still, a surprisingly low number of these patients quit smoking. Recently published data on breast cancer is suggesting that smoking might increase both the overall mortality, as well as their risk of dying from their breast cancer. This could pose as a new powerful motivational factor when advising these patients on their lifestyle.

Materials and methods: A systematic review and meta-analysis on smoking status in women diagnosed with breast cancer, investigating their mortality rate and cause of death. All cohort studies published within the last ten years were included. Twelve studies, with a total of 400 944 women diagnosed with primary invasive breast cancer, was included.

Results: Data on overall mortality and breast cancer-specific mortality was analyzed. Hazard Ratio (HR) for breast cancer associated death in former smokers was 1.02 [0.93, 1.12] and for current smokers 1.28 [1.17, 1.41] when compared to never smokers. For all-cause death, the HR for former smokers was 1.12 [1.04, 1.19], and for current smokers 1.52 [1.32, 1.76] when compared to never smokers.

Conclusions: This large systematic review and meta-analysis found a 28% increase in breast cancer-associated mortality in those who were current smokers compared to never smokers. The mortality in former smokers was equal to the one found in never smokers. This indicates that breast cancer patients, ceasing to smoke, can lower their risk of dying from their breast cancer disease dramatically. Possibly regaining the risk of a never smoker. Passing this information on to our patient could motivate more of them to quit smoking and decrease the mortality of this disease.

2.

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Title

Hydrochlorothiazide use and risk of non-melanoma skin cancer

Background

Hydrochlorothiazide is photosensitizing and has been linked to lip cancer, but it is unclear whether hydrochlorothiazide use increases the risk of non-melanoma skin cancer (NMSC) in general. To study the association between hydrochlorothizide use and NMSC risk using the Danish nationwide demographic, prescription, and disease registries.

Methods

From the Danish Cancer Registry, we identified patients (cases) with a first diagnosis of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), the two major types of NMSC, between 2004 and 2012. For each case, we selected 20 population controls matched by age and sex using risk-set sampling. Cumulative hydrochlorothiazide use was assessed using data on filled prescription captured in the Danish Prescription Registry. Using conditional logistic regression, we calculated odds ratios (ORs) for BCC and SCC associated with hydrochlorothiazide use, adjusting for pre-defined potential confounders. We further examined doseresponse effects and performed additional analysis for comparable drugs with similar indications as hydrochlorothiazide.

Results

We identified 71,625 cases of BCC and 8,652 cases of SCC. High use of hydrochlorothiazide (≥50,000 mg) was associated with ORs of 1.30 (95% confidence interval [CI] 1.24-1.37) for BCC and 3.80 (95% CI 3.51-4.12) for SCC. We found clear dose-response relationships between hydrochlorothiazide use and both BCC and SCC; the highest cumulative dose category (≥200,000 mg HCTZ) had ORs of 1.59 (95% CI 1.43-1.76) and 6.78 (95% CI 5.83-7.90) for BCC and SCC, respectively. The use of drugs with similar indications, including other diuretics, calcium-channel blockers, and inhibitors of the renin-angiotensin system, was not associated with increased ORs for BCC or SCC.

Conclusion

Hydrochlorothiazide use is associated with an increased risk of NMSC, particularly SCC.

<u>3.</u>

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Title

Surgical-site Infection Following Lymph Node Surgery in Malignant Melanoma Patients Suggests Increased Susceptibility to Lymphedema: A Retrospective Cohort Study

Background:

The incidence of malignant melanoma (MM) is rising worldwide. Lymphedema is one of the most dreaded complications following any cancer treatment with lymph node involvement. Prevention of lymphedema is of essence as treatment options are limited. Several inevitable lymphedema risk factors have been identified; however potentially preventable factors such as seroma and surgical-site infection have yet to be asserted.

Methods:

To evaluate the impact of seroma and surgical-site infection for the onset of lymphedema, we included all MM patients treated with sentinel lymph node biopsy and/or lymphadenectomy at the axilla or inguinal region in the period of 2008-2014. Data regarding treatment and diagnosis was retrieved from registries and electronic patient files.

Results:

A total of 640 unique axillary and inguinal incision sites were included, of which 70 correlating limbs developed lymphedema. Postoperative complications were most frequent following inguinal lymphadenectomy (86% developed seroma, surgical-site infection, a need for reoperation and/or lymphedema). Multivariate cox regression showed that surgical-site infection was an independent risk factor for lymphedema (HR 8.47, 95%CI 4.37-16.46), and multivariate logistic regression revealed that seroma was an independent risk factor for developing surgical-site infection (OR 7.28, 95%CI 4.18-12.69).

Conclusion:

Seroma was the most prevalent complication following both sentinel lymph node biopsy and lymphadenectomy, and significantly correlated to surgical-site infection and subsequent lymphedema. Future studies should examine modalities to reduce seroma and its following complications.

<u>4</u>

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Title

Melanoma-related limb lymphoedema

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Aim/background: A focus of the PhD study *Health-related quality of life and surgical morbidity in melanoma patients* was to describe melanoma-related limb lymphoedema (LE) and the effect of LE on health-related quality of life (HRQoL) in melanoma patients.

Material and Method: This cross-sectional study consisted of a survey, a clinical examination and DXA scan of the study participants. The inclusion criteria were confirmed primary cutaneous melanoma, age 18-75, no previous or current evidence of metastatic disease, wide local excision (WLE) and unilateral axillary or inguinal sentinel lymph node biopsy (SLNB) and/or complete lymph node dissection (CLND) at least one year prior to the study. Health-related quality of life was evaluated with official cancer generic and symptom specific questionnaires. The clinical diagnosis of LE was based on the history, patients' symptoms and clinical findings. DXA scans of the limbs were performed to describe the volume and tissue composition (fat mass and lean mass).

Results: Of the 431 patients included (68% of eligible patients), 109 patients (25%) had clinical melanoma-related limb lymphoedema. Lymphoedema was present in 10 patients (5%) after axillary SLNB, in 13 patients (31%) after axillary CLND, in 53 patients (35%) after inguinal SLNB, and in 33 patients (83%) after inguinal CLND. The only treatment related risk factor statistically significant in univariate and multiple analyses was WLE on the leg in the inguinal SLNB subgroup. The majority of LE was classified as mild with the increase in volume particularly attributed to an increase in fat mass. The negative impact of LE on HRQoL in melanoma patients was statistically and clinically significant in multiple domains including global health status, role, and social functioning, pain, fatigue, financial difficulties and body image.

Conclusion: The study emphasises the importance of increasing awareness, and improving prevention and treatment of LE in melanoma patients.

<u>5.</u>
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The impact of autologous breast reconstruction on pain, lymphedema, AoDL, anxiety and depression

Introduction

Mastectomy can cause persistant pain, lymphedema and increase in psychiatric disease and anxiety. Autologous breast reconstruction (ABR) is a complex reconstructive procedure and it is well known that extensive surgery can cause long-term negative side effects such as pain. ABR is the most cosmetically satisfiying and natural looking reconstructions and previous literature has suggested an added beneficial effekt of ABR on both pain, lymphedema and activity of daily living. The present study was designed to

examine the direct effect of ABR on the above parameters in a nationwide cross-sectional questionnaire study.

Material and Methods

Patients included were treated with or without reconstruction after mastectomy for primary breast cancer in Denmark between January 2004 and December 2012. Patients who had undergone delayed unilateral ABR using a free abdominal flap (DIEP or MS2-TRAM), with a minimum of 3 years follow up was extracted from the microsurgical database. Matching controls were identified in the Danish Breast Cancer Cooperative Group database. Women were randomly selected as a *control* if the following criteria with respect to the case were met: age +/-3 years, same mastectomy year, same adjuvant treatment and same lymph node status. Patients with a previous cancer or metastases/recurrence were excluded. The response rate was 76% (554/731) for mastectomy and 84% (214/256) for patients treated with ABR. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated and the Wald χ 2 test was used to test the overall significance of each parameter. Associations between pairs of variables were analysed by Fisher's Exact Test. Two-tailed *p*-values were calculated and the level of significance was set at 5%. Analyses were carried out to assess possible selection bias between cases and controls.

Results

We found no significant difference in *pain* between patiens who had undergone ABR (OR 0,77, CI 0.52-1.14, P= 0,18) and no significant difference regarding *lymphedema* (OR 1.23, CI 0.84-1.82, P=0.28). ABR does not reduce patient *anxiety* (OR 0.70, CI 0.46-1.07, P=0.1) nor does it affect *depression* (OR 0.46, CI 0.19-1.14, P=0.08) and *activity of daily living* (OR 0.93, CI 0.67-1.31, P=0.70)

Conclusion

Contrary to previous reports, we find that ABR offers no beneficial effect on pain lymphedema anxiety depression and activity of daily living. However, it does not increase the prevalence of these symptoms.

6. Patient-Reported Outcomes in Weight Loss and Body Contouring Surgery: A Cross-sectional Analysis using the BODY-Q

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BACKGROUND Health-related quality of life (HR-QOL) and satisfaction with appearance are important outcomes in bariatric and body contouring surgery. In order to investigate these outcomes, scientifically sound and clinically meaningful patient-reported outcome (PRO) instruments are needed. Our study aims was to measure HR-QOL and appearance in a cohort of Danish patients at different phases in the weight

loss journey: pre-bariatric surgery, post-bariatric surgery, pre-body contouring surgery and post-body contouring surgery.

MATERIAL AND METHOD From June 2015 to June 2016, a cross sectional sample of 493 bariatric and body contouring patients were recruited from 4 different hospital departments. Patients were asked to fill out the BODY-Q - a new PRO instrument designed specifically to measure HR-QOL and appearance over the entire patient journey, from obesity to post body contouring surgery. Data were collected using REDCap, and analyzed using SPSS software.

RESULTS For all appearance and HR-QOL scales the mean score was significantly lower in the pre-bariatric surgery group compared with the post-body contouring group. Furthermore, the correlation between BMI and mean scores was significant for all appearance and HR-QOL scales, with higher scores associated with lower BMI. The mean score for the group reporting no excess skin compared to the group reporting a lot of excess skin was significantly higher for 5/7 appearance scales and 4/5 HR-QOL scales.

CONCLUSION Our study provides evidence to suggest that body contouring plays an important role in the weight loss patient journey and that patients need access to treatments.

7.

Tc-99m-human serum albumin transit time as a measure of arm breast cancer-related lymphedemaNavid M. Toyserkani^{1,3}, MD; Svend Hvidsten², MSc; Siavosh Tabatabaeifar^{1,3}, MD; Jane A. Simonsen², MD;
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Abstract

Background: Lymphoscintigraphy has often been used for evaluating arm lymphatic dysfunction, but no optimal approach for quantification has so far emerged. We propose a quantifiable measure of lymphatic function which we applied in patients treated for breast cancer.

Methods: Eleven patients, aged 34-68 years, with unilateral arm lymphedema following breast cancer treatment underwent bilateral lymphoscintigraphy using intradermal injection in both hands of technetium-99m-labelled human serum albumin and sequential 5 min imaging for five hours. The mean transit time (MTT) in the arms was calculated based on time activity curves generated from injection site and arm regions. Visual lymphedema scoring was performed based on dermal backflow and lymph node presence. Excess arm volume was calculated from circumference measurements.

Results: The MTT (mean \pm SD) was significantly longer in the lymphedema arm than in the normal arm: 60.1 \pm 27.7 min vs. 5.4 \pm 2.5 min (mean difference 54.7 min, 95% CI 36.5-72.9 min, p< 0.0001). Patients with previous erysipelas infection had significantly longer MTT than other patients (mean difference 43.7 min 95%, CI 18.6-68.7 min, p< 0.001). There was a positive correlation between MTT and excess arm volume (r= 0.64, p= 0.04) and number of lymph nodes removed (r= 0.65, p= 0.03), but no correlation between visual score and MTT.

Conclusion: Measurements of MTT were able to discriminate lymphedema from healthy arm, and MTT correlated with relevant markers for lymphedema severity. We encourage further research using the MTT approach for monitoring lymphedema and evaluation of treatment response.

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