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Surgical treatment of keratinocyte carcinoma in Danish hospitals 2007-2021: Time trends and impact of patient and tumor characteristics on treatment choices

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Summary The incidence of keratinocyte carcinoma (KC) is rising globally, significantly burdening healthcare resources. Treatment options include medical treatment, non-invasive procedures, and surgery, each associated with their distinct benefits and risks. With advanced treatment, the procedures become increasingly invasive for the patients and expensive for the society.

This nationwide cohort study examined the current surgical treatment trends for KC, including factors influencing the likelihood of undergoing reconstructive surgery. We retrieved data on all first-time incidences of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) that were treated at a Danish hospital in the calendar years 2007–2021, corresponding to 34,205 patients with BCC and 17,625 patients with SCC. Descriptive statistics were used to study the development of reconstructive surgery, and the associations between demographic factors, tumor-related factors, and comorbidity, and the use of reconstructive procedures were analyzed using multivariable logistic regression.

Among the patients, 26% with BCC and 35% with SCC received reconstructive surgery as part of their surgical treatment. The volume of surgical treatment increased with time, but the proportion

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of reconstructive procedures for surgically treated KC decreased in the study period. The likelihood of undergoing reconstructive surgery was higher for men and increased with age. Patients with BCC and high comorbidity burden or those who stayed in assisted living facilities were less likely to undergo reconstructive surgery. This was not the case for patients with SCC.

The rapid increase in surgical treatment for KC at Danish hospitals, with a notable increase in reconstructive procedures, reflects the global development in KC cases and highlights the continued need for tailored management strategies.

Keratinocyte carcinoma (KC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is a growing global public health concern, with its incidence rising steadily,[1] particularly among older individuals.[2] In the coming years, the considerably aging Danish population is expected to increase the burden on healthcare resources for KC treatment.[3,4]

Treatment options for KC vary based on tumor type, size, location, and the resources and comorbidities of the individual patient. In Denmark, initial diagnosis and intervention are managed in the primary healthcare sector, including primary care physicians and private practice dermatologists. Less invasive treatments, such as topical therapies, cryotherapy, and photodynamic therapy, are often preferred for superficial lesions with minimal risk of local recurrence and metastasis.[5] However, more complex and aggressive cases require management in hospital settings to ensure optimal outcomes.

In hospitals, KC treatment includes advanced modalities such as systemic and targeted medical therapies, radiation therapy, and surgical management.[6–8] Multidisciplinary collaboration among dermatologists, plastic surgeons, and oncologists may be essential to ensure effective tumor control while achieving satisfactory aesthetic and functional outcomes.[9] Surgical interventions remain one of the cornerstones of curative treatment, allowing precise tumor removal while preserving healthy tissue.[10] Several tumors can be treated with simple excision and primary closure, but larger tumors or those located in challenging anatomical regions may require reconstructive surgery and the use of advanced techniques, such as skin transplants, local skin flaps, and intraoperative histological examination for comprehensive margin control.[11,12] As the surgical treatments become increasingly specialized, the associated costs and risks of managing complications may increase, making it important to determine which patients are suitable candidates for advanced procedures.[13] More specifically, patients with KC vary widely in age, comorbidities, and frailty,[14] highlighting the need for a nationwide population-based examination of how advanced surgical techniques are applied in various patient categories, to potentially mitigate the future strain on healthcare resources.

Aim

The purpose of the study (conducted according to the principles of the strengthening the reporting of observational studies in epidemiology (STROBE) statement)[15] was to describe time trends in the use of surgical treatments for KC in a hospital setting, and to identify patient and tumor characteristics associated with the selection of reconstructive (i.e., more advanced) surgery through adjusted analyses.

Materials and methods

Study design

This is a nationwide population-based registry study.

Study population

This study included all patients aged ≥20 years with a first-time diagnosis of KC in Denmark from January 1, 2007 to December 31, 2021.

Registries

In the Danish Cancer Registry,[16] non-melanoma skin cancer (NMSC) is classified under ICD-10 code C44. The registry holds detailed information on morphology, tumor (T) category, and topography for first-time cases of BCC, SCC, and other (rare) histological types of NMSC. In this study, we only included BCC tumors (morphology code M-809×3) and SCC tumors (morphology codes M-807×3 and M-80833/M-80843). For further analyses, we divided T category into T1 and ≥T2 according to the UICC TNM-classification. Topography was divided into anatomical location in the head/neck region and other locations.

The National Patient Register[17] is an administrative register containing data from all hospitalizations at somatic wards in Denmark since 1977. We used the registry to collect data on KC treatments in Danish hospitals. Patient records with relevant diagnosis (C44) and surgical procedure codes identified patients who underwent surgery, defined as those with a dermato-surgical procedure code within 90 days of the initial BCC or SCC diagnosis. Codes for skin transplantation and skin flaps identified reconstructive surgeries, and codes for the use of intraoperative histological techniques were also included. Additionally, information on comorbidity was collected to calculate the Charlson Comorbidity Index (CCI)[18] score, based on conditions recorded up to 5 years before the KC diagnosis, grouped into scores of 0, 1–2, and 3+.

The Danish Registry of Pathology[19] provided information on the use of intraoperative histological techniques when this was missing in The National Patient Register.

We received information on assisted living residence in the year prior to diagnosis from Statistics Denmark.

The unique and personal Danish civil registration number was used for each patient as a common identifier to merge data.

Statistical analyses

Descriptive statistics showed the proportion of tumors treated in primary care versus hospital settings, surgical versus non-surgical treatment in Danish hospitals, and presented the distribution of the use of reconstructive techniques for patients with KC.

The associations between demographic factors, T category, and anatomical location, and comorbidity with reconstructive procedures were analyzed using uni- and multivariable logistic regression, where the model was adjusted for sex, age, year of surgery, T category, anatomical location, comorbidity, and assisted living. Patients with unknown T category were included in the analysis; however, imputation was not done. Age groups were divided in 20–49, 50–59, 60–69, 70–79 and 80+ year olds. The results are reported as odds ratios (OR) with 95% confidence intervals (CI). Analyses were conducted in Stata version 18 (StataCorp. 2023. College Station, TX: StataCorp LLC.) A P-value < 0.05 was considered significant. Because of the intrinsic differences between the two types of KC, results were analyzed and presented separately for BCC and SCC.

Results

From 2007 to 2021, 183,338 patients were diagnosed with a first incidence of BCC, and 42,233 with first incidence of SCC. For BCC, 42,904 (23%) patients were treated in Danish hospitals, with 34,205 undergoing surgery. Reconstructive interventions were required for 8770 patients. For SCC, 20,295 (48%) patients were treated in hospitals, with 17,625 undergoing surgery and 6253 requiring reconstructive procedures (Figure 1).

Treatment in a hospital setting

The number of diagnosed BCC cases increased each year in the observation period. The number of cases treated in primary care and hospital settings increased, as did the proportion of patients treated in hospitals, rising from 16% in 2007 to 24% in 2021 (Figure 2a). Comparable to BCC, the number of diagnosed SCC cases rose over the years. However, the percentage of patients treated in a hospital setting differed markedly. Most patients were predominantly treated in primary care at the beginning and end of the observation period, whereas from 2014 to 2019, most patients were treated in a hospital setting (Figure 2e).

Surgical and non-surgical treatment

Over the 15-year period, the number of surgical interventions in a hospital setting increased from 1211 in 2007 to 3000 in 2021 for BCC, equaling an increase of 148%, with a slight dip around 2020–2021 (Figure 2b). Non-surgical treatment also rose in the study period from 325 to 741 (128% increase). Surgical treatment of SCC cases increased from 598 in 2007 to 1788 in 2021 (increase of 199%; Figure 2f). Non-surgical treatment rose from 115 to 231 (100% increase) in the same period. Most patients, 64% of BCC and 79% of SCC cases, who received treatment in a hospital were also treated in plastic surgery departments.

Reconstructive surgery

Most BCC tumors (25,435 (74%)) were excised without the need for reconstructive surgery. A total of 4537 skin grafts and 4683 skin flaps were performed over the years. The amount of reconstructive procedures increased from 370 in 2007 to 783 in 2021, but the proportion of total surgeries

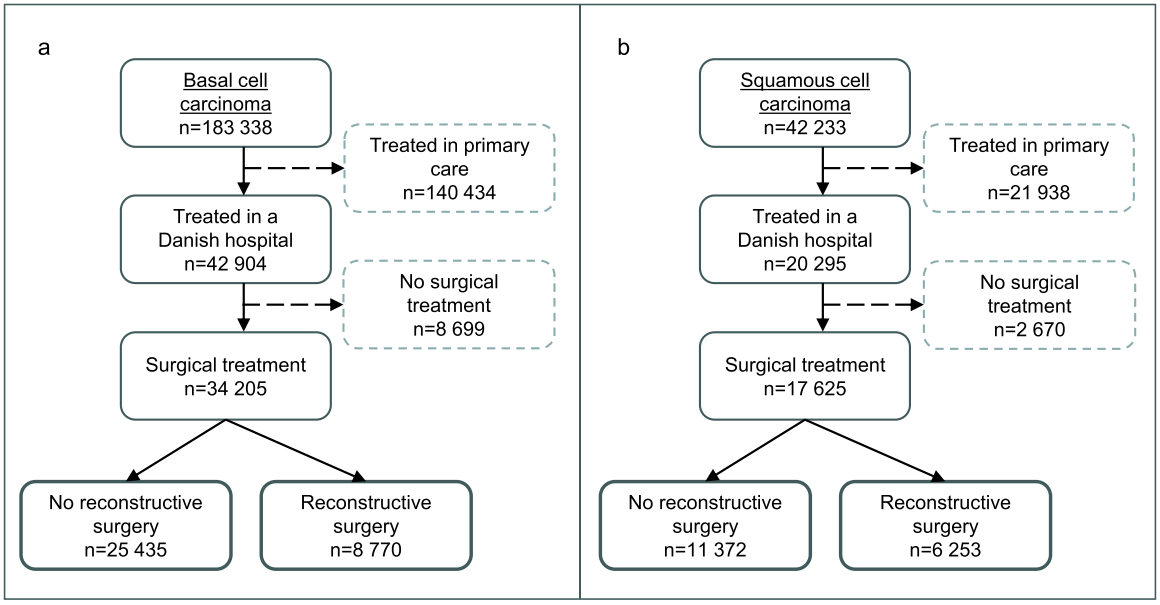

Figure 1 Flowchart on different treatment modalities for all first time diagnosed patients with a) **basal cell carcinoma** and b) **squamous cell carcinoma** in Denmark, 2007–2021.

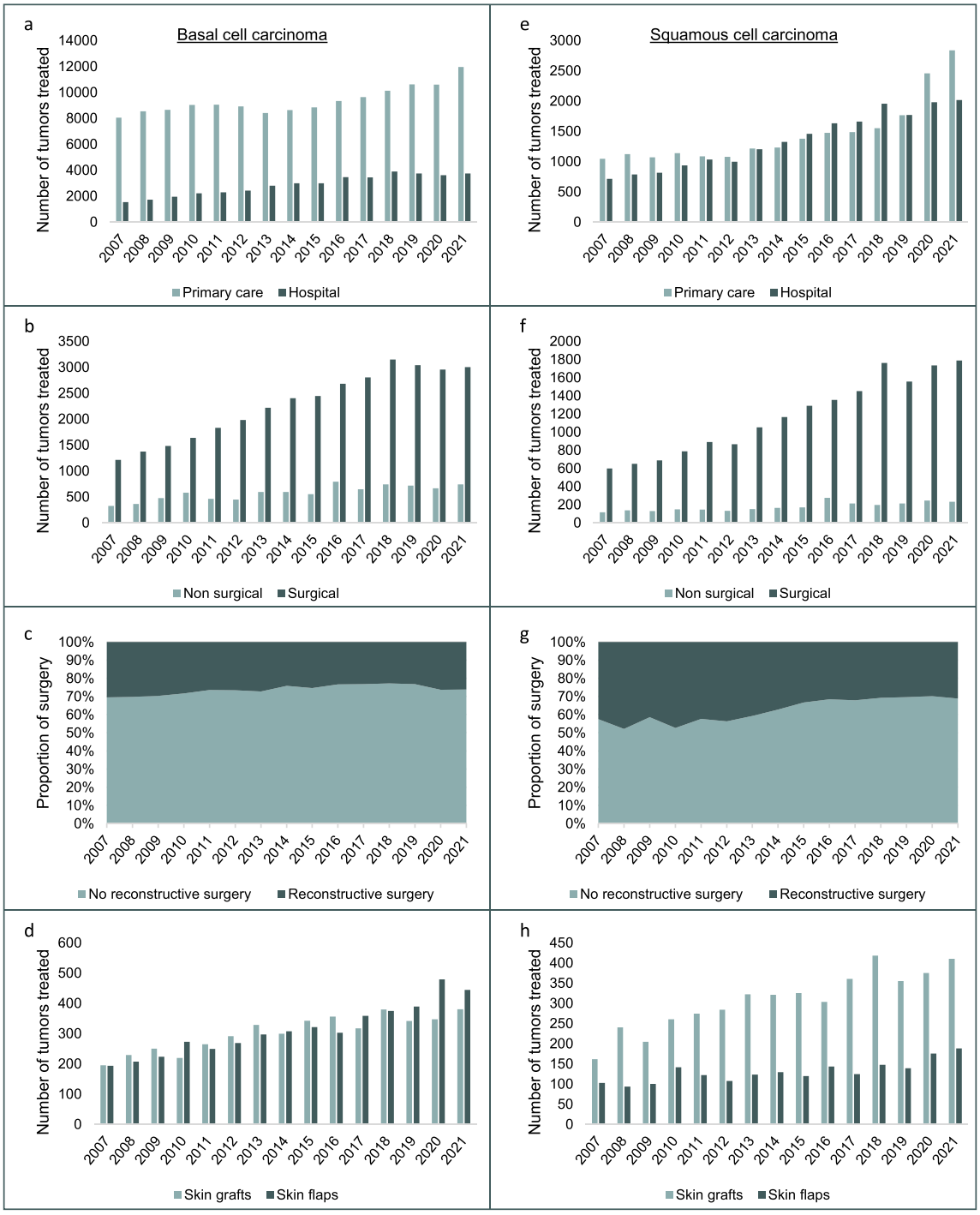

Figure 2 Development on the treatment modalities for patients with KC, 2007–2021. **Basal cell carcinoma**: a) number of tumors treated in primary care or hospital, b) number of tumors non-surgically and surgically treated in a hospital setting, c) proportion of tumors treated with and without reconstructive surgery, and d) number of skin grafts and skin flaps performed. **Squamous cell carcinoma**: e) number of tumors treated in primary care or hospital, f) number of tumors non-surgically and surgically treated in a hospital setting, g) proportion of tumors treated with and without reconstructive surgery, and h) number of skin grafts and skin flaps performed.

decreased from 31% to 26% (Figure 2c). Skin grafts increased from 195 to 380 and skin flaps from 193 to 444 (Figure 2d). Intraoperative histological examination were used in 3712 BCC cases, more frequently in combination with skin flaps (55%) than skin grafts (24%) (Figure 3a). Among the 18,268 surgically treated patients with BCC with tumors in the head/neck region, detailed anatomical information and data on reconstructive surgical techniques were available for only 12,682 patients (Figure 4a). Most tumors were located on the scalp or forehead. For tumors on the nose,

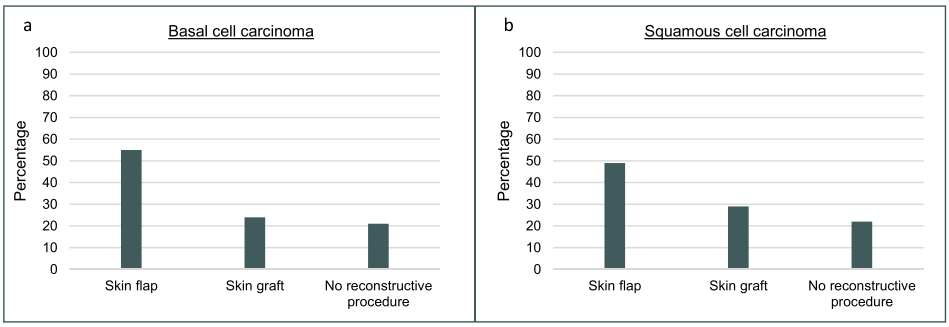

Figure 3 Proportion of different types of reconstructive methods used in combination with intraoperative histological examination. a) **Basal cell carcinoma**, intraoperative histological examination was used in the treatment of 3712 patients. b) **Squamous cell carcinoma**, intraoperative histological examination was used in the treatment of 1428 patients.

over 50% required reconstructive procedures, compared to a lower rate of only 9% for tumors in the neck area.

Similar to BCC, most surgically treated SCC tumors did not require reconstructive surgery (11,372 patients (65%)). Over the 15 years of observation, 4611 skin grafts and 1949 skin flaps were performed. Reconstructive procedures increased from 254 in 2007 to 557 in 2021; however, the proportion of these procedures out of total surgeries declined from 42% to 31% (Figure 2g). Skin grafts increased from 161 to 410 and skin flaps from 102 to 188 (Figure 2h). In 1428 SCC cases, intraoperative histological examination was used. As with BCC, this procedure was used more frequently with skin flaps (49%) than skin grafts (29%) (Figure 3b). Among the 9413 surgically treated patients with SCC with tumors in the head/neck region, detailed data were available for 7884 patients. Similar to BCC, most tumors were on the scalp or forehead, where 54% of the surgically treated cases involved reconstructive surgeries. Tumors on the nose required the highest rate of reconstructive surgery at 64% (Figure 4b).

Association between patient and tumor characteristics and reconstructive surgery

Table 1 describes the association between demographic factors, tumor-related variables, comorbidity, dependency on care, and rate of reconstructive surgery among patients with KC.

After adjusting for age, year of surgery, T category, anatomical location, and comorbidity, male sex was found to be associated with a higher rate of reconstructive surgery for BCC and SCC, with ORs of 1.06 (95% CI: 1.01–1.11) and 1.26 (95% CI: 1.17–1.34), respectively. The 70–79 year age group was used as the baseline for BCC cases, as this was the largest group. All the younger age groups had lower odds of reconstructive treatment, whereas those aged 80+ years had higher odds (OR 1.12, 95% CI: 1.05–1.20). For SCC, we chose the age group 80+ years as the baseline, and found lower odds of reconstructive surgery in all younger age groups from 20–79.

Fifteen percent of the BCC tumors requiring reconstructive surgery were a T category of ≥T2, equaling an OR of 1.70 (95% CI: 1.57–1.83) when comparing with cases that were surgically treated without reconstructive procedures. In 63% of the BCC cases requiring excision reconstructive surgery, the tumors were located in the head and neck area, whereas 50% of the cases treated without the need for reconstructive surgery, corresponded to an OR of 1.67 (95% CI: 1.59–1.76). For SCC, the percentage of ≥T2 tumor in the group treated with reconstructive surgery was 22%, whereas the proportion was 10% for tumors excised without the use of reconstructive procedures (OR 2.42, 95% CI: 2.22–2.64). The proportion of tumors located in the head and neck area among those treated with reconstructive techniques were 59% (OR 1.34, 95% CI: 1.26–1.43).

Most BCC cases had a Charlson Comorbidity Score of 0, in those treated with and without reconstructive surgery (76% and 77%). Higher comorbidity scores were significantly associated

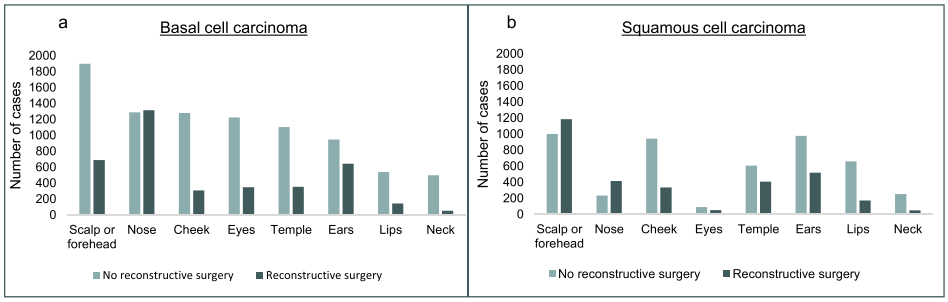

Figure 4 Distribution of reconstructive techniques based on detailed anatomical locations for patients with tumors in the head and neck region. a) **Basal cell carcinoma**, data on anatomical location and use of reconstructive surgery were available for 12,682 patients with head/neck tumors. b) **Squamous cell carcinoma**, data on anatomical location and use of reconstructive surgery were available for 7884 patients with head/neck tumors.

Table 1 Associations between year of surgery, demographic, tumor-related, and health-related factors with the rate of reconstructive procedures in surgically treated patients with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in Danish hospitals.

	BCC (n = 34 205)				**SCC** (n = 17 625)			
	No reconstructive surgery	Reconstructive surgery	Crude OR [95% CI]	Adjusted OR[a] [95% CI]	No reconstructive surgery	Reconstructive surgery	Crude OR [95% CI]	Adjusted OR[a] [95% CI]
Number of cases	25,435	8770	-	-	11,372	6253	-	-
Sex, n (%)								
Female	12,595 (50)	4169 (48)	1	1	4798 (42)	2237 (36)	1	1
Male	12,840 (50)	4601 (52)	**1.08 [1.03–1.14]**	**1.06 [1.01–1.11]**	6574 (58)	4016 (64)	**1.31 [1.23–1.40]**	**1.26 [1.18–1.34]**
Age at diagnosis, n (%)								
20–49	2948 (12)	576 (7)	**0.51 [0.46–0.56]**	**0.52 [0.47–0.57]**	269 (2)	109 (2)	**0.61 [0.48–0.76]**	**0.63 [0.50–0.80]**
50–59	3821 (15)	1063 (12)	**0.72 [0.67–0.79]**	**0.72 [0.67–0.78]**	727 (6)	253 (4)	**0.52 [0.45–0.61]**	**0.58 [0.50–0.68]**
60–69	6253 (25)	2026 (23)	**0.84 [0.79–0.90]**	**0.83 [0.78–0.89]**	1985 (18)	876 (14)	**0.66 [0.60–0.73]**	**0.69 [0.63–0.76]**
70–79	7324 (29)	2812 (32)	1	1	4124 (36)	2168 (35)	**0.79 [0.73–0.85]**	**0.83 [0.77–0.89]**
80+	5089 (20)	2293 (26)	**1.17 [1.10–1.25]**	**1.13 [1.06–1.21]**	4267 (38)	2847 (45)	1	1
Year	-	-	**0.98 [0.97–0.99]**	**0.98 [0.97–0.98]**	-	-	**0.94 [0.94–0.95]**	**0.94 [0.94–0.95]**
Tumor classification, n (%)								
T1	21,300 (84)	7101 (81)	1	1	9702 (85)	4587 (73)	1	1
≥T2	2241 (9)	1303 (15)	**1.75 [1.62–1.88]**	**1.70 [1.57–1.83]**	1123 (10)	1376 (22)	**2.59 [2.38–2.83]**	**2.42 [2.22–2.64]**
Unknown	1894 (7)	364 (4)	**0.58 [0.51–0.65]**	**0.60 [0.54–0.68]**	457 (5)	290 (5)	1.12 [0.97–1.30]	1.06 [0.91–1.23]
Head/neck area, n (%)								
No	12,675 (50)	3262 (37)	1	1	5625 (49)	2587 (41)	1	1
Yes	12,760 (50)	5508 (63)	**1.68 [1.60–1.76]**	**1.67 [1.59–1.76]**	5747 (51)	3666 (59)	**1.39 [1.30–1.48]**	**1.34 [1.26–1.43]**
Comorbidity, n (%)								
None	19,413 (76)	6723 (77)	1	1	7569 (67)	4083 (65)	1	1
1–2	4810 (19)	1639 (19)	0.98 [0.92–1.05]	**0.91 [0.85–0.97]**	2885 (25)	1657 (27)	1.06 [0.99–1.14]	1.02 [0.95–1.10]
3+	1121 (5)	408 (4)	0.97 [0.87–1.09]	**0.87 [0.78–0.98]**	918 (8)	513 (8)	1.04 [0.92–1.16]	0.97 [0.86–1.09]
Assisted living, n (%)								
No	24,974 (98)	8600 (98)	1	1	10,991 (97)	5999 (96)	1	1
Yes	461 (2)	170 (2)	1.07 [0.90–1.28]	**0.81 [0.67–0.97]**	381 (3)	254 (4)	**1.22 [1.04–1.44]**	1.03 [0.87–1.23]

Results are presented as odds ratios (OR) with 95% confidence interval (95% CI), and results in bold are considered significant with a p-value < 0.05.

[a] Adjusted for sex, age, year of surgery, T category, anatomical location, comorbidity, and assisted living.

with lower odds of reconstructive surgery: OR 0.91 (95% CI: 0.85–0.97) for scores of 1–2 and OR 0.87 (95% CI: 0.78–0.98) for scores of ≥3. Patients in assisted living facilities had lower odds of reconstructive surgery (OR 0.81, 95% CI: 0.67–0.97) as well. Regarding SCC, the percentages of patients with a Charlson Comorbidity Score of 0 were 67% and 66% for the patients who did not and those who needed reconstructive surgery, respectively. No significant relationship was found between the comorbidity score or assisted living and reconstructive procedures after adjustment.

Discussion

This study revealed a rapid increase in surgical treatment for KC at Danish hospitals, with a notable rise in reconstructive procedures. A clear distinction was found between BCC and SCC regarding factors related to reconstructive surgery. For BCC, a higher comorbidity burden and assisted living were associated with a lower likelihood of advanced surgery, even after adjusting for confounders. However, this trend was not observed for SCC.

The primary goal of treatment is to remove all cancerous tissue with clear margins and minimize recurrence risk using the most cost-effective method that the patient can accept.[20] Although less invasive treatments exist, surgery is often the first choice, especially for SCC, to minimize the risk of local recurrence and metastasis.[21] In this study, 34,205 out of 183,338 BCC cases (19%) and 17,625 out of 42,233 SCC cases (42%) were surgically treated in a Danish hospital.

Reconstructive surgery was defined as receiving a skin graft, local skin flap, or both within 90 days of KC diagnosis. Most surgically treated skin lesions were excised and not subsequently treated using reconstructive surgery. Although other studies report skin flaps as the norm for tumors in the head and neck area,[22] approximately 50% of such tumors were treated without the need for reconstructive surgery in our study. In Denmark, even small KCs are often referred to hospitals for treatment, possibly explaining this difference. The number of reconstructive procedures increased over the years, which is expected given the increase in KC cases. However, the proportion relative to total surgeries is decreasing. Our previous research indicates that more KC cases are diagnosed at earlier stages, where tumors are smaller and easier to manage.[2] This trend persists despite the lack of formal screening or public education programs, likely driven by increased personal vigilance, societal awareness, and informal education through social media, the internet, and news outlets. The increase in the number of KC cases has also drawn attention in the Danish media.[23] Additionally, greater medical vigilance during routine exams and advancements in diagnostic technology may contribute to more frequent and earlier detection of skin cancers. These findings underscore the importance of early detection of KC, which may also potentially reduce treatment costs.[24]

Margin control surgery using intraoperative histological techniques remains a cornerstone of advanced surgical treatment for KC. These include Mohs micrographic surgery and frozen section histology. Mohs micrographic surgery is especially effective for KC with unfavorable oncological characteristics such as location in the facial region, as the technique offers nearly 100% microscopic margin assessment, enabling targeted re-excision if needed.[25] However, Mohs micrographic surgery requires specialized training and is considered too expensive for routine use in Danish hospitals. Frozen section histology is a well-established alternative, providing similar benefits in ensuring clear margins before closure and is available in Danish hospitals with specialized surgical and pathology departments.[26] Tumor tissue is sent to a pathologist for immediate margin assessment, which requires less specialized surgical training. Frozen section histology is recommended when selecting skin flaps for reconstruction[27] and have been found to be accurate in detecting the presence of tumor involvement at the surgical margins 85% of the time compared with permanent sections.[28] In our study, intraoperative histological techniques were used in 44% of BCC cases and 36% of SCC cases treated with skin flaps. We lack data on re-excision rates for cases not using intraoperative histological procedures, highlighting the need for further investigation. Additionally, we do not have data on surgical margins or recurrence rates for patients treated with frozen section histology or other methods, as this information is not available in the registers.

A noteworthy finding is the association between the use of reconstructive surgical techniques and certain patient groups. Tumors with a T category of ≥T2 and/or those located in the head and neck area were significantly associated with higher odds of reconstructive procedures for BCC and SCC patients. Old age and male sex were also associated with the use of reconstructive surgery, even after adjusting for T category and anatomical location in the head and neck area. This association may be explained by differences in tumor locations in the face, as men and older patients are more prone to have tumors on the ears and scalp, where reconstructive techniques are often needed.[29,30]

In this context, we found that patients with a higher comorbidity burden or those in assisted living are less likely to receive reconstructive surgery for BCC, even after adjusting for anatomical location and T category. This is likely because the risk of complications outweighs the benefits of extensive surgery in these groups, when the patient's remaining lifespan must be considered. Reconstructive surgery often requires several hospital visits throughout the treatment course, which can be intolerable for patients with multiple comorbidities or immobility. For such patients, surgery with primarily palliative intent may be preferable, and in some cases of BCC, a margin of 3 mm can be considered acceptable, as minimizing the risk of local recurrence might not necessarily be a priority.[31] For lesions that are too large or anatomically complex for direct closure, the surgeon may have opted for healing by secondary intention. Although we lack data on the frequency of this approach, it is often considered less invasive and may be preferable for this frail patient group with BCC. Regarding SCC cases, we found no such associations. SCC is more aggressive and often requires extensive surgery with wider margins,[32] necessitating reconstructive surgery to maintain appearance and functionality, even for patients with comorbidities or in assisted care.

The strengths of this study include its robust register-based design, using national data, which provides a comprehensive and representative sample of KC cases surgically treated in a hospital setting. The national scope enhances the generalizability of the findings. However, there are limitations to this study. The reliance on clinician-reported data can introduce reporting bias, including misclassification and underreporting of procedures. Standardized coding may oversimplify clinical details, and registries often lack key confounding variables, which can limit causal inferences. Additionally, the study is limited to data reported from hospitals, restricting the insights into patient management in primary care settings.

Conclusion

This study provides valuable insights into the trends of surgical treatment in a hospital setting for KC. As the incidence of KC increases, the demand for surgical treatments will rise, highlighting the need for a well-trained healthcare workforce. Continued efforts in early detection and tailored approaches for specific patient group is essential to ensure optimal use of healthcare resources in the future.

Ethical approval

The project was approved by the National Danish Health Authority and Statistics Denmark. All data linkage was conducted in compliance with the Danish Act on Processing of Personal Data. Data management was sanctioned by the Danish Data Protection Agency through local authorities. As this is a registry-based study with no direct contact with individual patients, no additional approvals were required under Danish law.

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Conflict of interest

None declared.

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