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ARTICLE

DaPeCa5 – obesity at the time of diagnosis does not predict poor cancer-specific survival in patients with penile squamous cell carcinoma – a Danish National study

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ABSTRACT

Background: Conflicting data on the prognostic significance of obesity in penile cancer have been presented in recent years.

Objective: The objective of this study was to investigate obesity as a prognostic factor in patients with penile squamous cell carcinoma (pSCC) in a large national Danish cohort. Furthermore we aimed to compare the BMI of pSCC patients to a large age-matched cohort of healthy men.

Methods: We evaluated 429 patients with invasive pSCC from a national retrospective penile cancer cohort and defined a body mass index (BMI) at 30 kg/m^2 as obese. Furthermore, we considered if a fitted model for BMI and mortality could define a critical BMI tipping point for increasing mortality by the means of BMI categories of 1 kg/m^2 width. We compared 29 pSCC patients with reported unintended weight loss at diagnosis to 400 with no reported weight loss. Cox regression with 95% confidence intervals was used for penile cancer-specific survival analysis. The comparison between 325 age-matched pSCC patients and 11,238 healthy men from an existing contemporary health database was done by nonparametric tests.

Results: There was no difference in cancer specific survival between patients with a BMI below and above 30 kg/m^2, cox hazard ratio (HR) 0.74 (0.47–1.18), $p = .20$, but 37 kg/m^2 was a tipping point for increasing mortality, HR = 2.10 (1.06–4.18), $p = .035$. Unintentional weight loss prior to diagnosis significantly predicted worse cancer specific outcome, cox hazard ratio 6.0 (3.5–10.0), $p < 001$ and cox hazard ratio adjusted for American Joint Committee of Cancer (AJCC)-stage at 1.8 (1.1–3.1), $p = .03$. Age-matched pSCC patients had a significantly higher BMI than healthy males, 28.4 ± 5.5 kg/m^2 vs. 26.2 ± 3.6 kg/m^2, $p < .0001$ and were more likely to smoke, $p < .0001$, and report alcohol intakes over 14 units/week, $p < .0001$.

Conclusion: In this Danish cohort, BMI above 30 kg/m^2 at diagnosis does not affect prognosis, but BMI at and above 37 kg/m^2 at diagnosis predicts poor prognosis. Unintentional weight loss is a predictor of high stage and poor prognosis. PSCC patients have a significantly higher BMI than age-matched healthy males.

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Penile cancer; squamous cell carcinoma; obesity; prognosis; weight loss; mortality; cause specific survival

Introduction

Penile squamous cell carcinoma (pSCC) is a rare diagnosis with an incidence of 0.5 – 2.1/100,000 men in Europe and North America [1–4]. PSCC is often diagnosed with a considerable delay [5]. A number of known risk factors for pSCC exist including phimosis, human papilloma virus infection, and tobacco use [6].

Urologists working at specialised penile cancer centres observe that a significant group of patients presenting with SCC of the penis tend to be obese. Obese penile carcinoma patients may be diagnosed at later stages of the disease compared with non-obese patients. It has been hypothesized that obese patients due to hampered visual genital inspection, impaired genital cleansing, reduced possibilities for self-examination and lowered compliance with healthcare systems have an increased risk of penile carcinoma and a delayed recognition of symptoms that leads to presentation at a more advanced stage [7]. This finding in an American dataset, however, has recently been challenged in a large European cohort where no association between American Joint Committee of Cancer (AJCC)-stage and BMI was found [8].

In some cancers low BMI and weight loss in the period leading to cancer diagnosis has been associated with worse prognosis leading to an inverse relationship between BMI and survival sometimes referred to as the obesity cancer paradox [9]. Generally in large populations, J-shaped relationships between all cause mortality and BMI are observed, and mortality from any cancer follows this with a flat J-shaped pattern estimating the mortality risk to reach a nadir at BMIs

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in the range of 21–25 kg/m^2, with inverse associations below, and positive associations above [10].

This study aims to investigate the prognostic importance of BMI at diagnosis and unintentional weight loss prior to diagnosis in a large nationwide retrospective Danish cohort of men with invasive pSCC to add data to the controversial debate on the prognostic significance of BMI in pSCC.

Furthermore, we age-matched the current penile cancer cohort to an existing contemporary major Danish general health database in order to compare BMI, tobacco use and alcohol consumption of men with penile carcinoma to that of healthy controls.

Methods

pSCC patients

We assessed 429 patients diagnosed with pSCC from a National Danish retrospective penile cancer cohort from a 10-year period. The cohort database was established by chart review at the only five Danish university hospitals treating penile cancer during the period. Patient characteristics are summarised in Table 1.

Unintended weight loss

We compared 29 pSCC patients with reported unintended weight loss at diagnosis to 400 with no reported weight loss.

Cancer-free controls

Data for the healthy control group, consisting of 11,238 healthy individuals, was derived from the national health and morbidity studies by Department of Public Health, University of Southern Denmark. Data were collected through self-administered questionnaires with a mixed-mode approach, allowing for the invited individuals to complete either a web questionnaire or an identical paper questionnaire. Survey invitations were sent by regular postal mail [11].

Age-matching

In the comparison between pSCC patients and healthy men, 104 pSCC patients older than 75 years were omitted from the pSCC cohort in order to age-match the 11,238 healthy controls, leaving 325 pSCC patients for comparison.

Statistical analysis

We assessed the role of BMI as a prognostic factor by splitting the retrospective cohort in two at BMI below and above 30 kg/m^2. Cox regression with 95% confidence intervals was used for penile cancer-specific survival analysis. In the survival estimates for patients reporting unintentional weight loss prior to diagnosis we utilized a cox regression model adjusting for AJCC-stage [12]. Due to limited sample size the model did not allow for further adjusting variables.

We considered an alternative non-linear parameterization of BMI in fine categories of 1 kg/m^2 width (<18 kg/m^2, 18–18.99 kg/m^2, 19–19.99 kg/m^2 and so on), and plotted cox hazard ratios with 95% confidence intervals for each BMI category-split with a two-term fractional polynomial fit to investigate if a critical BMI tipping point for increasing mortality was present in this cohort [10].

Penile Cancer-specific death was defined as death from penile carcinoma or death from complications due to treatment for penile carcinoma. Patients alive at the end of follow-up were censored at that date.

We compared BMI and smoking between penile carcinoma cases and healthy controls by nonparametric tests. For

Table 1. BMI and Penile Cancer.

Characteristics Cohort	pSCC patients	Age-matched pSCC patients	Cancer free healthy males	*p*-value
Patients (n)	429	325	11238	
Age				
Yr, Mean (SD)	66.1 (12.4)	61.0 (9.2)	60.3 (10.7)	.17[a]
Range	25.3–102.3	25.3–74.8	–	
BMI				
kg/m^2, mean (SD)	28.0 (5.3)	28.4 (5.5)	26.2 (3.6)	<.00001[a]
kg/m^2, Range	14.5–60.4	15.5–60.4	–	
Smoking				
Never, *n* (%)	170 (40)	124 (38)	–	
Current Daily, *n* (%)	216 (50)	172 (53)	1521 (38.5)	<.00001[b]
Former, *n* (%)	38 (9)	27 (8)	–	
Unknown, n (%)	5 (1)	2 (1)	–	
Circumcision or phimosis surgery before diagnosis				
No, *n* (%)	365 (85)	278 (85)	–	
Yes, *n* (%)	6 (15)	47 (15)	–	
Phimosis at diagnosis				
No, *n* (%)	179 (42)	141 (43)	–	
Yes, *n* (%)	250 (58)	184 (57)	–	
Unintentional weightloss in the period before diagnosis				
No, *n* (%)	400 (93)	302 (93)	–	
Yes, *n* (%)	29 (7)	23 (7)	–	
Exceeding alcohol limits (14 units/ week)				
No, *n* (%)	329 (77)	234 (72)	9362 (83)	<.00001[b]
Yes, *n* (%)	100 (23)	91 (28)	1876 (17)	

[a]Unpaired samples ttest. [b]Chi square test.

statistical analysis we used Stata Statistical Software: Release 13, TX: Statacorp. A *p*-value of .05 or less was considered statistically significant.

Results

Patient characteristics

In the current penile cancer cohort 216 out of 429 (50%) men were current smokers at the time of diagnosis, see Table 1. In the age-matched cohort of 325 pSCC patients 161 (49.5%) were smokers. In healthy men the proportion of current smokers was reported at 38.5%, <.00001 [11]. Penile SCC patients had a significantly higher BMI compared to controls 28.4 ± 5.5 kg/m^2 vs. 26.2 ± 3.6 kg/m^2, $p < .0001$, and were more likely to consume more that 14 units of alcohol per week 28% vs. 17%, $p < .00001$.

BMI and AJCC stage

Fifty-six percent of patients (242 of 429) were American joint committee of cancer stage I. No significant mean BMI differences were found between AJCC stage groups, see Table 2.

BMI and survival

The median follow-up of the patients was 72.8 ± 48 months. Cox hazard ratio when comparing penile cancer patients with a BMI below and above 30 kg/m^2 was 0.74 (0.47–1.18), $p = .20$ (Figure 1), whereas BMI at 37 kg/m^2 was a tipping point for increasing mortality, HR = 2.10 (1.06–4.18), $p = .035$, Figure 2.

Unintended weight loss and survival

When comparing patients with reported unintended weight loss at diagnosis ($n = 29$) and patients where weight loss was not mentioned in the medical history ($n = 400$), the hazard ratio was 6.0 (3.5–10.1) $p < .001$, In a cox regression model adjusting for AJCC-stage the hazard ratio was 1.8 (1.1–3.1), $p = .03$. Hence, unintentional weight loss predicts markedly worse penile cancer specific survival. Thirteen of 29 patients (45%) with reported unintended weight loss at diagnosis were AJCC stage 5.

Discussion

Conflicting data on the prognostic significance of obesity in penile cancer have been presented in recent years. An

Table 2. AJCC stage compared to mean BMI.

AJCC	All pSCC patients *n* (%)	BMI (CI)	SCC patients who reported weightloss *n* (%)
Stage I	242 (56)	28.2 (27.7−28.8)	5 (17)
Stage II	71 (17)	27.7 (26.5−28.9)	7 (24)
Stage III	33 (8)	27.6 (25.9−29.3)	0 (0)
Stage IV	26 (6)	28 (24.9−31.1)	4 (14)
Stage V	57 (13)	28.2 (26.7−29.6)	13 (45)
Total (*n*)	429 (100)		29 (100)

pSCC: penile squamous cell carcinoma; AJCC: American Joint Committee on Cancer; BMI: body mass index.

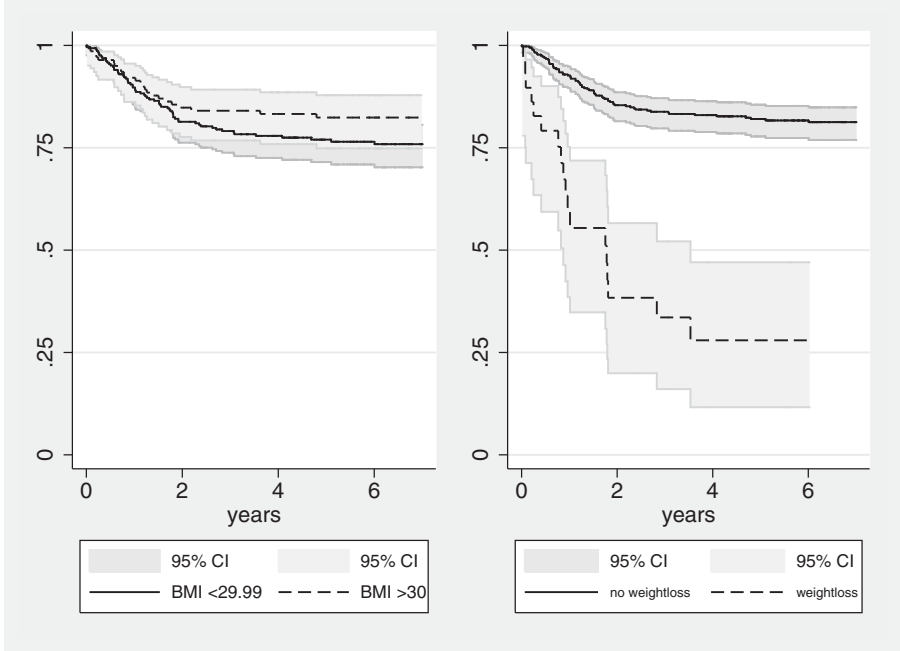

Figure 1. (a) Kaplan-Maier survival estimates, no survival difference between patients with BMI under and over 30 kg/m^2. Cox hazard ratio 0.74 (0.47–1.18), $p = .20$. (b) Kaplan-Maier survival estimates, significantly worse outcome in patients with unintended weight loss preceding the cancer diagnosis, cox hazard ratio 6.0 (3.5–10.1) $p < .001$. BMI, body mass index, kg/m^2.

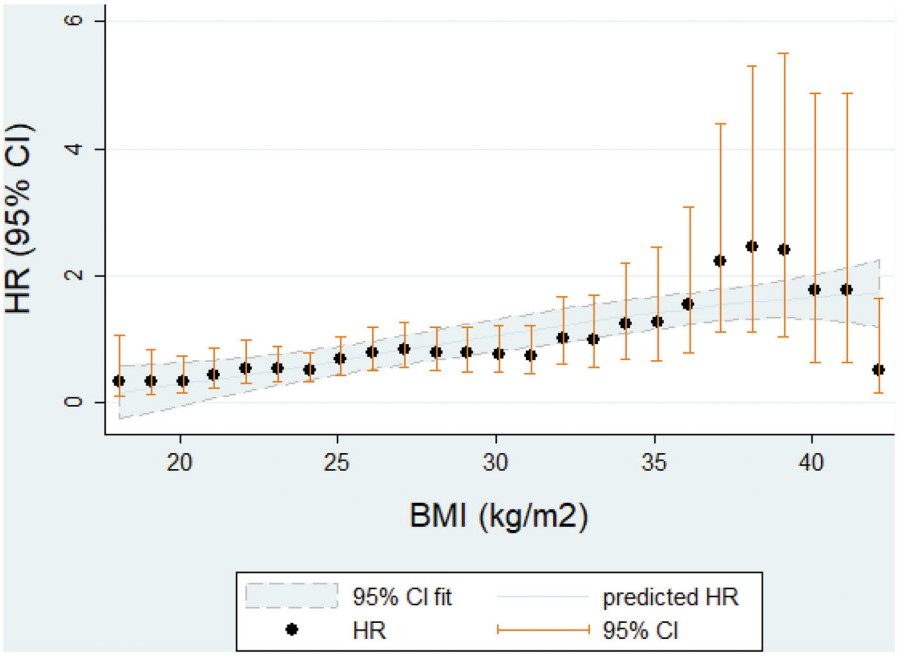

Figure 2. Cox Hazard ratios for BMI categories of 1 kg/m^2 width (<18 kg/m^2, 18–19.09 kg/m^2, 19.1–20.09 kg/m^2 and so on), plotted cox hazard ratios with 95% confidence intervals for each BMI category-split with a two-term fractional polynomial fit, establishing 37 kg/m^2 as a tipping point for increasing mortality, HR = 2.10 (1.06–4.18), $p = .035$. BMI, body mass index, kg/m^2.

American study found that higher BMI was associated with worse AJCC stage at diagnosis. Reportedly on multivariate ordinal logistic regression, every

5-unit increase in BMI was associated with 49% increased odds of higher stage [7]. On the contrary, a Dutch study found no correlation between patient BMI and AJCC stage [8]. In the current study, we aimed to investigate this controversial issue in our retrospective Danish Penile Cancer Database and our results are in line with the Dutch study with no difference in BMI between the different AJCC groups of the Danish SCC cohort.

In the current study we did a separate survival analysis for 29 pSCC patients reporting unintended weight loss in the period preceding pSCC diagnosis. Not surprisingly, this small subgroup of patients was more likely to be diagnosed at at higher AJCC stage and had worse cancer specific outcome. Unintended weight loss at diagnosis is likely to indirectly indicate widespread disease and/or rapid cancer growth with high metabolic needs and increased calorie consumption. This phenomenon is well-known in other cancers and may sometimes lead to the paradoxical interpretation that obesity may protect against cancer. This paradox is known as the obesity paradox in cancer [9,13]. However, a group of patients is expected to not report their weight loss or the physician did not note it in the record. The reported effect will probably be smaller, if all degrees of weight loss were captured.

On the other hand it has indeed been demonstrated in breast, colorectal and prostate cancer that increasing BMI decrements prognosis. Studies have confirmed that obese patients or even those with an overweight BMI at time of diagnosis have a poorer cancer-specific outcome than those with a normal BMI [14–16].

BMI and pSCC survival

In the study by Barnes et al. higher BMI was related to a higher AJCC stage at pSCC diagnosis and they hypothesize that a worse prognosis in obese patients might be multi-factorial related to different aspects such as the proposed idea that obese patient would have a poorer genital hygiene, self-examination and lowered compliance with healthcare systems and thereby delay identification of a likely cancer by both patient and physicians [7]. Additionally, lichen sclerosus have recently been found to be more common in obese men [16]. Lichen sclerosus is a chronic inflammatory disease of the glans penis linked to penile cancer [17]. While this study only had a small cohort ($n = 97$), it is possible that BMI plays a role in the pathogenesis of LS. Another possible pathogenic mechanism is that an enclosed penis is more likely to develop penile carcinoma despite neonatal circumcision and lack of HPV infection [18,19]. At this stage, we must consider these suggestions highly speculative.

In our study, and in the Dutch cohort presented by Djajadiningrat et al., mean BMI is considerably lower than in the Barnes cohort. The Dutch cohort [8] had a mean BMI of 26.8 kg/m^2 ($n = 433$). The Danish cohort of the current study had a mean BMI of 28.4 ± 5.5 kg/m^2 ($n = 429$) and the mean BMI in US cohort presented by Barnes is 31.8 ± 8.3 kg/m^2 ($n = 101$). The higher BMI in the US cohort can be contributed to the fact that obesity is more common among men in the United States than it is in Europe [20]. Thus the negative effect on AJCC stage and survival of increasing BMI reported by Barnes et al. might only penetrate in populations above a certain level of obesity. Exploring this question in our current cohort we plotted cox hazard ratios with 95% confidence intervals for each 1 kg/m^2 BMI category-split to investigate, if we could define a critical BMI tipping point for

increasing mortality. The tipping point in this Danish cohort was 37 kg/m^2. This finding might support the hypothesis, that increasing BMI mainly aggravates the prognosis in pSCC only in the WHO obesity classes II and III [21]. Cases of extreme obesity may even challenge nodal staging and restrict treatment options.

Another marked difference between the European and the US cohort is the free and public access to health care and centralized penile cancer management in Holland and Denmark as compared to the more diverse and restricted pay per service approach still dominating US health care. In that respect the negative effect on AJCC stage and survival of increasing BMI reported by Barnes et al. might in part be explained by difficulties in approach to health care by obese people without health insurance in the US as opposed to free and easy access for obese Dutch and Danish patients with pSCC. Since 2009 Danish citizens have the right to a Cancer Care Pathway when a primary care physician suspects cancer which increases the likelihood of timely diagnosis, proper, homogenous and due treatment [5]. Additionally, the US study is at risk of selection bias and limited generalizability because of referral patterns at an academic medical center in the US [7].

The discussed differences highlights the need for further studies to analyse the importance of obesity in the pathogenesis of penile cancer, as mortality is high for advanced penile cancer and therapeutic options limited [22].

In the current study on the Danish pSCC cohort comparing the BMI of 325 age-matched pSCC patients to the BMI of 11,238 cancer-free healthy Danish males we found a significantly elevated BMI in the pSCC patients who were also significantly more likely to be smokers and to consume above 14 units of alcohol per week than controls. Due to the retrospective study design and the differing methods of data collection this cannot be considered proof of associations or risk. However, these data indirectly supports the correlations revealed in a prospectively designed case-control study [6].

Limitations and strengths

The main limitation of this study is the retrospective study design. However, our retrospective cohort represents a complete national dataset, which limits potential selection bias. Thorough and strict record-keeping tradition at all participating centres made the maintained data of great completeness and high quality. In the comparison between pSCC patients and healthy cancer free age-matched males a major limitation is different modes of data collection with extraction of data form medical records for the pSCC patients and individual response to self-administered questionnaires in the national health and morbidity studies for the healthy males. It might be expected that self reported alcohol-consumption, smoking habits and self reported body weight tends to be biased by the current social norms of health behaviour leading to underreporting as compared to the medical history taking situation, where the ethics and hierarchy of the patient – doctor relationship is still at stake. If this speculation on report bias is true, the differences between the pSCC patients and the healthy males are estimated larger than the true difference between the groups. For this reason we only employed non-parametric tests in this part of the study and adapted discussions and conclusions accordingly.

Conclusion

In the present study we found that pSCC patients have a significantly higher BMI than healthy males. In this Danish cohort, BMI above 30 kg/m^2 at diagnosis does not affect prognosis, but BMI at and above 37 kg/m^2 at diagnosis predicts poor prognosis. Not surprisingly, unintended weight loss preceding pSCC diagnosis predicts an elevated AJCC stage and a poor prognosis.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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