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Comorbidity in HPV+ and HPV− oropharyngeal cancer patients: A population-based, case-control study

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ABSTRACT

Objectives: Comorbid conditions impact outcome for patients treated for oropharyngeal squamous cell carcinoma (OPSCC) and serve as competing risk factors for death. The purpose of this study was to examine differences in comorbidities in patients with OPSCC and known HPV-DNA.

Material and methods: We included patients diagnosed with OPSCC in Eastern Denmark in 2000–2014. Patients were linked to the Danish National Patient Register to identify comorbidities based on the Charlson Comorbidity Index (CCI) at time of diagnosis and following cancer treatment. Patients were age-and sex-matched in a 1:10 ratio with a reference group and stratified according to HPV-status.

Results: In total 1,499 patients (55.0% HPV+) and 14,990 controls were included. Significantly more HPV+ patients had no comorbidities compared to HPV− patients at time of diagnosis (RR: 1.5 (1.3;1.6), n = HPV+: 522, HPV−: 302) and following treatment (RR 1.5 (1.4;1.6), n = HPV+: 342, HPV−: 142). Most prevalent comorbidity was malignancy not including OPSCCs. HPV+ patients had an increased risk of having AIDS before their OPSCC diagnosis compared to the reference population (OR: 4.8 (1.8;12.9)). HPV− patients had increased risk of multiple comorbidities including cerebrovascular disease (OR: 1.9 (1.4;2.5)), peripheral vascular disease (OR: 1.7 (1.9;3.7)), dementia (OR: 2.9 (1.4;5.8)), ulcer disease (OR: 2.6 (1.9;3.5)), liver disease, mild (OR: 9.5 (7.0;13.0)) and severe (OR: 13.9 (5.8;22.8)).

Conclusion: This study showed that HPV− patients had more comorbidities than HPV+ patients at the diagnosis time and following treatment. Irrespective of HPV-status, OPSCC patients had a significant increased risk of (secondary) malignancy compared to the reference population.

Introduction

In Scandinavia, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing mainly because of a rise in human papillomavirus (HPV)-related disease [1–3]. Patients with HPV-positive (HPV+) OPSCC tend to be younger, more often non-smokers, and exhibit better survival compared to patients with smoking and alcohol-induced HPV-negative (HPV−) OPSCC [4]. The HPV+ OPSCCs have shown different molecular and histopathological characteristics when compared to HPV− OPSCCs [5,6], with the consequence that OPSCC today is staged by TNM classification based on HPV-positivity (i.e. by using the surrogate marker, p16), or not [7,8].

Medical comorbidities not only serve as competing risk factors for death but might also affect the ability to complete therapy and adhere to follow-ups. The comorbidity burden of head and neck cancer is recognized as an influencing factor on mortality with death from non-malignant causes reaching 35% at 5 years in these patients [9–12]. Further, comorbidities are strongly correlated with predicted outcome [13], have been proven to influence the treatment-decision in head and neck cancer (HNC) patients and are associated with increased risk of complications [14]. As HPV+ OPSCC patients exhibit superior survival outcome even when adjusted for smoking status, gender, age, and tumor stage [15] we hypothesize that the increased survival in this patient group could, in part, be due to difference in comorbidities between HPV+ and HPV− patient. HPV+ OPSCC patients have been shown to have fewer comorbidities at the time of diagnosis compared to the HPV− OPSCC patients [16]. However, studies specifically for OPSCC patients and, data on expected comorbidity (e.g. compared with

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Table 1
Weighted CCI score at time of cancer diagnosis.

Weighted score	HPV+ count (%)	Median age (95% CI)	Non-smokers* count (%) Unknown smoking history count (U)	HPV− count (%)	Median age	Non-smokers* count (%) Unknown smoking history count (U)	Relative risk (95% CI)	p
0	522 (63.4%)	58 (57; 59)	182 (34.5%) U:39	302 (44.7%)	59 (58; 60)	27 (8.9%) U: 20	1.42 (1.28; 1.56)	0.001
1	86 (10.4%)	61.5 (58; 65)	22 (25.6%) U:3	124 (18.4%)	61 (59; 65)	7 (5.6%) U:15	0.72 (0.60; 0.85)	0.001
2	102 (12.4%)	61 (58; 65)	35 (34.3%) U:6	130 (19.3%)	63.5 (61; 65)	14 (10.8%) U:10	0.77 (0.66; 0.90)	0.001
3	28 (3.4%)	63 (56; 66)	2 (7.1%) U:2	50 (7.4%)	60 (58; 64)	6 (10.0%) U:2	0.64 (0.47; 0.87)	0.004
4	7 (0.9%)	72 (53; 92)	3 (42.9%) U:0	31 (4.6%)	64 (58; 66)	2 (6.5%) U:4	0.33 (0.17; 0.64)	0.001
≥5	79 (9.6%)	60 (55;66)	27 (34.2%) U:8	38 (5.6%)	60.5 (55; 66)	1 (2.6%) U:3	1.25 (1.09; 1.43)	0.001
Total	824 (100%)			675 (100%)				

* Smoking history of <1 pack years.

the background population), and the distinct differences for patients stratified on HPV-status remains sparse. The purpose of this study was to report comorbidities based on the Charlson Comorbidity Index (CCI) among patients with HPV+ OPSCC and HPV− OPSCC compared to the background population, and to report differences in comorbidity before and after treatment.

Methods

The Eastern Denmark Region holds 46% of the Danish population with approximately 2.4 million inhabitants. All patients registered with OPSCC (ICD-10: DC01, DC02.4, DC05.1, DC05.2, DC09.0, DC09.1, DC09.2, DC09.8, DC09.9, DC10.2, DC10.3, DC10.8, and DC10.9) in Eastern Denmark from 2000 to 2014 were identified through the Danish Head and Neck Cancer group (DAHANCA) database and validated through the national Danish Pathology Data Registry (DPDR), as previously described [1,12,17]. The OPSCC diagnosis was confirmed by an expert head and neck pathologist [17–19]. Patients were stratified according to HPV-status. Tumors were deemed HPV-positive when they were both HPV+ and p16+ [1]. Using personal identification numbers all patients included in the study were linked to the Danish National Patient Register (DNPR) [20]. DNPR contains information on all inpatient consultation as well as outpatient (ambulatory) hospital consultations after 1995 according to the ICD-classification in Denmark. Each patient was matched on age, sex, and calendar time with ten control subjects from the general population (henceforth the "reference population") at the date of diagnosis of the HNC for the included patients. Thus, no control subjects from the reference population had been diagnosed with an OPSCC at the time of matching. Smoking data was collected through medical files for each case. Smoking data for the reference group was not available. The medical comorbid disease burden was evaluated by means of the Charlson Comorbidity Index (CCI) at time of diagnosis and at the last date of follow-up (the April 30th 2016) [21]. CCI consists of 19 medical conditions weighted from one to six based on its potential to influence mortality, with a maximal score possible of 33. The use of CCI in the Danish National Patient Register has an overall positive predictive value of 98% [22]. Records of any OPSCC diagnosis were excluded from calculations of the CCI score. Furthermore, age was not included in the CCI calculations.

Statistical analysis

Statistical analysis was performed in the statistical environment R [23]. The relative risk (RR) and odds ratio (OR) calculations were performed with the 'fmsb' package [24]. Patients were descriptively grouped according to their weighted CCI score both at time of diagnosis and after the cancer diagnosis. The RR of having a specific weighted CCI score for HPV+ patients compared to HPV− patients were calculated. The number of patients as well as controls with each comorbidity was described and OR was calculated to assess the likelihood of having a comorbidity in patients, respectively all OPSCC patients, HPV+ patients, and HPV− patients, compared to the reference population.

Results

A total of 1,499 OPSCC patients (55.0% HPV+, n = 824) and 14,990 age- and sex-matched controls were included. Median age at diagnosis was significant different between the HPV-groups; 61.0 years (95% CI 60.2; 61.7) for HPV− patients and 59.3 years (95% CI 58.4; 60.1) for HPV+ patients ($p < 0.05$). A history of smoking was defined as 20 pack years or more, and 70.2% of HPV− patients had a history of smoking compared to only 39.4% of HPV+ patients (Supplementary Table 1). Significantly more HPV− patients had comorbidities compared to HPV+ patients at the time of diagnosis with 55.3% (n = 373/675) of HPV− patients and 36.7% of HPV+ patients (n = 302/824) having comorbidities. The same trend accounts after the cancer treatment with 79.0% of HPV− patients (n = 533/675 and 58.5% of HPV+ patients (n = 482/824) having comorbidities.

Weighted CCI score

At the time of diagnosis 63.4% of HPV+ patients had a CCI score of zero, indicating no comorbidities, compared to 44.7% of HPV− patients (Table 1). HPV− patients were more prone to be found in the categories of a weighted CCI score of one, two, three, and four compared to HPV+ patients with collectively 49.6% of HPV− patients found in one of these categories compared to 27.1% of the HPV+ patients. However, more HPV+ patients were found to have a weighted CCI score of five or more compared to HPV− patients with 9.6% and 5.6% of HPV+ and HPV− patients, respectively. Overall, significantly more HPV+ patients did not have a comorbidity compared to HPV− patients both at the time of cancer diagnosis (RR: 1.4 (95% CI 1.3; 1.6)) and in regards to comorbidities acquired after the cancer diagnosis (RR 1.5 (95% CI 1.4; 1.6)).

At the last follow-up date only 41.5% of HPV+ patients and 21.0% of HPV− patients were categorized as having no comorbidity with a CCI score of zero (Table 2). An increase in number of patients were found for the category of a weighted CCI score of five or more where 20.2% of HPV+ patients and 20.3% of HPV− patients were found after the OPSCC diagnosis with no statistically significant difference between the two HPV groups.

We calculated a modified CCI score, not including secondary

Table 2
Weighted CCI score after cancer diagnosis.

Weighted score	HPV+ count (%)	Median age (95% CI)	Non-smokers* count (%) Unknown smoking history count (U)	HPV− count (%)	Median age	Non-smokers* count (%) Unknown smoking history count (U)	Relative risk (95% CI)	p
0	342 (41.5%)	57.5 (57; 59)	134 (39.2%) U: 24	142 (21.0%)	59 (52;58)	13 (9.2%) U: 17	1.49 (1.36; 1.62)	0.001
1	88 (10.7%)	59 (57; 63)	27 (30.7%) U: 5	87 (12.9%)	62 (59; 67)	7 (8.0%) U: 10	0.9 (0.77; 1.06)	0.2
2	146 (17.7%)	60 (58; 63)	43 (29.5%) U:10	175 (25.9%)	61 (60; 63)	16 (9.1%) U: 14	0.79 (0.69; 0.9)	0.0001
3	65 (7.9%)	62 (59; 65)	15 (23.1%) U: 4	93 (13.8%)	61 (60; 64)	8 (8.6%) U: 6	0.73 (0.6; 0.88)	0.001
4	17 (2.1%)	63 (57; 72)	5 (29.4%) U: 2	41 (6.1%)	64 (59; 66)	2 (4.9%) U: 4	0.52 (0.35; 0.78)	0.002
≥5	166 (20.2%)	59 (57; 61)	53 (31.9%) U: 13	137 (20.3%)	59 (57; 61)	4 (2.9%) U: 10	1 (0.89; 1.12)	0.9
Total	824 (100%)			675 (100%)				

malignancy and metastatic malignancy, to investigate the comorbidity score in HPV+ and HPV− patients not comprising their cancer risk. Overall, both at the time of the cancer diagnosis (Supplementary Table 2) and after the cancer diagnosis we found (Supplementary Table 3) the same trends regarding CCI scores and trends in comparison between HPV+ and HPV− patients (RR) as the calculated CCI score including the cancer risk. We could however not find a significant difference in risk of having a CCI score of 5 or more at the time of diagnosis for HPV+ when excluding malignancy from the CCI score as we found with the CCI score including secondary malignancy.

Comorbidities

We compared the risk of specific comorbidities in patients with OPSCC to a reference group at the time of the cancer diagnosis and at the last day of follow up.

At the time of diagnosis (Table 3) the most common comorbidity in patients with OPSCC was malignancy including leukemia, lymphoma, or localized solid tumor not including the OPSCC diagnosis (n = 290), followed by metastatic malignancy (n = 89) and cerebrovascular disease (n = 88). We found that patients with OPSCC had a significantly higher risk of malignancy compared to the reference population with an OR of 94.4 (95% CI 67.0; 133.0). Further, OPSCC patients had an increased risk of metastatic solid tumor with an OR of 236.5 (95% CI 86.7; 644.9). Besides the increased risk of malignancy a significantly higher risk of cerebrovascular disease (OR: 1.4 (95% CI 1.1; 1.8)), ulcer disease (OR: 1.5 (95% CI 1.2; 2.0)), peripheral vascular disease (OR: 1.6 (95% CI 1.2; 2.1), and liver disease both mild (OR: 4.9 (95% CI 3.7; 6.5)) and severe (OR: 7.3 (95% CI 4.6; 11.7)) were observed for patients with OPSCC compared to the reference population.

When stratified according to HPV-status malignancy was the most frequent comorbidity in both HPV+ (n = 120) and HPV− patients (n = 170). Compared to the reference population, we found a significantly increased risk of malignancy for both HPV+ (OR: 67.1 (95% CI 46.2; 97.4)) and HPV− patients (OR: 99.1 (95% CI 69.1; 142.1)). We further identified an increased risk of metastatic solid tumor in both HPV+ patients compared to the reference population (OR: 304.8 (95% CI 110.6; 840.1) and HPV− patients compared to the reference population (OR: 138.1 (95% CI 47.8; 399.2)) with no significantly difference in the increased risk observed for HPV+ and HPV− patients. Besides malignancy, the only comorbidity with a significant increased risk in HPV+ OPSCC patients was HIV/AIDS with an OR of 4.8 (95% CI 1.8; 12.9). HPV− patients had increased risk of several comorbidities compared to the reference population. The comorbidity found to have the highest increased risk in HPV− patients compared to the reference population was liver disease with an OR of severe liver disease at 13.9 (95% CI 8.5; 22.8) and mild liver disease with an OR of 9.5 (95% CI 7.0; 13.0)). HPV− patients further had an increased risk of cerebrovascular disease (OR: 1.9 (95% CI 1.4; 2.5)), peripheral vascular disease (OR: 2.7 (95% CI 1.9; 3.7)), dementia (OR: 2.9 (95% CI 1.4; 5.8), and ulcer disease (OR: 2.6 (95% CI 1.9; 3.5)). No patients with HPV- OPSCC were found to have AIDS.

The most common comorbidity acquired after the OPSCC treatment in patients with OPSCC continued to be malignancy (n = 349) (Table 4) with more HPV- OPSCC patients having another malignancy besides the OPSCC (n = 227/675, 33.6%) than HPV+ OPSCC patients (n = 172/824, 20.9%). When stratified according to HPV-status we observed that HPV+ OPSCC patients still had increased risks of malignancy, both metastatic (OR: 5.8 (95% CI 4.4; 7.5)) and non-metastatic (OR: 2.0 (95% 1.7; 2.4)) compared to the reference population. HPV+ OPSCC patients furthermore had a significantly lower risk of peripheral vascular disease (OR: 0.5 (95% CI 0.3; 0.9)) compared to the reference population. HPV− patients continued to have increased risk of malignancy, both metastatic (OR: 7.8 (95% CI 6.0; 10.2)) and non-metastatic (OR: 3.8 (95% CI 3.2; 4.5)), liver disease, both mild (OR: 2.1 (95% CI 1.1; 4.2)) and severe (OR: 2.9 (95% CI 1.4; 6.2)), and ulcer disease (OR: 2.0 (95% CI 1.2; 3.3)). In HPV− OPSCC patient we found a significantly lower risk of myocardial infarction after treatment when compared to the reference populating with an OR of 0.3 (95% CI 0.1; 0.7). We found that the risk of diabetes mellitus both with chronic complications (OR: 0.1 (95% CI 0.02; 0.9)) and without chronic complications (OR: 0.3 (95% CI 0.2; 0.7) was significantly lower in patients with HPV− OPSCC.

Malignancy

The most common location of malignancy not including OPSCCs for both HPV+ and HPV− patients was oral cavity cancer applicable both at the time of cancer diagnosis (HPV+ n = 43, HPV− n = 94) and at the last day of follow up (HPV+ n = 51, HPV− n = 105) (Table 5).

At the time of the cancer diagnosis, the second most common cancer location in HPV- OPSCC patients was hypopharyngeal cancer (n = 26). For HPV+ OPSCC patients hypopharyngeal cancer (n = 19) and cancer of the reproductive organs (n = 19) was the second most common location of malignancy. Cancer of the reproductive organs included cervical cancer (n = 2), cancer of the ovary (n = 1), testicles (n = 5), external genitalia (n = 1), and prostate (n = 10).

At the last day of follow up the second most common location of malignancy in HPV− OPSCC patients was lung cancer (n = 45) followed by hypopharyngeal cancer (n = 22). For HPV+ OPSCC patients the second most common cancer location was lung cancer (n = 27) followed by cancer of the skin (n = 22).

Table 3
The odds ratio of specific comorbidities at the time of diagnosis was calculated for patients with OPSCC compared to an age-and sex-matched reference group, for HPV + OPSCC patients compared to the reference group, and HPV − OPSCC patients compared to the reference group.

	Control count	OPSCC count	OR (95% CI)	p-value	HPV+ count	OR HPV + (95% CI)	p	HPV− count	OR HPV − (95% CI)	p-value
Myocardial infarction	587	61	1.04 (0.8; 1.36)	0.8	29	0.9 (0.61; 1.31)	0.6	32	1.22 (0.85; 1.76)	0.3
Congestive heart failure	255	32	1.26 (0.87; 1.83)	0.2	18	1.29 (0.79; 2.08)	0.3	14	1.22 (0.71; 2.1)	0.5
Peripheral vascular disease	372	57	1.55 (1.17; 2.06)	0.002	14	0.68 (0.4; 1.17)	0.2	43	2.68 (1.94; 3.71)	> 0.01
Cerebrovascular disease	644	88	1.39 (1.11; 1.75)	0.005	36	1.02 (0.72; 1.44)	0.9	52	1.86 (1.39; 2.5)	> 0.01
Dementia	70	11	1.58 (0.83; 2.98)	0.2	2	0.52 (0.13; 2.12)	0.4	9	2.88 (1.43; 5.79)	0.003
Chronic pulmonary disease	658	72	1.10 (0.86; 1.41)	0.5	35	0.97 (0.68; 1.37)	0.8	37	1.26 (0.9; 1.78)	0.2
Connective tissue disease	267	28	1.05 (0.71; 1.55)	0.8	19	1.3 (0.81; 2.08)	0.3	9	0.75 (0.38; 1.45)	0.4
Ulcer disease	445	67	1.53 (1.18; 1.99)	0.001	18	0.73 (0.45; 1.18)	0.2	49	2.56 (1.89; 3.48)	> 0.01
Liver Disease - mild	149	70	4.88 (3.65; 6.52)	> 0.01	11	1.35 (0.73; 2.5)	0.3	59	9.54 (6.98; 13.03)	> 0.01
Liver Disease - moderate/severe	43	31	7.34 (4.61; 11.68)	> 0.01	5	2.12 (0.84; 5.37)	0.1	26	13.93 (8.5; 22.8)	> 0.01
Diabetes Mellitus – Uncomplicated	773	77	1.0 (0.78; 1.27)	1.0	52	1.24 (0.93; 1.66)	0.1	25	0.71 (0.47; 1.06)	0.09
Diabetes Mellitus – organ damage	254	27	1.06 (0.71; 1.59)	0.8	20	1.44 (0.91; 2.28)	0.1	7	0.61 (0.28; 1.29)	0.2
AIDS	19	5	2.64 (0.98; 7.07)	0.05	5	4.81 (1.79; 12.92)	0.002	0	0 (0; NaN)	NaN
Hemiplegia	22	1	0.45 (0.06; 3.37)	0.4	1	0.83 (0.11; 6.14)	0.9	0	0 (0; NaN)	NaN
Renal kidney disease – moderate /severe	168	20	1.19 (0.75; 1.90)	0.4	9	0.98 (0.5; 1.92)	1.0	11	1.47 (0.79; 2.72)	0.2
Leukemia, lymphoma, or localized solid tumor	38	290	94.38 (66.96; 133.02)	> 0.01	120	67.07 (46.21; 97.35)	> 0.01	170	99.10 (69.14; 142.05)	> 0.01
Metastatic solid tumor	4	89	236.48 (86.71; 644.91)	> 0.01	62	304.83 (110.61; 840.07)	> 0.01	24	138.12 (47.79; 399.23)	> 0.01

Odds ratio: OR, Confidence interval: CI.

Discussion

This large, population-based study reports that the risk of comorbidities are significantly higher in OPSCC patients compared to an age and sex-matched reference population; and that HPV − patients have an increased risk of higher number of comorbid conditions compared to the reference population as well as to HPV + patients, providing additional evidence of the difference between the two OPSCC groups.

Overall, significantly more HPV + patients had no comorbid condition compared to HPV − patients, both at time of diagnose and at the last day of follow up. It has been proven that HPV-p16 status is an independent predictor of overall survival in OPSCC patients even when adjusted for smoking status, gender, age, and tumor stage [15]. A higher comorbidity score at the time of diagnosis has been associated to poorer survival [25,26], and the fact that HPV − patients have a higher CCI score at the time of diagnosis could be a contributing factor to the poorer survival observed in this patient group compared to HPV + patients [4].

Both HPV + and HPV − patients had an increased risk of malignancy, both metastatic and non-metastatic compared to the reference population. Metastatic disease could likely be OPSCC failures at M-sites or seemingly likely new primary cancers. The high smoking consumption in both HPV-groups could explain the most common location of malignancy (e.g. secondary primary cancer); being oral cavity cancer. A likely bias to this is the misclassification of T-site OPSCC failures being re-classified as new oral cavity cancers–or vice versa.

More HPV − patients had a non-metastatic malignancy than HPV + patients which could be a result of HPV − OPSCC being an alcohol and tobacco associated cancer, risk factors with known oncogenic properties in several organs and is a known cause of several types of cancer including lung cancer [27], breast cancer [28], liver cancer [29] etc. We observed that the second most common location of malignancies in HPV − patients was lung cancer supporting this argument. We further found that hypopharyngeal cancer (n = 22) and esophageal cancer (n = 19) was the third and fourth most common location for secondary malignancy in HPV − OPSCC patients which corresponds to the fact that alcohol and tobacco are risk factors for both OPSCC, hypopharyngeal cancer, and esophageal cancer [30].

The increased risk of malignancy in HPV − patients could be another contributing factor to the improved survival observed for HPV + patients when comparing the groups.

HPV − patients had a significantly higher risk of liver disease compared to the reference population correlated with the fact that alcohol is a dominant risk factor in development of OPSCC [31] and a cause of liver disease. We found that the risk of liver disease, ulcer disease, and cerebrovascular disease were increased in HPV- OPSCC patients and not HPV + OPSCC patients. Comorbidities all connected independently to decrease survival in OPSCC patients [26].

We found that HPV + OPSCC patients had a significantly increased risk of HIV/AIDS compared to the reference population. As both HIV/AIDS and HPV are sexually transmitted viruses, the increased risk could be an indicator of a more promiscuous lifestyle in HPV + patients, however it should be noted that the absolute number of patients with HIV/AIDS was five. These results are similar to other studies describing an increased prevalence of HNC in HIV/AIDS-infected patients [32,33], and it has been proven that the incidence of HPV + OPSCC is higher in HIV-positive patients compared to the general population [34]. These findings have led to the speculations as to whether the increased risk of HNC in HIV-infected patients is related to the HIV-infection or whether it is coincidental [32]. So far, HNC has not been categorized as an AIDS-defining cancer and more studies on this matter are needed. Lastly, it should be noted that treatment of HIV is based on immunosuppression, which could contribute to an increased cancer risk in HIV positive patients.

Interestingly, we found that HPV + patients had a significantly

Table 4
The odds ratio of specific comorbidities acquired from the date of the OPSCC diagnosis to the last date of follow up was calculated for patients with OPSCC compared to an age-and sex-matched reference group, for HPV+ OPSCC patients compared to the reference group, and HPV− OPSCC patients compared to the reference group.

	Control count	OPSCC count	OR (95% CI)	p	HPV+ count	OR HPV + (95% CI)	p	HPV− count	OR HPV− (95% CI)	p
Myocardial infarction	359	18	0.50 (0.3; 0.8)	0.004	13	0.65 (0.37; 1.14)	0.13	5	0.30 (0.13; 0.74)	0.009
Congestive heart failure	322	27	0.84 (0.6; 1.2)	0.4	10	0.56 (0.30; 1.05)	0.07	17	1.18 (0.72; 1.93)	0.52
Peripheral vascular disease	412	27	0.65 (0.4; 0.96)	0.03	12	0.52 (0.29; 0.93)	0.03	15	0.80 (0.48; 1.35)	0.41
Cerebrovascular disease	612	63	1.03 (0.8; 1.3)	0.8	39	1.17 (0.84; 1.63)	0.36	24	0.87 (0.57; 1.31)	0.50
Dementia	134	11	0.82 (0.4; 1.5)	0.5	5	0.68 (0.28; 1.66)	0.39	6	0.99 (0.44; 2.26)	0.99
Chronic pulmonary disease	482	47	0.97 (0.7; 1.3)	0.9	24	0.90 (0.60; 1.37)	0.63	23	1.06 (0.69; 1.63)	0.78
Connective tissue disease	166	11	0.66 (0.4; 1.2)	0.2	8	0.88 (0.43; 1.79)	0.71	3	0.40 (0.13; 1.25)	0.12
Ulcer disease	190	30	1.59 (1.1; 2.4)	0.02	13	1.25 (0.71; 2.20)	0.44	17	2.01 (1.22 ; 3.33)	0.006
Liver Disease - mild	96	12	1.25 (0.7; 2.3)	0.5	3	0.57 (0.18; 1.79)	0.33	9	2.10 (1.05; 4.17)	0.03
Liver Disease - moderate/severe	61	12	1.98 (1.1; 3.7)	0.03	4	11.94 (0.43; 3.29)	0.73	8	2.94 (1.40; 6.16)	0.004
Diabetes Mellitus – Uncomplicated	447	22	0.48 (0.3; 0.8)	0.001	15	0.60 (0.36; 1.01)	0.06	7	0.34 (0.16; 0.72)	0.005
Diabetes Mellitus – organ damage	186	6	0.32 (0.1; 0.7)	0.006	5	0.49 (0.20; 1.18)	0.11	1	0.12 (0.02; 0.85)	0.03
AIDS	3	0	NA		0	NA		0	NA	
Hemiplegia	14	1	0.71 (0.1; 5.4)	0.7	1	1.30 (0.17; 9.90)	0.80	0	NA	
Renal kidney disease – moderate /severe	227	20	0.88 (0.5; 1.1)	0.2	12	0.96 (0.54; 1.72)	0.89	8	0.78	0.5
Leukemia, lymphoma, or localized solid tumor	1767	349	2.27 (2.0; 2.6)	0.0001	172	1.97 (1.66; 2.35)	0.0001	227	3.79 (3.21; 4.48)	0.0001
Metastatic solid tumor	260	158	6.68 (5.4; 8.1)	0.0001	76	5.8 (4.41; 7.51)	0.0001	82	7.83 (6.03; 10.18)	0.0001

Odds ratio: OR, Confidence interval: CI.

lower risk for peripheral vascular disease compared to the reference population, and that HPV− patients had a significantly lower risk of myocardial infarction and diabetes mellitus compared to the reference population at the last day of follow-up. It has been suggested, that a low body mass index is associated to an increased risk of head and neck cancer [35] and that the prevalence of diabetes mellitus decreases with lower body mass index [36] which could explain why HPV− patients had a lower risk of diabetes. The lower risk of peripheral vascular disease in HPV+ patients and the lower risk of myocardial infarction in HPV− patients could be speculated to be due to underdiagnostics of these disease in the two OPSCC patient groups. In parallel with the latter, we did not find a significantly increased risk of chronic pulmonary disease in HPV− patients, which is in contrast to the fact that most HPV− patients had a history of smoking. However, information on comorbidities of OPSCC patients is limited and further studies to elaborate the association between these comorbidities and OPSCC patients are needed.

One of the strengths in this study is that the Danish universal, tax-financed health care systems diminish selection bias. A limitation to our study is that information on comorbidity is based on accuracy of clinicians and misclassifications or coding errors may thus be present. Furthermore, only comorbidities treated at hospitals are included, thus

Table 5
Anatomical location of further malignancies in patients with OPSCC.

	At the time of diagnosis				At the last date of follow up			
	HPV−		HPV+		HPV−		HPV+	
	Count	% of patients	Count	% of patients	Count	% of patients	Count	% of patients
Oral cavity	94	13.9	43	5.2	105	15.6	51	6.2
Hypopharyngeal	26	3.9	19	2.3	22	3.3	13	1.6
Laryngeal	4	0.6	3	0.4	15	2.2	4	0.5
Sinonasal and nasopharynx	1	0.1	1	0.1	2	0.3	7	0.8
Major salivary glands	1	0.1	3	0.4	1	0.1	3	0.4
Thyroid	0	0	0	0	1	0.1	3	0.4
Head and neck Unspecified	5	0.7	1	0.1	15	2.2	3	0.4
Skin	12	1.8	14	1.7	8	1.2	22	2.7
Malignant melanoma	1	0.1	5	0.6	2	0.3	3	0.4
Gastrointestinal canal	15	2.2	3	0.4	21	3.1	18	2.2
Mamma	6	0.9	6	0.7	8	1.2	4	0.5
Female and male genital organs*	11	1.6	19	2.3	1	0.1	16	1.9
Lung	6	0.9	1	0.1	45	6.7	27	3.3
Inner organs	1	0.1	0	0.0	9	1.3	3	0.4
Urinary tract	2	0.3	3	0.4	0	0.0	7	0.8
Blood and lymphatic tissue	3	0.4	6	0.7	5	0.7	6	0.7
Connective tissue	2	0.3	1	0.1	1	0.1	0	0.0
Centrale nervous system	2	0.3	0	0	2	0.3	3	0.4
Peripheral nerves	1	0.1	1	0.1	0	0.0	0	0.0

23 HPV− patients and 9 HPV+ patients had more than one cancer diagnosis at the date of diagnosis. 37 HPV− patients and 19 HPV+ patients had more than one cancer diagnosis at the last day of follow up. 36 patients acquired a malignancy in the same location as they previously had a malignancy before their OPSCC diagnosis.

* Includes cervical cancer, testicular cancer, prostate cancer, penile cancer, cancer of the external genitalia, and cancer of the ovary.

comorbidities treated by a general practitioner may not be registered in DNPR and are thus not to be found in the CCI. A further limitation to our study is the lack of information regarding smoking history among our reference population. Lastly, information on missed treatment days was not included and thus could be a potential limitation to our study as poorly controlled disease could affect the prognosis.

In conclusion, we have demonstrated that the risk of comorbidities is significantly increased in OPSCC patients compared to controls, mostly pronounced in HPV− patients. Patients with HPV- OPSCC carry a much higher burden of competing risk factors for death.

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Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.06.035.

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