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ORIGINAL ARTICLE

Human papillomavirus-driven head and neck cancers in Japan during 2008–2009 and 2018–2019: The BROADEN study

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Abstract

There is limited understanding of epidemiology and time trends of human papilloma virus (HPV)-driven head and neck cancers (HNC) in Japan, especially outside of the oropharynx. To assess HPV-driven HNC, a non-interventional study (BROADEN) of HNC patients diagnosed in 2008–2009 and 2018–2019 was conducted in Japan. Adult patients with oropharyngeal, nasopharyngeal, laryngeal, hypopharyngeal or oral cavity cancers were included in this study. HPV was centrally tested using p16INK4a immunohistochemistry, HPV-DNA PCR and HPV E6*I mRNA. HPV attributability required positivity in at least two tests (p16INK4a immunohistochemistry, HPV-DNA PCR, HPV E6*I mRNA) in the oropharynx, and HPV-DNA and HPV E6*I

Abbreviations: AF, attributable fraction; AJCC, American joint committee on cancer; APC, annual percentage change; BML, biomedical laboratory; DEIA, DNA enzyme immunoassay; DKFZ, Deutsches Krebsforschungszentrum; EBV, Epstein–Barr virus; ERC, ethics review committee; FFPE, formalin-fixed paraffin-embedded; HNC, head and neck cancer; HPV, human papilloma virus; ICO, Institute of Oncology; IHC, immunohistochemistry; IRB, institutional review board; LIPA, line probe assay; NCR, national cancer registry; OPC, oropharyngeal cancer; OR, odds ratio; SCC, squamous cell carcinoma; SPF, short-fragment.

Miquel Angel Pavón and Tim Waterboer contributed equally to this work.

mRNA positivity for non-oropharynx sites. Nineteen hospitals included a total of 1108 patients, of whom 981 had valid samples. Men accounted for 82% of HNC diagnoses. Patients in the earlier cohort were younger and included a higher percentage of smokers. There was an increasing trend of HPV-driven oropharyngeal cancer over the last decade, from 44.2% to 51.7%. HPV attribution in nasopharyngeal cancers was 3.2% in 2008–2009 and 7.5% in 2018–2019; and 4.4% and 0% for larynx respectively. In total, 95.2% of HPV-driven HNC were attributed to HPV genotypes included in the 9-valent HPV vaccine being HPV16 the most prominent genotype. These results suggest that an epidemiologic shift is happening in Japan, with a decrease in smoking and alcohol use and an increase in HPV-driven HNC. The increasing trend of HPV-driven HNC in Japan highlights the need for preventive strategies to mitigate the rise of HPV-driven HNC.

KEYWORDS
HPV attributability, HPV genotype, HPV-driven HNC, HPV-driven vaccine, oropharyngeal cancer

1 | INTRODUCTION

Head and neck cancer (HNC) is the seventh most common cancer worldwide with more than 666,000 new diagnoses and an estimated 325,000 deaths in 2020.[1,2] HNC incidence is two-to-five-fold higher in men versus women.[3,4]

In Japan, the annual incidence of HNC was nearly 27,000 new cases in 2019, with 10,000 deaths reported in 2009.[5–7] Incidence increased from 1993 to 2015,[8,9] with the highest APC observed in OPC at 5.0% and 7.6%, followed by oral cavity cancer at 1.2% and 1.9% for men and women respectively. Hypopharyngeal cancer has also shown an increasing incidence in men (APC of 4.1%), but a downward trend was observed for nasopharyngeal (−2.7%) and laryngeal cancers (−1.1%).[8]

Tobacco use and alcohol consumption are well known risk factors for HNC, especially in Japan and other Asian countries where inactive heterozygous aldehyde dehydrogenase polymorphism is strongly associated with poor outcomes of hypopharyngeal cancer.[10] Importantly, over the last 15 years, HPV infection has emerged as an etiological factor, especially for OPC.[11,12] Data related to HPV attributability of HNC in Japan over time are limited, especially outside the oropharynx.

Previous studies used a variety of biomarkers to assess HPV status and distinguish between HPV-associated and non-HPV-associated HNC such as amplification of viral DNA (HPV-DNA), HPV E6/E7 oncogene transcript detection, *in situ* hybridization targeting both DNA and RNA, and $p16^{INK4a}$ IHC assays.[13,14] Single $p16^{INK4a}$ IHC is highly sensitive in OPC but less specific than a combination of HPV-DNA detection and $p16^{INK4a}$ IHC, or HPV E6/E7 RNA detection to diagnose HPV-driven HNC.[15,16] Noteworthy, $p16^{INK4a}$ is now included in clinical oncology guidelines for HPV assessment in OPC and for clinical decision-making.[17]

Globally, the prevalence of HPV-associated HNC is estimated at 30.8% for OPC, followed by laryngeal (2.4%), and oral cavity (2.2%) cancers.[18] In Japan, some studies have shown the prevalence of HPV-positive OPC to range between 31% and 64%.[19–25] However, a robust HPV attributability definition in HNC has not been defined until now, and numbers provided in different reports derive from different testing techniques. Sensitive and specific HPV diagnostic tests are required to ensure the identification of a genuine HPV-driven oncogenic process rather than a transient or non-related infection.[26] In Japan, most studies describing HPV attributability of HNC are limited by small sample sizes.

The aim of the BROADEN Japan study was to determine the burden of HPV-driven HNC and their associated genotypes in five anatomic sites using a combination of multiple detection methods (HPV-DNA, $p16^{INK4a}$ and E6*I mRNA) in two time periods (2008–2009 and 2018–2019).

2 | MATERIALS AND METHODS

2.1 | Study design and patients

The BROADEN Japan study is part of a large multi-country, non-interventional, cross-sectional study of patients diagnosed with HNC.[27] The present analysis is focused on the burden of HPV-driven HNC in Japan. This study was designed to estimate the fraction of HNC that was attributable to HPV per anatomic site (oropharynx, hypopharynx, larynx, nasopharynx, and oral cavity) during two different time periods (2008–2009 and 2018–2019). Anatomic sites were defined based on International Classification Disease (ICD) codes as previously published.[27] Men and women ≥18 years of age, diagnosed in 2008–2009 or 2018–2019 with a primary HNC and with a pre-treatment biopsy or resection sample obtained as part of regular clinical practice were retrospectively included in this study. A consecutive-retrospective approach was used by hospitals to select patients to avoid any selection bias.

2.2 | Participating hospitals

Patient data were collected from 19 hospitals across Japan (Figure S1). All participating hospitals had a local pathology laboratory or biobank to process the FFPE tissue blocks. Most of the participating hospitals ($n=16$, 84.2%) were university or academic institutions. The total number of patients diagnosed with HNC by anatomic site during the two study periods and the percentage of these patients with FFPE tissue samples available are provided in Table S1. Availability of FFPE tissue samples ranged from 70.6% to 84.2%.

To ensure patient representativeness across participating hospitals, the number of patients with HNC at each anatomic site was defined based on two criteria: (1) the total number of HNC diagnoses by hospital, and (2) the tumor block sectioning method. The number of patients enrolled from self-sectioning institutions was limited to half of the total sample size to maximize the number of FFPE blocks sectioned centrally. The number of patients per anatomical location by each site was provided to the sites before starting the data collection.

2.3 | Determining the fraction of HNC attributable to HPV

HPV-driven OPC was defined by at least two positive tests (HPV-DNA PCR, $p16^{INK4a}$ IHC, or E6*I mRNA PCR). HPV-driven non-OPC was defined by positivity on two tests (HPV-DNA PCR and E6*I mRNA PCR).

2.4 | Data collection

Demographics, tumor characteristics and diagnostic data, smoking status and alcohol consumption were retrospectively collected by participating hospitals via medical record review.[27] Central Laboratories (Catalan ICO, Barcelona, Spain, and German Cancer Research Center DKFZ, Heidelberg, Germany) reassessed and reported the data on the histological diagnosis and performed HPV testing (PCR-DNA, $p16^{INK4a}$, and E6*I mRNA PCR).

The details of tumor block sectioning, HPV-DNA, p16INK4a IHC and HPV E6*I mRNA detection, and quality control applied to the study samples are mentioned in the Appendix S1 section.

2.5 | Statistical analysis

Statistical analyses were conducted using SAS® statistical software. HPV attributable fractions (HPV-AF) were calculated for each anatomic site including all participant hospitals in Japan. The calculation of the fraction of patients with HNC attributable to HPV considered the number of patients with HPV-related cancer, as per the results of the central laboratories, and the total number of patients evaluated within the defined time period. APC of HPV-AF was calculated for OPC using HPV-AF from both study periods. For HPV-driven HNC, HPV genotypes were defined based on E6*I mRNA results for mRNA-positive samples and based on HPV-DNA results for HPV attributable cases with positivity on HPV-DNA and p16INK4a only. Patient and HNC characteristics were described according to HPV status. Age was categorized as ≤53, 54–61, 62–70 and ≥71 years as reported previously.[28] HPV attributable fraction was provided by patient characteristics and HPV genotypes in each anatomic site. Univariable and multivariable logistic regression models were used to assess the relationship between patient characteristics and HPV attributability, presented with OR and adjusted OR, respectively.

3 | RESULTS

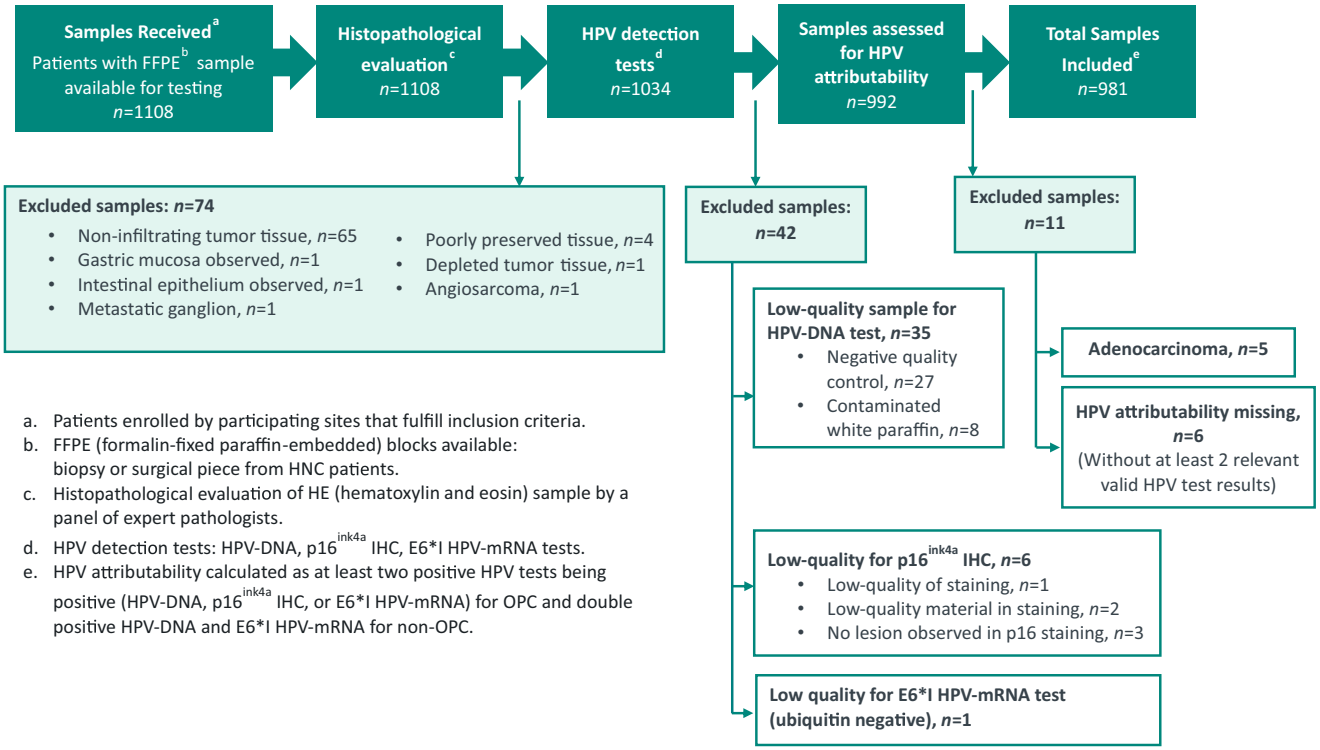
3.1 | Patient demographic and clinical characteristics

In total, 1108 patients were enrolled, of which 981 (456 and 525 from the time periods of 2008–2009 and 2018–2019, respectively) were included in the final analyses. Figure 1 shows a flowchart of cases included in the study, describing the number of HNC patients enrolled, the number with histopathological evaluation, the tissue tested for molecular HPV markers, the reasons for exclusion of samples, and the final number of cases included in statistical analyses. Five patients with adenocarcinoma were recruited into the study but excluded from statistical analyses. All five adenocarcinomas were non-HPV attributable.

Overall, 82.0% of the study population was male ($n=804$). Patients diagnosed with HNC in 2008–2009 were younger compared with those diagnosed in 2018–2019 (mean of 64.3 vs. 67.0 years old, $p<0.001$). A larger proportion of HNC patients from 2008–2009 was current smokers compared with those from 2018–2019 (50.4% vs. 37.0%, $p<0.001$) (Table 1), a difference that was more pronounced among men (from 57.2% to 40.2%, $p<0.01$) than in women (from 17.7% to 23.3%, $p=0.17$). The percentage of heavy drinkers was higher in men (36.0% in 2008–2009 and 39.8% in 2018–2019) than in women (10.2% and 19.1%, respectively) (Tables S2 and S3), with no statistically significant differences by time period. AJCC version 8 was commonly used in the second time period (2018–2019) and tended to provide lower TNM stages compared with the AJCC version 7 as version 8 defines lower TNM stages in patients with $p16^{INK4a}$ positive.

3.2 | HPV attributability based on $p16^{INK4a}$, HPV-DNA and HPV E6*I mRNA

HPV was tested in 478 OPC and 503 non-OPC HNC tumors. In total, 231 OPC tumors were HPV attributable. In total, 211 FFPE samples were positive on all three HPV tests, seven positive on HPV-DNA PCR and E6*I mRNA (two had $p16^{INK4a}$ IHC tests unavailable), five positive on HPV-DNA PCR and $p16^{INK4a}$ IHC, and eight positive on $p16^{INK4a}$ IHC and E6*I mRNA. Among OPC



a. Patients enrolled by participating sites that fulfill inclusion criteria.
b. FFPE (formalin-fixed paraffin-embedded) blocks available: biopsy or surgical piece from HNC patients.
c. Histopathological evaluation of HE (hematoxylin and eosin) sample by a panel of expert pathologists.
d. HPV detection tests: HPV-DNA, $p16^{ink4a}$ IHC, E6*I HPV-mRNA tests.
e. HPV attributability calculated as at least two positive HPV tests being positive (HPV-DNA, $p16^{ink4a}$ IHC, or E6*I HPV-mRNA) for OPC and double positive HPV-DNA and E6*I HPV-mRNA for non-OPC.

FIGURE 1 Flowchart of cases included in the study.

cases, 5.9% of $p16^{INK4a}$ positive samples (14/238) were non-HPV attributable (false HPV attributable) and 2.1% of $p16^{INK4a}$ IHC negative samples (5/233) were HPV attributable (false non-HPV attributable).

Among the seven HPV-attributable nasopharyngeal cancers (NPC), all were positive for all three HPV tests. Among the NPC cases, 30.0% of $p16^{INK4a}$ IHC-positive samples (3/10) were non-HPV attributable (false HPV attributable) and none of the $p16^{INK4a}$ IHC negative samples (0/114) were HPV attributable (false non-HPV attributable). Two laryngeal cancers were HPV attributable, one with positivity to all three HPV tests and one with HPV-DNA PCR and E6*I mRNA PCR positive results. Among the 11 oral cavity cases and five hypopharynx cases with $p16^{INK4a}$ IHC positive, all were non-HPV attributable (false HPV attributable). A description of HPV attributability based on results obtained in HPV-DNA PCR, $p16^{INK4a}$ and E6*I mRNA is provided in Table 2.

3.3 | HPV attributability by anatomic site of HNC and time period

There was an increasing trend of HPV attribution among OPC cases over the last decade, from 44.2% (95% CI: 37.5%, 51.1%; 2008–2009) to 51.7% (95% CI: 45.5%, 57.9%; 2018–2019), but this difference was not statistically significant (Figure 2). APC for HPV-attributable OPC of 1.6% per year was observed. This trend was mostly observed among men, with an HPV-AF of 41.6% (95% CI: 34.4%, 49.1%) in 2008–2009 and 51.6% (95% CI: 44.8%, 58.3%) in 2018–2019. Among women, the HPV-AF was 59.4% (95% CI: 40.6%, 76.3%) in 2008–2009 and 52.5% (95% CI: 36.1%, 68.5%) in 2018–2019 (Figure S2).

Compared with OPC cases, a lower percentage of NPC was attributable to HPV with 3.2% and 7.5% in 2008–2009 and 2018–2019, respectively. In 2008–2009, 4.4% of laryngeal cancers were HPV attributable, but no HPV-attributable cases were observed in 2018–2019 (Figure 2). No cases of hypopharynx and oral cavity type HNC were HPV attributable in either study time period.

3.4 | Histopathological diagnosis

The most common histopathological diagnoses among OPC were keratinizing SCC (192), non-keratinizing SCC (147) and basaloid SCC (106) with HPV-AF of 28.1%, 57.1%, and 75.5% respectively. NPC were mainly non-keratinizing SCC (89), and only 3.4% of those were HPV driven. Laryngeal and oral cavity cancers were mainly keratinizing SCC (65 and 161, respectively), but none of those cancers was HPV driven. Hypopharyngeal cancers were mainly non-keratinizing SCC and keratinizing SCC, but none of them was HPV-driven (Table S4).

3.5 | HPV genotypes

Among HPV-positive HNC cases, HPV genotypes included in the 9-valent vaccine were detected in 94.6% of HNC overall, and 95.2%

TABLE 1 Description of demographic, behavior, and clinical characteristics of Japanese patients during the two study time periods.

Time period	Overall (*N* = 981)	2008–2009 (*N* = 456)	2018–2019 (*N* = 525)	*p*-value*
Gender *n* (%)				
Male	804 (82.0%)	374 (82.0%)	430 (81.9%)	0.9635
Female	177 (18.0%)	82 (18.0%)	95 (18.1%)	
Age				
Mean (SD)	65.7 (11.9)	64.3 (11.8)	67.0 (11.8)	0.0001
Age (categorical)				
≤53 years	145 (14.8%)	69 (15.1%)	76 (14.5%)	0.0005
54–61 years	186 (19.0%)	107 (23.5%)	79 (15.0%)	
62–70 years	283 (29.9%)	141 (30.9%)	152 (29.0%)	
≥71 years	357 (36.4%)	139 (30.5%)	218 (41.5%)	
Smoking status *n* (%)				
Current smoker	354 (42.8%)	181 (50.4%)	173 (37.0%)	<0.0001
Ex-smoker	259 (31.3%)	87 (24.2%)	172 (36.8%)	
Non-smoker	214 (25.9%)	91 (225.3%)	123 (26.3%)	
Alcohol consumption *n* (%)				
Heavy drinker	308 (34.3%)	122 (32.0%)	186 (36.0%)	0.4309
Occasional drinker	323 (36.0%)	144 (37.8%)	179 (34.7%)	
Non-drinker	266 (29.7%)	115 (30.2%)	151 (29.3%)	
TNM version at HNC diagnosis				
TNM version 7	404 (41.2%)	360 (78.9%)	44 (8.4%)	<0.0001
TNM version 8	577 (58.8%)	96 (21.1%)	481 (91.6%)	
TNM stage (version 7)				
Stage I	37 (9.3%)	33 (9.3%)	4 (9.1%)	0.2114
Stage II	90 (22.6%)	85 (24.0%)	5 (11.4%)	
Stage III	80 (20.1%)	67 (18.9%)	13 (29.5%)	
Stage IVa	153 (38.4%)	133 (37.6%)	20 (45.5%)	
Stage IVb	27 (6.8%)	26 (7.3%)	1 (2.3%)	
Stage IVc	11 (2.8%)	10 (2.8%)	1 (2.3%)	
Missing (*N*)	5	6	0	
TNM stage (version 8)				
Stage I	137 (24.6%)	15 (16.7%)	122 (26.1%)	0.3122
Stage II	128 (22.9%)	25 (27.8%)	103 (22.0%)	
Stage III	111 (19.9%)	20 (22.2%)	91 (19.4%)	
Stage IVa	139 (24.9%)	25 (27.8%)	114 (24.4%)	
Stage IVb	36 (6.5%)	5 (5.6%)	31 (6.6%)	
Stage IVc	7 (1.3%)	0 (0.0%)	7 (1.5%)	
Missing (*N*)	19	6	13	

Abbreviations: HNC, head and neck cancer; SD, standard deviation; TNM, tumor, node, and metastasis.

*p-value corresponding to the comparison of patient characteristics between time periods for each variable.

of OPC, 71.4% of NPC, and 100% of laryngeal cancers. HPV16 was the most predominant HPV genotype detected among HPV attributable OPC (90.0%). Other HPV types identified in OPC were HPV58 (2.2%), HPV18 and HPV35 (1.7% each), and HPV56 (1.3%). Among NPC, HPV18 (42.9%), followed by HPV16 (28.6%) were the predominant HPV genotypes detected. In HPV-driven larynx cancers HPV31 and HPV52 were identified (Table 3).

3.6 | Factors associated with HPV attributability in OPC

Factors associated with OPC HPV attribution were assessed in the combined cohort of patients from the two study time periods. Among OPC patients, younger age, non-smoker status and less alcohol consumption were significantly associated with higher HPV-AF.

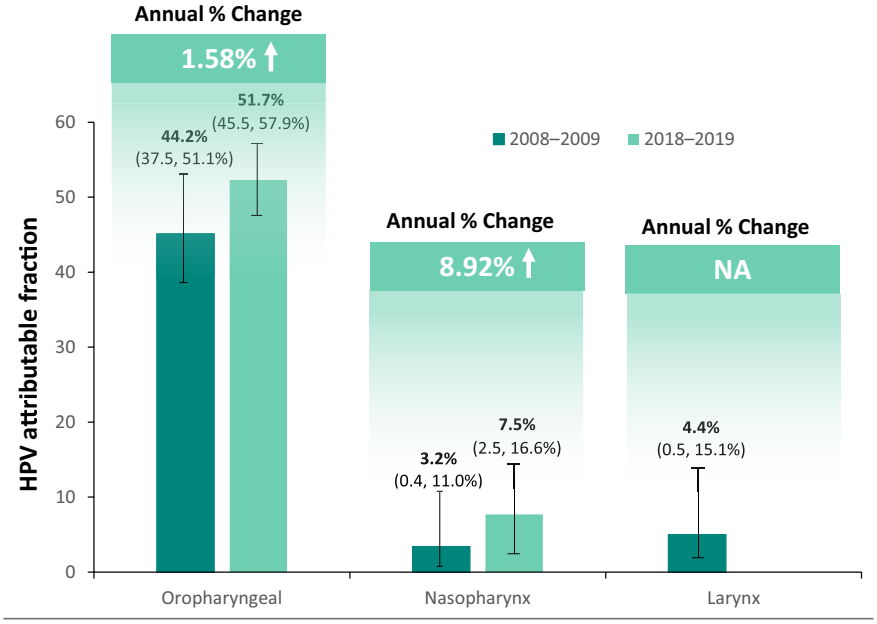
TABLE 2 Description of HPV attributability based on results obtained in DNA, $p16^{INK4a}$ and E6*I mRNA.

	DNA result	$p16^{INK4a}$ result	E6*I mRNA result	HPV attributability		Number (%) of patients		
OPC cancers						**OPC ($n=471$)**		
	+	+	+	Attributable		211 (44.8%)		
	+	+	−	Attributable		5 (1.1%)		
	+	−	+	Attributable		5 (1.1%)		
	+	NA	+	Attributable		2 (0.4%)		
	−	+	+	Attributable		8 (1.7%)		
	+	−	−	Non-attributable		4 (0.8%)		
	−	+	−	Non-attributable		14 (3.0%)		
	−	−	+	Non-attributable		1 (0.2%)		
	−	−	−(10%)/NA[a]	Non-attributable		17 (3.6%)/204 (43.3%)		
Non-OPC cancers					**Nasopharynx ($n=124$)**	**Larynx ($n=88$)**	**Hypopharynx ($n=91$)**	**Oral cavity ($n=174$)**
	+	+	+	Attributable	7 (5.6%)	1 (1.1%)	0	0
	+	−	+	Attributable	0	1 (1.1%)	0	0
	+	+	−	Non-attributable	0	0	0	0
	+	−	−	Non-attributable	4 (3.2%)	2 (2.3%)	0	2 (1.1%)
	−	+	+	Non-attributable[b]	0	0	1 (1.1%)	1 (0.6%)
	−	+	−	Non-attributable	3 (2.4%)	1 (1.1%)	4 (4.4%)	10 (5.7%)
	−	−	+	Non-attributable	0	0	0	1 (0.6%)
	−	−	−(10%)/NA[a]	Non-attributable	14 (11.3%)/96 (77.4%)	8 (9.1%)/75 (85.2%)	12 (13.2%)/74 (81.3%)	15 (8.6%)/145 (83.3%)

Abbreviations: HPV, human papillomavirus; NA, not available; OPC, oropharyngeal cancer.

[a]RNA was only tested in 10% of samples negative for both DNA and $p16^{INK4a}$.

[b]Attributable for HPV sensitivity analysis.



HPV-driven	96	135	2	5	2	0
Total	217	261	63	67	45	49

No cases of hypopharynx and oral cavity type HNC were HPV attributable in either study time period

FIGURE 2 HPV attributable fraction by anatomic sites of HNC in two time periods. Numerator for the calculation of the HPV-AFs was the subset of patients diagnosed with HNC attributable to HPV based on positivity to at least two test (HPV-DNA PCR, $p16^{INK4a}$ IHC and/or E6*I mRNA PCR) for OPC and positivity on HPV-DNA PCR and E6*I mRNA PCR for non-OPC. The denominator was the total number of patients diagnosed with HNC and tested for HPV by the central laboratory in 2008–2009 and 2018–2019.

TABLE 3 HPV genotypes identified in study samples determined by central laboratory.

	HPV-driven OPC ($N = 231$)	HPV-driven nasopharynx cancer ($N = 7$)	HPV-driven larynx cancer ($N = 2$)
HPV genotypes			
HPV11	1 (0.4%)	0	0
HPV16	208 (90.0%)	2 (28.6%)	0 (0.0%)
HPV18	4 (1.7%)	3 (42.9%)	0 (0.0%)
HPV31	0 (0.0%)	0 (0.0%)	1 (50.0%)
HPV33	2 (0.9%)	0	0
HPV35	4 (1.7%)	1 (14.3%)	0
HPV39	1 (0.4%)	0	0
HPV45	1 (0.4%)	0	0
HPV52	1 (0.4%)	0	1 (50.0%)
HPV56	3 (1.3%)	0	0
HPV58	5 (2.2%)	0	0
HPV59	0	1 (14.3%)	0
HPV74	1 (0.4%)	0	0
HPV untypable (identified in DNA)	3 (1.3%)	0	0
High-risk 9-valent vaccine	220 (95.2%)	5 (71.4%)	2 (100.0%)

Note: Three HPV-driven OPC patients presented co-infection with more than 1 HPV genotype confirmed with mRNA: 1 patient presented co-infection with HPV16 and HPV18, one patient with HPV16 and HPV35, and one patient with HPV11 and HPV16. One additional patient presented co-infection with HPV16 and HPV18 based on DNA, but co-infection was not confirmed with mRNA.

Abbreviations: HNC, head and neck cancer; HPV, human papillomavirus; OPC, oropharyngeal cancer.

HPV-AF was higher in patients diagnosed at younger ages, ranging from 66.1% in patients diagnosed below 54 years old to 40.6% in patients diagnosed over 71 years old ($p < 0.001$). HPV-AF was also higher in non-smokers compared with current smokers (68.3% vs. 37.9%) ($p < 0.001$) and non-drinkers or occasional drinkers compared with heavy drinkers (63.8% vs. 37.3%) ($p < 0.001$). Adjusted OR derived from the multivariable logistic regression model confirmed younger age, non-smoker status and less alcohol consumption as factors associated with higher HPV-AF (Table 4). Additional subanalyses were performed by time period (Tables S5 and S6) and gender (Tables S7 and S8). Similar risk factors were observed in both time periods and genders with a higher statistical significance in 2018–2019 and in men, probably due to the higher number of patients.

4 | DISCUSSION

The BROADEN study highlights the increasing trend in the incidence of HPV-driven OPC over time in Japan (from 44.2% during 2008–2009 to 51.7% during 2018–2019) using a stringent HNC classification and robust methodology. These results are aligned with prior smaller studies, showing that the incidence of HPV-positive cancer has been increasing in Japan in the last few decades.[29–31] This is the first study performed in an Asian country, Japan, showing the same epidemiological trend of HPV-driven HNC as in Europe and the United States.[12,32,33]

The increase in HPV-driven OPC observed in this study might continue in the future. In 2019, 4551 patients were newly diagnosed with OPC according to the NCR in Japan (3579 men and 972 women). Applying the HPV-AF obtained in the second time period in BROADEN to the HNC cases reported in the NCR in 2019, it is estimated that 2380 OPCs (1872 men and 508 women) were HPV driven in Japan. This number is projected to increase to a total of 4851 (3588 men and 1263 women) by 2029 [assuming an APC of OPC of 5% in men and 7.4% in women,[8] and the APC of HPV attributable OPC derived from this study (1.5%/year)]. This increasing trend over time mainly impacts men, with the global incidence of OPC more than 2.5-fold higher in the male versus female population.[3,4,34] Changes in sexual practices, including the earlier age of sexual initiation, increased number of sexual partners, and increasing practice of oral sex may be driving oral-HPV infection and development of HPV-related HNC.[32,33] Conversely, a decrease in HNC due to smoking and alcohol use was observed in Japan.

In Japan, there is limited evidence about HPV attributability at other anatomic sites and one strength of the current study is that non-OPC are included for HPV attributability.[24] This study shows that in 2008–2009 HPV attributable cancers were identified in larynx (4.4%) and nasopharynx (3.2%), while in 2018–2019 were only

TABLE 4 HPV attributable OPC by demographic and behavior characteristics of OPC patients according to HPV attributability and OR obtained from univariable and multivariable analysis.

OPC	HPV attributable ($N = 231$)	OR (95% CI)	Adjusted OR[b] (95% CI)
Gender *n* (%)			
Male	191 (47.0%)	Reference	Reference
Female	40 (55.6%)	1.41 (0.85, 2.33)	0.60 (0.32, 1.15)
Age at HNC diagnosis			
Mean (SD)	65.0 (11.0)	0.77 (0.65, 0.92)[a,**]	–
Age at HNC diagnosis *n* (%)			
≤53 years	37 (66.1%)	Reference	Reference
54–61 years	50 (52.1%)	0.56 (0.28, 1.11)	0.64 (0.30, 1.37)
62–70 years	73 (48.3%)	0.48 (0.25, 0.91)*	0.47 (0.23, 0.98)*
≥71 years	71 (40.6%)	0.35 (0.19, 0.66)**	0.26 (0.12, 0.56)***
Smoking status *n* (%)			
Current smoker	64 (37.9%)	0.28 (0.17, 0.48***	0.27 (0.15, 0.50)***
Ex-smoker	54 (42.9%)	0.35 (0.20, 0.60)***	0.41 (0.23, 0.74)**
Non-smoker	69 (68.3%)	Reference	Reference
Unknown	44	–	–
Alcohol consumption *n* (%)			
Heavy drinker	59 (37.3%)	0.35 (0.21, 0.56)***	0.41 (0.23, 0.71)**
Occasional drinker	66 (45.5%)	0.48 (0.30, 0.79)**	0.58 (0.33, 1.02)
Non-drinker	81 (63.3%)	Reference	Reference
Unknown	25	–	–

Note: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. [a]OR provided for each increase of 10 years in age.
[b]Adjusted OR derived from multivariable logistic regression model. Multivariable model only includes age reported as categorical variable, not as continuous variable.

Abbreviations: CI, confidence interval; HNC, head and neck cancer; HPV, human papillomavirus; OPC, oropharyngeal cancer; OR, odds ratio; SD, standard deviation.

identified in nasopharynx (7.5%). Interestingly, no HPV-AF was observed in oral cavity and hypopharynx cancer even though previous studies reported a possible association with HPV. The lack of HPV-driven oral cancers can be explained by the stringent selection of ICD codes in BROADEN study to avoid tumor site misclassification, especially for "Tongue NOS" that represents an uninterpretable mixture of oropharynx and oral cavity tumors.[21] The use of different criteria to define HPV status limits the comparability of results between studies, and explains the differences seen between the BROADEN Japan study and prior studies.

HPV attributability is an important factor to consider clinically. HPV is usually assessed in OPC using $p16^{INK4a}$ IHC, which supports clinical decision-making.[17] The BROADEN study showed excellent concordance between $p16^{INK4a}$ positivity and HPV attributability in OPC. In non-OPC, there is a lack of a standard definition of HPV attributability. $p16^{INK4a}$ IHC as the sole method to detect HPV attributability in non-OPC has been dismissed by the scientific and medical community as it is not clear whether $p16^{INK4a}$ immunoreactivity indicates oncogenic HPV infection or risk of progression.[35] The BROADEN study also shows a high percentage of false HPV-attributable cases (71.4%) when $p16^{INK4a}$ is the only criteria to be used in HNC outside OPC, reinforcing the low predictive value of $p16^{INK4a}$ IHC as an HPV biomarker in non-OPC.

Previous smaller studies have shown that HPV16 was present in 67.8% to 91.1% of OPC HPV-positive samples.[21,23] BROADEN Japan confirms these previous results (90.0%). Outside of HPV16, other genotypes were more common in non-OPC (HPV31, HPV52, HPV35 and HPV59), which supports the variability in genotypes that has been observed in prior studies.[32,36,37] Among the HPV-attributable HNC, the BROADEN Japan study found that 95.2% of cases are attributable to HPV types targeted by the 9-valent HPV vaccine. Without any preventive measures in place, HNC is likely to continue to increase in Japan. This is especially important to consider in this country where the HPV vaccination program has only been implemented in girls, leaving men at continued risk of the vaccine-preventable HPV types associated with these cancers.

The study has certain limitations that need to be considered. Although the number of participant hospitals was large and distributed across the country, participant hospitals may not be fully representative of all those in Japan. Due to the epidemiology of the disease, a low number of women were included, limiting the precision of HPV attributability analysis by gender. The combination of multiple testing techniques used in the BROADEN study makes the comparison with previous Japanese studies challenging. Like HPV, EBV, is known to be associated with nasopharyngeal cancer. However, EBV data are not systematically reported in clinical patient charts and no data related to EBV were collected in this study.

The BROADEN study also has several strengths that minimize the impact of the mentioned limitations. This study included a combination of HPV testing methods, with centralization and quality control of the entire process overseen by an international scientific group of advisers. The quality control process allowed the identification and exclusion of samples with DNA quality issues and avoided false HPV-negative results, which may be expected to be more frequent in older samples. The exclusion of these samples discards the possibility of explaining differences in HPV attributability between periods due to test sensitivity or tissue conservation issues. Centralized FFPE tissue block sectioning, certification of the sectioning process, as well as the testing of blank paraffin blocks were performed to minimize the risk of cross-contamination and potentially false-positive results in PCR-based HPV testing methods. Two characteristics of the sample population observed in the study support the representativeness of the study sample. Large values obtained in terms of sample availability confirm the inclusion of most patients with HNC diagnosis, with low risk of selection bias associated with the availability of tissue samples. Older age at HNC diagnosis, especially in the second study time period, is consistent with increasing life expectancy in Japan. Interestingly, in the United States, the burden of HPV-related OPC is now shifting to older ages suggesting continued persistence of oral-HPV infections, with possibly greater penetrance at older ages.[38]

This study is the largest and most comprehensive assessment of HPV attribution in HNC conducted in Japan. This study highlights the burden of HPV in HNC, especially in oropharyngeal and nasopharyngeal cancers. HPV-AF is highest in OPC reaching 51.7% in 2018–2019. If HPV-driven HNC continues to increase in Japan, especially in men for whom alcohol and smoking behaviors are decreasing, the burden will be substantial in the future.

AUTHOR CONTRIBUTIONS

Ken-ichi Nibu: Investigation; supervision; writing – review and editing. **Nobuhiko Oridate:** Conceptualization; methodology; writing – review and editing. **Yuki Saito:** Investigation; writing – review and editing. **Montserrat Roset:** Conceptualization; data curation; formal analysis; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Marta Fores Maresma:** Project administration; writing – original draft; writing – review and editing. **Daniel Cuadras:** Data curation; formal analysis. **Edith Morais:** Conceptualization; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Craig Roberts:** Conceptualization; methodology; writing – review and editing. **Ya-Ting Chen:** Writing – review and editing. **Jacque Spitzer:** Project administration; writing – original draft; writing – review and editing. **Kayo Sato:** Writing – review and editing. **Itori Saito:** Writing – review and editing. **Ichiro Tazaki:** Writing – review and editing. **Omar Clavero:** Investigation; writing – review and editing. **Lea Schroeder:** Investigation; writing – review and editing. **Laia Alemany:** Conceptualization; investigation; methodology; writing – review and editing. **Hisham Mehanna:** Conceptualization; methodology; writing – review and editing. **Haitham Mirghani:** Conceptualization; methodology; writing – review and editing. **Anna R. Giuliano:** Conceptualization; methodology; writing – review and editing. **Miquel Angel Pavón:** Conceptualization; investigation; methodology; writing – review and editing. **Tim Waterboer:** Conceptualization; investigation; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors report the conflicts of interest as follows: KN and NO reported support from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway NJ, USA (MSD) during the conduct of the study; M.R., M.F., and D.C. reported being an employee of IQVIA during the conduct of the study; E.M. reported being an employee of MSD France and stockholder in Merck & Co., Inc., Rahway, NJ, USA during the conduct of the study; C.R. and Y.T.C. reported being an employee and stockholder of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA during the course of the study; J.S. reported being an employee of Merck & Co., Inc. during the conduct of the study; K.S. and I.T. reported being an employee of MSD K.K., Tokyo, Japan and stockholder of Merck & Co., Inc., Rahway, NJ, USA during the course of the study; I.S. reported being an employee of MSD K.K., Tokyo, Japan during the conduct of the study; O.C., L.A. and M.P. reported support to his institution from MSD, Roche, GSK, IDT, Hologic, and Seegene; in addition, L.A. and M.P. reported receiving consulting fees, honoraria, and support for attending meetings and participation on an Advisory Board from MSD, Inc for the conduct of this study; Hi.M. reported receiving consulting fees, honoraria, and support for attending meetings and participation on an Advisory Board from MSD, Inc for the conduct of this study, other grants and honoraria from AstraZeneca, Seagen, and Nanobiotix, and stockholder of Warwickshire Head Neck Clinic and Docspert; Ha.M. reported receiving consulting fees, honoraria, and support for attending meetings and participation on an Advisory Board from MSD; A.G. reported receiving consulting fees, honoraria, and support for attending meetings and participation on an Advisory Board from MSD for the conduct of this study; L.S. declare no potential competing interests; T.W. serves on advisory boards from MSD; No other disclosures were reported.

ETHICS STATEMENTS

Approval of the research protocol by an Institutional Reviewer Board: The BROADEN Japan study was approved by the IRB/ERC from each of the participating hospitals. This study was also conducted in compliance with the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: All patients received the consent form adhering to IRB/ERC requirements, laws, and sponsor requirements. Waivers for patient informed consent were obtained according to local regulations. In cases in which waivers were not applicable, the investigator obtained consent in writing or by other appropriate methods from living patients or next of kin for deceased patients.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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