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High incidence of multiple primary carcinomas in HCV--infected patients with oral squamous cell carcinoma

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Hepatitis C virus (HCV) infection has been associated with several extrahepatic manifestations. Oral cancer is one of them. We investigated the association among oral squamous cell carcinoma (OSCC), multiple primary cancers (MPCs), insulin resistance and HCV infection.

Material/Methods: Upper gastrointestinal tract examination and determination of the presence of HCV infection were routinely done for 60 primary OSCC patients. Occurrence of MPCs was evaluated between 1992 and 2008.

Results: Of the 60 patients, 21 (35%: 15 males and 6 females; mean age 67.3±11.9 years) developed MPCs. Antibodies to HCV were found in 26.7% (16/60) of cases. The incidence of MPCs in HCV-infected OSCC cases was 62.5% (10/16 cases, P<0.01 vs the non-HCV-infected OSCC group); for cases without HCV infection it was 25% (11/44 cases). In HCV-infected cases, 10 MPCs with patients, hepatocellular carcinoma (HCC) was the most common outcome (5 cases), whereas gastric cancer was the most common outcome (6 cases) in non-HCV-infected 11 MPCs. In logistic regression analysis, the adjusted odds ratios on staging IV, anti-HCV positive, and over 70 years old were 15.50, 13.45, and 4.46, respectively, indicating that there were significant differences. Furthermore, the patients with HCV-infected MPCs had hyperinsulinemia.

Conclusions: HCV infection was strongly associated with the occurrence of MPCs as well as primary OSCC. HCV-infected OSCC patients in Japan should receive medical treatment to inhibit development of HCC. In patients with HCV infection, it is important to clinically examine organs other than the liver.

key words: **multiple primary cancers (MPCs) • oral squamous cell carcinoma (OSCC) • hepatitis C virus (HCV) • hepatocellular carcinoma (HCC) • lichen planus • insulin resistance • extrahepatic manifestations**

Abbreviations: **anti-HCV** – anti-bodies to HCV; **anti-HBc** – antibody to hepatitis B core antigen; **CLEIA** – chemiluminescent enzyme immunoassay; **HBsAg** – hepatitis B surface antigen; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **HOMA-IR** – homeostasis model assessment; **IFN** – interferon; **MPCs** – multiple primary cancers; **OSCC** – oral squamous cell carcinoma

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Background

The development of multiple primary cancers (MPCs) is frequently detected in patients with oral squamous cell carcinoma (OSCC). Patients with OSCC are at risk of developing second cancers or MPCs, particularly at sites within the upper digestive tract and airway [1,2]. Routine upper gastrointestinal panendoscopy identifies synchronous MPCs in 9–14% of patients [3].

In recent years in Japan, there has been an upward trend in MPCs in patients with head and neck cancer [4]. The reasons behind this are increases in carcinoma itself, progress in diagnostic techniques, improvements in treatment outcomes, and increased mean survival time.

Since 1981, malignant neoplasms have been the leading cause of death in Japan. During the past 20 years, primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), has ranked third in men and fifth in women in Japan as the cause of death from malignant neoplasms [5]. The number of deaths from HCC is expected to increase by 2010–15 [6]. Of the HCC cases in Japan, ~16% are caused by hepatitis B virus (HBV) infection and~80% by hepatitis C virus (HCV) infection. The increase in incidence of HCC in Japan has largely been attributable to HCV infection. Geographically, HCC is more frequent in western than eastern Japan.

HCV infection has also been associated with extrahepatic manifestations and immune-mediated phenomena [7]. For example, HCV is associated with the development of OSCC. We reported for the first time an association between HCV and OSCC [8], and provided evidence, at the national level in Japan, for the high prevalence of HCV infection in patients with OSCC [9]. The subjects included 305 patients with OSCC and 276 patients with non-malignant disease (the control group) from five geographically-distinct institutions. The incidence of HCV infection in Japanese OSCC patients has been reported as 16.7–24.0% [8,9]. We also investigated the prevalence of HCV infection in oral cancer patients with MPCs [10]. Of 327 patients with OSCC, 59 (18.0%) exhibited MPCs. In the OSCC patients with MPCs, serum HCV antibodies (anti-HCV) and HCV RNA were detected in 36.7% and 28.6%, respectively [10].

Meanwhile, insulin resistance emerges as a very important host factor in patients with chronic hepatitis C. Hyperinsulinaemia is associated with accelerated HCC growth [11]. We concluded that HCV infection induces insulin resistance, which causes an increase in the incidence of extrahepatic manifestations such as lichen planus in HCV-infected individuals [12,13]. Lichen planus is an inflammatory disease of the skin and oral mucosa. The HCV infection rates in lichen planus patients are high especially in Japan [14]. Oral lichen planus should be considered as a precancerous lesion, particularly in patients presenting HCV infection [15]. Prevalence of smoking history, presence of hypertension, extrahepatic malignant tumor, and insulin resistance were significantly higher in 17 patients with lichen planus than in 70 patients without lichen planus [13].

In the current study, we surveyed the incidence of MPCs in OSCC patients with or without HCV infection and investigated the relationship between OSCC and insulin resistance.

Material and Methods

Subjects

This retrospective study included 60 primary OSCC patients who had visited our clinic at the Kurume University Hospital in Japan for the first time between November 1992 and December 1994. The 60 patients with OSCC included 39 males and 21 females. Their ages ranged from 32 to 85 years, with an average age of 64.8±13.7 years. These patients resided in the northern Kyushu region of Japan where the prevalence of HCV infection is the highest in the country [5,16]. The stages of OSCC were as follows; stage I (15 cases), II (24), III (6), and IV (15).

MPCs were identified according to the definition proposed by Warren and Gates: there must be histological evidence of malignancy in each tumor, they must be separated from each other by normal tissue, and one tumor must not be a metastasis of another [17]. Patients with multiple OSCCs were excluded from the study. MPCs detected <6 months after OSCC diagnosis were defined as synchronous; those detected >6 months after diagnosis were defined as metachronous [17].

Methods

Upper gastrointestinal tract examinations were routinely performed in all OSCC patients using an endoscope. This was done on the first visit or first day of medical treatment in order to confirm the presence of MPCs such as carcinomas of the larynx, pharynx, esophagus, and stomach regardless of whether symptoms were present.

Sera from all 60 OSCC patients were used for the following liver function tests at the time of the first visit to our hospital: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), total protein (TP), and albumin (Alb). Sera were also examined for the presence or absence of HCV or HBV infection. Anti-HCV antibodies and hepatitis B virus surface antigen (HBsAg) were measured by a chemiluminescent enzyme immunoassay (CLEIA) kit and a chemiluminescent immunoassay (CLIA), respectively. In 59 of 60 patients, HCV RNA in serum was detected using the Amplicore HCV test. In 58 of 60 patients, antibody to hepatitis B core antigen (anti-HBc) was found using a CLEIA kit. Ultrasonographic examination for all subjects was performed in order to examine the shape of the liver and lesions occupying the liver. Computed tomography and liver biopsy were performed in some patients.

Plasma glucose levels were measured by a glucose oxidase method for all subjects and serum insulin levels were measured using a sandwich enzyme immuno assay kit (EIKEN CHEMICAL, Tokyo, Japan). Insulin resistance was calculated on the basis of fasting levels of plasma glucose and insulin, according to the homeostasis model assessment (HOMA-IR) method [18]. The formula for the HOMA-IR is: HOMA-IR = fasting glucose (mg/dL) × fasting insulin (μU/mL)/405.

Their district, a history of liver dysfunction, blood transfusion, alcohol consumption, and smoking at the time of the first medical examination were collected as background information; OSCC was based upon their medical record cards.

Table 1. Incidence difference of MPCs depend on the presence or absence of HCV infection.

		Anti-HCV negative n=44 (%)		Anti-HCV positive n=16 (%)		P value A versus B
Age	Mean (year) ±SD	64.3±14.5		66.1±11.0		NS
Sex	Male	30	(68.2)	9	(56.2)	NS
	Female	14	(31.8)	7	(43.8)	
MPCs	Number	11	(25.0)	10	(62.5)	p<0.01
	Primary oral SCC					
	Tongue	2	(18.2)	6	(60.0)	
	Gingiva	5	(45.5)	3	(30.0)	
	Buccal mucosa	2	(18.2)	0	(0.0)	
	Sinus	1	(9.1)	0	(0.0)	
	Oropharynx	1	(9.1)	1	(10.0)	
	Number of MPCs					
	Double		(81.8)	10	(100.0)	
	Triple		(9.1)	0	(0.0)	
	Quadruple		(9.1)	0	(0.0)	
	Organ of MPCs	Stomach	6	Liver	5	
		Esophagus	2	Colon	2	
		Skin	2	Lung	1	
		Thyroid	1	Throid	1	
		Pharynx	1	Bone marrow*	1	
		Kidney	1			
		Liver	1			
		Total	14	Total	10	
	Occurrence time					
	Synchronus		6		5	
	Metachronus		6**		5	

* Acute myeloid leukemia (AML); ** One patient with quadruple cancer had cancer of the gingiva-esophagus (synchronous)-skin (synchronous)-hypopharynx (metachronous). SD – standard deviation; NS – no significance.

We observed the occurrence of MPCs from the first medical examination day to the last check-up day or nearest day preceding October 17, 2008. MPCs were diagnosed based on histopathology by the pathology laboratory which collected samples from all other medical departments of our hospital; or the diagnosis was made at other medical institutions.

Furthermore, the 60 patients whom we followed were divided into four groups: (i) MPCs with HCV infection, (ii) MPCs without HCV infection, (iii) non-MPCs with HCV infection, (iv) non-MPCs without HCV infection. We examined insulin resistance in these four groups.

Statistical analysis

All data are expressed as mean ± standard error. Differences between two groups were analyzed using the Mann-Whitney U test and the Chi-square test. Differences were judged significant for $p<0.05$ (two-tailed). Adjusted odds ratios were calculated using logistic regression analysis. All statistical analyses were conducted using JMP Version 6 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05.

Results

Incidence of MPCs

The details of the 60 patients studied are shown in Table 1. The mean period of follow-up was 2914.6±1536.7 days. Of the 60 patients with OSCC, 21 (35%: 15 males and 6 females; mean age 67.3±11.9 years) developed MPCs. Among the 21 patients, there were a total of 24 affected organs. The affected organs were: 6 liver cases (25%), 6 stomach (25%), 2 esophagus (8.3%), 2 colon (8.3%), 2 thyroid (8.3%), 2

Table 2. Background factors of 60 patients in onset of OSCC.

		Total n=60 (%)		Group A MPCs n=21 (%)		Group B Non-MPCs n=39 (%)		P value A versus B
Age	Mean (year) ±SD	64.8 ± 13.7		67.3 ± 11.9		63.4 ± 14.4		NS
Age group	20-69 years old	35	(58.3)	10	(47.6)	25	(64.1)	NS
	70 years or older	25	(41.7)	11	(52.4)	14	(35.9)	
Sex	Male	39	(65.0)	15	(71.4)	24	(61.5)	NS
	Female	21	(35.0)	6	(28.6)	15	(38.5)	
Stage	I	15	(25.0)	4	(19.0)	11	(28.2)	NS
	II	24	(40.0)	6	(28.6)	18	(46.2)	
	III	6	(10.0)	2	(9.5)	4	(10.3)	
	IV	15	(25.0)	9	(42.9)	6	(15.4)	
Period of follow-up	Mean (days) ±SD	2914.6±1536.7		3512.3±1355.0		2675.5±1457.9		NS
History of liver dysfunction	Yes	16	(26.7)	10	(47.6)	6	(15.4)	p<0.01
	No	41	(68.3)	9	(42.9)	32	(82.1)	
	Unknown	3	(5.0)	2	(9.5)	1	(2.6)	
History of blood transfusion	Yes	7	(11.7)	5	(23.8)	2	(5.1)	p<0.05
	No	48	(80.0)	13	(61.9)	35	(89.7)	
	Unknown	5	(8.3)	3	(14.3)	2	(5.1)	
Alcohol consumption	Yes	29	(48.3)	11	(52.4)	18	(46.2)	NS
	No	29	(48.3)	10	(47.6)	19	(48.7)	
	Unknown	2	(3.3)	0	(0.0)	2	(5.1)	
Smoking history	Yes	24	(40.0)	10	(47.6)	14	(35.9)	NS
	No	34	(56.7)	11	(52.4)	23	(59.0)	
	Unknown	2	(3.3)	0	(0.0)	2	(5.1)	

OSCC – oral squamous cell carcinoma; MPCs – multiple primary cancers; SD – standard deviation, NS: no significance.

skin (8.3%), 1 pharynx (4.2%), 1 kidney (4.2%), 1 lung (4.2%), and 1 bone marrow (leukemia, 4.2%). Nineteen patients had second primary cancers: one patient had three, and one patient had four primary cancers.

Incidence of HCV infection

Anti-HCV were detected in sera from 16 of the 60 patients with oral cancer (26.7%). The diagnosis of liver disease following the development of primary OSCC included: asymptomatic HCV carrier 6.3% (1/16), past HCV infection 6.3% (1/16), chronic hepatitis C 25% (4/16), liver cirrhosis 37.5% (6/16), HCC with liver cirrhosis 18.8% (3/16), and HCC post interferon (IFN) treatment for chronic hepatitis C 6.3% (1/16). Just after we succeeded in eliminating HCV by IFN treatment, a 38-year-old man developed simultaneous HCC and OSCC. The incidence of MPCs in an HCV-infected OSCC or in a non-HCV-infected OSCC patient was 62.5% (10/16 cases, P<0.01 vs the non-HCV-infected OSCC group) and 25% (11/44), respectively. In 10 MPC patients who were HCV-infected, HCC was the most common carcinoma (5 cases); In 11 MPC patients who were not HCV-infected, gastric cancer was the most common (6 cases).

Risk factors by univariate analysis

We compared characteristics of 21 subjects who had MPCs (group A) and 70 subjects who did not have MPCs (group B). The average age in group A was 67.3±11.9 years; there were 15 males and 6 females. The average age in group B was 63.4±14.4 years; there were 24 males and 15 females. Table 2 shows clinical features of groups A and B. A history of liver dysfunction in group A was found in 10 (47.6%, p<0.01 vs group B); a history of blood transfusion in group A was found in 5 (23.8%, p<0.05 vs group B).

We analyzed for differences between these two groups in AST, ALT, ALP, γGTP, LDH, TP, Alb, insulin, blood glucose level, and HOMA-IR. The laboratory data of both groups are shown in Table 3. Prevalence of anti-HCV antibodies was significantly higher in group A than in group B (p<0.01).

Significant differences in the development of MPCs included a history of liver dysfunction, blood transfusion, and anti-HCV positivity.

Table 3. Laboratory data of 60 patients in onset of OSCC.

		Total n=60	Group A MPCs n=21	Group B Non-MPCs n=39	P value A versus B
AST (IU/L)	(Mean ± SD)	31.1±23.5	34.6±22.4	29.1±24.1	NS
ALT (IU/L)	(Mean ± SD)	19.5±18.5	22.7±15.4	17.7±19.9	NS
ALP (IU/L)	(Mean ± SD)	15.6±2.0	33.2±2.1	7.1±1.9	NS
γ-GTP (IU/L)	(Mean ± SD)	23.4±20.5	25.5±18.7	22.3±21.3	NS
LDH (IU/L)	(Mean ± SD)	337.1±66.8	351.1±56.5	330.4±70.8	NS
TP (g/dL)	(Mean ± SD)	7.6±0.5	7.7±0.5	7.6±0.5	NS
Alb (g/dL)	(Mean ± SD)	4.0±0.4	3.9±0.3	4.0±0.4	NS
Insulin (μU/L)	(Mean ± SD)	11.9±9.4	14.1±9.0	10.8±9.5	NS
Blood glucose level (mg/dL)	(Mean ± SD)	90.9±40.6	89.8±19.3	91.5±47.7	NS
HOMA-IR	(Mean ± SD)	3.0±3.7	3.3±2.3	2.9±4.2	NS
Anti-HCV	Positive	16 (26.7%)	10 (47.6%)	6 (15.4%)	p<0.01
	Negative	44 (73.3%)	11 (52.4%)	33 (84.6%)	
HCV RNA	Positive	13 (21.7%)	7 (33.3%)	6 (15.4%)	
	Negative	46 (76.7%)	13 (61.9%)	33 (84.6%)	NS
	Uncertain	1 (1.7%)	1 (4.8%)	0 (0.0%)	
HBsAg	Positive	1 (1.7%)	0 (0.0%)	1 (2.6%)	NS
	Negative	59 (98.3%)	21 (100.0%)	38 (97.4%)	
Anti-HBc	Positive	39 (65.0%)	14 (66.7%)	25 (64.1%)	
	Negative	19 (31.7%)	5 (23.8%)	14 (35.9%)	NS
	Uncertain	2 (3.3%)	2 (9.5%)	0 (0.0%)	

SD – standard deviation; NS – no significance; AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; γ-GTP – gammaglutamyl transpeptidase; LDH – lactate dehydrogenase; TP – total protein; Alb – albumin; HOMA IR – homeostasis model assessment.

Multivariate analysis

According to multivariate analysis, three factors – stage IV, anti-HCV positivity, and over 70 years old – were identified as factors associated with OSCC patients having an increased chance of developing MPCs. The adjusted odds ratios for these three factors were 15.50, 13.45, and 4.46, respectively, and each was statistically significant (Table 4).

Table 4. Results of multivariate analysis.

	Adjusted odds ratio (95% confidence interval)		P value
Stage IV	15.50	(0.39–2.58)	P=0.0124
Anti-HCV positive	13.45	(0.50–2.30)	P=0.0039
70 years or older	4.46	(0.04–1.56)	P=0.0480

Insulin resistance for the four groups

Of the 60 subjects (16 anti-HCV antibody positive and 44 anti-HCV negative), 10 had MPCs with HCV infection (group 1), 11 had MPCs without HCV infection (group 2), 6 lacked MPCs but had HCV infection (group 3), and 33 lacked MPCs and HCV infection (group 4). Fasting insulin levels at the time of the first visit to our hospital were: 16.3±7.9, 12.1±9.5, 13.5±12.6, or 10.3±8.7, in groups 1, 2, 3 and 4, respectively. Fasting insulin levels for group 1 was significantly higher than for group 4 (p=0.01, Figure 1A). HOMA-IR values seven years prior in groups 1, 2, 3, and 4 were, respectively, 3.5±1.6, 3.0±2.7, 3.1±3.0, and 2.9±4.4. A HOMA-IR value for group 1 was significantly higher than for group 4 (p=0.01, Figure 1B).

Discussion

We have already reported a high incidence of HCV among patients with OSCC [8,9]. Furthermore, we investigated the characteristics and incidence of MPCs in patients with OSCC treated between 1974 and 1995, suggesting that HCV infection increases the risk of developing MPCs [10].

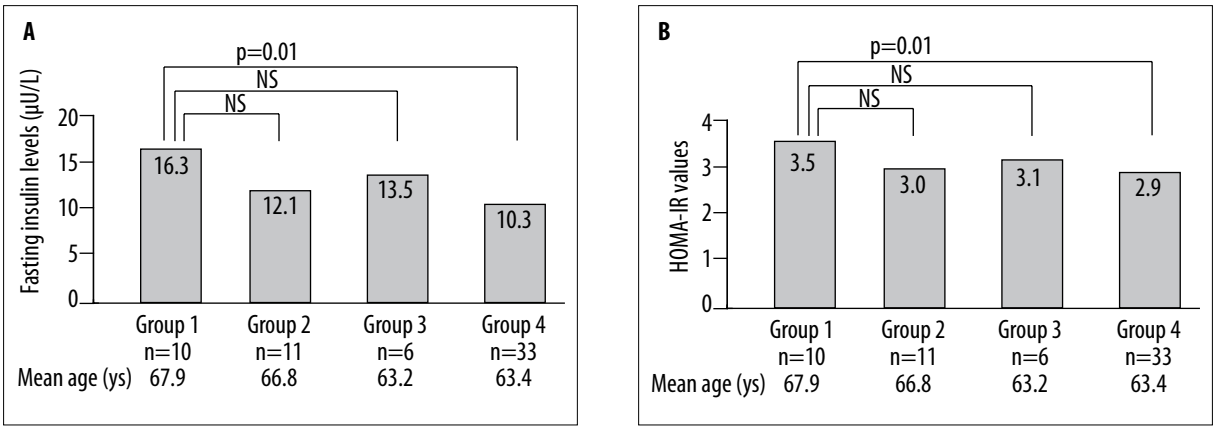

Figure 1. Association of carcinomas with insulin resistance depend on the presence or absence of OSCC and HCV infection. (**A**) Fasting serum insulin levels and (**B**) HOMA-IR values.

In the present study, the incidence of MPCs in patients with OSCC was 35% (21/60 patients) during 2914.6±1536.7 days of follow-up. The incidence of anti-HCV positivity was 26.7% (16/60 patients). The incidence of MPCs in an OSCC patient that was HCV-infected was significantly higher than in one that was not infected (62.5% vs 25%, $p<0.01$). HCC was the most common form of HCV-infected MPCs, and gastric cancer was the most common form of non-HCV-infected MPCs. These findings suggest a strong association between HCV infection and OSCC. The incidence of MPSc with the exclusion of 5 HCC in an OSCC patient that was HCV-infected was also higher than in one that was not infected (45.1% vs 25%). The affected carcinomas in extrahepatic organs of OSCC patients with HCV infection were: 2 colons, 1 lung, 1 thyroid, and 1 bone marrow (leukemia). Even excluding HCC, HCV-infected patients were at a high risk of developing extrahepatic MPCs.

Multivariate analysis demonstrated that stages of OSCC, being anti-HCV positive, and being over 70 years old increased the risk that patients with OSCC would develop MPCs. In OSCC patients who are HCV-infected, it is important to clinically examine the liver other than the oral cavity and gastrointestinal regions.

HCV infection induces not only chronic liver disease but also extrahepatic manifestations. Indeed, we experienced and reported five head and neck SCC among HCV-infected patients: (i) the patient who developed buccal mucosa cancer after IFN therapy for chronic hepatitis C [19], (ii) the patient who had simultaneous double primary cancers, including tongue cancer and HCV-related HCC [20], (iii) the patient who developed tongue cancer during the treatment of HCV-related liver disease [20], (iv) the patient with chronic hepatitis C, who developed worsening of lichen planus lesions during treatment with IFN plus ribavirin [21] and subsequently developed larynx cancer, and (v) the patient who developed tongue cancer during treatment for chronic hepatitis C [22].

It is presumed that between 1 and 2 million Japanese people are chronically infected with HCV. Because many such people are unaware that they are infected, carriers may develop liver cirrhosis and HCC, and this poses a serious problem. HCV-related HCC has increased and is now the cause of a majority of cases in Japan. Thus, the increased rates of death due to primary liver cancer in Japan appear to reflect the increase in numbers of HCV-related HCC [5]. IFN therapy, an antiviral agent, contributes to the prevention of occurrence of HCC and to improvement in long-term prognosis [23,24]. HCV-infected OSCC patients should also receive medical treatment to inhibit development of HCC, especially in Japan where the average life expectancy has increased year after year. In 2006, the life expectancies at birth were 79.0 years for males and 85.8 for females (Abridged Life Table, Ministry of Health, Labour and Welfare). Meanwhile, in patients with HCV infection, it is important to clinically examine organs other than the liver.

Satoh et al reported autopsy cases collected from the Annual of the Pathological Autopsy Cases in Japan, which is issued by the Japanese Society of Pathology for the past five years 1997–2001 [4]. A total of 134,997 cases had autopsies in Japan over five years. Of these, 321 were tongue cancer. The incidence of MPCs, affecting both the tongue and other organs, was reported to be 35.2% (113/321). In cases of double cancers including tongue cancer, commonly occurring cancers were reported to be lung, liver, esophagus, and thyroid. We think that there is a strong relation between OSCC and HCV infection, as can be seen from the fact that the second most common MPCs with tongue cancer, according to the results of autopsies, is liver cancer (reported by Satoh et al).

Several studies and our previous reports suggest that HCV infection antedates insulin resistance [25,26]. We showed molecular mechanisms for HCV core-induced insulin resistance [26]. Meanwhile, in a large population-based cohort study, Park et al. reported that among male cancer survivors, prediagnosis smoking, alcohol consumption, obesity, and insulin resistance (all risk factors for cancer development) affected cancer prognosis [27]. Previous studies in breast, prostate, and colorectal cancers demonstrated that insulin resistance can influence outcomes through systemic consequences of hyperinsulinemia [28–30]. Insulin receptors are overexpressed in those cancer tissues, so high insulin levels could promote the selective growth advantage of cancer cells [28–30]. We conclude that HCV infection induces insulin resistance and may cause lichen planus, a precancerous lesion [12,13]. In the present study,

the MPC patients who were HCV-infected had hyperinsulinemia. Insulin resistance may be involved in the development of MPCs in patients with HCV infection, although the mechanisms are unclear.

CONCLUSIONS

We demonstrated a high incidence of MPCs in HCV-infected OSCC patients. Risk factors for MPCs developing in OSCC patients are high stage of primary cancer, HCV infection, and older age. Our study emphasizes the importance of periodic examination of the oral cavity among patients with HCV infection. Success in the detection and treatment of MPCs at early stages requires close cooperation between different medical specialists.

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