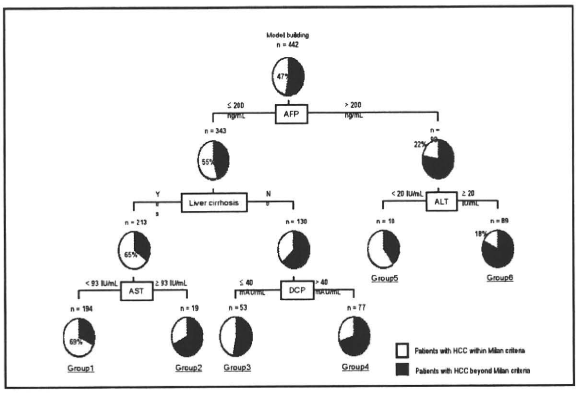
(2. 2) 樹形モデルの結果

663 名のデータを学習データ(n=442)とテストデータ(n=221)に無作為に分け、Milan criteria を2値の反応変数、13個のリスク因子を説明変数にとって樹形モデルを学習データにあてはめた。

図2:非 B 非 C 肝細胞癌の臨床プロファイル



樹形モデルでは APF, Liver cirrhosis, AST, DCP,ALT の5つのリスク因子が用いられ6つの臨床プロファイルが作成された(図2)。この臨床プロファイリングの精度を検討するために、テストデータを用い感度、特異度、誤判別率を求め、それぞれ 73%,67%,30%であった。

D. 考察

分岐鎖アミノ酸食品の市販後調査データの解析は、データのアンバランスにより非常に困難なデータ解析となったが、データのバランス化により有効性が示唆される結果が得られえら。現在、2重盲検無作為化比較試験が実施されており、この比較試験の解析により科学的根拠の高い結果が得られると期待している。

非 B 非 C 型肝癌患者の予測因子に関する解析では、具体的な仮説検証、具体的な治療効果の検討を目的にしておらず、このようなデータの解析では、交絡因子を考慮しないことによる見せ掛けの相関が生じたりする。更に臨床的根拠に基づくリスク因子モデルが存在しないので、病期進展に関与するリスク因子の検討は探索的観点から行うべきであると判断し、探索的データ解析を行った。

E. 結論

肝炎・肝硬変に対する抗ウイルス剤以外の治療法に関する研究における生物統計学的解析の有用性について考察し、実際のデータを用いて妥当性のあるデータ解析結果を得た。研究目的、研究デザイン、有効性評価項目の選択、臨床仮説の具体性、疾病モデル・疾病過程のメカニズムなど多様な事柄が、適切な生物統計学的解析手法の選択に影響する。今回行った探索的データ解析から得られた結果より、新たな仮説を打ち立てて、仮説検証を目的とした Randomized Controlled Trials の計画・実施を通した科学的根拠の集積が行われることを期待する。

F. 研究発表

1. 論文発表

1. Okamatsu Y, Matsuda K, Hiramoto I, Tani H, Kimura K, Yada Y, Kakuma T, Higuchi S, Kojima M, Matsuishi T. Ghrelin and leptin modulate immunity and liver function in overweight children. Pediatrics International, 2009 Feb;51(1):9-13.
2. Hayamizu K, Yamashita N, Hattori S, Kakuma T. A Change-Point Regression Approach for Efficacy Evaluation of Dietary Supplements. J. Clin. Biochem. Nutr., 44, 285-290, 2009
3. Data Mining Revealed Complex Interactions of Risk Factors and Clinical Feature Profiling Associated with Staging of non-HBV non-HCV-Hepatocellular Carcinoma. Takumi Kawaguchi, Tatsuyuki Kakuma Hiroshi Yatsuhashi, Hiroshi Watabebe, Hideki Saitsu, Kazuhiko Nakao, Akinobu Taketomi, Satoshi Ohta, Akinari Tabaru, Kenji Takenaka, Toshihiko Mizuta, Kenji Nagata, Yasuji Komorizono, Kunitaka Fukuizumi, Masataka Seike, Shuichi Matsumoto, Tatsuji Maeshiro,

Hirohito Tsubouchi, Toyokichi Muro, Osami Inoue, Motoo Akahoshi, Michio Sata, The Liver Cancer Study Group of Kyushu. (Submitted for publication)

2. 学会発表

特記事項なし

G. 知的財産権の出願・登録状況

(予定を含む)

1. 特許取得

特記事項なし

2. 実用新案登録

特記事項なし

3. その他

特記事項なし

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Kawaguchi T, Nagao Y, Sata M.	Taste Alteration in Palliative Care	Victor R Preedy	Handbook of Nutrition and Diet in Palliative Care	Taylor & Francis Group, LLC.	Boca Raton, FL 33487 , USA	2011	In Press
長尾由実子、佐田通夫	肝炎ウイルスによる肝外病変.	幕内雅敏・菅野健太郎・工藤正敏	今日の消化器疾患治療指針 第３版	医学書院	東京	2010	592-595
長尾由実子、佐田通夫	九州Ｘ町の疫学研究ー肝疾患並びに肝外病変の病態と治療の方策ー	河田純男・佐田通夫・新澤陽英・齋藤貴史	HCV 感染の natural course を探る： わが国におけるコホート研究	山形大学出版会	山形	2010	23-32
長尾由実子，佐田通夫	Ｃ型肝炎でみられる肝外病変にはどのようなものがあるのか？	河田純男，佐々木 裕	現場の疑問に答える 肝臓病診療 Q&A	中外医学社	東京	2009	113-116
川口 巧，佐田通夫	Ｑ17．肝癌の発生に肥満，糖尿病は影響するか？	河田純男，佐々木裕	現場の疑問に答える 肝臓病診療 Q&A	中外医学社	東京	2009	67– 70
中村徹，佐田通夫	血管内皮前駆細胞を用いた肝臓再生療法	「肝胆膵」編集委員会	肝胆膵	アークメディア	東京	2008	459-466
中村徹，佐田通夫	自己末梢血単核球細胞を用いた非代償性肝硬変症に対する肝臓再生医療の開始 －基礎研究から臨床研究へ －	学術アドバイザー 小俣政男	消化器疾患における Translational Research	アークメディア	東京	2008	63-68
中村徹	非代償性肝硬変患者に対する自己末梢血単核球細胞移植再生療法	小寺弘晃	Liver Forum in Kyoto 第10回学術集会	メディカルトリビューン社	東京	2008	41-46
長尾由実子，佐田通夫	Q6 最近ロ内炎がよく出来ます。肝臓が悪いことと関係があるのでしょうか？	松崎靖司，宜保行雄	患者さんの質問に答える慢性肝疾患診療 改訂２版	南山堂	東京	2008	19-21
長尾由実子，佐田通夫	Q58 キャリアの血液に触れたのですが，どのように対処したらよいでしょうか？	松崎靖司，宜保行雄	患者さんの質問に答える慢性肝疾患診療 改訂２版	南山堂	東京	2008	188-190

長尾由実子, 佐田通夫	C 型肝炎患者が専門医に聞く 88 の質問.	長尾由実子, 佐田通夫	C 型肝炎患者が専門医に聞く 88 の質問. 追補版.	新興医学出版社	東京	2008	1-132
川口 巧, 佐田通夫	Q8 シカやイノシシの生肉を食べると肝炎になるという記事を読みました。好物なのですが肝炎にかからぬようにワクチンを打っていただけますか？	松崎靖司, 宜保行雄	患者さんの質問に答える慢性肝疾患診療 改訂 2 版	南山堂	東京	2008	26-27
川口 巧, 佐田通夫	Q56 海外旅行に行くのですが、ウイルス性肝炎の予防接種は必要ですか？	松崎靖司, 宜保行雄	患者さんの質問に答える慢性肝疾患診療 改訂 2 版	南山堂	東京	2008	183-185
川口 巧, 佐田通夫	Q57 ウイルス性肝炎のワクチンはないのですか？	松崎靖司, 宜保行雄	患者さんの質問に答える慢性肝疾患診療 改訂 2 版	南山堂	東京	2008	186-187

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kawaguchi T, Shiba N, Maeda T, et al.	Hybrid-Training of Voluntary and Electrical Muscle Contractions Reduces Steatosis, Insulin Resistance and IL-6 Levels in Patients with NAFLD: A Pilot Study.	J Gastroenterol		In Press.	2011
Kawaguchi T, Shiba N, Takano Y, Maeda T, Sata M.	Hybrid-Training of Voluntary and Electrical Muscle Contractions Decreased Fasting Blood Glucose and Serum Interleukin-6 Levels in Elderly People: A Pilot Study.	Appl Physiol Nutr Metab		In Press.	2011
Itou M, Kawaguchi T, Taniguchi E, et al.	Supplementation before Endoscopic Therapy for Esophageal Varices Reduces Mental Stress in Patients with Liver Cirrhosis.	Hepatogastroenterology		In Press.	2011
Kawaguchi T, Itou M, Taniguchi E, et al.	Serum Level of Free Fatty Acids is Associated with Nocturnal Hypoglycemia in Cirrhotic Patients with HCV Infection: A Pilot Study.	Hepatogastroenterology		In Press.	2011
Fujimoto K, Kawaguchi T, Nakashima O, Ono J, Ohta J, Kawaguchi A, Tonan T, Ohshima K, Yano H, Hayabuchi N, Izuhara K, Sata M.	Periostin, a matrix protein, has potential as a novel serodiagnostic marker for cholangiocarcinoma.	Oncology Report		In Press	2011

Taura N, Fukushima N, Yatsuhashi H, Takami Y, Seike M, Watanabe H, Mizuta T, Sasaki Y, Nagata K, Tabara A, Komorizono Y, Taketomi A, Matsumoto S, Tamai T, Muro T, Nakao K, Fukuizumi K, Maeshiro T, Inoue O, Sata M	The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased in Kyushu area	Med Sci Monit.	17(2)	PH7-11	2011
Takahashi M, Maruyama H, Ishibashi H, Yoshikawa M, Yokosuka O	Contrast-enhanced ultrasound with perflubutane microbubble agent: evaluation of differentiation of hepatocellular carcinoma.	AJR Am J Roentgenol.	196巻	W123-131	2011
Sogawa K, Kodera Y, Satoh M, Kawashima Y, Umemura H, Maruyama K, Takizawa H, Yokosuka O, Nomura F.	Increased Serum Levels of Pigment Epithelium-Derived Factor by Excessive Alcohol Consumption-Detection and Identification by a Three-Step Serum Proteome Analysis.	Alcohol Clin Exp Res.	35巻	211-217	2011
Fujiwara K, Kojima H, Yasui S, Okitsu K, Yonemitsu Y, Omata M, Yokosuka O.	Hepatitis A viral load in relation to severity of the infection.	J Med Virol.	83巻	201-207	2011
Bekku D, Arai M, Imazeki F, Yonemitsu Y, Kanda T, Fujiwara K, Fukai K, Sato K, Itoga S, Nomura F, Yokosuka O.	Long-term follow-up of patients with hepatitis B e antigen negative chronic hepatitis B.	J Gastroenterol Hepatol.	26巻	122-128	2011
Nagao Y, Matsuoka H, Kawaguchi T, Sata M.	Aminofeel® improves the sensitivity to taste in patients with HCV-infected liver disease.	Med Sci Monit	16	7-12	2010
Nagao Y, Sata M.	Dental problems delaying the initiation of interferon therapy for HCV-infected patients.	Virol J	7	192	2010
Nagao Y, Sata M.	Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan.	Virol J	7	375	2010
佐田通夫、長尾由実子、大坪維範、岡村 孝.	C型肝炎. HCV感染とB cell clonality、口腔癌、インスリン抵抗性についての検討	犬山シンポジウム記録刊行会	27	137-142	2010
長尾由実子、佐田通夫.	C型肝炎の臨床最前線. IFN治療普及のための戦略.	肝胆膵	61	28-35	2010
Sakata M, Kawaguchi T, Taniguchi E, et al.	Oxidized albumin is associated with water retention and severity of disease in patients with chronic liver diseases.	e-SPEN, the European e-Journal of Clinical Nutrition and	5	e247-e53	2010

		Metabolism			
Sakata S, Kawaguchi T, Taniguchi E, et al.	Redox state of albumin is not associated with colloid osmotic pressure.	Mol Med Rep.	3	685-7	2010
Kawaguchi T, Sata M.	Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulin sensitization.	World J Gastroenterol	16	1943-52	2010
Kawaguchi T, Taniguchi E, Itou M, Sumie S, Yamagishi S, Sata M.	The pathogenesis, complications and therapeutic strategy for hepatitis C virus-associated insulin resistance in the era of anti-viral treatment.	Rev Recent Clin Trials	5	147-57	2010
Kawaguchi T, Yamagishi SI, Sata M.	Structure-function relationships of PEDF.	Curr Mol Med	10	302-11	2010
Kanda T, Jeong SH, Imazeki F, Fujiwara K, Yokosuka O.	Analysis of 5' nontranslated region of hepatitis a viral RNA genotype I from South Korea: comparison with disease severities.	PLoS One.	5巻	e15139	2010
Fujiwara K, Yasui S, Okitsu K, Yonemitsu Y, Oda S, Yokosuka O.	The requirement for a sufficient period of corticosteroid treatment in combination with nucleoside analogue for severe acute exacerbation of chronic hepatitis B.	J Gastroenterol.	45巻	1255-1262	2010
Kasuga A, Mizumoto H, Matsutani S, Kobayashi A, Endo T, Ando T, Yukisawa S, Maruyama H, Yokosuka O.	Portal hemodynamics and clinical outcomes of patients with gastric varices after balloon-occluded retrograde transvenous obliteration.	J Hepatobiliary Pancreat Sci.	17巻	898-903	2010
Ishibashi H, Maruyama H, Takahashi M, Fujiwara K, Imazeki F, Yokosuka O.	Assessment of hepatic fibrosis by analysis of the dynamic behaviour of microbubbles during contrast ultrasonography.	Liver Int.	30巻	1355-1363	2010
Yasui S, Fujiwara K, Yonemitsu Y, Oda S, Nakano M, Yokosuka O.	Clinicopathological features of severe and fulminant forms of autoimmune hepatitis.	J Gastroenterol.			2010
Yang L, Kiyohara T, Kanda T, Imazeki F, Fujiwara K, Gauss-Müller V, Ishii K, Wakita T, Yokosuka O.	Inhibitory effects on HAV IRES-mediated translation and replication by a combination of amantadine and interferon-alpha.	Virol J.	7巻	212	2010
Chiba T, Seki A, Aoki R, Ichikawa H, Negishi M, Miyagi S, Oguro H, Saraya A, Kamiya A, Nakauchi H, Yokosuka O, Iwama A.	Bmi1 promotes hepatic stem cell expansion and tumorigenicity in both Ink4a/Arf-dependent and -independent manners in mice.	Hepatology.	52巻	1111-1123	2010

Imada H, Kato H, Yasuda S, Yamada S, Yanagi T, Kishimoto R, Kandatsu S, Mizoe JE, Kamada T, Yokosuka O, Tsujii H.	Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis.	Radiother Oncol.	96巻	231-235	2010
Imada H, Kato H, Yasuda S, Yamada S, Yanagi T, Hara R, Kishimoto R, Kandatsu S, Minohara S, Mizoe JE, Kamada T, Yokosuka O, Tsujii H.	Compensatory enlargement of the liver after treatment of hepatocellular carcinoma with carbon ion radiotherapy - relation to prognosis and liver function.	Radiother Oncol.	96巻	236-242	2010
Maruyama H, Okugawa H, Ishibashi H, Takahashi M, Kobayashi S, Yoshizumi H, Yokosuka O.	Carbon dioxide-based portography: an alternative to conventional imaging with the use of iodinated contrast medium.	J Gastroenterol Hepatol.	25巻	1111-1116	2010
Aoki R, Chiba T, Miyagi S, Negishi M, Konuma T, Taniguchi H, Ogawa M, Yokosuka O, Iwama A.	The polycomb group gene product Ezh2 regulates proliferation and differentiation of murine hepatic stem/progenitor cells.	J Hepatol.	52巻	854-863	2010
Kanda T, Imazeki F, Nakamoto S, Okitsu K, Fujiwara K, Yokosuka O.	Internal ribosomal entry-site activities of clinical isolate-derived hepatitis A virus and inhibitory effects of amantadine.	Hepatol Res.	40巻	415-423	2010
Maruyama H, Okabe S, Ishihara T, Tsuyuguchi T, Yoshikawa M, Matsutani S, Yokosuka O.	Long-term effect of endoscopic injection therapy with combined cyanoacrylate and ethanol for gastric fundal varices in relation to portal hemodynamics.	Abdom Imaging.	35巻	8-14	2010
Ito K, Arai M, Imazeki F, Yonemitsu Y, Bekku D, Kanda T, Fujiwara K, Fukai K, Sato K, Itoga S, Nomura F, Yokosuka O.	Risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. Scand	J Gastroenterol.	45巻	243-249	2010
Komatsu N, Yutani S, Yamada A, Shichijo S, Yoshida K, Itou M, Kuromatsu R, Ide T, Tanaka M, Sata M, and Itoh K	Prophylactic effect of peptide vaccination against hepatocellular carcinoma associated with hepatitis C virus	Experimental and Therapeutic Medicine	1(4)	619-626	2010
Imafuku S, Nakayama J	Questionnaire-based survey of the treatment of patients with psoriasis and hepatitis C in Japan.	J Eur Acad Dermatol Venereol	24	1114-1116	2010
Tonan T	Chronic hepatitis and cirrhosis on MR imaging	Magn Reson Imaging Clin N Am	18(3)	383-402	2010
Kawaguchi T, Yamagishi S, Itou M, Okuda K, Sumie S, Kuromatsu R, Sakata M, Abe M, Taniguchi E, Koga H, Harada M, Ueno T, Sata	Pigment epithelium-derived factor inhibits lysosomal degradation of Bcl-xL and apoptosis in HepG2 cells.	Am J Pathol.	176	168-176	2010

M.					
Maruyama H, Okugawa H, Kobayashi S, Yoshizumi H, Yokosuka O.	Pre-treatment hemodynamic features involved with long-term survival of cirrhotic patients after embolization of gastric fundal varices.	Eur J Radiol.	75	32-37	2010
Kanda T, Gauss-Müller V, Cordes S, Tamura R, Okitsu K, Shuang W, Nakamoto S, Fujiwara K, Imazeki F, Yokosuka O.	Hepatitis A virus (HAV) proteinase 3C inhibits HAV IRES-dependent translation and cleaves the polypyrimidine tract-binding protein.	J Viral Hepat	17	618-623	2010
Nakamoto S, Imazeki F, Fukai K, Fujiwara K, Arai M, Kanda T, Yonemitsu Y, Yokosuka O.	Association between mutations in the core region of hepatitis C virus genotype 1 and hepatocellular carcinoma development.	J Hepatol.	52	72-78	2010
Maruyama H, Takahashi M, Ishibashi H, Okabe S, Yoshikawa M, Yokosuka O	Changes in tumor vascularity precede microbubble contrast accumulation deficit in the process of dedifferentiation of hepatocellular carcinoma.	Eur J Radiol.	75	102-106	2010
Maruyama H, Ishihara T, Ishii H, Tsuyuguchi T, Yoshikawa M, Matsutani S, Yokosuka O.	Blood flow parameters in the short gastric vein and splenic vein on Doppler ultrasound reflect gastric variceal bleeding.	Eur J Radiol.	75(1)	41-45	2010
Nagao Y, Matsuoka H, Seike M, Yamasaki K, Kato J, Nakajima T, Miyazaki Y, Ohno T, Inuzuka S, Ohira H, Yokosuka O, Yatsuhashi H, Mori T, Honda K, Kawaguchi T, Ide T, Sata M.	Knowledge about *Vibrio vulnificus* infection in Japanese patients with liver diseases: A prospective multicenter study.	Med Sci Monit	15	115-120	2009
Nagao Y, Sata M.	High incidence of multiple primary carcinomas in HCV-infected patients with oral squamous cell carcinoma.	Med Sci Monit	15	453-459	2009
長尾由実子, 佐田通夫.	C型肝炎ウイルス感染者における医療連携の在り方.	医療情報誌シュネラー	71	20-25	2009
長尾由実子	進歩する肝疾患診療と病診連携 「インターフェロン治療の理解・認知不足の背景を探る一患者・医師対象アンケート調査からの考察一」	Medical Tribune		144	2009
長尾由実子, 今福信一, 佐田通夫	ご存じですか？ビブリオ・バルニフィカス感染症	中外製薬株式会社		1-4	2009
Ide T, Hino T, Ogata K, Miyajima I, Kuwahara R, Kuhara K, Sata M.	A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C.	Am J Gastroenterol	104	70-75	2009

Kawaguchi T, Taniguchi E, Morita Y, Shirachi M, Tateishi I, Nagata E, Sata M.	Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection.	Liver Int.	30	479-486	2009
Kawaguchi T, Yamagishi S, Sata M.	Branched-chain amino acids and pigment epithelium-derived factor: novel therapeutic agents for hepatitis c virus-associated insulin resistance.	Curr Med Chem.	16	4843-4857	2009
Taura N, Yatsuhashi H, Nakao K, Ichikawa T, Ishibashi H.	Long-term trends of the incidence of hepatocellular carcinoma in the Nagasaki prefecture, Japan.	Oncol Rep.	21(1)	223-227	2009
Chiba T, Kamiya A, Yokosuka O, Iwama A.	Cancer stem cells in hepatocellular carcinoma: Recent progress and perspective.	Cancer Lett	286(2)	145-153	2009
Okugawa H, Maruyama H, Kobayashi S, Yoshizumi H, Matsutani S, Yokosuka O.	Therapeutic effect of balloon-occluded retrograde transvenous obliteration for gastric varices in relation to haemodynamics in the short gastric vein.	Br J Radiol.	82(983)	930-935	2009
Yonemitsu Y, Imazeki F, Chiba T, Fukai K, Nagai Y, Miyagi S, Arai M, Aoki R, Miyazaki M, Nakatani Y, Iwama A, Yokosuka O.	Distinct expression of polycomb group proteins EZH2 and BMI1 in hepatocellular carcinoma.	Hum Pathol	40(9)	1304-1311	2009
Fujiwara K, Kojima H, Yonemitsu Y, Yasui S, Imazeki F, Miki M, Suzuki K, Sakaida I, Okita K, Tanaka E, Omata M, Yokosuka O.	Phylogenetic analysis of hepatitis A virus in sera from patients with hepatitis A of various severities.	Liver Int.	29(6)	838-845	2009
Maruyama H, Takahashi M, Ishibashi H, Okugawa H, Okabe S, Yoshikawa M, Yokosuka O.	Ultrasound-guided treatments under low acoustic power contrast harmonic imaging for hepatocellular carcinomas undetected by B-mode ultrasonography.	Liver Int.	29(5)	708-714	2009
Nakamoto S, Kanda T, Yonemitsu Y, Arai M, Fujiwara K, Fukai K, Kanai F, Imazeki F, Yokosuka O.	Quantification of hepatitis C amino acid substitutions 70 and 91 in the core coding region by real-time amplification refractory mutation system reverse transcription-polymerase chain reaction.	Scand J Gastroenterol	44(7)	872-877	2009
Yutani S, Komatsu N, Shichijo S, Yoshida K, Takedatsu H, Itou M, Kuromatu R, Ide T, Tanaka M, Sata M, Yamada A, Itoh K.	Phase I clinical study of a peptide vaccination for hepatitis C virus-infected patients with different human leukocyte antigen-class I-A alleles.	Cancer Sci.	100(10)	1935-1942	2009

Niu Y, Komatsu N, Komohara Y, Matsueda S, Yutani S, Ishihara Y, Itou M, Yamada A, Itoh K, Shichijo S.	A peptide derived from hepatitis C virus (HCV) core protein inducing cellular responses in patients with HCV with various HLA class IA alleles.	J Med Virol.	81(7)	1232-1240	2009
Sato T, Kurokawa M, Nakashima Y, Ida T, Takahashi T, Fukue Y, Ikawa M, Okabe M, Kangawa K, Kojima M.	Ghrelin deficiency does not influence feeding performance.	Regul Pept.	145	7-11	2008
Chiba T, Miyagi S, Saraya A, Aoki R, Seki A, Morita Y, Yonemitsu Y, Yokosuka O, Taniguchi H, Nakauchi H, Iwama A..	The polycomb gene product BMI1 contributes to the maintenance of tumor-initiating side population cells in hepatocellular carcinoma.	Cancer Res	68 (19)	7742-7749	2008
Maruyama H, Okugawa H, Yoshizumi H, Kobayashi S, Yokosuka O.	Hemodynamic features of gastrorenal shunt: a Doppler study in cirrhotic patients with gastric fundal varices.	Acad Radiol.	15(9)	1148-1154	2008
Tomizawa M, Toyama Y, Ito C, Toshimori K, Iwase K, Takiguchi M, Saisho H, Yokosuka O.	Hepatoblast-like cells enriched from mouse embryonic stem cells in medium without glucose, pyruvate, arginine, and tyrosine.	Cell Tissue Res	333 (1)	17-27	2008
Kobayashi S, Maruyama H, Okugawa H, Yoshizumi H, Matsutani S, Ebara M, Yokosuka O.	Contrast-enhanced US with Levovist for the diagnosis of hepatic hemangioma: time-related changes of enhancement appearance and the hemodynamic background.	Hepatogastroenterology	55 (85)	1222-1228	2008
Tada M, Kanai F, Tanaka Y, Tateishi K, Ohta M, Asaoka Y, Seto M, Muroyama R, Fukai K, Imazeki F, Kawabe T, Yokosuka O, Omata M.	Down-regulation of hedgehog-interacting protein through genetic and epigenetic alterations in human hepatocellular carcinoma.	Clin Cancer Res	14 (12)	3768-3776.	2008
Inada M, Yokosuka O.	Current antiviral therapies for chronic hepatitis B.	Hepatol Res.	38(6)	535-542.	2008
Maruyama H, Yoshikawa M, Yokosuka O.	Current role of ultrasound for the management of hepatocellular carcinoma.	World J Gastroenterol	14(11).	1710-1719	2008
Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H.	Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients.	Liver Int	28 (3)	355-362	2008

Fujiwara K, Yasui S, Yonemitsu Y, Fukai K, Arai M, Imazeki F, Suzuki A, Suzuki H, Sadahiro T, Oda S, Yokosuka O.	Efficacy of combination therapy of antiviral and immunosuppressive drugs for the treatment of severe acute exacerbation of chronic hepatitis B.	J Gastroenterol.	43(9)	711-719	2008
Ogata K, Kashiwagi T, Iwahashi J, Hara K, Honda H, Ide T, Kumashiro R, Kohara M, Sata M, Watanabe H, Hamada N.	A mutational shift from domain III to II in the internal ribosome entry site of hepatitis C virus after interferon-ribavirin therapy	Arch Virol	153(8)	1575-1579	2008
Kuwahara R, Kumashiro R, Ide T, Koga Y, Hino T, Hisamochi A, Tanaka K, Ogata K, Koga H, Takao Y, Sata M.	Predictive factors associated with the progression to hepatic failure caused by Lamivudine-Resistant HBV	Dig Dis Sci	53(11)	2999-3006	2008
Nagao Y, Kawasaki K, Sata M.	Insulin resistance and lichen planus in patients with HCV-infectious liver diseases.	J Gastroenterol Hepatol	23	580-585	2008
Nagao Y, Matsuoka H, Kawaguchi T, Ide T, Sata M.	HBV and HCV infection in Japanese dental care workers.	Int J Mol Med	21	791-799	2008
Kawaguchi T, Nagao Y, Matsuoka H, Ide T, Sata M.	Branched-chain amino acid-enriched supplementation improves insulin resistance in patients with chronic liver disease.	Int J Mol Med	22	105-112	2008
Nagao Y, Hiromatsu Y, Nakashima T, Sata M.	Graves' ophthalmopathy and tongue cancer complicated by peg-interferon α-2b and ribavirin therapy for chronic hepatitis C: A case report and review of the literature.	Molecular Medicine Reports	1	625-631	2008
Nagao Y, Kawakami Y, Yoshiyama T, Sata M	Analysis of factors interfering with the acceptance of interferon therapy by HCV-infected patients.	Med Sci Monit	14	45-52	2008
長尾由実子, 川口 巧, 井出 達也, 佐田 通夫.	HCV あるいは HBV 感染者における歯科治療時の自己申告調査	感染症誌	82	213-219	2008
長尾由実子, 佐田通夫.	日常診療に必要なウイルス肝炎の知識と対策　A 型肝炎の現況と予防.	臨床と研究	85	964-968	2008
長尾由実子, 佐田通夫.	C型肝炎ウイルス感染者に対するインターフェロン治療の状況- 患者と医師のアンケート調査から- .	HCV News letter	3	1-4	2008
長尾由実子, 今福信一, 佐田通夫.	肝臓病の方の皮膚や粘膜には、さまざまな症状が現れます。とくにインターフェロン治療中には注意が必要です。- 肝臓病と皮膚・粘膜の病気- .	肝外病変シリーズ	2	1-22	2008

今福信一, 中山樹一郎	シクロスポリン投与中の乾癬患者におけるテルミサルタンの腎機能及び血圧に対する効果・安全性の検討	西日本皮膚科	70.	204-207	2008
今福信一, 中山樹一郎	乾癬のシクロスポリン 1.2mg/kg 療法	西日本皮膚科	70	436-441	2008
Kawaguchi T, Taniguchi E, Itou M, Ibi R, Okada T, Mutou M, Shiraishi S, Uchida Y, Otsuka M, Umeki Y, Oriishi T, Hayabuchi H, Tanaka S, Takakura M, Sata M.	Body cell mass is a useful parameter for assessing malnutrition and severity of disease in non-ascitic cirrhotic patients with hepatocellular carcinoma or esophageal varices.	Int J Mol Med	22	589-594	2008
Kawaguchi T, Taniguchi E, Itou M, Mutou M, Ibi R, Shiraishi S, Okada T, Uchida Y, Otsuka M, Tonan T, Fujimoto K, Oriishi T, Tanaka S, Takakura M, Sata M.	Supplement improves nutrition and stresses caused by examination-associated fasting in patients with liver cirrhosis.	Hepatol Res	38	1178-1185	2008
Itou M, Kawaguchi T, Taniguchi E, Sumie S, Oriishi T, Mitsuyama K, Tsuruta O, Ueno T, Sata M.	Altered expression of glucagon-like peptide-1 and dipeptidyl peptidase IV in patients with HCV-related glucose intolerance.	J Gastroenterol Hepatol	23	244-251	2008
Ohno. T, Tanaka. Y, Sugauchi. F, Orito. E, Hasegawa. I, Nukaya. H, Kato. A, Matunaga. S, Endo. M, Yoshito. T, Sakakibara. k, Mizokami. M	Suppressive effect of oral administration of branched-chainamino acid granules on oxidative stress and inflammation in HCV−positive patients with liver cirrhosis	Hapatol Res	38	683-688	2008
Gohara S, Shichijo S, Komatsu N, Okuda S, Yutani S, Itoh K	Detection of IgE antibody specific to a hepatitis C virus-derived peptide being recognized by cellular immunity in patients with HCV infection.	Viral Immunol	21(3)	365-369	2008

Ⅳ．研究成果の刊行物・別刷

18 Taste Alteration in Palliative Care

Takumi Kawaguchi, Yumiko Nagao, and Michio Sata

CONTENTS

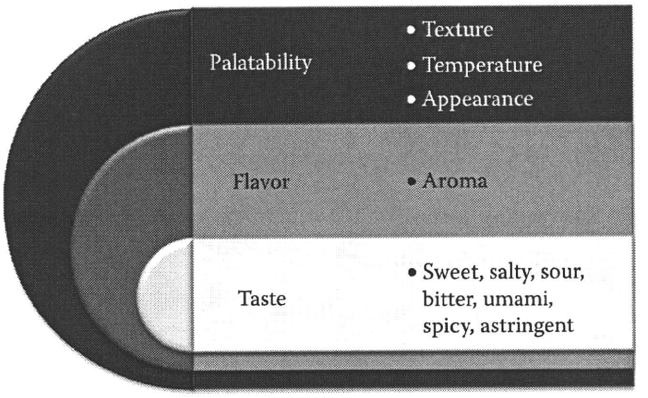
18.1 INTRODUCTION

Sufficient food intake is indispensable for maintaining nutritional status as well as quality of life in patients with cancer (Kawaguchi et al. 2006). Food intake is affected by multiple factors including sensory properties. Texture, temperature, and appearance of food are properties that regulate food intake (Kawaguchi et al. 2006). In addition, taste is a notable factor in sensory-specific satiety, as shown in Figure 18.1 (Rolls, Hetherington, and Burley 1988).

In patients with cancer, taste alterations are frequently seen because of not only therapeutic intervention such as chemotherapy and radiotherapy, but also cancer itself (Ravasco 2005). Taste alteration causes a decrease in dietary food intake and subsequent malnutrition. Malnutrition is a primary morbidity and has an impact on quality of life in patients with cancer (Ottery 1994). Thus, the management of taste alterations is important in palliative care (Table 18.1).

18.2 TYPES OF TASTE ALTERATIONS

Two types of taste alterations are seen in patients with cancer. Hypogeusia and ageusia are changes in taste acuity. Dysgeusia and phantogeusia are changes in taste quality (Hong et al. 2009) (Table 18.2).



AU: Figure legend has been merged. Please review for all figures.

FIGURE 18.1 Factors associated with dietary food intake. This figure shows factors associated with dietary food intake. In addition to taste, flavor and palatability affect dietary food intake.

18.2.1 Assessments of Taste Alteration

Au: "acuity to determine" Please check meaning

Taste alteration is assessed by taste acuity to determine recognition and detection thresholds for any of the five basic tastes: sweet, sour, salty, bitter, and umami (a Japanese word for delicious) (Wismer 2008). This examination can assess precise taste alteration; however it is not always available for patients in palliative care because of its complicated procedure.

Taste alteration can be assessed by questionnaires. Among a variety of patient-reported tools for taste alteration, the 14-questionnaire scored tool is evaluated in patients with advanced cancer (Hutton, Baracos, and Wismer 2007). The tool shows a significant correlation between the self-perceived chemosensory experience, energy intake, and quality of life (Hutton et al. 2007), suggesting a usefulness in palliative care.

18.2.2 Mechanisms of Taste Alteration

Taste alterations are induced by anticancer therapy and/or cancer itself (Ravasco 2005). Although the mechanisms of taste alteration are largely unknown, impairment of sensory receptor cells and zinc deficiency are well-known causative factors for taste alteration (Hong et al. 2009). Turnover rates of sensory receptor cells for taste are about 7–10 days. Since these high turnover cells are sensitive for radiation and chemotherapy (Hong et al. 2009), anticancer therapy may cause taste alteration. Zinc is a trace element that is involved in the sensitivity of taste (Henkin et al. 1976). Some anticancer agents bind with zinc and inhibit an activation of sensory receptor cells. In addition,

TABLE 18.1
Key Features of Taste

1. Taste is the sense that distinguishes the flavor or savor of dissolved substances by contact with the taste receptors on the tongue
2. Humans can detect seven taste qualities: sweet, sour, salty, bitter, umami, spicy, and astringent
3. Taste alterations are frequently seen in patients with cancer, because of not only therapeutic intervention, but also cancer itself
4. Taste alterations reduce interest in food, resulting in decreased dietary food intake and subsequent malnutrition
5. Malnutrition is a major morbidity and reduces quality of life in patients with cancer

Note: This table lists the key facts of taste alterations in patients with cancer. The management of taste alterations is important in palliative care.

AU: Are the legends under the table necessary? Additional legend information has been changed as Table footnote. Please review for all tables.

TABLE 18. 2
Definitions of Taste Alterations

Abnormalities	Definition
Changes in taste acuity	
Hypogeusia	Decreased sensitivity to taste perception
Ageusia	Loss of taste perception
Changes in taste quality	
Dysgeusia	Distorted sensitivity to taste perception
Phantogeusa	Perception of metallic or salty taste

Note: This table lists definitions of taste alterations. Symptoms of taste alterations are classified into changes in taste acuity and in taste quality.

a depletion of serum zinc is frequently seen in patients with hypermetabolism, malnutrition, and cachexia (Hong et al. 2009). Abnormalities in digestive tract also affect taste sensitivity and other possible mechanisms of taste alteration are summarized in Table 18.3.

18.3 PRACTICAL METHODS AND TECHNIQUES

18.3.1 Modification of Food

18.3.1.1 Flavors

Since taste is modified by flavors, adding flavor to foods is a strategy to alleviate taste alteration (Schiffman 2007) (Figure 18.2). In patients with breast or lung cancer, aromatic flavors improved nutritional status and physical function compared to those in the control group (Schiffman 2007). In addition, flavoring is reported to enhance patient compliance and quality of life (Steinbach et al. 2009).

TABLE 18.3
Mechanisms of Taste Alteration in Patients with Cancer

Mechanisms
Impairment of sensory receptor cells by anti-cancer therapy
Zinc deficiency
Oral mucositis
Oral infection
Reflux esophagitis
Gastric ulcer
Impairment of peristaltic movement in digestive tract
Impairment of chorda tympani nerve
Changes in tumor necrosis factor-α, interleukin-1β, and interleukin-6
Increased oxidative stress
Cachexia

Note: This table lists mechanisms of taste alteration in patients with cancer. Not only anticancer agents, but also various factors including gastrointestinal disorders, affect taste alteration.

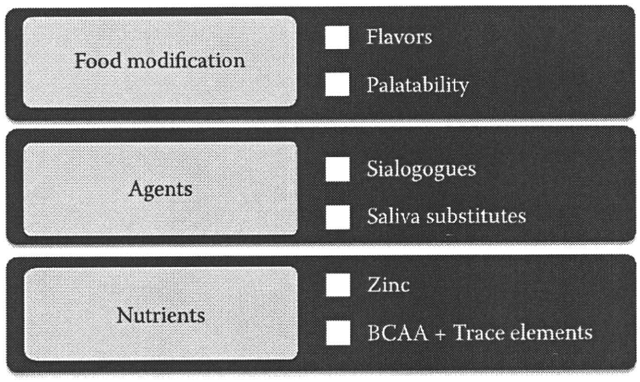


FIGURE 18.2 Therapeutic approach to taste alteration of cancer patients in palliative care. This figure shows a therapeutic approach to taste alteration of cancer patients in palliative care. A holistic approach is recommended in order to alleviate taste alteration.

18.3.1.2 Palatability

Au: Should this read "Smith, Smith, and Houpt 2010" as in reference list?

Temperature of food is an important palatability regulating food intake (Smith et al. 2009) (Figure 18.1). Warming of foods activates thermosensitive molecules in the taste transduction pathway, leading to changes in taste (Ullrich et al. 2005). The bitter taste of the branched-chain amino acids (BCAA)-enriched supplement is significantly improved by prewarming at 60°C compared to that served at 25°C. BCAA is stable at 60°C and warming of food results in an increased calorie intake and improvement of nutritional status in cirrhotic patients with hepatocellular carcinoma (Itou et al. 2009). Texture and appearance of food are also important palatabilities regulating food intake.

18.3.2 Agents

18.3.2.1 Sialogogues

Decreased salivary secretion is involved in taste alteration and therefore, sialogogues or saliva substitutes may improve taste alteration. Nizatidine, a histamine H2 receptor antagonist, is known to stimulate salivary secretion. Nizatidine inhibits acetylcholine esterase and subsequently increases acetylcholine, which stimulates muscarinic receptors of salivary glands (Nin et al. 2008). Cevimeline hydrochloride, a muscarinic acetylcholine receptor agonist, increases the salivary flow rate significantly (Vissink et al. 2004). These sialogogues may help patients with preserved salivary gland cells.

Chinese-Japanese herbal medicines are known to stimulate salivary secretion. Byakkokaninjinto increases the expression of aquaporin 5, a regulator of salivary secretion, through activation of muscarinic M3, and stimulates salivary secretion (Yanagi et al. 2008). Bakumondo-to is another Chinese-Japanese herbal medicine, which promotes salivary gland cell proliferation and enlarges the mean size of secretion granules (Kagami et al. 1996). These sialogogues may also have benefit in patients with preserved salivary gland cells.

18.3.2.2 Saliva substitutes

In patients with devastating damage to salivary glands, saliva substitutes are effective for taste alteration. There are now a variety of saliva substitutes available such as gel, carmellose spray, oil, and mucin spray (Momm et al. 2005). Significant benefits of different saliva substitutes on taste alteration are shown in patients treated by radiotherapy for head and neck cancer (Momm et al. 2005). Since palatability differs with each patient and no severe adverse effects of saliva substitutes are reported, testing different saliva substitutes is an effective approach to taste alteration in patients with cancer.

18.3.3 Nutrients

18.3.3.1 Zinc

Zinc is a well-known nutrient associated with taste alteration and zinc supplementation improves taste disorders (Henkin et al. 1976). Although its mechanism remains unclear, zinc plays important roles in the physiology of taste function. Zinc is involved in the synthesis of gustin, a salivary protein regulating taste (Shatzman and Henkin 1981). In patients with cancer, zinc supplementation improves taste disorders in cancer patients treated by chemotherapy (Yamagata et al. 2003). However, it is also reported that zinc does not prevent taste alterations in cancer patients treated by radiotherapy (Halyard et al. 2007). Thus, zinc supplementation does not always improve taste alterations and the effects of zinc on taste may differ with types of cancer, its treatments, or nutritional status.

18.3.3.2 BCAA

BCAA are amino acids that cannot be synthesized endogenously in humans (Kawaguchi, Yamagishi, and Sata 2009). BCAA are constituents of protein and are known to have some relevant pharmacologic properties in muscle-protein synthesis, the immune system, ammonia metabolism, and glucose metabolism (Kawaguchi et al. 2009). Recently, the Department of Digestive Disease Information & Research, Kurume University School of Medicine and Seikatsu Bunkasya Co. Inc. (Tokyo, Japan) developed the BCAA-enriched supplement Aminofeel®) (Tokyo, Japan) (Kawaguchi et al. 2007) and found that it improves taste alterations in patients with chronic liver diseases (Nagao et al. 2010). As the supplement contains not only BCAA, but also zinc, the impact of BCAA on alleviation of taste sensitivity remains unclear. However, the effect of zinc on taste improvement is still controversial (Halyard et al. 2007) and BCAA may alleviate taste alteration associated with chronic liver disease. In patients with cancer, decreased serum BCAA levels are frequently seen (Choudry et al. 2006), so BCAA may improve taste alterations in patients with cancer (Kawaguchi et al. 2009). Furthermore, BCAA has an ability to synthesize muscle protein. Moreover, BCAA has the potential to suppress cancer proliferation through improvement of insulin resistance (Kawaguchi et al. 2009). For these reasons, BCAA supplementation is recommended for patients in palliative care.

Au: Please provide the opening bracket for 'Aminofeel®)'

18.4 CONCLUSION

Taste alteration has a variety of etiologies and therefore the management of taste alteration in palliative care is still challenging. In order to alleviate taste alteration and subsequently improve food intake and quality of life, holistic approaches are needed. In addition, current care regarding these issues is not sufficient and further research into the pathogenesis of and development of new treatments for taste alteration is required.

Au: "current care regarding these issues" Please check meaning.

SUMMARY POINTS

- Since taste alteration is frequently seen in patients with cancer, routine assessment for taste alteration is recommended.
- A variety of etiologies may underlie taste alteration.
- Modification of food is an approach to taste alteration. Use of flavors or warming of food may improve taste alteration.
- Sialogogues and saliva substitutes are useful agents that may have a beneficial effect on taste alteration. Various types of saliva substitutes are now available and it is therefore recommended to test different saliva substitutes.
- Supplementation of zinc may alleviate taste alteration. Aminofeel®, a supplement including BCAA plus trace elements, has the potential to affect taste alteration.

ACKNOWLEDGMENTS

This chapter is based upon work supported in part by a Grant-in-Aid for Young Scientists (B) (No. 19790643 to T.K.), a Grant-in-Aid for Scientific Research (C) (No. 21590865 to M.S.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, a Health and Labour Sciences Research Grant for Research on Hepatitis from the Ministry of Health, Labour and Welfare of Japan, and a Grant for Cancer Research from the Fukuoka Cancer Society.

AU: Please review placement of abbreviations is fine here?

LIST OF ABBREVIATION

BCAA Branched-chain amino acids

REFERENCES

Choudry, H. A., M. Pan, A. M. Karinch, and W. W. Souba. (2006). Branched-chain amino acid-enriched nutritional support in surgical and cancer patients. *J Nutr* 136:314S–18S.

Halyard, M. Y., A. Jatoi, J. A. Sloan, J. D. Bearden 3rd, S. A. Vora, P. J. Atherton, E. A. Perez et al. (2007). Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central Cancer Treatment Group (N01C4). *Int J Radiat Oncol Biol Phys* 67:1318–22.

Henkin, R. I., P. J. Schecter, W. T. Friedewald, D. L. Demets, and M. Raff. (1976). A double blind study of the effects of zinc sulfate on taste and smell dysfunction. *Am J Med Sci* 272:285–99.

Hong, J. H., P. Omur-Ozbek, B. T. Stanek, A. M. Dietrich, S. E. Duncan, Y. W. Lee, and G. Lesser. (2009). Taste and odor abnormalities in cancer patients. *J Support Oncol* 7:58–65.

Hutton, J. L., V. E. Baracos, and W. V. Wismer. (2007). Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. *J Pain Symptom Manage* 33:156–65.

Itou, M., T. Kawaguchi, E. Taniguchi, S. Shiraishi, R. Ibi, M. Mutou, T. Okada et al. (2009). Heating improves poor compliance of branched chain amino acids-rich supplementation in patients with liver cirrhosis: A before after pilot study. *Mol Med Report* 2:983–87.

Kagami, H., K. Horie, H. Nishiguchi, T. Shigetomi, and M. Ueda. (1996). Effect of 'bakumondo-to', a Chinese-Japanese herbal medicine, on cultured and dispersed salivary gland cells. *J Ethnopharmacol* 53:89–95.

Kawaguchi, T., E. Taniguchi, M. Itou, J. Akiyoshi, S. Itano, M. Otsuka, S. Iwasaki et al. (2006). Appearance-specific satiety increases appetite and quality of life in patients with metastatic liver tumor: A case report. *Kurume Med J* 53:41–46.

Kawaguchi, T., E. Taniguchi, M. Itou, S. Sumie, T. Oriishi, H. Matsuoka, Y. Nagao, and M. Sata. (2007). Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: Report of two cases. *Liver Int* 27:1287–92.

Kawaguchi, T., S. Yamagishi, and M. Sata. (2009). Branched-chain amino acids and pigment epithelium-derived factor: Novel therapeutic agents for hepatitis C virus-associated insulin resistance. *Curr Med Chem* 16:4843–57.

Momm, F., N. J. Volegova-Neher, J. Schulte-Monting, and R. Guttenberger. (2005). Different saliva substitutes for treatment of xerostomia following radiotherapy. A prospective crossover study. *Strahlenther Onkol* 181:231–36.

Nagao, Y., H. Matsuoka, T. Kawaguchi, and M. Sata. (2010). Aminofeel® improves the sensitivity to taste in patients with HCV-infected liver disease. *Med Sci Monit* (in press).

Nin, T., M. Umemoto, A. Negoro, S. Miuchi, and M. Sakagami. (2008). Nizatidine enhances salivary secretion in patients with dry mouth. *Auris Nasus Larynx* 35:224–29.

Ottery, F. D. (1994). Cancer cachexia: Prevention, early diagnosis, and management. *Cancer Pract* 2:123–31.

Ravasco, P. (2005). Aspects of taste and compliance in patients with cancer. *Eur J Oncol Nurs* 9 (Suppl 2): S84–91.

Rolls, B. J., M. Hetherington, and V. J. Burley. (1988). Sensory stimulation and energy density in the development of satiety. *Physiol Behav* 44:727–33.

Schiffman, S. S. (2007). Critical illness and changes in sensory perception. *Proc Nutr Soc* 66:331–45.

Shatzman, A. R., and R. I. Henkin. (1981). Gustin concentration changes relative to salivary zinc and taste in humans. *Proc Natl Acad Sci U S A* 78:3867–71.